Connectivity-based approaches in stroke and recovery of function

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Lancet Neurol 2014; 13: 206–16

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After focal damage, cerebral networks reorganise their structural and functional anatomy to compensate for both the lesion itself and remote effects. Novel developments in the analysis of functional neuroimaging data enable us to assess in vivo the specific contributions of individual brain areas to recovery of function and the effect of treatment on cortical reorganisation. Connectivity analyses can be used to investigate the effect of stroke on cerebral networks, and help us to understand why some patients make a better recovery than others. This systems-level view also provides insights into how neuromodulatory interventions might target pathological network configurations associated with incomplete recovery. In the future, such analyses of connectivity could help to optimise treatment regimens based on the individual network pathology underlying a particular neurological deficit, thereby opening the way for stratification of patients based on the possible response to an intervention.

Introduction

Stroke is a leading cause of long-term disability (WHO atlas of heart disease and stroke 2004).[1] In countries with well developed health care systems, stroke-associated mortality has continuously declined in the past decade because of improvements in acute stroke treatment (eg, recanalisation therapy, decompressive therapy) and medical care (stroke units).[1] The increasing proportion of stroke survivors is, however, associated with a growing number of patients living with a persistent neurological deficit; despite intensive rehabilitation, more than half of all stroke patients are greatly disabled.[1] Many of these patients show persistent motor symptoms, which affect their functional independence in everyday life.[2] In view of our ageing societies, the burden of stroke is expected to rise further in the next decades, thus an urgent need emerges to further our understanding of the neurobiological factors that determine functional outcome to inform novel treatment approaches. Functional neuroimaging paves the way for non-invasive insights into the neural mechanisms underlying recovery of function and reorganisation of brain networks.

Importantly, recent developments in computational neuroscience enable us to move beyond the mere localisation of brain activity. In particular, they allow us to consider the dynamics within an ensemble or an entire network of areas sustaining a particular cognitive process or behaviour. Such analyses open up new vistas on the pathophysiology underlying stroke-induced neurological deficits and the network changes underlying recovery of function.

In this Review, we discuss recent data obtained by neuroimaging experiments that provide new insights into the mechanisms underlying recovery of function from a systems-level approach. We first summarise data obtained from animal studies that show physiological mechanisms engaged in functional recovery. We next review novel methods that non-invasively assess connectivity of brain areas and changes thereof during cortical reorganisation in patients who have had a stroke. We focus on MRI-based imaging techniques, which because of their excellent spatial resolution, enable us to study the contribution of distinct anatomical areas to recovery. Other effective brain mapping methods such as electroencephalography, magnetoencephalography, and transcranial magnetic stimulation are also briefly discussed; a more elaborate assessment of these electrophysiological methods is however beyond the scope of this Review. Finally, we aim to reconcile the findings obtained by different approaches (including functional MRI [fMRI], electrophysiological studies, and animal data) to provide a comprehensive picture of reorganisation processes after stroke. Such neuroimaging-based analyses could eventually be used to inform novel treatment strategies for neurorehabilitation.

Stroke and disconnection concepts in the nervous system

Nearly 100 years ago, the Russian-Swiss neurologist Constantin von Monakow coined the concept of diaschisis, which postulates that an acute lesion to a part of the brain consecutively leads to a reduction of excitatory input into regions remote from but connected to the lesion.[3,4] The resulting depression of the functionality of interconnected regions (so-called passive inhibition) was assumed to contribute to the neurological deficit of the patient.[5] Von Monakow further hypothesised that recovery of function is mainly caused by a reactivation of initially deafferented brain regions. By contrast, other neuroscientific pioneers of that time, such as Eduard Hitzig, Hermann Munk, and Wilhelm Trendelenburg, suggested that recovery of function could be driven by intact areas, which take over functions from the lesioned region (vicariation theory).[5,6] Likewise, collateral sprouting from intact regions to perilesional cortex was discussed as a mechanism supporting recovery (Constantin von Monakow, Santiago Ramón y Cajal).[3,5,7]

Together, important concepts of how the brain compensates for lesion-induced neurological impairment have been developed in the past century. However, when these concepts were formulated, experimental evidence

for the disconnection concept was predominantly based on post-mortem analyses of lesion location and degenerated fibre tracts, which are structural endpoints of a long cascade of processes evoked by the lesion. Hence, such data do not allow us to study in vivo the temporal dynamics underlying recovery of function. Importantly, no information about the actual role of specific anatomical areas in the process of recovery—ie, transient excitatory or inhibitory effects—can be inferred from structural lesion data. Finally, localisation of symptoms is not equivalent with localisation of function, a fact already emphasised by von Monakow.[3]

Spontaneous recovery

Animal studies have shown many biochemical and cellular processes triggered by stroke. For example, inflammatory responses such as activation of glial cells, cytokines, and other immunomodulators, and activation of neural stem cells and changes in genetic machinery, lead to enhanced expression of neuroprotective proteins, nerve growth factors, and neurotransmitter receptors.[8–11] Importantly, these effects take place within minutes and hours after a stroke, and do not only occur in the vicinity of the lesion, but also in remote areas and in the contralateral hemisphere.[12,13] In part, such processes subserve the formation of new synapses and the sprouting of axons to rewire surviving tissue, especially in peri-infarct cortex.

For example, stroke models in non-human primates showed that after focal damage to the hand area in primary motor cortex (M1), the cortical representation of the digits could expand into intact cortex that had formerly been occupied by the shoulder and elbow representations.[14] This cortical plasticity was associated with recovery of hand motor skills.[14,15] Furthermore, higher motor regions contribute to recovery of hand motor function after stroke. Neurons in the ventral premotor cortex after M1 injury were shown to form new terminals with surviving neurons in the perilesional zone.[16,17] Additionally, premotor areas develop new connections with spinal neurons to substitute the lesion-induced loss of M1 fibres.[18]

These cortical processes are supplemented by sprouting of descending fibre tracts originating from brainstem structures such as the red nucleus or the reticular formation.[19,20] About 10–15% of corticospinal tract fibres remain uncrossed at the level of the medullary pyramids, which implies that descending fibre tracts originating from the intact motor cortex might also take over functions from the lesioned hemisphere.[21] However, these uncrossed fibre tracts do not have measurable effect on spinal neurons of the distal upper limb (ie, wrist and fingers), which makes it rather unlikely that they contribute greatly to recovery of manual dexterity.[19] This does not mean that motor areas of the intact hemisphere have no role in recovery of hand motor function after stroke. For example, Nishimura and colleagues[22] showed that in macaque monkeys pharmacological inactivation of contralesional (ie, intact) M1 1 week after an experimental lesion to the corticospinal tract impaired recovery of hand function. This finding provides strong evidence that the intact hemisphere contributes to functional recovery early after stroke, probably via transcallosal rather than corticospinal signals.[19,22] Neural signals that seem to be associated with axonal sprouting between contralesional areas and the perilesional cortex are low-frequency synchronisations of neuronal activity—ie, electrophysiological phenomena similar to those seen during the formation of new connections in the developing brain.[23]

Neuroimaging of activity and connectivity

The development of non-invasive functional imaging techniques has greatly advanced our understanding of the neural mechanisms underlying behaviour and its disturbances after brain lesions in humans. These techniques not only enable us to directly test in vivo the relation between structural or functional disruptions and clinical manifestations of disease, but also warrant the opportunity for multiple testing and monitoring of treatment effects. In particular, PET and fMRI are frequently used to investigate changes in neural activity (figure 1). Neither technique directly measures neuronal activity but rather their metabolic results—ie, changes of blood flow, oxygen content, or glucose consumption.[25,26] Therefore, to obtain valid information, it is necessary to ensure that patients undergoing fMRI do not have a haemodynamically relevant stenosis or small vessel disease. Other in-vivo techniques such as electroencephalography and magnetoencephalography work at the level of spontaneous intrinsic electrical oscillations, and are hence more directly related to neuronal activity (albeit at the cost of anatomical precision). Magnetoencephalography, although technically more demanding than electroencephalography, has the advantage that the neural signals are not distorted by extracerebral tissue.[27]

All these techniques go beyond the mere localisation of neural activity to provide structure–function relations of the brain. Additionally, functional neuroimaging allows us to compute how activity in one region is related to activity in another region. This relation is referred to as functional connectivity.[28] The concept of functional connectivity assumes that two or more regions belong to the same functional network if their activation timecourses correlate with each other. Different approaches can be used to assess functional connectivity (figure 2).[30–32]

However, functional connectivity estimates do not provide information about how a functional interaction between two or more areas is expressed—ie, whether connectivity exists because area X affects area Y or vice versa. Such information about causality (or directionality) between activation time series is inferred from models of effective connectivity (figure 2A, right).[28] These models rely on mathematical assumptions that define

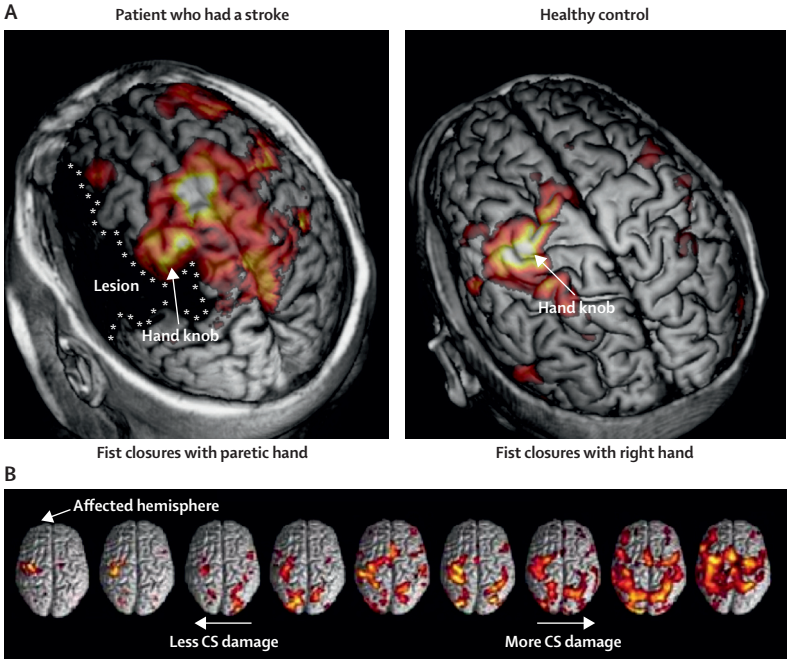

Figure 1: **Representative functional MRI blood oxygenation level-dependent activity reconstructions after stroke in the motor system**

(A) Patient with persistent hemiparesis more than 10 years after stroke (left) and an age-matched healthy control (right) during a fist closure task. In the healthy control, activity is strongly lateralised to the left hemisphere with movements of the right hand. By contrast, fist closures with the paretic hand were associated with enhanced and more extended neural activity in both hemispheres. Over-activity is particularly seen in the supplementary motor area region (see activity maximum along the interhemispheric fissure) and in the intact cortex adjacent to the lesion, which has spared the motor hand area formation (white arrows; asterisks delineate lesion region). Furthermore, additional clusters of activity are evident in prefrontal cortex, which might show higher cognitive control when doing this relatively simple task. (B) Different appearances of functional MRI activity in patients who had chronic stroke with corticospinal tract damage and different lesion volumes. Increased damage was associated with a greater amount of over-activity. CS=corticospinal. Adapted from Ward,[24] with permission from Minerva Medica.

causality. One model is dynamic causal modelling,[33] which uses a biophysically validated haemodynamic forward model to explain changes in neural activity evoked by a given task as a function of changes in excitatory or inhibitory connectivity.[32,33] Dynamic causal modelling could be more robust in clinical populations than other fMRI-based connectivity approaches because the haemodynamic response is estimated specifically for each region. This accommodates, at least to a certain degree, changes in vascular responsiveness caused by disease. Notably, causality in dynamic causal modelling refers to the modelling of brain activity, rather than the relation between activity or connectivity and behaviour. At present, dynamic causal modelling is limited to a maximum of 8–10 regions. Further technical details on dynamic causal modelling and other approaches to functional or effective connectivity have been described elsewhere.[34,35]

A complementary approach to connectivity offered by neuroimaging is diffusion-based MRI (dMRI). This technique images the random diffusion of water in intracellular and extracellular spaces. Particularly in white matter, the mobility of water molecules is restricted by microstructural barriers—eg, along bundles of axons (figure 3A).[37] Diffusion-tensor imaging makes use of this anisotropic diffusion behaviour by estimating the preferred diffusion direction (fractional anisotropy) in each voxel. This approach not only enables us to detect disease-associated changes in diffusion properties in a given white matter voxel, but also allows the reconstruction of entire fibre tracts.[38] At present, dMRI at standard magnetic resonance field strengths (1·5–3·0 Tesla) provides a voxel resolution of 1–2 mm edge length. This in turn means that diffusion-tensor imaging values do not show single fibres, but rather information pooled along thousands of axons (even at the ultra-high magnetic field strength encountered in 7 Tesla scanners).

Imaging motor recovery

Both PET and fMRI have been used to investigate changes in neural networks after brain lesions. A frequent finding is that ischaemic lesions alter neural activity in both the affected and the unaffected hemisphere (figure 1). Studies of animal models and patients who have had a stroke show that in the first few days after stroke, brain activity is typically reduced in the lesioned hemisphere.[39–41] Thereafter, neural activity gradually increases concurrent to functional recovery, both in the lesioned and the unaffected, healthy hemisphere.[41–43] In particular, patients with severe motor deficits show greater recruitment of motor and non-motor (eg, prefrontal) areas of the unaffected hemisphere than that reported for healthy controls (figure 1).[44] Similar effects have been observed in animal models of stroke.[45]

The changes in neural activity are closely linked to behavioural recovery. For example, in humans bilateral increases in fMRI motor activity of M1, the supplementary motor cortex, the lateral premotor cortex, and the superior parietal cortex in the first 2 weeks after stroke correlate with greater improvements of hand motor function during this period.[41] A magnetoencephalography correlate of poor recovery is the appearance of abnormal low-frequency magnetic activity in the perilesional cortex, particularly in patients with large cortical lesions.[46] In the weeks and months after stroke, cortical over-activity in these areas usually decreases to levels seen in healthy controls, particularly in patients with better recovery.[42,43,47] Furthermore, patients with better motor recovery show stronger coherence between ipsilesional M1 magnetoencephalography signals and electroencephalography activity of the paretic hand.[48] These electrophysiological data converge with findings from a recent meta-analysis of 43 fMRI experiments, which showed that the patients with better motor performance had a greater likelihood of activation in ipsilesional M1.[49] Therefore, restitution of ipsilesional M1 function seems to be crucially associated with functional recovery.

By contrast, patients featuring persistent fMRI over-activity of the unaffected hemisphere in the chronic phase (ie, 6–12 months after stroke) usually show poor recovery. These patients often present with more extensive anatomical damage to the corticospinal system (figure 1B).[24] Consistently, transient downregulation of contralesional M1 excitability has been used to improve motor function of the paretic hand, suggesting an inhibitory role of this area for functional recovery.[50–52]

However, some patients with good functional recovery can also show fMRI over-activity in contralesional motor areas.[49] Likewise, magnetoencephalography experiments on corticomuscular coherence demonstrated significant contributions of contralesional areas in the frontal and parietal regions to muscular activity of the paretic hand (in addition to ipsilesional sources).[53] In patients who had a congenital stroke, corticomuscular coherence during movements of the paretic hand was even shown exclusively in the unaffected hemisphere.[54] Likewise, interfering with neural activity in the contralesional dorsal premotor cortex, M1, or superior parietal cortex by means of 20 Hz transcranial magnetic stimulation resulted in significant deterioration of performance in patients.[55]

Therefore, the exact functional role that brain regions such as the contralesional M1 have during recovery seems to be complex. Most likely, time since stroke, severity of deficit at baseline, lesion size, location, and other biological factors (eg, age of the patient) all contribute to interindividual differences.

Neuroimaging of structural connectivity

A key factor affecting brain networks after stroke is the anatomical damage. Lesion location rather than the mere size of the lesion accounts for the neurological sequelae after stroke.[56,57] For example, severe hemiplegia could be caused by a small lesion confined to the posterior limb of the internal capsule. This anatomically specific effect arises from disruption of the corticospinal tract fibres connecting cortical motor areas with motor neurons in the spinal cord.[58] Diffusion-tensor imaging studies consistently show that the more corticospinal tract fibres that are damaged, the more severe the motor deficits are (figure 3).[36,59] In particular, lesions affecting fibres originating from the M1 and dorsal premotor cortex seem to determine motor performance after stroke.[60]

Furthermore, histological analysis of rat stroke models suggests that corticospinal tract lesions lead to secondary demyelination of transcallosal fibres between motor areas.[61] Consistently, remote effects of stroke lesions on the integrity of transcallosal fibres have been reported in human studies using diffusion-tensor imaging.[36,62] Notably, patients with pronounced degeneration of transcallosal motor fibres are also more likely to show pathologically enhanced motor activity in the contralesional hemisphere (figure 3B).[36] Therefore, chronic stroke over-activity in the unaffected hemisphere might be caused by disturbances in interhemispheric inhibition.

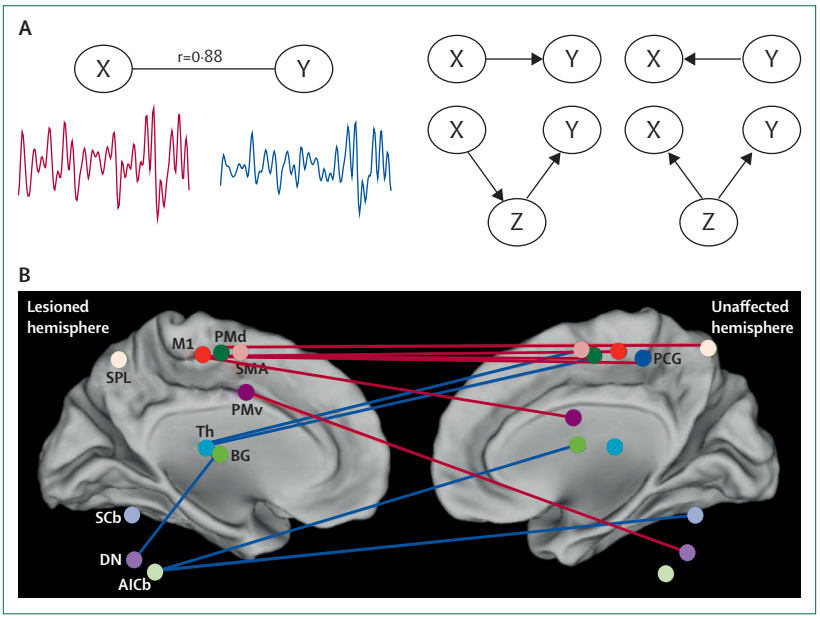

Figure 2: **Functional connectivity analysis of functional MRI time series**
(A) Left: Example of correlated blood oxygenation level-dependent resting-state activity between area X and area Y (primary motor cortex in the left and right hemisphere). Right: The models show possible explanations for correlated activity, which cannot be resolved by functional connectivity analyses, but can with models of effective connectivity revealing directional influences. (B) Longitudinal changes of functional resting-state connectivity in the motor system after stroke. Red lines denote increases in connectivity over time, blue lines show decreases. In particular, connectivity of ipsilesional M1 and contralesional motor areas increases with recovery, whereas connectivity between subcortical areas decreases. SPL=superior parietal lobe. PMd=dorsal premotor cortex. PMv=ventral premotor cortex. M1=primary motor cortex. Th=thalamus. BG=basal ganglia. SCb=superior cerebellum. DN=dentate nucleus. AICb=anterior inferior cerebellum. PCG=postcentral gyrus. Adopted from Wang and colleagues,[29] with permission from Oxford University Press.

Another factor that affects the potential for recovery is global white matter changes caused by small-vessel disease.[63] Likewise, the integrity of fibre tracts of the unaffected hemisphere is indicative of motor outcome after stroke.[64] However, invasive studies in monkeys showed that the contralesional corticospinal tract has no relevant role in the recovery of hand motor function.[19] Rather, fibre tracts from brainstem structures, such as the red nucleus or the reticular formation, seem to contribute to recovery of upper limb function in non-human primates.[19,20] Whether or not such compensatory pathways also exist in human beings remains to be elucidated. First evidence for this hypothesis stems from a recent diffusion-tensor imaging study, which suggests that improved motor function in chronic stroke is associated with stronger structural connectivity between the motor cortex and the red nucleus.[65] Hence, greater recruitment of the cortico-rubro-spinal system might help to compensate for pyramidal tract lesions in patients who have had a stroke.

Neuroimaging of functional connectivity

The widespread but specific structural changes observed in patients who have had a stroke are mirrored by distinct changes of functional interactions between cortical areas.

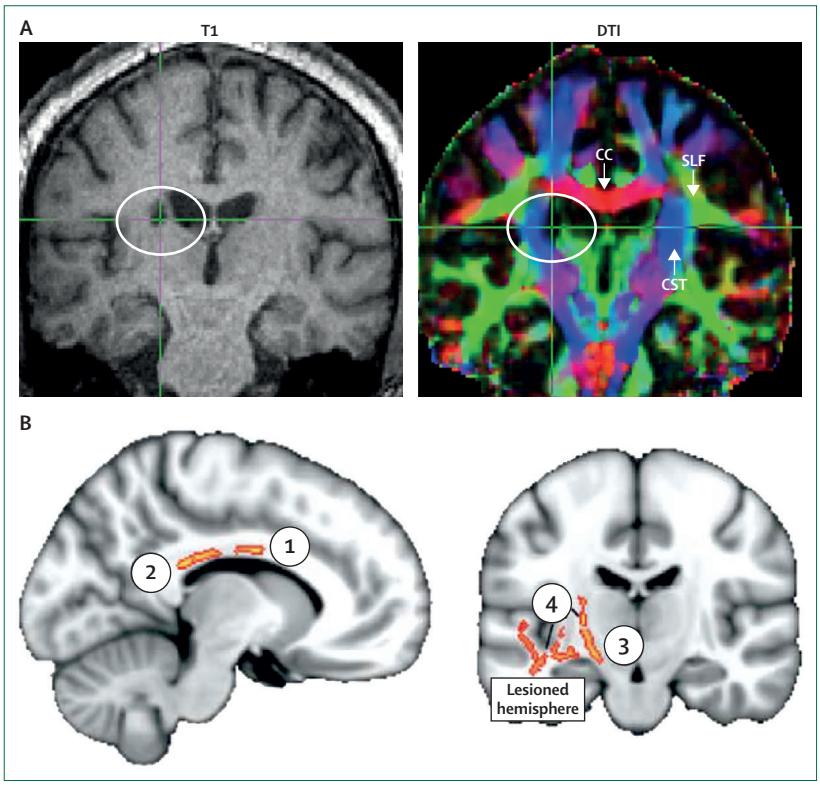

Figure 3: **Diffusion-tensor imaging of fibre tracts in patients who have had a stroke with motor deficits**
(A) Individual MRIs showing a T1-weighted anatomical image (left) and a diffusion-tensor imaging MRI volume sampled with 60 directions (right). The principal diffusion directions are colour-coded (red=medial-lateral; green=anterior-posterior; blue= superior-inferior). A paraventricular lesion leads to a partial interruption of the corticospinal tract (blue descending fibres). (B) Group data showing voxel-wise positive correlations between diffusion fractional anisotropy and fMRI over-activity (laterality index) for a group of 18 patients who had a chronic stroke. Significant effects ($p<0·05$) were seen in four clusters, two of them situated in the body of the corpus callosum (1, 2), and two (3, 4) in the internal capsule extending into the adjacent inferior longitudinal and fronto-occipital fasciculi (4). The same clusters also correlate with the severity of motor impairment (Action Research Arm Test). Hence, patients with the greatest reductions of fractional anisotropy in the corpus callosum and along the corticospinal tract have both greater motor impairment and less lateralised fMRI activation patterns during movements of the paretic hand. T1=T1 weighted MRI. DTI=diffusion-tensor imaging. CC=corpus callosum. SLF=superior longitudinal fasciculus. CST=corticospinal tract. fMRI=functional MRI. Adapted from Wang and colleagues,[36] with permission from John Wiley and Sons.

In neuroimaging, functional connectivity between brain regions can be measured in two different functional states: during a particular task or in the absence of a structured task—ie, during rest.[31] During rest, participants are requested to lie motionless in the scanner without thinking of something particular (but to stay awake). Resting-state blood oxygenation level-dependent activity is then acquired and analysed for correlated low-frequency (<0·1 Hz) fluctuations.

Several studies showed that, at rest, cortical areas belonging to the same functional system have correlated fMRI activity. For example, even in the absence of overt movements, the primary motor cortex exhibits coherent activity with other motor areas in both hemispheres.[31,32] The advantage of resting-state measurements in stroke research is that they do not impose particular demands on the patient's ability to comply.[35]

Functional connectivity and recovery

Functional connectivity analyses based on resting-state fMRI have identified stroke-induced disturbances of the functional network architecture in both animals and patients (figure 2B). For example, resting-state measurements in rats recovering from induced stroke showed that impaired sensorimotor performance was associated with a loss of interhemispheric connectivity between sensorimotor regions, whereas recovery of function weeks after stroke was paralleled by normalisation of interhemispheric connectivity.[66] Similar effects have been reported in fMRI studies of stroke in human beings.[67] Converging evidence stems from electroencephalography studies, which showed that the disruption of coherent resting-state oscillations in the α-band (but not in other bands) highly correlates with specific motor or cognitive deficits.[68,69]

Recovery from motor deficits is typically associated with a steady increase of resting-state connectivity, particularly between the ipsilesional M1 and contralesional areas (figure 2B).[29,70] Magnetoencephalography-based analyses of resting-state functional connectivity in patients who had subacute stroke showed a close relation between improved recovery scores sampled during 2–3 months and initially higher connectivity estimates within the motor system.[71] Likewise, with fMRI, Park and colleagues[72] reported that patients with higher interhemispheric connectivity between motor areas in the acute phase show improved motor recovery 6 months after stroke.

Importantly, these effects seem to be anatomically and behaviourally specific. For example, patients with motor impairments but without visuospatial neglect show pathological connectivity in the motor system but not in attention-related networks.[67] Consistently, lesion studies suggest that these effects arise from damage to specific fibre pathways. For example, in both human and animal stroke models, reduced interhemispheric connectivity between motor areas is directly related to the integrity of the corticospinal tract after stroke.[61,73] Therefore, white matter lesions do not only interrupt output fibres of the cortex (thereby disconnecting motor neurons from spinal neurons), but also trigger remote changes of corticocortical processing. Notably, the corticospinal tract does not only contain corticofugal projections, but also ascending fibres into the motor cortex. Disruption of these input fibres might lead to a functional deafferentation of the target region (eg, M1). This deafferentation theory is supported by findings from transcranial magnetic stimulation studies suggesting that corticospinal tract lesions activate intracortical inhibitory circuits in M1, which reduce the excitability of cortical motor neurons.[74,75] Likewise, pontine lesions affect functional connectivity between M1 and the contralateral cerebellum.[76] Together, these findings sampled in different species and brain regions suggest that focal lesions cause system-wide changes in structural and functional connectivity, which contribute to behavioural

impairment. This systems-based view on the effect of stroke also explains the clinical notion that lesions in very different parts of the brain can result in similar behavioural deficits.

Effective connectivity after stroke

A severe restriction of functional connectivity analyses is that they do not provide information about the directionality of functional interactions. By contrast, models of effective connectivity explicitly test the effect that one area exerts on another.[28] So far, most studies on effective connectivity changes after stroke focus on dynamic causal modelling of fMRI activity.

Dynamic causal modelling applied to fMRI data obtained from healthy individuals suggests that movements of the right or left hand lead to an increase of excitatory effects from premotor areas exerted on the contralateral M1 activity, whereas ipsilateral M1 activity is suppressed (figure 4A).[78] The amount of inhibitory coupling estimated by fMRI dynamic causal modelling correlates with interhemispheric inhibition effects measured with transcranial magnetic stimulation, thereby providing validity for the dynamic causal modelling approach.[79] In patients who have had a stroke, excitatory influences in the lesioned hemisphere are reduced in the subacute to chronic phase, particularly between the supplementary motor area and M1, but also between premotor areas.[77,80] Importantly, during movements of the paretic hand, some patients show additional negative influences exerted from the contralesional M1 on the ipsilesional M1 activity. These influences are not observed in healthy controls and correlate with the degree of motor impairment (figure 4B, C).[77] Hence, the more impaired a patient is, the more the contralesional M1 exerts an inhibitory influence on the ipsilesional M1, which further reduces the motor output of the lesioned hemisphere beyond that which could be due only to the anatomical damage. Similar effects have been seen in a paired-pulse transcranial magnetic stimulation study during movement preparation of the paretic hand.[81]

Effective connectivity and recovery

Longitudinal studies of changes of fMRI effective connectivity in stroke showed that in the first few days after ischaemia, coupling of the ipsilesional supplementary motor area and ventral premotor cortex with ipsilesional M1 was significantly reduced.[82] Coupling parameters between these areas increased with recovery and predicted a better outcome 3–6 months later. Thus, there seems to be a tight relation between changes of motor system activity, premotor–M1 connectivity, and early recovery after stroke (figure 5). Furthermore, changes of interhemispheric connectivity between the two M1 regions depend on the time elapsed since stroke: in the acute phase, inhibitory effects exerted from the ipsilesional on the contralesional M1 have been shown to be

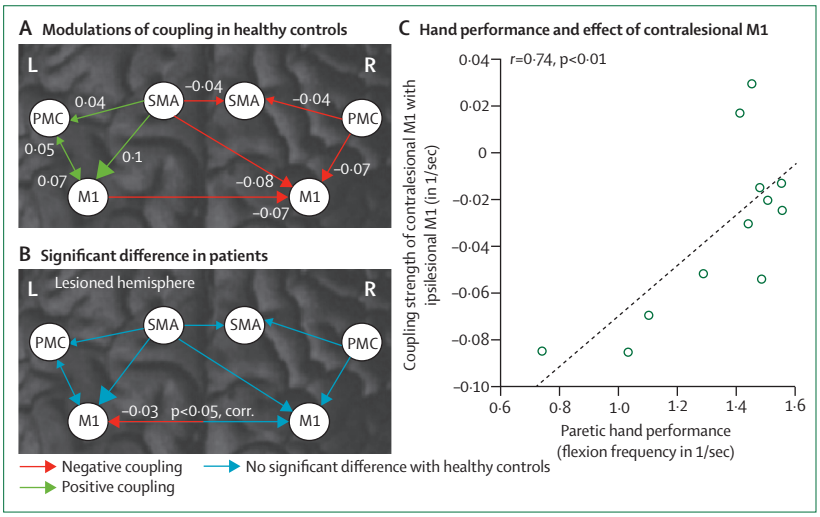

Figure 4: **Effective connectivity during hand movements in healthy controls and patients with persistent motor deficits in the subacute to chronic phase post stroke**
(A) In healthy controls, unilateral hand movements are associated with increased coupling of premotor areas with contralateral (active) motor area (green arrows; numbers by the arrows refer to coupling strength in Hz), whereas activity in the ipsilateral hemisphere is suppressed (red arrows). (B) In patients with persistent hemiparesis, the contralesional M1 exerts an inhibitory influence (red arrow) on the ipsilesional M1 (blue arrows indicate no difference to controls). (C) The amount of inhibitory coupling exerted by contralesional M1 correlates with the degree of motor impairments—ie, the greater the inhibitory coupling the greater the impairment. PMC=lateral premotor cortex. SMA=supplementary motor area. M1=primary motor cortex. Adapted from Grefkes and colleagues,[78] with permission from John Wiley and Sons.

significantly reduced, particularly in patients with the worst impairment. About 2 weeks later, the contralesional M1 starts to exert a positive effect on the ipsilesional M1, suggesting a supportive role for motor performance during the subacute phase (figure 5). With further recovery in the subsequent months, ipsilesional motor areas re-establish their inhibitory effects on the contralesional M1, eventually resulting in connectivity patterns similar to those seen in healthy individuals (figure 4A). In some patients with good motor recovery, the contralesional M1 seems to maintain a supportive effect on ipsilesional M1 activity (figure 4C, figure 5).[82] These findings are supported by transcranial magnetic stimulation, electroencephalography, and magneto-encephalography data, which show that in patients with good recovery, the contralesional hemisphere contributes to the degree of recovered function.[48,55,83] With dynamic causal modelling analyses of magneto-encephalography data, similar effects have been reported for the language system.[84]

However, in patients with poor functional recovery, the contralesional M1 seems to lose its supporting effects (figure 4C).[77,82] The shift from an early, supportive role of the contralesional M1 into an inhibitory one probably constitutes a maladaptive process that contributes to reduced motor performance of the paretic hand.[82] The neurobiological factors causing this maladaptive development are unknown, but are, at least in part, related to lesion location.[77,85] For example, patients with lesions in the basal ganglia or interhemispheric fibres are more likely

to develop abnormal inhibition phenomena at the cortical level.[77,86] As such, interhemispheric inhibitory effects seem to arise at later stages during recovery,[82] and might be related to secondary degenerative processes (neuronal or axonal degeneration, ineffective sprouting). Support for this hypothesis stems from diffusion-tensor imaging studies showing a degeneration of transcallosal fibres in patients with over-activity of contralesional M1.[36] However, because of the scarcity of data, these conclusions are preliminary and need to be systematically tested in future studies. Additionally, cross-validation experiments are needed to show the electrophysiological and anatomical underpinnings of connectivity parameters derived from functional neuroimaging (eg, by combining fMRI dynamic causal modelling with electroencephalography, transcranial magnetic stimulation, or animal data).[79,87–89]

Treatment implications

The question of whether or not contralesional areas support recovery of function is highly relevant with respect to the development of new treatment approaches. For example, non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation can be used to either enhance or suppress neural activity of the stimulated region.[50,52,90,91] However, so far, data are inconsistent about the treatment efficacy of these approaches; some patients have improved after stimulation-induced suppression of contralesional M1, but some have not.[91]

A reason for these conflicting observations could be that the inhibitory stimulation protocols applied to the contralesional M1 might only be effective in patients with abnormal interhemispheric inhibition. As outlined, contralesional over-activity is not equivalent to maladaptive interhemispheric inhibition (figure 5). This issue can be resolved by means of connectivity analyses in order to guide therapeutic interventions. For example, repetitive transcranial magnetic stimulation-induced inhibition of the contralesional M1 had the greatest effect on behavioural improvements in patients who

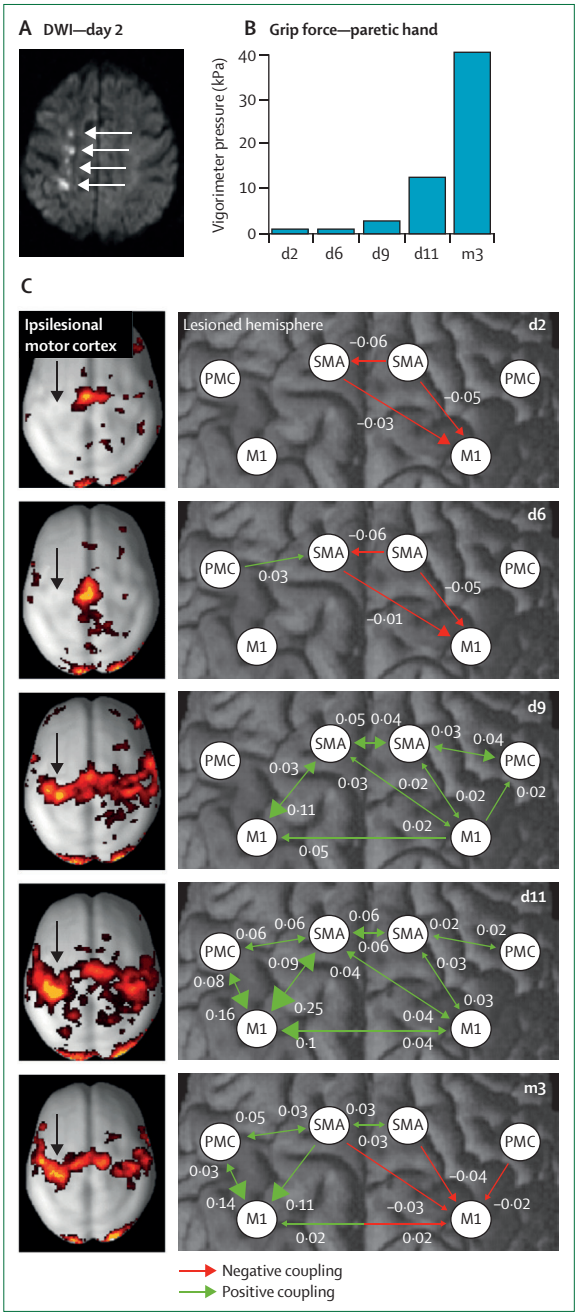

Figure 5: **Dynamic causal modelling of motor activity in a patient recovering from first-ever stroke**

(A) Many acute ischaemic lesions (arrows) in white matter of the middle cerebral artery territory 2 days after thromboembolic stroke. The patient, who was on warfarin because of chronic atrial fibrillation, had stopped her medication 1 week before symptom onset (hemiplegia). The cause for the watershed-like distribution might be a transient occlusion of the right middle cerebral artery in the presence of well developed collaterals. The small lesion volume with only little overlap with the corticospinal tract is likely to have facilitated the rapid recovery of the patient. (B) Grip force measurements during recovery using a squeeze-ball vigorimeter. In the first 6 days (d2, d6), the patient was unable to move the stroke-affected hand (hemiplegia). At day 9 (d9), minimal finger movements were possible. 2 days later (d11), the patient was able to move the entire hand. At 3 months post stroke (m3), grip force had fully recovered. (C) Changes in movement-related blood oxygenation level-dependent activity and effective connectivity. Attempts to move the paralytic hand were initially associated with an increase in supplementary motor area activity, but not of the ipsilesional primary sensorimotor cortex (black arrows). Note the breakdown of effective connectivity in both hemispheres. Minimum motor recovery (day 9) induced significant increases of activity not only in the ipsilesional motor cortex, but also in contralesional sensorimotor areas. This phase was characterised by a general upregulation of excitatory influences, which further increased with advancing recovery. Note the supportive influences from the contralesional M1 on ipsilesional M1 activity at days 9 and 11. Full motor recovery after 3 months was associated with a reduction of over-activity and recurrence of inhibitory effects onto contralesional motor areas. Of note, this patient, who had full recovery, still featured coactivation of the contralesional M1, which according to dynamic casual modelling had a supporting effect on ipsilesional M1 activity. DWI=diffusion-weighted imaging. Numbers by the green and red arrows refer to coupling strength in Hz. PMC=lateral premotor cortex. SMA=supplementary motor area. M1=primary motor cortex. Data from the patient cohort published by Rehme and colleagues.[82]

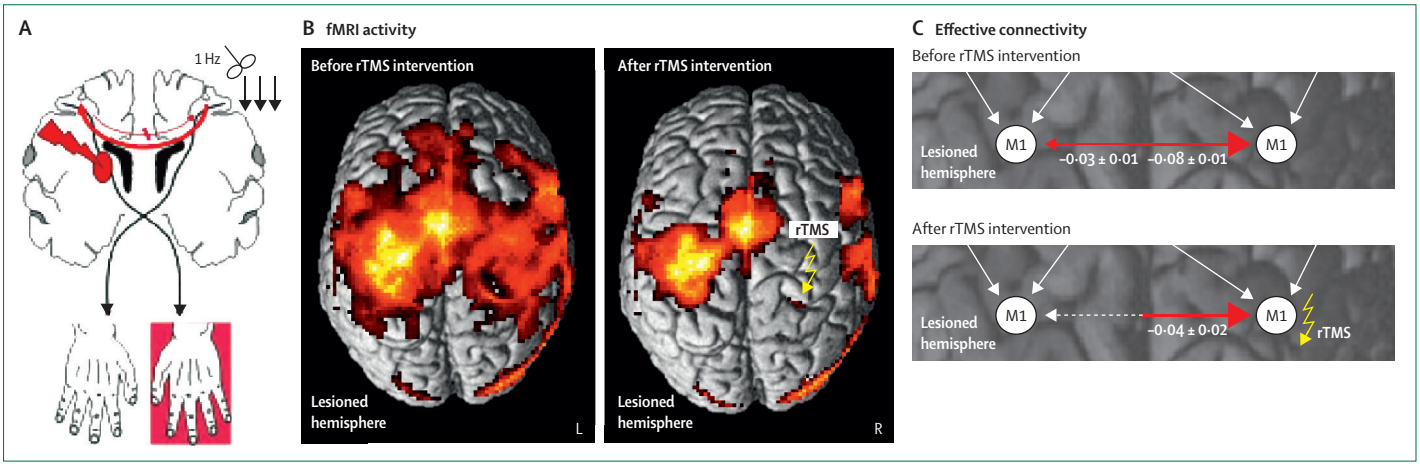

Figure 6: **Modulation of brain networks by means of repetitive transcranial magnetic stimulation**
A cohort of 11 patients, 1·9 months after a stroke (ranging from 1–3 months) with motor deficits (mean ARAT 45·5, range 41–57; mean MRC 4·3, range 4–5), were stimulated with inhibitory 1-Hz repetitive transcranial magnetic stimulation. The functional improvements after stimulation were variable. Although fist closure frequency improved on average by about 4% (compared with baseline), maximum finger tapping frequency of the index finger improved by about 28%. (A) Stimulation site over contralesional M1 using an inhibitory 1-Hz repetitive transcranial magnetic stimulation protocol. (B) Effect of inhibitory repetitive transcranial magnetic stimulation on over-activity in the contralesional hemisphere. (C) Effect of inhibitory repetitive transcranial magnetic stimulation applied over contralesional M1 on interhemispheric inhibition. After treatment, negative coupling effects from contralesional M1 were absent. This effect correlated with improvement in motor performance of the paretic hand. fMRI=functional MRI. rTMS=repetitive transcranial magnetic stimulation. ARAT=action research arm test. M1=primary motor cortex. Red lines=inhibitory coupling. Solid white lines=influences from premotor regions. Dashed lines=absent coupling after stimulation. Numbers by the arrows refer to coupling strength in Hz. Adapted from Grefkes and colleagues,[92] with permission from Elsevier.

showed the strongest reduction of interhemispheric inhibition after the intervention, providing strong evidence for the interhemispheric inhibition theory as a factor underlying motor impairment after brain lesions (figure 6).[92] Suppression of the contralesional M1 by repetitive transcranial magnetic stimulation was also associated with a more effective coupling between the ipsilesional supplementary motor area and the ipsilesional M1. Similar effects have been observed in resting-state fMRI studies, in which effective connectivity from the premotor cortex to the ipsilesional M1 increased after 3 weeks of intensive rehabilitation in subacute stroke.[93] Thus, improved motor performance after intervention might result from a remodelling of the neural network architecture of the entire motor system towards a more physiological state (ie, stronger facilitation from the premotor cortex, less inhibition from the contralesional M1).[92,94–96]

Conclusions and future directions

Connectivity-based analyses of neuroimaging data allow new insights into the pathophysiology underlying stroke-induced deficits, as they provide an in-vivo systems-level perspective of the specific outcomes that a lesion has on neural networks. Therefore, these approaches do not only enable us to test established (but mostly theoretically founded) concepts of disconnection syndromes in an experimental setting, but also to extend these by providing the opportunity to study recovery of function over time. Furthermore, they enable us to investigate the specific contributions of brain areas to recovery of function, the effect of therapies on cortical reorganisation, and the reasons why some patients improve and others do not. Importantly, MRI-based techniques have an excellent spatial resolution, which offers us the opportunity to move from a conceptual basis of cortical reorganisation towards an anatomical or neurobiological explanation of the underlying processes. Already, these studies have shown that there is no unique reorganisation scheme with supportive or maladaptive effects of certain brain areas, a finding which has substantial implications when designing new rehabilitation schemes. Connectivity analyses of non-invasive neuroimaging data might help to identify brain regions suitable for neuromodulatory approaches—ie, where enhancement or suppression of activity will support the effect of training or other therapies.[85,97] Whether or not this conjecture will ultimately be proven feasible in a clinical environment remains to be elucidated.

An important limitation of all non-invasive brain mapping techniques (including electroencephalography, magnetoencephalography, and transcranial magnetic

Search strategy and selection criteria

We searched PubMed from January, 1990, to August, 2013. Search items were combinations of "stroke", "neuroimaging", "functional connectivity", "effective connectivity", "DTI", and "motor system". For some sections of this Review, additional keywords such as "animal", "rat", "monkey", and "transcranial magnetic stimulation", "electroencephalography", or "magnetoencephalography" were used. The final reference list is based on the relevance of the articles to the scope of this Review.

stimulation) is that they do not record microstructural information at the level of axons and synapses. Complementing connectivity studies of the human brain with animal studies might help to overcome this limitation. Because network analyses are computationally demanding and require a high amount of methodological expertise, it seems necessary to develop standardised and robust connectivity protocols (eg, based on resting-state fMRI), which can be integrated into clinical routine to allow a reliable estimation of network disturbances at a single-subject level. Such a development would be a major step forward into an era of personalised medicine in neurorehabilitation.

Contributors

CG searched for the relevant literature, wrote the first draft of the manuscript, and designed the figures. GRF critically revised the first draft and all subsequent versions of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

CG is supported by grants from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG GR 3285/2–1 and GR 3285/5–1). Additional support from the Marga-and-Walter-Boll Foundation to GRF is gratefully acknowledged.

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