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Motor Imagery After Stroke:

Relating Outcome to Motor Network Connectivity

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Abstract

Objective—Neuroplasticity is essential for recovery after stroke and is the target for new stroke therapies. During recovery from subcortical motor stroke, brain activations associated with movement may appear normal despite residual functional impairment. This raises an important question: how far does recovery of motor performance depend on the processes that precede movement execution involving the premotor and prefrontal cortex, rather than recovery of the corticospinal system alone?

Methods—We examined stroke patients with functional magnetic resonance imaging while they either imagined or executed a finger-thumb opposition sequence. In addition to classical analyses of regional activations, we studied neuroplasticity in terms of differential network connectivity using structural equation modeling. The study included 8 right-handed patients who had suffered a left-hemisphere subcortical ischemic stroke with paresis, and 13 age-matched healthy controls.

Results—With good functional recovery, the regional activations had returned to normal in patients. However, connectivity within the extended motor network remained abnormal. These abnormalities were seen predominantly during motor imagery and correlated with motor performance.

Interpretation—Our results indicate that neuroplasticity can manifest itself as differences in connectivity among cortical areas remote from the infarct, rather than in the degree of regional activation. Connection strengths between nodes of the cortical motor network correlate with motor outcome. The altered organization of connectivity of the prefrontal areas may reflect the role of the prefrontal cortex in higher order planning of movement. Our results are relevant to the assessment and understanding of emerging physical and neurophysiological therapies for stroke rehabilitation.

The human brain reorganizes itself throughout life, in health and disease. This neuroplasticity not only underpins human adaptation and learning,¹ but is especially important for recovery after brain injury. Understanding and influencing the processes of neuroplasticity are therefore crucial in providing more effective therapies for patients. Functional neuroimaging can reveal the alterations in large-scale brain networks following brain injury,^{2,3} physical training,^{4–6} and pharmacological therapy.⁷

After a subcortical stroke, functional magnetic resonance imaging (fMRI) during movement reveals cortical reorganization that is associated with the recovery of function.^{8–10} The reorganization includes overactivity of cortical motor areas,¹¹ alterations in the inter-hemispheric balance,^{4,9,12–15} and dysfunctional coupling between cortical regions.^{10,16}

However, the cortical activation patterns associated with some motor tasks may appear normal in patients despite residual functional impairment.^{11,13,14,17–19} An explanation for this paradox is that hemiparetic stroke disrupts both corticospinal output and important motor processes prior to the execution of movement, for example, motor attention, imagination, preparation, or planning.^{18,20}

We set out to examine the extent to which recovery of motor performance after stroke is associated with changes in the movement-related cognitive processes that precede movement, as opposed to changes in corticospinal function. There are 3 key aspects to our study. First, we studied a carefully selected subgroup of patients with a left hemisphere subcortical stroke. Changes in their cortical motor systems are therefore not confounded by cortical infarction, and can be interpreted as remote neuroplasticity. Second, we studied both motor imagery (MI) and executed movement (EM). Motor imagery utilizes many aspects of the motor system,^{21–24} and has been suggested as an adjunct to rehabilitative physical therapies as well as a method to study the motor system without actual movement. For example, in stroke patients with normal activations during executed movement, motor imagery has been associated with abnormal hemispheric lateralization that in turn correlated with recovery of motor function.²⁰ The third critical aspect was that rather than simply defining the activation within isolated regions, we analyzed the interactions between brain regions by structural equation modeling of the fMRI signal in an anatomically specified causal model.^{25,26} Inferences about changing regional neuronal interactions can be made from the changing interactions at the level of blood oxygenation level-dependent (BOLD) fMRI signals.^{27,28} In the absence of significant neuronal loss or regeneration, such changes in connectivity are heavily dependent on changes in synaptic density, structure, and efficacy.²⁹ Inferences can be drawn in terms of changes in systems-level effective connectivity, in which the strength of a physiological connection between 2 regions (eg, path coefficient) is modulated by experimental context (eg, MI vs EM) and/or condition effects (eg, patient group).

We used fMRI to examine the connectivity within the extended motor network during motor imagery and executed movement in subcortical stroke patients who were nearly fully recovered. Our first hypothesis was that although activations may normalize after stroke, analysis of effective connectivity would reveal persisting abnormalities. Our second hypothesis was that atypical connectivity will be more prominent during motor imagery than executed movement, because of the emphasis on the cognitive processes that precede movement execution. Finally, we predicted that connectivity among prefrontal and premotor cortex would correlate with upper limb motor function.

Materials and Methods

Subjects

Eight patients (6 females; mean age, 67 years; standard deviation [SD], 11 years) were prospectively recruited from local stroke services. Inclusion criteria were that the stroke was the first clinical stroke episode in previously right-handed adults, affected the left hemisphere subcortically, and was associated with right hemiparesis involving the hand with reduced power (nadir) 2/5 on the Medical Research Council scale.³⁰ Exclusion criteria included carotid artery stenosis/occlusion; neglect or inattention; inability to pass the Chaotic Motor Imagery Assessment Battery^{20,23,24,31}; renal and liver impairment; concurrent treatment with a selective serotonin reuptake inhibitor or benzodiazepine; significant small vessel disease on routine computed tomography; current depression; and contraindications to MRI.

Thirteen right-handed control subjects (9 males; mean age, 57.6 years; SD, 8.5 years) were recruited through local advertisement. Control subjects had no history of neurological or psychiatric disorder and were not taking regular medication. All subjects gave written consent in accordance with the declaration of Helsinki. The protocol was approved by the Cambridge Research Ethics Committee.

Chaotic Motor Imagery Assessment Battery

Chaotic motor imagery is defined as either an inability to perform motor imagery accurately or temporal uncoupling of otherwise accurate imagery.²³ Subjects were assessed using the Chaotic Motor Imagery Assessment Battery,^{20,23,24} which has 3 components that provide an objective measure of motor imagery compliance (see online supplementary material for a full description). The first component used a hand mental rotation task to assess implicit motor imagery; subjects who score below 75% are excluded. The second component used a variation of the fMRI task with a variable block length to ensure motor imagery performance. The third component used principles of motor control to ensure subjects are using motor imagery; subjects using alternative cognitive strategies such as counting are excluded. During all motor imagery tasks, subjects were instructed to perform first-person motor imagery; not to view the scene from the 3rd person; and not to count, or assign numbers or tones to each finger. Subjects were excluded if they were unable to perform motor imagery.

Additional Tests

Patients were assessed with the National Institutes of Health Stroke Scale; the Action Research Arm Test (a quantitative test of upper limb extremity function measuring grasp)^{32,33}; and the Motricity Index,³⁴ which measures the motor function of the arm in terms of pinch, elbow flexion, and shoulder abduction as well as the leg and trunk. Thumb to index finger tapping over 15 seconds (TIT ratio) and mirror synkinesia were also measured. Vasomotor reactivity was assessed in patients using transcranial Doppler.³⁵

fMRI

MOTOR PARADIGM AND FMRI—The fMRI used an established block design,^{24,36} with auditory pacing (1Hz) of a right-hand finger-thumb opposition sequence (2, 3, 4, 5, 2...) with 2 separate runs (MI & Rest and EM & Rest). Subjects were instructed to keep their eyes closed. We used individually calibrated bilateral fiberoptic gloves (Fifth Dimension Technologies, Pretoria, South Africa) to monitor finger movements, to exclude inappropriate movement, and to assess the performance of motor imagery. After each motor imagery block, subjects confirmed whether the finger they were currently imagining was the correct “stop finger” for the length of sequence. After scanning, subjects were asked to rate the difficulty of motor imagery performance on a 7-point scale.³⁷

A 3-Tesla Bruker (Billerica, MA) MRI scanner was used to acquire T2-weighted and proton density anatomical images and T2*-weighted MRI transverse echo-planar images sensitive to the BOLD fMRI signal (64 × 64 × 23; field of view, 20 × 20 × 115; 23 slices of 4mm; repetition time, 1.5 seconds; echo time, 30 milliseconds; voxel size, 4 × 4 × 4). Each run was preprocessed separately using Statistical Parametric Mapping software (SPM 5, Wellcome Trust Centre for Neuroimaging, London, UK). Images were corrected for acquisition delays, spatially realigned (movement <1.5mm), transformed into the standard space of the Montreal Neurological Institute,³⁸ and smoothed with a Gaussian kernel full width at half maximum of 6mm.

STATISTICAL NONPARAMETRIC MAPPING: VOXEL-BASED ANALYSIS OF REGIONAL EFFECTS—A first-level general linear model was used for each subject. The

block design (task vs Rest) was convolved by the canonical hemodynamic response function (high pass filter 128 seconds). Contrast images (either [MI vs Rest] or [EM vs Rest]) were entered into second-level models using the Statistical nonParametric Mapping (SnPM) toolbox (SnPM 5b, www.sph.umich.edu/ni-stat/SnPM/). SnPM was used at the second level for several reasons. First, with low subject numbers, the correction for multiple comparisons using SPM's random field theory is too conservative. Second, the heterogeneity of the stroke group could lead to violations of the assumptions of equal and normally distributed error variance across groups. One-sample pseudo *t* tests were used to examine the effects of the tasks, whereas pseudo paired *t* tests were used to compare tasks within subjects. Pseudo unpaired *t* tests examined task differences between groups. A threshold of $p < 0.05$ corrected (family wise error) was used for all contrasts based on permutations tests.

STRUCTURAL EQUATION MODELING OF NETWORK CONNECTIVITY—The structural model (Fig 1A) included an extended cortical motor network that has been implicated in stroke recovery. The specific connections were based on consensus human and primate data (www.cocomac.org). The coordinates for the regions were taken from the nearest maxima in a second-level fixed-effect group model generated using SnPM (MI and EM vs Rest) from all subjects with a threshold of $p < 0.05$ corrected (familywise error) (Fig 1B).

The first eigenvector of the adjusted BOLD signal was extracted from a 6mm sphere for each region from each subject. These time series were used for structural equation modeling^{27,28,39,40} to estimate the affects of an experimental manipulation on task-related effective connectivity within the specified anatomical model. These changes in connectivity represent psychophysiological interactions within hypothesis-led stationary causal models.²⁸

Inferences at the group level used the subject-specific path coefficients in a 3-way repeated-measures analysis of variance (ANOVA) with within-subject factors of Task (MI vs EM) and Connections (20 connections shown in Fig 1A). Group was a between-subject factor (Control vs Stroke). Significant effects were explored with post hoc *t* tests. Given our hypothesis that effective connectivity would correlate with measurement of motor function, we performed 2-tailed Spearman correlations between path coefficients and measurements of upper limb function.

Results

The demographic details of participants are shown in Table 1. The results of the behavioral assessment are shown in Table 2. For patients, Figure 2 shows the T2 structural scans at the maximum infarct size slice. Vasomotor reactivity was normal in all patients.

SnPM: Voxel-Based Analysis of Regional Effects

Motor imagery and executed movement (vs Rest) were associated with similar activations throughout the motor network in both groups (Fig 3, Table 3) including primary motor cortex (BA4), primary sensory cortex, supplementary motor area (SMA), prefrontal cortex (PFC), bilateral dorsal premotor cortex, parietal cortex, right cerebellum, and inferior frontal cortex (IFC).

Comparing the 2 tasks (EM > MI), executed movements were associated with greater activation in premotor and motor cortex in both groups (Table 4). In keeping with our previous work in stroke patients³⁶ and in healthy volunteers (unpublished), we did not find greater activations for the reverse contrast (MI > EM) in either group. On direct comparison, there were no differences between the stroke patients and the control group for either task, at

standard threshold ($p < 0.05$ familywise error corrected) or at a reduced exploratory threshold ($p < 0.001$ uncorrected).

Structural Equation Modeling of Network Connectivity

From the ANOVA of connectivity parameters there were significant effects of Task ($F_{1,19} = 5.1$; $p < 0.05$) and Connection ($F_{9,6,182.0} = 8.5$; $p < 0.0001$). There was no overall effect of Group ($F_{1,19} = 2.021$; $p = 0.171$). There was a significant interaction between Task and Connection ($F_{9,9,188.4} = 1.86$; $p < 0.05$), indicating that the 2 tasks manifested different connectivity in some connections. There was a 3-way interaction between Task, Connection, and Group ($F_{9,9,188.4} = 1.82$; $p < 0.05$), indicating that the task-related differences at a subset of connections was itself different between the 2 groups. The results are summarized in Figure 4. Figure 4A shows within group results, and Figure 4B shows between group results.

Comparing motor imagery to motor execution (MI > EM), overlapping patterns emerge (Fig 4A). Most significantly, there was a reduction in the coupling between premotor and motor cortices in both groups. In control subjects, there was a significant difference in the effective connectivity of the prefrontal cortex, in keeping with regional activation patterns in healthy volunteers.^{41–44} In patients, there was also a reduction in the coupling between the left premotor cortex and supplementary motor area, whereas control subjects had differences in right prefrontal to premotor connections.

Significant differences in connectivity between the stroke patients and the controls were also found (Fig 4B). The stroke patients showed reduced connectivity between the supplementary motor area and the ipsilesional premotor cortex in both tasks. However, there were differences between groups that were only seen during motor imagery. This included 1) increased coupling between both the ipsilesional prefrontal cortex and premotor cortex, and the ipsilesional prefrontal cortex and supplementary motor area; and 2) a significant reduction in coupling between the ipsilesional premotor cortex and supplementary motor area (Fig 4B). Thus, patients who have recovered from stroke showed abnormal coupling among frontal brain regions despite normal activations within these regions during motor imagery. Significant correlations between motor functions and the effective connectivity among prefrontal and premotor regions were found. Figure 5 shows the connections that were tested based on our hypothesis. There were no significant correlations during executed movement, so only the significant correlations during motor imagery are presented. The connectivity from contralesional prefrontal cortex to the supplementary motor area correlated positively with the Motricity score (Spearman rho = 0.770; $p < 0.05$; Fig 5A); that between the contralesional premotor cortex and the supplementary motor area correlated positively with the TIT ratio (Spearman rho = 0.762; $p < 0.05$; Fig 5B); and that from the ipsilesional premotor cortex to the ipsilesional BA4 correlated positively with both the Motricity score (Spearman rho = 0.825; $p < 0.05$; Fig 5D) and the TIT ratio (Spearman rho = 0.714; $p < 0.05$; Fig 5E). There was no significant correlation between the TIT ratio and Motricity scores. In contrast, a negative correlation was identified for connectivity between supplementary motor area and ipsilesional BA4 and the Motricity scores (Spearman rho = -0.784 ; $p < 0.05$; Fig 5C). No correlation was found between the time since stroke and either the effective connectivity or the motor scores.

In summary, as motor function improved, the coupling during motor imagery increased in 3 connections (ipsilesional premotor to primary motor cortex; contralesional prefrontal cortex to supplementary motor area; contralesional premotor cortex to supplementary motor area) and decreased in 1 connection (supplementary motor area to ipsilesional BA4).

Discussion

There are 3 principal findings from this study. First, after subcortical stroke there is evidence for cortical neuroplasticity, both in terms of regional activation,^{4,10,11,14,15} and also in terms of the changes in connectivity within distributed brain networks. These changes in network connectivity were observed most clearly during motor imagery. Second, plasticity occurred in cortical areas that were remote from the subcortical infarct. This means that the cortical changes were not the result of local cortical injury, but a response to injury elsewhere in the motor system. Third, the changes in connectivity during motor imagery correlated with motor function. These effects would not have been revealed by a classical analysis of neuroimaging data based on regional activations or by the study of executed movement alone.

One interpretation of the correlations between motor function and connection strength with motor imagery is that enhanced cortico-cortical interactions facilitate recovery. However, our data alone cannot refute the alternative hypothesis that better recovery leads to better connectivity by an unknown mechanism. Nevertheless, the higher connectivity between ipsilesional premotor and primary motor cortex in patients with better motor function is in keeping with previous work showing the importance of premotor cortex to functional recovery after subcortical stroke.^{45,46} Conversely, patients with a persistent motor deficit had low connectivity between premotor and primary motor cortex together with higher connectivity between supplementary motor area and primary motor cortex. This accords with results from healthy subjects in whom the coupling between the SMA and primary motor cortex is inhibitory.^{47,48}

In contrast to interactions with the supplementary motor area, the interactions among other areas including the prefrontal cortex were enhanced. This increased connectivity may have facilitated recovery of motor function (Fig 5C), although it may also reflect recovery enabled by another mechanism. Although this causal relationship is ambiguous in an observational study, the prefrontal cortex has been implicated in several functions related to both motor imagery and executed movement. These functions are candidate mechanisms if recovery does indeed result from greater cortical connectivity. For example, attention to action has been associated with greater activation and connectivity in prefrontal and premotor cortex.⁴⁰ Although this mechanism cannot be excluded here because of ceiling effects, the behavioral data for motor imagery (Table 2) suggest that attention to action is not the principal mechanism underlying recovery. For example, there was no difference in the motor imagery score between the groups. The prefrontal cortex is also associated with motor learning, although this mechanism is less likely to underlie our results, given the extensive training of subjects before scanning.

Instead, we propose that the abnormal organization of connectivity of the prefrontal areas in the patients is due to the important role of the prefrontal cortex in motor preparation and planning. This role exists for both imagined and executed movement.^{49–51} Although planning is common to both tasks, studies of healthy volunteers have suggested that prefrontal cortex activity is more prominent during motor imagery in the absence of motor execution.^{41–44} Although we did not reproduce this result in either of our subject groups, this is consistent with our previous work in both stroke patients³⁶ and healthy volunteers (unpublished). One explanation for this apparent discrepancy is that unlike previous studies, our subjects were screened for chaotic motor imagery (see Results), and compliance during scanning was strictly monitored. Motor imagery differs from executed movement in that the motor program is not “discharged” or executed, but it is rehearsed “online” in an active state.^{23,24,52} This rehearsal of the motor planning program may underlie the increased connectivity in our patients.

The role of the prefrontal cortex in recovery from subcortical motor stroke is relevant to the development of transcranial direct current stimulation (tDCS) as a potential therapy to improve motor function.¹⁰ tDCS montages often place the inhibitory (cathodal) electrode over the contralesional prefrontal regions, with the stimulatory (anodal) electrode over the affected motor cortex. The prefrontal cortical location might affect other cognitive processes,⁵³ and our study provides grounds for careful consideration of potential interactions between the effects of tDCS and the timing of therapy or the combination with physical rehabilitation strategies and motor imagery.

One other major study has examined motor network connectivity after stroke using executed movement. Grefkes et al¹⁶ identified residual differences in regional activations as well as differences in transcallosal connectivity between the primary motor areas. They also found a significant reduction in the cortical coupling between the supplementary motor area and ipsilesional primary motor cortex, which increased with better motor performance. Similarly, during executed movement we found a reduction of connectivity between supplementary motor area and dorsal premotor cortex, which is situated immediately anterior to the primary motor region. This small anatomical difference could represent a functionally meaningful difference related to cognitive processes prior to execution or movement. However, methodological differences between the 2 studies are more likely to account for the apparent discrepancy. These include individual variation of anatomy in the small study populations, the severity of residual deficits, and the time since stroke. Another difference from our study is the use of structural equation modeling rather than dynamic causal modeling to assess connectivity. Despite these differences, the similarity of changes in connectivity across both studies highlights the additional information available from connectivity analyses in the context of motor recovery after stroke.

This study also has several limitations arising from inclusion criteria, group size, and the structural equation modeling method itself. For example, we found no difference between groups in terms of regional activations (even with an exploratory use of a lower threshold of $p < 0.001$ uncorrected). Although a similar lack of difference was observed in a previous study,³⁶ it is possible that significant differences might emerge with larger groups. Nevertheless, we show that changes in connectivity can be seen even when significant changes in regional activation are not apparent. This study included patients with good functional outcome in order to contrast the results during motor imagery with executed movement. However, the tasks and connectivity analysis could also usefully be extended to patients with more severe deficits of the type studied by Grefkes et al.¹⁶

Structural equation modeling of changes in brain network connectivity has been used in diverse clinical contexts^{40,54,55} and simulations of lesions.²⁵ Our anatomical network model was confined to regions implicated in motor recovery after stroke, and we cannot infer changes among other regions. Moreover, structural equation modeling cannot be used to infer whether changes in connectivity are due to direct or indirect pathways, nor whether excitatory or inhibitory synaptic changes mediate the changes in connectivity; the method supports systems-level conclusions regarding regional interactions. Although structural equation modeling can be used to test a model that embodies causal interactions (effective connectivity⁵⁶), we do not claim that the changes in connectivity that we observed were the cause of improved outcome, even though they positively correlated with outcome. This qualification is important in considering the impact of our results on rehabilitation strategies, to which we now turn.

Although our observations are based on a small number of highly selected stroke patients, they have implications for developing and assessing stroke rehabilitation strategies. For example, they support the use of motor imagery training²³ and mirror therapy⁵⁷ as means to

promote activity within the motor system after stroke. It is possible that both pharmacological and nonpharmacological approaches can enhance distributed cortical connectivity and thereby facilitate recovery from stroke. However, further studies including longitudinal design are needed to establish a causal link between increased connectivity and recovery. It would be of particular interest to study whether effective therapy by motor imagery or mirror training enhances connectivity in the motor system. Our data suggest that for such studies the formal analysis of effective connectivity may be more sensitive than classical analysis of regional activations, and complement behavioral tests of recovery in heterogeneous patient populations.

The heterogeneity of stroke patients must also be considered. It is possible that benefits of motor imagery may not apply to patients with chaotic motor imagery. These patients were excluded from our study and may require alternative strategies for therapy.^{20,23} Additional inclusion criteria were used. We restricted the study to right-handed patients with subcortical stroke affecting the dominant hand. Stringent selection has the advantage of minimizing patient variance and hence increasing power, reducing common confounds and preventing ambiguity over interpretation of tasks that patients cannot perform.⁵⁸ However, it also restricts the generalization of inferences to other patients.

In conclusion, this study shows abnormal cortico-cortical connectivity in the motor system after subcortical stroke even after significant recovery. Moreover, the strength of connectivity among frontal motor regions correlated with motor function. We propose that the altered connectivity from the prefrontal cortex relates to its role in planning movement. Our results underpin the concepts of recovery of function that are relevant to the development (and assessment) of physical or neurophysiological therapies for stroke. Key questions for future studies will be the generalization of our findings to other stroke syndromes, and the causal relationship between changing connectivity and motor recovery.

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References

1. Wolpert D, Ghahramani Z. Computational principles of movement neuroscience. *Nat Neurosci*. 2000; 3(suppl):1212–1217. [PubMed: 11127840]
2. Cramer S. Repairing the human brain after stroke. II. Restorative therapies. *Ann Neurol*. 2008; 63:549–560. [PubMed: 18481291]
3. Cramer S. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol*. 2008; 63:272–287. [PubMed: 18383072]
4. Johansen-Berg H, Dawes H, Guy C, et al. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*. 2002; 125:2731–2742. [PubMed: 12429600]
5. Dong Y, Dobkin BH, Cen SY, et al. Motor cortex activation during treatment may predict therapeutic gains in paretic hand function after stroke. *Stroke*. 2006; 37:1552–1555. [PubMed: 16645139]
6. Takahashi CD, Der-Yeghiaian L, Le V, et al. Robot-based hand motor therapy after stroke. *Brain*. 2008; 131:425–437. [PubMed: 18156154]
7. Nagano-Saito A, Leyton M, Monchi O, et al. Dopamine depletion impairs frontostriatal functional connectivity during a set-shifting task. *J Neurosci*. 2008; 28:3697–3706. [PubMed: 18385328]

8. Fregni F, Pascual-Leone A. Hand motor recovery after stroke: tuning the orchestra to improve hand motor function. *Cogn Behav Neurol*. 2006; 19:21–33. [PubMed: 16633016]
9. Calautti C, Baron J-C. Functional neuroimaging studies of motor recovery after stroke in adults: a review. *Stroke*. 2003; 34:1553–1566. [PubMed: 12738893]
10. Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. *Arch Neurol*. 2004; 61:1844–1848. [PubMed: 15596603]
11. Calautti C, Leroy F, Guincestre J-Y, Baron J-C. Dynamics of motor network overactivation after striatocapsular stroke: a longitudinal PET study using a fixed-performance paradigm. *Stroke*. 2001; 32:2534–2542. [PubMed: 11692013]
12. Calautti C, Naccarato M, Jones PS, et al. The relationship between motor deficit and hemisphere activation balance after stroke: a 3T fMRI study. *Neuroimage*. 2007; 34:322–331. [PubMed: 17045490]
13. Cramer SC, Nelles G, Benson RR, et al. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*. 1997; 28:2518–2527. [PubMed: 9412643]
14. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*. 2003; 126:2476–2496. [PubMed: 12937084]
15. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of outcome after stroke: a cross-sectional fMRI study. *Brain*. 2003; 126:1430–1448. [PubMed: 12764063]
16. Greffkes C, Nowak D, Eickhoff S, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol*. 2008; 63:236–246. [PubMed: 17896791]
17. Gerloff C, Bushara K, Sailer A, et al. Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. *Brain*. 2006; 129:791–808. [PubMed: 16364955]
18. Raghavan P, Krakauer JW, Gordon AM. Impaired anticipatory control of fingertip forces in patients with a pure motor or sensorimotor lacunar syndrome. *Brain*. 2006; 129:1415–1425. [PubMed: 16597653]
19. Chollet F, DiPiero V, Wise R, et al. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann Neurol*. 1991; 29:63–71. [PubMed: 1996881]
20. Sharma N, Simmons LH, Jones PS, et al. Motor imagery after subcortical stroke: a functional magnetic resonance imaging study. *Stroke*. 2009; 40:1315–1324. [PubMed: 19182071]
21. Jeannerod M, Decety J. Mental motor imagery: a window into the representational stages of action. *Curr Opin Neurobiol*. 1995; 5:727–732. [PubMed: 8805419]
22. Lotze M, Cohen LG. Volition and Imagery in neurorehabilitation. *Cogn Behav Neurol*. 2006; 19:135–140. [PubMed: 16957491]
23. Sharma N, Pomeroy VM, Baron J-C. Motor imagery: a backdoor to the motor system after stroke? *Stroke*. 2006; 37:1941–1952. [PubMed: 16741183]
24. Sharma N, Jones PS, Carpenter TA, Baron J-C. Mapping the involvement of BA 4a and 4p during motor imagery. *Neuroimage*. 2008; 41:92–99. [PubMed: 18358742]
25. Kim J, Horwitz B. How well does structural equation modeling reveal abnormal brain anatomical connections? An fMRI simulation study. *Neuroimage*. 2009; 45:1190–1198. [PubMed: 19349234]
26. Penny WD, Stephan KE, Mechelli A, Friston KJ. Modelling functional integration: a comparison of structural equation and dynamic causal models. *Neuroimage*. 2004; 23(suppl 1):S264–S274. [PubMed: 15501096]
27. Buchel C, Friston KJ. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. *Cereb Cortex*. 1997; 7:768–778. [PubMed: 9408041]
28. Friston KJ, Buchel C. Attentional modulation of effective connectivity from V2 to V5/MT in humans. *Proc Natl Acad Sci U S A*. 2000; 97:7591–7596. [PubMed: 10861020]
29. Hayashi Y, Majewska AK. Dendritic spine geometry: functional implication and regulation. *Neuron*. 2005; 46:529–532. [PubMed: 15944122]
30. Oldfield R. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971; 9:97–113. [PubMed: 5146491]

31. Simmons L, Sharma N, Baron J, Pomeroy V. Feasibility study of motor imagery after stroke. *Neurorehabil Neural Repair*. 2008; 22:458–467. [PubMed: 18780881]
32. Lang CE, Wagner JM, Dromerick AW, Edwards DF. Measurement of upper-extremity function early after stroke: properties of the action research arm test. *Arch Phys Med Rehabil*. 2006; 87:1605–1610. [PubMed: 17141640]
33. Hsieh C-L, Hsueh IP, Chiang F-M, Lin P-H. Inter-rater reliability and validity of the Action Research arm test in stroke patients. *Age Ageing*. 1998; 27:107–113. [PubMed: 16296669]
34. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. *J Neurol Neurosurg Psychiatry*. 1990; 53:576–579. [PubMed: 2391521]
35. Markus HS, Harrison MJ. Estimation of cerebrovascular reactivity using transcranial Doppler, including the use of breath-holding as the vasodilatory stimulus. *Stroke*. 1992; 23:668–673. [PubMed: 1579964]
36. Sharma N, Simmons L, Jones PS, et al. Motor imagery after sub-cortical stroke: an fMRI study. *Stroke*. 2009; 40:1315–1324. [PubMed: 19182071]
37. Alkadhi H, Brugger P, Boendermaker SH, et al. What disconnection tells about motor imagery: evidence from paraplegic patients. *Cereb Cortex*. 2005; 15:131–140. [PubMed: 15238440]
38. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994; 18:192–205. [PubMed: 8126267]
39. Rowe JB, Siebner H, Filipovic SR, et al. Aging is associated with contrasting changes in local and distant cortical connectivity in the human motor system. *Neuroimage*. 2006; 32:747–760. [PubMed: 16797190]
40. Rowe J, Stephan KE, Friston K, et al. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain*. 2002; 125:276–289. [PubMed: 11844728]
41. Hanakawa T, Dimyan MA, Hallett M. Motor planning, imagery, and execution in the distributed motor network: a time-course study with functional MRI. *Cereb Cortex*. 2008; 18:2775–2788. [PubMed: 18359777]
42. Binkofski F, Amunts K, Stephan K, et al. Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. *Hum Brain Mapp*. 2000; 11:273–285. [PubMed: 11144756]
43. Gerardin E, Sirigu A, Lehericy S, et al. Partially overlapping neural networks for real and imagined hand movements. *Cereb Cortex*. 2000; 10:1093–1104. [PubMed: 11053230]
44. Lacourse MG, Orr ELR, Cramer SC, Cohen MJ. Brain activation during execution and motor imagery of novel and skilled sequential hand movements. *Neuroimage*. 2005; 27:505–519. [PubMed: 16046149]
45. Fridman EA, Hanakawa T, Chung M, et al. Reorganization of the human ipsilesional premotor cortex after stroke. *Brain*. 2004; 127:747–758. [PubMed: 14749291]
46. Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci U S A*. 2002; 99:14518–14523. [PubMed: 12376621]
47. Kasess CH, Windischberger C, Cunnington R, et al. The suppressive influence of SMA on M1 in motor imagery revealed by fMRI and dynamic causal modeling. *Neuroimage*. 2008; 40:828–837. [PubMed: 18234512]
48. Solodkin A, Hlustik P, Chen EE, Small SL. Fine modulation in network activation during motor execution and motor imagery. *Cereb Cortex*. 2004; 14:1246–1255. [PubMed: 15166100]
49. Marois R. The cortical basis of motor planning: does it take two to tango? *Nat Neurosci*. 2002; 5:1254–1255. [PubMed: 12447378]
50. Connolly JD, Goodale MA, Menon RS, Munoz DP. Human fMRI evidence for the neural correlates of preparatory set. *Nat Neurosci*. 2002; 5:1345–1352. [PubMed: 12411958]
51. Rowe JB, Owen AM, Johnsrude IS, Passingham RE. Imaging the mental components of a planning task. *Neuropsychologia*. 2001; 39:315–327. [PubMed: 11163609]
52. Jeannerod M. Mental imagery in the motor context. *Neuropsychologia*. 1995; 33:1419–1432. [PubMed: 8584178]

53. Fecteau S, Knoch D, Fregni F, et al. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J Neurosci.* 2007; 27:12500–12505. [PubMed: 18003828]
54. Laird AR, Robbins JM, Li K, et al. Modeling motor connectivity using TMS/PET and structural equation modeling. *Neuroimage.* 2008; 41:424–436. [PubMed: 18387823]
55. Rosenbaum RS, Furey ML, Horwitz B, Grady CL. Altered connectivity among emotion-related brain regions during short-term memory in Alzheimer's disease. *Neurobiol Aging.* (in press).
56. de Marco G, Devauchelle B, Berquin P. Brain functional modeling, what do we measure with fMRI data? *Neurosci Res.* 2009; 64:12–19. [PubMed: 19321134]
57. Pomeroy VM, Clark CA, Miller JS, et al. The potential for utilizing the “mirror neurone system” to enhance recovery of the severely affected upper limb early after stroke: a review and hypothesis. *Neurorehabil Neural Repair.* 2005; 19:4–13. [PubMed: 15673838]
58. Price C, Friston K. Scanning patients with tasks they can perform. *Hum Brain Mapp.* 1999; 8:102–108. [PubMed: 10524600]

Fig 1.

(A) The anatomical model used for structural equation modeling. The arrows indicate whether the connections were modeled as uni- or bidirectional. The model structure was designed a priori and represents the extended cortical motor network based on the likely presence of connections between homologous regions reported in animal and human neuroimaging literature (including the CoCoMac database, www.cocomac.org). PFC = prefrontal cortex; PM = dorsal premotor cortex; M1 = primary motor cortex (BA4); SMA = supplementary motor area. (B) Second-level fixed-effect group model generated using Statistical Parametric Mapping software that included both tasks (vs Rest) from all subjects with a threshold of $p < 0.05$ corrected (familywise error) to produce the coordinates (the nearest maxima) for the anatomical model. This includes the prefrontal (left hemisphere: BA10 $x = -20$, $y = 52$, $z = 0$; right hemisphere: $x = 26$, $y = -54$, $z = -6$), dorsal premotor (left hemisphere: $x = -38$, $y = -12$, $z = 64$; right hemisphere: $x = 44$, $y = -6$, $z = 58$), primary motor (left hemisphere: $x = -41$, $y = -16$, $z = 52$; right hemisphere: $x = 36$, $y = -30$, $z = 54$), parietal BA7 (left hemisphere: $x = -32$, $y = -48$, $z = 62$; right hemisphere: $x = 42$, $y = -46$, $z = 60$) cortex bilaterally, and the supplementary motor area ($x = -2$, $y = 2$, $z = 56$).

Fig 2. Structural T2-weighted magnetic resonance imaging of stroke patients indicating the subcortical lesions. The slice is chosen for each patient at the maximum extent of the infarct.

Fig 3. Second-level voxel-based cortical activation maps (Statistical nonParametric Mapping toolbox: pseudo *t* maps thresholded at $p < 0.05$ corrected for familywise error).

Fig 4.

Illustration of the differences in the connectivity parameters for each path of the anatomical model. (A) and (B) are the within-group results, whereas (C) and (D) are the between-group differences for each task. (A) Differences in path coefficients for the comparison of motor imagery versus executed movement in aged-matched controls. (B) Differences in path coefficients for the comparison of motor imagery versus executed movement in the stroke patients. (C) Differences in path coefficients for the comparison of stroke patients versus aged-matched controls during motor imagery. (D) Differences in path coefficients for the comparison of stroke patients versus aged-matched controls during executed movement. Green arrow = increased connectivity; red arrow = reduced connectivity. * $p < 0.05$; ** $p < 0.01$. PFC = prefrontal cortex; PM = premotor cortex; SMA = supplementary motor area; M1 = primary motor cortex.

Fig 5.

Spearman's correlations ($p < 0.05$) between connectivity of the prefrontal regions during motor imagery of the stroke patients and motor performance. Of note, there were no significant correlations during executed movement; therefore, only the significant correlations during motor imagery are presented. (A) Correlation between the connectivity coefficient (contralateral prefrontal cortex [PFC] cortex to supplementary motor area [SMA]) and Motricity arm score. (B) Correlation between the connectivity coefficient (contralateral premotor cortex [PM] to SMA) and thumb to index finger tapping over 15 seconds (TIT) ratio. (C) Correlation between the connectivity coefficient (SMA to ipsilateral primary motor cortex [M1]) and Motricity arm score. (D) Correlation between

the connectivity coefficient (ipsilesional premotor cortex to ipsilesional primary motor cortex) and Motricity arm score. (E) Correlation between the connectivity coefficient (ipsilesional premotor cortex to ipsilesional primary motor cortex) and TIT ratio.

Table 1

Stroke Patients' Clinical Characteristics

Patient	Age, y	Sex	Time Since Stroke, d	Affected Hand	Site of Lesion	Stroke Syndrome	TIT Ratio	NIHSS/42	ARAT/57	Motricity Index (Arm)/100	Motricity (Arm+Leg+Trunk)/300
S1	70	F	132	R	L Pons	L Lac	0.78	0	57	77	269
S2	46	M	138	R	L IC	L Lac	0.68	1	57	100	300
S3	56	M	703	R	L IC	L Lac	1.20	1	57	100	300
S4	70	M	7	R	L IC	L Lac	0.67	4	57	93	269
S5	66	F	7	R	L IC	L Lac	0.94	0	57	100	300
S6	74	M	7	R	L IC	L Lac	1.09	0	57	100	300
S7	70	M	173	R	L IC	L Lac	0.56	1	49	84	268
S8	81	M	198	R	L IC	L Lac	1.16	0	57	100	300
Mean	66.6		170.6				0.89	0.875	56	94.25	288
SD	10.9		228				0.25	1.4	2.8	9.0	16.2

TIT ratio = thumb to index finger tapping over 15 seconds; NIHSS = National Institutes of Health Stroke Scale; ARAT = Action Research Arm test; F = female; R = right; L = left; Pons = pontine lesion; Lac = lacunar stroke syndrome; M = male; IC = internal capsule lesion; SD = standard deviation.

Table 2

Chaotic Motor Imagery Assessment: Individual and Group Mean Scores for Accuracy, Break Point, and Self-Assessment of the Motor Imagery Task

Subject	Hand Rotation, % Correct ^a	Finger Sequence ^b	Break Point, MI-EM % ^c	Subjective Post-MRI MI Score
C1	91		-50	7
C2	97		0	6
C3	91		-28	6
C4	93		-5	5
C5	94		-9	6
C6	88		-30	7
C7	86		-24	5
C8	94		-25	6
C9	99		-25	4
C10	90		-69	7
C11	100		-43	4

Subject	Hand Rotation, % Correct ^a	Finger Sequence ^b	Break Point, MI-EM % ^c	Subjective Post-MRI MI Score
C12	100		-44	5
C13	95		-18	5
Mean (SE)	94 (0.2)		-28 (5)	Median 6, range (4–7)
S1	91		-14	6
S2	89		-42	4
S3	95		-67	5
S4	85		-20	4
S5	100		-21	4
S6	94		-6	6
S7	77		-19	6
S8	98		-69	7
Mean (SE)	91 (2)		-32 (7)	Median 5.5, range (4–7)

^aNinety-six A4-sized picture cards of hands were presented, and subjects were asked to identify whether the picture was of a left or right hand. Entry criteria include performance over 75%.

^bSubjects are asked to perform motor imagery of a finger sequence task (2,3,4,5,2...; paced using auditory cues at 1Hz). = performed accurately.

^cSubjects performed a finger-tapping sequence using executed movement and then using motor imagery. Pacing rate starts at 40 beats/min and is increased by 10 beats every 5 seconds. The break point is defined as the time when the subject is unable to perform the task accurately. Subjects are excluded if the break point is greater for motor imagery than for executed movement.

MI = motor imagery; EM = executed movement; MRI = magnetic resonance imaging; SE = standard error.

Table 3

Details of Peaks of Activations for Executed Movement and Motor Imagery Against Baseline Aged-Matched Controls and Stroke Patients

Task/Subjects	Cluster Size, Voxels	Pseudo t Value	Coordinates			Location	
			x	y	z		
Executed movement-age-matched controls	76	6.81	-55	11	31	L	PFC
	2917	8.92	-40	-11	59	L	PMd
	130	5.83	42	-13	60	R	PMd
		5.44	36	1	61	R	PMd
	694	8.49	-2	-1	55	L	SMA
	2917	9.93	-34	-15	49	L	BA4
		9.41	-48	-21	51	L	S1
		9.14	-46	-23	47	L	S1
	885	7.09	65	-14	21	R	S1
	885	5.19	32	-35	42	R	Inf.P
	1140	10.07	20	-53	-19	R	CB
		7.35	6	-63	-12	R	CB
	483	6.78	-24	-53	-21	L	CB
		5.60	-20	-65	-15	L	CB
Motor imagery-age-matched controls	12	5.06	-51	10	36	L	PFC
	112	6.74	-55	12	-1	L	IFC
	282	6.89	44	6	51	R	PMd
		6.84	42	5	53	R	PMd
	474	6.83	-34	-15	49	L	BA4
		6.23	-28	-1	50	L	PMd
	569	6.80	-46	-18	38	L	BA4
		6.57	-40	-27	46	L	S1
	98	6.00	50	-30	55	R	S1
	112	5.81	46	-22	36	R	S1
	569	5.46	-53	-32	27	L	Inf.P
	98	5.09	40	-29	40	R	Inf.P
	83	5.66	-30	-51	60	L	Sup.P
	27	5.34	18	-53	-18	R	CB
Executed movement-stroke patients	27	6.62	28	-3	48	R	PMd
	45	6.49	32	-3	65	R	PMd
	641	6.35	-44	-16	60	L	PMd
	32	5.80	0	1	53		SMA
	32	5.80	-2	-7	54	L	SMA
	641	8.05	-40	-17	49	L	BA4
	641	7.62	-38	-34	64	L	S1

Task/Subjects	Cluster Size, Voxels	Pseudo <i>t</i> Value	Coordinates			Location	
			x	y	z		
Motor imagery-stroke patients	641	6.26	-42	-31	46	L	Inf.P
	58	7.16	-18	-63	57	L	Sup.P
	60	6.67	22	-50	-19	R	CB
	4	5.72	6	66	8	R	PFC
	12	5.70	58	16	-6	R	IFC
	234	6.63	-2	3	62	L	SMA
	69	6.30	30	0	46	R	PMd
	35	5.76	42	1	55	R	PMd
	25	5.85	-40	-15	49	L	BA4
	17	6.02	48	-28	57	R	S1
	45	5.87	-38	-33	42	L	Inf.P
	56	6.15	30	-62	-27	R	CB

Coordinates are given in Montreal Neurological Institute standard space.

L = left; PFC = prefrontal cortex; PMd = dorsal premotor cortex; R = right; SMA = supplementary motor cortex; BA4 = primary motor cortex; S1 = primary sensory cortex; Inf.P = inferior parietal lobe; CB = cerebellum; IFC = inferior frontal cortex; Sup.P = superior parietal lobe.

Table 4

Details of Peaks of Activations for Executed Movement (vs Rest) > Motor Imagery (vs Rest) and the Reverse for Each Group

Task	Cluster Size, Voxels	Pseudo, <i>t</i> Value	Coordinates			Location
			x	y	z	
Aged-matched controls						
Executed movement > motor imagery	486	7.09	−36	−17	54	L BA4
		7.04	−38	−16	63	L PMd
Motor imagery > executed movement	Nil	N/A	N/A	N/A	N/A	N/A
Stroke patients						
Executed movement > motor imagery	30	7.45	−36	−18	65	L PMd
	36	6.50	−38	−19	49	L BA4
Motor imagery > executed movement	Nil	N/A	N/A	N/A	N/A	N/A

Coordinates are given in Montreal Neurological Institute standard space.

L = left; BA4 = primary motor cortex; PMd = dorsal premotor cortex; N/A = not applicable.