Cortical Reorganization After Stroke: How Much and How Functional?

Christian Grefkes¹,² and Nick S. Ward³,⁴

Abstract
The brain has an intrinsic capacity to compensate for structural damage through reorganizing of surviving networks. These processes are fundamental for recovery of function after many forms of brain injury, including stroke. Functional neuroimaging techniques have allowed the investigation of these processes in vivo. Here, we review key advances over the past two decades that have shed light on the neural mechanisms enabling recovery of motor function after stroke. We first provide an overview on invasive stroke models in non-human primates that provided insights into lesion-induced changes in the cortical representations of the upper limb. We then present key findings from neuroimaging studies in human stroke patients, which suggest that the role of contralesional motor hemisphere in supporting recovered function depends on factors such as time since stroke, lesion location and anatomical region. More recently, research has been directed at understanding how surviving brain regions influence one another during movement. It appears that it is not only the corticospinal tract but also brainstem pathways and interhemispheric connections that affect cortical reorganization patterns and functional recovery. In summary, neuroimaging opens the way for greater understanding of the mechanisms of recovery and potentially improves our ability to deliver effective restorative therapy.

Keywords
functional neuroimaging, motor system, connectivity, transcranial magnetic stimulation (TMS), fMRI

Stroke: Epidemiology and Causes
Stroke is a common neurological disease in industrialized countries. According to estimations published by the World Health Organization, 15 million people per year worldwide suffer a stroke, making it the third leading cause of death after coronary heart disease and cancer (WHO Atlas of Heart Disease and Stroke, 2004; http://www.who.int/cardiovascular_diseases/resources/atlas). Approximately 80% to 90% of all strokes are caused by an interruption of blood supply due to an obstructed blood vessel (ischemic stroke), whereas intracranial bleedings are found in 10% to 15% (hemorrhagic stroke). As a consequence, brain tissue in the affected vascular territories becomes dysfunctional, and ultimately necrotic. Brain edema and subsequent herniation of brain tissue are poor prognostic indicators for survival (Hacke and others 1996). However, over the past few decades, mortality from stroke has continuously declined because of advances in acute treatment together with improvements in primary and secondary prevention of stroke. However, only a small fraction (5% to 15%) of all stroke patients is eligible for acute treatments such as thrombolysis or thrombectomy, because of the narrow window of opportunity in acute stroke. And even those that can be treated may still have a permanent neurological deficit due to irreversibly damaged brain tissue. Such deficits are often found in the motor domain. In the acute phase, more than 80% of the patients present with motor impairments such as hemiparesis or loss of manual dexterity (Bonita and Beaglehole 1988). In the ensuing weeks and months, substantial recovery may occur even in patients with initially severe motor deficits, especially when patients receive some form of training like physical or occupational therapy (Maulden and others 2005). The rate of overall recovery is often greatest within the first 3 to 6

¹Department of Neurology, Cologne University Hospital, Cologne, Germany
²Max Planck Institute for Neurological Research, Cologne, Germany
³Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, UK
⁴The National Hospital for Neurology and Neurosurgery, London, UK

Corresponding Author:
Christian Grefkes, Department of Neurology, Cologne University Hospital, Kerpener Strasse 62, Cologne 50624, Germany. Email: christian.grefkes@uk-koeln.de
months after stroke onset (Bonita and Beaglehole 1988; Cramer 2008). Maximum improvement rates are found within the first 4 weeks post-stroke, and patients with less initial impairment show faster improvement with better final outcome compared to those with severe stroke (Cramer 2008; Hendricks and others 2002). Interestingly, it seems that recovery rates can differ for motor, language and cognitive impairments, suggesting that the underlying mechanisms of recovery may also be different for each domain (Cramer 2008; Hier and others 1983).

**Neurobiology Underlying Recovery of Function: Animal Studies**

A number of factors contribute to spontaneous functional recovery after stroke. Already within a few minutes after ischemia, a complex cascade of cellular and molecular processes is activated not only in the peri-lesional tissue but also in remote brain regions (Schallert and others 2000). These processes comprise inflammation, genetic changes in transcription and translation, secretion of growth factors, changes in neurotransmitter receptors, formation of new synapses, and sprouting of axons (Cramer 2008). All these processes facilitate the “rewiring” of neurons to compensate for the ischemia-induced loss of brain tissue. For example, tract-tracing studies in rats showed that 4 weeks after stroke neurons located in cortex (M1) next to the infarct give rise to new connections with surrounding tissue (Carmichael and others 2001). These processes might contribute to early functional reorganization. In macaque monkeys, 2 weeks after surgical removal of the thumb representation in primary motor cortex (M1), electrical responses can be elicited in a zone surrounding the infarct area that did not show thumb responses before surgery (Glees and Cole 1950). These changes are not limited to M1. For example, the size of the ventral premotor cortex—a region that is engaged during grasping movements (Rizzolatti and others 2002) and that shares extensive connections with M1 (Dum and Strick 2005)—increases in proportion to larger lesions in M1 (Frost and others 2003). These changes are accompanied by formation of new connections of ventral premotor cortex (PMv) with surviving, intact tissue concurrent to motor recovery (Danccause and others 2005).

However, a critical factor for early cortical reorganization phenomena seems to be task-specific practice. In healthy animals, immobilization of the distal forelimb for several months leads to a redistribution of cortical forelimb representations (Milliken and others 2013). In particular, the digit representations progressively decrease with longer immobilization period whereas wrist and forearm representation increase in spatial extent. Importantly, such reorganization phenomena are reversible after terminating immobilization and ensuing motor training (Milliken and others 2013). These results demonstrate the impact of training and restricting movements on cortical plasticity. Evidently, this is of great importance in the context of motor rehabilitation. In a seminal study, Nudo and others (1996) demonstrated that in monkeys receiving 4 weeks of retraining of skilled hand use after ischemic damage to the hand motor area, cortical representations of the digits, wrist, and forearm expanded into intact cortex that had been formerly occupied by the elbow and shoulder representation. In contrast, monkeys without training experienced a loss of the digit and wrist-forearm area in surviving tissue (Nudo and others 1996). These findings underpin the importance of early rehabilitative training for cortical reorganization and functional recovery after stroke. Furthermore, studies in macaques demonstrated changes in the unaffected hemisphere after lesions to the corticospinal tract, that is, the large fiber bundle that connects the motor cortex with spinal neurons (Nishimura and others 2007). Here, recovery of arm motor functions after a selective lesion of the lateral corticospinal tract at a high cervical level (segments C4/C5, thereby disconnecting motor fibers to the arm and hand) was associated with increases in cortical activity in bilateral primary motor cortex (M1) and cerebellar vermis 4 weeks after the lesion compared with preoperative activity levels (Fig. 1). Recovery at later stages (i.e., after 3 months) was associated with increased activity compared with preoperative levels in M1 contralateral to the affected hand as well as in PMv. Pharmacological inactivation of these areas by means of focal injections of muscimol, a GABA-A receptor agonist, reinstated the motor deficit, thereby demonstrating a causal role of these activation changes for recovered hand function, especially for the early period of recovery. Here, inactivation of either ipsilateral or contralateral M1 as well as contralateral PMv led to a marked deterioration of recovered hand function. In contrast, at later stages of recovery, inactivation of ipsilateral M1 had no effects on behavioral performance, and also contralateral M1 inactivation had only mild behavioral effects (Nishimura and others 2007). In summary, these findings imply that recovery of at least some function (1) relies on time-dependent changes in cortical activity and (2) also depends on motor areas ipsilateral to the affected hand during early recovery.

However, it remains unclear how ipsilateral motor areas contribute to functional recovery of the lesioned hand. In principle, there are two major routes by which ipsilateral M1 could contribute to hand motor recovery. One mechanism to support the lesioned motor system would be by transcallosal fibers, which are common between homotopic regions (Boussaoud and others 2005; Liu and others 2002; Rouiller and others 1994). Such connections could then be used to integrate areas from the
Figure 1. Changes in motor network activity in macaque monkeys following lesion of the corticospinal tract. (Upper left) Preoperative motor activity (regional cerebral blood flow, rCBF) during performance of precision grips relative to no movement. (Upper right) Increased activity (relative to preoperative levels) while performing precision movements with the affected hand after partial recovery (80% successful movement trials) early after the lesion (about 1 month post-lesion), and after full recovery (100% successful trials) at later stages of recovery (about 3 months post-lesion). (Lower panels) The effect of inactivation (intracortical muscimol injections) of M1 or ventral premotor cortex (PMv) on food retrieval at preoperative, early, and late recovery stages in two monkeys. From Nishimura and others (2007), with permissions.

intact hemisphere in the neuronal computations necessary for movement planning and execution. An alternative route by which M1 might contribute to motor function of the ipsilateral hand could be via uncrossed pyramidal tract fibers. Studies in primates suggest that approximately 10% to 15% of the fibers remain uncrossed and, therefore, connect to ipsilateral spinal motor neurons (Kuypers 1981). Accordingly, these fibers remain intact after a unilateral cerebral lesion, and might hence compensate for the loss of corticospinal input from the contralateral side.
However, in healthy primates direct ipsilateral corticospinal fibers appear to be absent for hand and finger muscles (Soteropoulos and others 2011; Zaaimi and others 2012). Also in monkeys having recovered from corticospinal tract lesions at the brainstem level, electrophysiological recordings did not find a functionally meaningful input from the ipsilateral pyramidal tract onto motor neurons innervating forearm muscles, and no input at all on motor neurons connecting to intrinsic hand muscles despite substantial recovery of hand motor function (Zaaimi and others 2012). Therefore, this pathway has to be considered of little relevance for recovery of hand motor function, at least in primate models. In contrast, the influence of the medial longitudinal fasciculus—a structure originating from medial brain stem nuclei—was found to be strongly enhanced (factor 2.5) for forearm flexors and intrinsic hand muscles in stroke animals compared with controls (Zaaimi and others 2012).

So it appears more likely, at least from an anatomical perspective, that pathways such as reticulospinal (Zaaimi and others 2012) or rubrospinal (Belhaj-Saif and Cheney 2000) tracts might convey ipsilateral motor signals after injury to contralateral corticofugal pathways. These pathways are more likely to originate from medial or lateral premotor cortical regions in both hemispheres (23% of supplementary motor area terminations remain ipsilateral and are located mainly in spinal laminae VII and VIII in primates; Dum and Strick 1996). Furthermore, this is a likely explanation why patients who rely on these non-monosynaptic pathways are more likely to engage motor patterns across multiple joints, for example, flexor synergy, rather than retaining control of individual muscles. Whether synergistic movements aid functional recovery or in fact represent maladaptive motor responses that hinder recovery of better quality motor patterns, is currently under debate.

Functional Neuroimaging and Cortical Reorganization in Humans

For obvious reasons, invasive investigations of neuronal response properties and axonal rewiring are not feasible in human stroke patients. Therefore, non-invasive approaches afforded by neuroimaging techniques are useful for investigating the neural mechanisms supporting recovery of function in humans. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are the two most commonly used techniques to map changes in the cortical architecture after stroke. PET detects changes in local perfusion and glucose metabolism by mapping the distribution of radioactive tracers in the brain. In contrast, fMRI makes use of the blood oxygenation level–dependent (BOLD) signal, which arises from differences in local magnetic field inhomogeneities caused by changes in blood flow and deoxyhemoglobin content in the “activated” tissue (Ogawa and others 1990). As fMRI is free of ionizing radiation, subjects can be scanned several times without any accumulation of potentially harmful side effects, which is of particular relevance when investigating longitudinal changes of brain activity or changes in brain networks evoked by therapeutic interventions.

The first experiments on motor system activity in patients suffering from motor deficits were conducted using PET. Chollet and others (1991) were among the first scientists to demonstrate that in a group of stroke patients who had recovered from hemiplegic movements of the affected hand do not only increase regional cerebral blood flow in the contralateral (i.e., ipsilesional) hemisphere but also in primary sensorimotor cortex in the ipsilateral (i.e., contralesional) hemisphere. The additional recruitment of ipsilateral motor areas was absent when subjects moved their unaffected hand. Subsequently, further PET (Weiller and others 1992) and fMRI studies (Grefkes and others 2008; Tombari and others 2004; Ward and others 2003a) confirmed that movements of the stroke affected hand are associated with enhanced neural activity not only in the lesioned hemisphere but also in the contralesional, that is, “healthy” hemisphere (Fig. 2). A recent meta-analysis on activation data derived from more than 50 neuroimaging experiments demonstrated that enhanced activity in contralesional primary motor cortex (M1), bilateral ventral premotor cortex and supplementary motor area (SMA) is a highly consistent finding after motor stroke compared with healthy controls for a wide range of hand motor tasks (Rehme and others 2012). Importantly, especially patients with poor motor outcome are more likely to recruit motor and non-motor areas in the unaffected hemisphere 3 months post-stroke (Calautti and others 2007; Ward and others 2003b). A similar modality-specific ‘over-activity’ was also reported for other functional systems, for example, for the attention system in patients with neglect or for the language system in patients with aphasia (Corbetta and others 2005; Saur and others 2006).

Longitudinal Changes in Motor System Activity After Stroke

Longitudinal assessments of changes in neural activation are of great importance when studying the neural mechanisms underlying recovery of function as they allow direct comparison of how functional recovery relates to reorganized cerebral network structures. One of the first longitudinal studies in recovering stroke patients was published by Marshall and others (2000). The authors compared fMRI motor activation patterns acquired in the first days after stroke with those obtained 3 to 6 months
post-stroke for a group of patients with lacunar strokes along the corticospinal tract. They found that movements of the paretic hand in the acute phase were associated with a stronger bilateralization of neural activity in sensorimotor cortex, which then returned to a more physiological, lateralized activation pattern after functional recovery 3 to 6 months post-stroke (Marshall and others 2000). Similar findings were obtained in a PET study assessing motor activity 7 weeks and 8 months after striatocapsular stroke (Calautti and others 2001). Ward and others (2003a) scanned patients with fMRI at multiple time points (6–10 sessions) post-stroke, starting around 2 weeks and ending 6 to 12 weeks after stroke, in combination with comprehensive behavioral tests. This design enabled changes in motor-related brain activity to be described not as a function of time, but as a function of recovery (Ward and others 2003a). The authors found that for a number of brain regions in ipsilesional and contralesional hemisphere (including M1, SMA, lateral premotor cortex, and subcortical regions) a decrease in “overactivity” correlated with better motor recovery over sessions. This study suggests that successful recovery is associated with a normalization of pathologically enhanced brain activity over time, which has been confirmed by a number of subsequent studies (Calautti and others 2010; Rehme and others 2012; Saur and others 2006; Tombari and others 2004).

However, the question arises how pathological over-activity develops in the first days after stroke in relation to clinical impairment. This issue was addressed by a serial fMRI study in which acute stroke patients with motor deficits were scanned several times in the first 2 weeks post-stroke starting within 3 days after symptom onset (Rehme and others 2011b) (Fig. 3). The authors found that in patients with only mild motor impairments, motor-related activity during movements of the affected hand was not different from healthy controls. In contrast, patients with initially severe motor deficits featured a general reduction of motor activity in the first 1 to 3 days after stroke, which in the ensuing 10 days gradually increased in both hemispheres over and above fMRI activity levels obtained for healthy controls. In a further fMRI session obtained after 4 months, cortical overactivity returned to levels observed in healthy controls concurrent with recovery of hand motor functions, thereby replicating the findings of Ward and others (2003a). Importantly, increases in neural activity in the first weeks after stroke significantly correlated with better motor recovery during that period (Fig. 3C). In summary, these results show that (1) overactivity after stroke does not occur instantaneously with stroke onset, but rather reflects a time-dependent reorganizational phenomenon and (2) these increases are indicative for better functional recovery early after stroke, suggesting a supportive role of contralesional motor areas for that period. This interpretation is supported by the monkey studies outlined above which showed that inactivation of contralesional M1 activity deteriorates motor performance of the stroke-affected hand in the early phase, but not 3 months after stroke (Nishimura and others 2007). In conclusion, longitudinal fMRI studies on recovery of motor function revealed that changes in neural activity are dynamic, and depend on the time that has elapsed since stroke onset as well as on the degree of motor impairment.

**Analyses of Network Connectivity After Stroke**

The studies presented thus far demonstrate activity changes in a number of cortical regions, some of which closely related to motor impairment and recovery thereof.
However, localizing additional activity in a certain brain region (i.e., motor cortex of the unaffected hemisphere) does not explain how this activity is integrated into the entire network subserving a particular task. Such questions can be answered using models of brain network connectivity. There are two different approaches to describe connectivity in fMRI data: (1) functional connectivity and (2) effective connectivity (Friston 1994). Functional connectivity refers to a correlation of the fMRI time courses between two (or more) brain regions. However, correlations have no directions and do not necessarily reflect causal interactions. Analyses of functional
connectivity are most frequently performed on resting-state fMRI time series reflecting spontaneous fluctuations of BOLD activity in absence of a structured cognitive, motor, or sensory task. In contrast, effective connectivity between two regions specifically describes the influence that one region exerts onto the activity of another. Estimation of effective connectivity always relies on some form of model and a priori assumptions, for example, as in structural equation modeling, Granger causality mapping, and dynamic causal modeling (DCM).

Connectivity studies using fMRI activity in the resting state, that is, in absence of a structured task, frequently demonstrated reduced functional connectivity between ipsilesional M1 and contralesional M1 as a function of motor impairment (Carter and others 2010; Carter and others 2012; Park and others 2011; Wang and others 2010). Other brain regions like contralesional premotor cortex and posterior parietal cortex were also found to have less functional connectivity with M1 of the lesioned hemisphere at rest (Wang and others 2010). Importantly, stronger functional connectivity of ipsilesional M1 with other brain areas in the early subacute phase post-stroke predicts a better functional recovery 6 months later (Park and others 2011). Similar relationships between functional resting-state connectivity and behavioral parameters were found for the language system (Warren and others 2009) or the attention system (He and others 2007).

Effective connectivity on the other hand can answer questions about the influence of one region on another (Friston 1994) and is usually employed during the performance of a particular task. As mentioned above, models of effective connectivity are much more complex as they rely on a number of a priori assumptions that are necessary to infer causal influences between activation time series (for an elaborated overview on the methodological backgrounds of different connectivity approaches, please refer to Eickhoff and Grefkes (2011) and Grefkes and Fink (2011), respectively). The validity of effective connectivity estimates can be tested by comparing them with data derived with other techniques. For example, Boudrias and others (2012) studied a group of healthy control subjects of different ages while performing a repetitive right hand grip task. They were able to show that during right hand grip, the influence of left M1 on right M1 diminished with advancing age. Importantly, the assessment of interhemispheric inhibition with transcranial magnetic stimulation (TMS) correlated with the assessment of interhemispheric coupling using DCM of fMRI data. Therefore, both approaches (TMS, DCM) seem to reflect the same physiological process (Boudrias and others 2012), thus providing face validity for the DCM approach within the cortical motor system.

In the past years, DCM of the cortical motor system has been used to investigate the effects of stroke on brain networks. For example, Grefkes and others (2008) found that in stroke patients in the subacute to chronic stage, effective connectivity between premotor areas and ipsilesional M1 is significantly reduced. In addition, especially patients with stronger motor impairment featured an inhibitory influence from contralesional (unaffected) M1 to ipsilesional M1 during movements of the paretic hand. These findings, hence, suggest that at least for some patients with stronger motor deficits, the unaffected hemisphere rather suppresses than supports activity in the lesioned hemisphere, which might further hinder the reduced cortical motor output when addressing the stroke-affected hand (Grefkes and others 2008). Effective connectivity can also be tested by TMS paradigms. At rest, the use of paired-pulse TMS was able to show that the contralesional dorsal premotor cortex (PMD) tends to inhibit ipsilesional motor cortex in well recovered patients, but becomes facilitatory in those with greater clinical impairment (Bestmann and others 2010). Concurrent TMS-fMRI was able to show that during affected hand movement greater clinical impairment was associated with a stronger facilitatory influence of contralesional PMd on two posterior parts of the ipsilesional sensorimotor cortex—parts of the ipsilesional hemisphere that are most likely to be able to generate descending motor signals to the spinal cord (Fig. 4) (Bestmann and others 2010).

### Functional Relevance of Lesion-Induced Overactivation

The question of whether these distributed cortical motor regions have any direct influence over recovering muscles was recently addressed by looking at coherence between oscillatory signals from the brain (measured with magnetoencephalography) and affected muscles (measured with electromyography) simultaneously during a simple isometric hand grip in chronic stroke patients (Rossiter and others 2013). Corticomuscular coherence here implies some kind of functional coupling between the cortical region and the ‘recovering’ muscle. The cortical source of the peak corticomuscular coherence was widely distributed in patients compared with controls (Fig. 5). In particular, peak corticomuscular coherence was seen in contralesional hemisphere in a number of patients, implying direct influence over affected muscle activity (Rossiter and others 2013).

The functional relevance of these overactivations can also be tested by transiently disrupting activity in a target brain region with TMS and measuring whether this causes a behavioral effect. TMS allows extremely short but strong (1–2 Tesla) magnetic pulses to be applied to the cortex through the skull (Barker and others 1985; Rothwell 1998). In studies involving adult patients with
small subcortical infarcts, the effect of disruption of secondary motor areas, in particular PMd, has been investigated. First, transiently disrupting activity in either ipsilesional or contralesional PMd with TMS can lead to worsening of recovered motor behaviors in some chronic subcortical stroke patients in a way that has no effect on healthy volunteers (Fridman and others 2004; Johansen-Berg and others 2002; Lotze and others 2006). However, there is evidence that the effect is dependent on residual impairment (and therefore on the anatomy of the damage). TMS to contralesional PMd is more disruptive in patients with greater impairment (Johansen-Berg and others 2002), whereas TMS to ipsilesional PMd is more disruptive in less impaired patients (Fridman and others 2004), implying a contralesional shift in balance of functionally relevant activity with greater impairment. The results of similar studies targeting disruption of contralesional M1 function by TMS depend on whether the motor task is a simple react time task (no disruption) (Johansen-Berg and others 2002; Werhahn and others 2003) or involves pressing sequences of buttons (disruption of timing) (Lotze and others 2006), suggesting a supportive role for contralesional M1 in some patients and in some more complex tasks. Overall, these findings suggest a functional role for the contralesional hemisphere in organizing movement of the impaired limb following stroke, but only in those patients that do not make a good functional recovery.

Figure 4. The influence of contralesional dorsal premotor cortex (PMd) on residual networks after stroke. (A) In a paired pulse transcranial magnetic stimulation (TMS) experiment, the resting-state influence of contralesional PMd on ipsilesional motor cortex is inhibitory in those patients with less impairment and facilitatory in those with more impairment. (B) The effect of TMS delivered to contralesional PMd (red symbol) during hand grip as measured with concurrent TMS-fMRI is seen primarily in ipsilesional sensorimotor cortex (blue arrow). This effect is facilitatory during hand grip in all patients, but more so in those with greater impairment. AH = affected hemisphere. Adapted from Bestmann and others (2010).

Figure 5. Corticomuscular coherence after stroke. (A) Lesion overlap of stroke patients from axial slices displayed on a template brain. This demonstrates the variety of cortical and subcortical damage across the group. The scale indicates the number of patients with overlapping damage in each area. (B) Three-dimensional plot of peak coherence coordinates for beta (left) and gamma (right) (grip performed with left hand). Control subjects are shown in blue and patients are shown in red. Results are displayed on a “glass brain” and shown from behind (top left), from the right side (top right) and from above (bottom left). These peaks of corticomuscular coherence were calculated using a Dynamical Imaging of Coherent Sources (DICS) beamformer. From Rossiter and others (2013), with permissions.
Another view is that cortical motor areas in the contralesional hemisphere, in particular M1, are pathologically overactive in some stroke patients and are in fact hindering recovery. The case for contralesional M1 hindering motor performance comes from both TMS (Murase and others 2004) and fMRI (Grefkes and others 2008) studies, which suggest that in some subcortical stroke patients, contralesional M1 although “active,” may exert an abnormally high degree of interhemispheric inhibitory drive toward ipsilesional M1 during attempted voluntary movement of the affected hand. This led to suggestions that contralesional M1 overactivity suppresses ipsilesional M1 activity, motor performance and therefore recovery.

The contradictory results with respect to the role of contralesional areas for motor performance and functional recovery might reflect different sets of reorganisation patterns that evolve from as yet unknown neurobiological factors. On one hand, the influence of contralesional M1 becomes increasingly inhibitory in patients with greater impairment (Grefkes and others 2008; Murase and others 2004). On the other, the influence of premotor cortex becomes increasingly facilitatory toward ipsilesional sensorimotor cortex in the same type of patients (Bestmann and others 2010). One possibility is that control of inhibition from contralesional M1 is normally managed by circuits in ipsilesional M1 that suppress inputs prior to movement. If these are damaged by stroke, then the influence of contralesional M1 will appear negative. Conversely inputs from contralesional premotor cortex may normally assist production of certain types of movement and this facilitation may increase after damage to the lesioned hemisphere. Although the physiological signatures for the interhemispheric influences of contralesional M1 and premotor cortex appear very different, what is common to both sets of observations is that the influences from contralesional to ipsilesional motor regions become systematically more abnormal in patients with more impaired clinical motor function. This conclusion is also supported by longitudinal studies on changes of motor cortex connectivity after stroke; here, motor system connectivity was strongly reduced right after stroke onset, and then reached values observed in healthy controls the better patients recovered (Rehme and others 2011a). Of note, 2 weeks after stroke, interhemispheric coupling between M1-M1 is positive, that is, contralesional M1 supported activity in the lesioned hemisphere during that time. Therefore, early over-activity of contralesional areas observed after stroke seems to contribute to recovery via transcallosal effects, which nicely matches data from stroke models obtained in monkeys (Nishimura and others 2007; Zaaimi and others 2012). However, patients in whom interhemispheric M-M1 coupling turned into inhibition after 3 to 6 months made less functional recovery (Rehme and others 2011a). Therefore, time is a critical factor that has to be taken into account when interpreting data on cortical reorganization after brain lesions (Nishimura and others 2007; Rehme and others 2011a; Ward and others 2003a).

**Therapeutic Implications**

The key point in thinking about these mechanisms is that interhemispheric influences are often thought of as a therapeutic target (Grefkes and Fink 2011; Hummel and Cohen 2006). In fact, a number of studies have been published that used cortical stimulation to suppress activity in the contralesional hemisphere in order to enhance training effects on upper limb function, via interhemispheric effects on ipsilesional M1 (Avenanti and others 2012; Grefkes and others 2010; Liepert and others 2007; Nowak and others 2008; Seniow and others 2012; Stagg and others 2012; Takeuchi and others 2005; Talelli and others 2007). However, there are also an increasing number of studies reporting absent repetitive TMS (rTMS) effects in stroke patients (Grefkes and Fink 2012). Therefore, the effects of rTMS intervention studies have been mixed, with more recent publications countering the early publication bias, raising the possibility that contralesional cortical motor regions actually contribute to motor recovery in some but not all stroke patients. This issue is further complicated as even in healthy subjects responses to TMS protocols is highly variable with some subjects responding in an expected manner (i.e., increases in motor-evoked potential amplitudes after “excitatory” rTMS) and some do not (Cárdenas-Morales and others 2013; Hamada and others 2012). In patients, additional neurobiological variance is introduced by differences in lesion location, premorbid condition, or medication.

One distinct possibility is that the effect is predicted by the constraints of the residual structural and functional architecture of the post-stroke motor system (Ward 2011). A few studies have examined the behavioral effects of combining fMRI of the motor system with either contralesional (Nowak and others 2008) or ipsilesional (Ameli and others 2009) rTMS. In both cases, behavioral improvements were associated with a “normalization” of motor-related activity as assessed with fMRI, that is, reduced overactivity of the contralesional hemisphere. As predicted, the behavioral (and neuroimaging) effects appeared to be related to the anatomical location of the lesions. Patients with subcortical lesions (i.e., intact cortical networks) were found to improve after non-invasive brain stimulation, whereas those patients featuring cortical lesions (involving premotor cortex but sparing the M1 hand knob region) did not respond or even deteriorated in terms of motor functions of the paretic hand (Ameli and others 2009). Therefore, stratifying patients based on an
understanding of the mechanisms of action of the inter-
vention and the residual architecture of the patient will be
ruel (Ward 2011). The take home message here is that
it is unlikely that the same treatment strategy will work to
the same degree in different types of patients, and at dif-
ferent times after stroke. Although this makes the field
more challenging, understanding these influences is also
the route toward both stratification of patients in clinical
trials and potentially also personalized medicine.

**Neuroimaging of Structural Damage**

An important factor determining the initial clinical deficit
and consequent cortical reorganization is likely to be the
atomy of the damage itself. Patients with larger in-
farct volumes tend to do worse, but information about the lo-
cation of the damage and which structures have been af-
ected seems to be even more important. For example,
even small lesions to the posterior limb of the internal
capsule often lead to severe hemiparesis as here motor
fibers of the corticospinal tract—the most important “ou-
put” bundle of the cortical motor system—converge in a
few square millimeters (Englander and others 1975;
Stinear and others 2007). Similar structure–function rela-
tionships were demonstrated for the language system in
aphasic stroke patients when the lesion affected distinct
pathways in the extreme capsule or arcuate fasciculus
(Kümmerer and others 2013).

An important technique to assess damage to fiber
tracts is diffusion MRI (dMRI; Le Bihan and Johansen-
Berg 2012). The physical basis behind this approach is
that in white matter tissue the spontaneous diffusion of
water molecules is constrained by the lipophilic mem-
branes of axons, which leads to a preferred diffusion in
the direction of the fiber bundles (“fractional anisotropy”
[FA]). Certain MR sequences in combination with math-
ematical algorithms enable the reconstruction of white
matter tracts based on dMRI information, for example by
means of diffusion tensor imaging (DTI) or Q-ball imag-
ing (Jbabdi and Johansen-Berg 2011).

There are now several studies that have used DTI to
assess the integrity of the descending corticospinal fibers
and linked this with motor impairment (Stinear and oth-
ers 2007; Wang and others 2012). More recently, attempts
have been made to look at body part specific tracts from
a number of different cortical motor regions to increase
spatial specificity. For example, Schulz and others (2012)
used probabilistic tractography to map corticospinal
fibers of M1, SMA, dorsal, and ventral premotor cortex.
The authors found that especially reductions in FA of
fibers originating from M1 and PMd correlated with impair-
ments in hand motor functions in chronic stroke
patients (Fig. 6) (Schulz and others 2012). However,
damage of not only corticospinal but also of transcallosal
fibers is closely related to motor deficits after stroke
(Wang and others 2012) but has received less attention
than descending fibers. As mentioned above, all motor
areas have interhemispheric connections to their contra-
lateral counterparts. These fibers cross the hemispheres in
middle parts of the corpus callosum (Hofer and Frahm
2006). Wang and others (2012) found that reductions in
FA of the corpus callosum correlate with a more bilateral
fMRI activation pattern in motor areas during movements
of the affected hand, especially in more impaired patients.
A fiber tracking analysis revealed that these changes in
corpus callosum integrity affected interhemispheric
fibers connecting cortical midline structures (sensorimo-
tor cortex, SMA, superior parietal lobe), as well as PMd
and multimodal cortex along the temporoparietal junc-
tion. Radlinska and others (2012) investigated fractional
anisotropy of the transcallosal motor fibers using DTI
within 3 weeks after stroke and another time at 6 months
after stroke. Whereas there were no differences in corpus
callosal DTI measures in the early phase (compared
with controls), patients featuring a stroke in the pyrami-
dal tract developed significant reductions in fractional
anisotropy in motor parts of the corpus callosum at later
stages post-stroke. Both studies (Radlinska and others
2012; Wang and others 2012) suggest that stroke-induced
lesions do not only lead to a degeneration of corticospinal
fibers within the lesioned hemisphere but also in destruc-
tive processes of transcallosal fibers which might ulti-
mately influence cortical reorganization and motor
recovery.

However, also the pre-morbid status in terms of white
matter lesions has a significant impact on motor recovery
after 3 months as demonstrated in a DTI study on a group
of acute stroke patients with pontine lesions (Förster
and others 2011). Another study showed that even in the unaf-
fected hemisphere, corticospinal tract fibers may show
reduced integrity in chronic stroke patients compared
with healthy controls (Borich and others 2012). In con-
trast, connections to the brainstem are enhanced in recov-
ered stroke patients as, for example, demonstrated for
fibers connecting M1 with the red nucleus (Rüber
and others 2012). Importantly, these increases in structural
connectivity correlated with better motor functions in
these patients, thereby suggesting a similar compensatory
function of the cortico-rubro-spinal system in humans as
discussed above for macaques (Belhaj-Saif and Cheney
2000). Therefore, a focal lesion induced by stroke impacts
on fiber tracts in the entire brain, including the unaffected
hemisphere, and these changes are closely linked to clini-
cal and behavioral parameters.

Of course, analysis of white matter damage does not
take into account the extent of damage to cortical regions,
which can also be influential in determining levels of
impairment (Zemke and others 2003). These factors and
Figure 6. Corticofugal pathways from cortical motor areas are affected in stroke. (A) Corticofugal tract originating from primary motor cortex (M1), dorsal (PMd), ventral (PMv) premotor, and supplemental motor area (SMA) connecting grip-related cortical seed areas and caudal pontine target zone ($z = -44$). Binarized common tracts include voxels shared by at least 5/9 control subjects. Tracts are overlaid on a common fractional anisotropy (FA) template. The two rows show axial slices in a rostrocaudal direction at given $z$ values in MNI (Montreal Neurological Institute) space. (B) Trajectory map for primary motor cortex (M1), dorsal (PMd), ventral (PMv) premotor, and supplemental motor area (SMA) connections at the level of the internal capsule ($z = 6$), showing a topographical distribution: M1 located posteriorly, PMd, PMv, and SMA following in a posteroanterior direction. Binarized common tracts include voxels shared by at least 5/9 control subjects, overlaid on a common axial ($z = 6$) FA template. Framed voxels indicate the center of each corticospinal tract (CST). Axes give $x$ and $y$ values in MNI space. (C) Tract-specific FA values given for CST originating from primary motor cortex (M1), dorsal (PMd), ventral (PMv) premotor, and supplemental motor area (SMA) as calculated at the level of the internal capsule. The proportional mean FA of all four tracts was significantly reduced in stroke patients compared with controls. Significant differences are indicated (*$P < 0.05$, †$P < 0.01$ Bonferroni corrected). All data are presented as mean ± standard error of the mean. (D) Tract-specific proportional FA values are plotted against normalized relative grip strength for CST originating from primary motor cortex (M1), dorsal (PMd), ventral (PMv) premotor, and supplemental motor area (SMA). $P$ (Bonferroni corrected) and $r$ values given. From Schulz and others (2012), with permission.
others are increasingly being considered as a tool for predicting outcomes after stroke (Stinear and Ward 2013). The overall aim of these approaches is that assessment of white matter pathway integrity can be used in the clinical routine. At present, there are a number of different methodological approaches but no particular consensus on the most appropriate. It seems logical that more widespread use of this approach will come if the analysis of structural MRI data can be automated. For example, automated segmentation of the lesion itself has been used in calculating the overlap with corticofugal pathways (Kou and others 2013). Performing tractography in patients themselves is fraught with difficulty but using “standard” templates of the corticofugal pathways to calculate either overlap with the lesion, or FA values within those templates, also appears to be potentially useful (Park and others 2013). There are already successful approaches to using lesion topography in predicting outcome in the language domain (Hope and others 2013; Price and others 2010), and it is likely that this approach will become the most useful, on the assumption that it incorporates important information on white matter and cortical damage.

**Conclusion and Outlook**

In summary, neuroimaging studies over the past 20 years have demonstrated reconfiguration of brain networks after focal brain damage. This reconfiguration does not appear to be simply a response to the lesion itself, but much of what is observed is functionally relevant. Residual functional networks seem to operate in a different way, with some brain regions adopting the characteristics of damaged or disconnected regions. This process varies across chronic stroke patients, but does so in a way that appears to be at least partially predictable. It is important to stress that this reorganization is often not successful in returning motor performance back to premorbid levels. It is less effective than that in the intact brain but will nevertheless support what recovered function there is. The exact configuration of this new motor system will be determined most obviously by the extent of the anatomical damage, but also on other factors, such as biological age, current drug treatments and possibly phenotype. In addition, we must not forget that the dose of treatment, most commonly physical therapies, is critical. How and whether adjuncts to physical therapy are effective will most likely come down to how well we understand the interaction between the mechanism of action of a given approach (e.g., pharmacological, cortical stimulation, cognitive/behavioral interventions) and the residual functional structural network architecture on the level of individual patients. Future work will take advantage of advanced neuroimaging techniques to determine whether assessment of individual post-stroke residual functional architecture can be a major predictor of outcome, opening the way for stratification of patients based on the likely response to an intervention.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: CG is supported by the German Research Foundation (DFG GR 3285/2-1; GR 3285/4-1), NW is supported The Wellcome Trust (WT088414AZ) and the European Commission under the 7th Framework Program–HEALTH–Collaborative Project Plasticise (Contract no. 223524)–www.plasticise.eu,

**References**


