tapraid5/zay-aon/zay-aon/zay01007/zay2633d07g | gockleyj | S=4 | 9/7/07 | 7:43 | Art: 21228

ORIGINAL ARTICLE

AQ: 1

Cortical Connectivity after Subcortical Stroke Assessed with Functional Magnetic Resonance Imaging

Christian Grefkes, MD,[1,2] Dennis A. Nowak, MD, PhD,[1,2] Simon B. Eickhoff, MD,[2] Manuel Dafotakis, MD,[1,2] Jutta Küst, PhD,[3] Hans Karbe, MD, PhD,[3] and Gereon R. Fink, MD, PhD[1,2]

Objective: This study aimed at identifying the impact of subcortical stroke on the interaction of cortical motor areas within and across hemispheres during the generation of voluntary hand movements.

Methods: Twelve subacute stroke patients with a subcortical ischemic lesion and 12 age-matched control subjects were scanned using 3-Tesla functional magnetic resonance imaging. Subjects performed visually paced hand movements with their left, right, or both hands. Changes of effective connectivity among a bilateral network of core motor regions comprising M1, lateral premotor cortex, and the supplementary motor area (SMA) were assessed using dynamic causal modeling.

Results: The data showed significant disturbances in the effective connectivity of motor areas in the patients group: Independently from hand movements, the intrinsic neural coupling between ipsilesional SMA and M1, and the interhemispheric coupling of both SMAs was significantly reduced. Furthermore, movements of the stroke-affected hand showed additional inhibitory influences from contralesional to ipsilesional M1 that correlated with the degree of motor impairment. For bimanual movements, interhemispheric communication between ipsilesional SMA and contralesional M1 was significantly reduced, which also correlated with impaired bimanual performance.

Interpretation: The motor deficit of patients with a single subcortical lesion is associated with pathological interhemispheric interactions among key motor areas. The data suggest that a dysfunction between ipsilesional and contralesional M1, and between ipsilesional SMA and contralesional M1 underlies hand motor disability after stroke. Assessing effective connectivity by means of functional magnetic resonance imaging and dynamic causal modeling might be used in the future for the evaluation of interventions promoting recovery of function.

Ann Neurol 2007;62:000–000

The motor system comprises a network of cortical and subcortical areas that interact by means of excitatory or inhibitory circuits finally leading to motor output. The balance within this network may be critically disturbed after stroke if the lesion either directly affects any of these areas or damages white matter fibers connecting critical regions. For example, disconnection of the spinal motor neurons from the motor cortex because of damage of the descending motor pathways (ie, the corticospinal tract) is widely assumed to be the major cause of impaired dexterity after subcortical stroke. However, data obtained using transcranial magnetic stimulation (TMS) of the motor cortex suggest that motor output from the lesioned hemisphere may be additionally influenced by pathologically enhanced inhibitory influences from the intact hemisphere.[1–3] Consistent with this finding, functional neuroimaging experiments demonstrated that neural activity in the primary motor cortex (M1) of the intact hemisphere is enhanced when patients move their paretic hand.[4,5] These data led to the hypothesis that subcortical stroke may alter transcallosal inhibition such that M1 of the unaffected hemisphere exerts an abnormally high inhibitory drive on the motor cortex of the lesioned hemisphere, thereby contributing to the impaired motor function of the paretic hand.[2] However, the neural mechanisms underlying such stroke-related disturbances in cortical networks leading to functional impairment remain to be elucidated.

Therefore, we aimed at identifying the impact of subcortical stroke lesions on the cortical networks controlling voluntary hand movements both within and across the hemispheres as assessed with functional magnetic resonance imaging (fMRI). Recent advances in modeling effective connectivity enabled inferring functional interactions between cortical areas in both time

From the [1]Department of Neurology, University of Cologne, Cologne; [2]Institute of Medicine and Brain Imaging Center West, Jülich Research Centre, Jülich; and [3]Neurological Rehabilitation Center "Godeshöhe," Bonn, Germany.

Received Apr 5, 2007, and in revised form Jul 7. Accepted for publication Aug 3, 2007.

Published online 00 Month 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21228

Address correspondence to Dr Grefkes, Department of Neurology, University of Cologne, Kerpener Strasse 62, 50924 Köln, Germany. E-mail: christian.grefkes@uk-koeln.de

Published by Wiley-Liss, Inc., through Wiley Subscription Services

and space.[6] In particular, the concept of dynamic causal modeling (DCM) is a promising approach to capture the intrinsic and task-dependent influences that a particular area exerts over the activity of another area, known as "effective connectivity."[6,7] Thus, we used DCM to test the hypothesis that connectivity among key regions of the motor system may be specifically altered in subcortical stroke patients suffering from a motor deficit of one hand. Effective connectivity was estimated in a bilateral cortical network of core motor regions including the primary motor cortex (M1), lateral premotor cortex (PMC), and supplementary motor area (SMA).

Subjects and Methods

Subjects

This study was approved by the local ethics committee. Twelve patients (mean age, 46.6 years) with mild weakness of one hand after a first-ever subcortical ischemic stroke in the left (n = 7) or right (n = 5) middle cerebral artery territory participated. Patients were selected according to the following criteria: (1) a stable unilateral motor deficit including the hand at least 5 weeks after the vascular incident (subacute phase); (2) subcortical location of the ischemic lesion within the territory of the middle cerebral artery; (3) no mirror movements of the unaffected hand; (4) a score of more than 25 points on the Folstein's Mini-Mental Status Examination[8]; (5) absence of aphasia, neglect, and apraxia; and (6) no visual field deficits. The following clinical scores were assessed on the day of examination: modified Rankin Scale, Mini-Mental Status Examination, and Medical Research Council scale for motor weakness of the affected hand. In addition, the maximum frequency of index finger tapping movements was averaged from three 5-second trials for both hands. Twelve age- and sex-matched healthy subjects (mean age, 46.4 years) with no history of neurological, psychiatric, or orthopedic diseases served as control subjects. Informed consent was obtained from each subject.

Experimental Procedures

Subjects were asked to perform stereotypical whole-hand fist closings with either the left, right, or both hands. Written instructions were displayed for 1.5 seconds on a video screen, indicating whether subjects had to move the left, right, or both hands. After a randomly jittered delay of 1.5 to 2.5 seconds, the instruction text was replaced by a black circle on a white screen, which started to blink in red at a rate of 1.5Hz. Subjects were instructed to perform fist closings at the same frequency coinciding with appearance of the red circle. Both hands rested in a supine position on cushions next to the subject's hips, and hand movements consisted of full finger flexion and extensions at the frequency of the visual cue. After 15 seconds, the circle disappeared, and a white screen indicated that subjects should rest their hand(s) for about 15 seconds until the next block of movements commenced. The whole fMRI session lasted approximately 12.5 minutes.

Before scanning, subjects were trained for task familiarization until stable performance was reached. Patients who could not achieve the requested frequency were instructed to perform as close as possible to the visual cue but to maintain correct fist openings and closings. Task performance (ie, the number of fist closures per block) was video-monitored over the whole experiment through the window of the magnetic resonance room using a video camera.

Functional Magnetic Resonance Imaging

fMRI scans were acquired on a Siemens Trio 3.0 T whole-body scanner (Siemens Medical Systems, South Iselin, NJ). We used a gradient echo planar imaging sequence with following imaging parameters: TR = 1,600 milliseconds, TE = 30 milliseconds, field of view = 200mm, 26 axial slices, slice thickness = 3.0mm, in-plane resolution = 3.1 × 3.1mm, echo planar imaging volumes = 457 (plus 4 dummy images). The slices covered a region extending from midprefrontal (rostral) to visual cortex (caudal). The cerebellum, prefrontal brain areas, orbitofrontal cortex, and anterior temporal cortex were outside the field of view because of the short TR (which, in turn, is a necessary prerequisite for accurate estimation of effective connectivity by means of DCM).

Additional high-resolution T1-weighted images were acquired using a three-dimensional magnetization-prepared, rapid acquisition gradient-echo sequence with the following parameters: TR = 2,250 milliseconds, TE = 3.93 milliseconds, field of view = 256mm, 176 sagittal slices, slice thickness = 1.0mm, in-plane resolution = 1.0 × 1.0mm. T2 fluid-attenuated inversion recovery images were acquired for all subjects to screen for brain lesions not evident on the T1 images: TR = 9,000 milliseconds, TE = 100 milliseconds, field of view = 220mm, 25 axial slices, slice thickness = 4mm, in-plane resolution = 0.9 × 0.9mm.

Imaging Data Processing

For imaging data preprocessing and statistical analysis, we used the Statistical Parametric Mapping software package (SPM5; Wellcome Department of Imaging Neuroscience, London, United Kingdom) for realignment of the echo planar imaging volumes, anatomical coregistration, spatial normalization to the reference space of the Montreal Neurological Institute, and smoothing (8mm isotropic kernel). For the DCM analysis, all subjects were analyzed in corrected left-right anatomical orientation, and only after estimation of the connectivity parameters were the DCM results sorted according to "affected" and "unaffected" hemisphere (see later). For the (visual) demonstration of neural activation in the group analysis, we reanalyzed the data of the five right-hemispheric stroke patients and flipped their data before normalization to the left hemisphere (to register the lesioned hemisphere to the same anatomical template in all subjects). After isotropic smoothing the data, box-car vectors for each condition were convolved with a canonical hemodynamic response function to create the regressors of interest for the subsequent general linear model.[9] Head movement estimates were used as confound regressors to exclude movement-related variance from the image time series. Voxels were identified as significant if their t values passed a height threshold of $t = 3.43$ ($p < 0.001$, uncorrected). Correction for multiple comparisons

was then applied on the cluster level ($p < 0.05$, family wise error corrected).

To demonstrate the location and variability of the stroke lesions, we used the software MRIcro (version 1.4, www.mricro.com) to delineate the ischemic lesions on the T1 volumes in combination with the T2 fluid-attenuated inversion recovery images. Right hemispheric lesions were flipped to the left hemisphere, and after normalization to the Statistical Parametric Mapping template, each lesion region of interest (ROI) was superimposed in three-dimensional space. The degree of overlap was color coded in a spectral sequence.

Connectivity Analysis

DCM was used to assess effective connectivity between the cortical motor areas activated by the aforementioned task. We focused our analysis on the core regions of the cortical motor system in both hemispheres of each subject: the primary motor cortex (M1), the SMA, the lateral PMC, and extrastriate visual cortex comprising area V5 at the occipitotemporal junction (Fig 1; $p < 0.05$, family wise error corrected on the voxel level). The latter region, which, in contrast with early retinotopic cortex, showed a well-defined local maximum in neural activity across all subjects, was defined as input region because subjects used the visual pacing cue as signal for moving the respective hand. The coordinates of the ROIs were determined in the respective baseline contrasts for each individual subject (left SMA/PMC/M1 in contrast "unimanual right vs baseline"; right SMA/PMC/M1 in contrast "unimanual left vs baseline").

F1

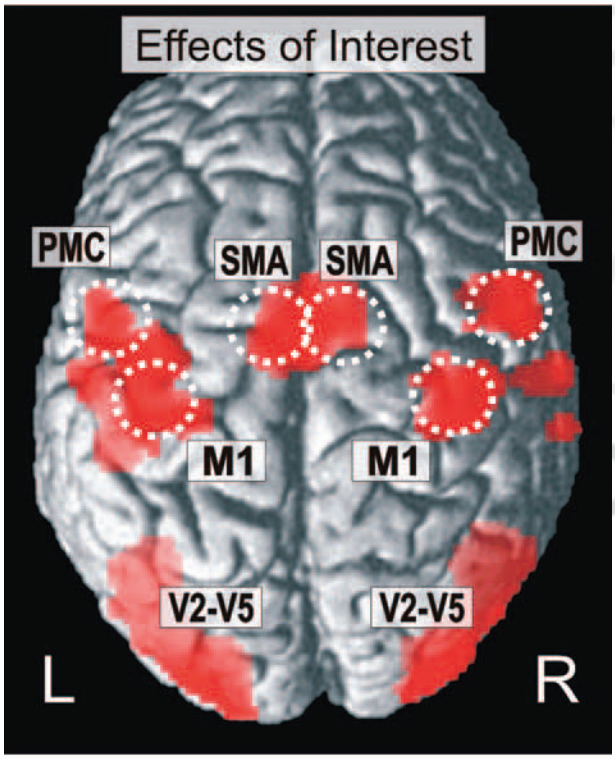


Fig 1. Regions of interest selected for the connectivity analysis based on significantly activated voxels during movements of the right or left hand in both groups (patients and healthy control subjects, F-test, p < 0.05*, corrected on the voxel level). Scans from patients with right-sided lesions were flipped, so that all patients were assumed to have left hemispheric lesions. Significant activations were found in primary sensorimotor cortex (with local maxima in M1), lateral premotor complex (PMC), supplementary motor area (SMA), and visual cortex.*

All three task conditions (unimanual right, unimanual left, bimanual) were modeled as experimental perturbations of the cortical network formed by these areas (outlined in Figs 1 and 3). Coupling parameters were obtained for the reciprocal interactions between SMA, PMC, and M1 within and across hemispheres. The statistical significance of the derived coupling parameters (the intrinsic connections and the task-dependent modulatory influences) were tested by means of a one-sample two-sided *t* test (software SPSS 12.0.1 for Windows; SPSS, Chicago, IL). Significant differences between patients and control subjects were assessed in a repeated-measures analysis of variance with "group" as fixed factor and the coupling parameters as within-subject variables. Post hoc *t* tests were calculated to identify statistically significant differences for the coupling parameters between patients and control subjects ($p < 0.05$, Bonferroni corrected for multiple comparisons). Because DCM data were analyzed according to "affected" and "unaffected" hemisphere and because of the sample size, inferences on the specific contribution of left- or right-sided lesions to cortical connectivity are beyond the scope of this article. Correlation analyses (Pearson's correlation coefficient *r*) were computed between significant coupling parameters and hand performance as assessed during scanning. Correlations were considered significant if their *p* value was less than 0.05.

Results

The clinical characteristics of the stroke patients are summarized in the Table. T1

Behavioral Data

Repeated-measures analysis of variance on the frequencies of fist closures with the between-subject factor "group" (patients; controls) and the within-subject factor "hand" (unimanual right, unimanual left, bimanual) demonstrated a significant main effect of both factors ("group" $F_{1, 22} = 5.54$; $p < 0.05$; "hand" $F_{2, 44} = 5.82$; $p < 0.01$). There was a significant group-by-hand interaction ($F_{2, 44} = 5.63$; $p < 0.01$). Post hoc *t* tests demonstrated that in patients movement frequencies of the affected hand were significantly lower (mean movement rate = 1.34 ± 0.25Hz) when compared with the unaffected hand (1.54 ± 0.02Hz) or with each hand of the healthy control subjects (right hand: 1.53 ± 0.04Hz; left hand: 1.54 ± 0.04Hz) ($p < 0.05$ for each comparison). There was no significant difference for the movement frequencies between the patients' unaffected hand and either hand of the healthy control subjects ($p > 0.70$). However, for bilateral hand movements, movement frequencies were significantly lower in patients (1.39 ± 0.20Hz) than those of the healthy control subjects (1.53 ± 0.04Hz) ($p <$

COLOR

AQ: T1

Table.

Patient No.	Age (yr)	Sex	Affected Hand	Site of Lesion	Time after Stroke (wk)	MRC Scale Score	mRS Score	Tapping Frequency (affected hand/ nonaffected hand)[a]	MMSE Score
1	47	M	R	L IC	10	4+	1	3.7/4.8	30
2	49	M	L	R CR	9	4	1	2.3/4.4	27
3	48	F	R	L IC/BG	7	4+	1	3.2/4.2	30
4	39	M	R	L CR	5	4+	1	3.6/5.1	26
5	52	F	L	R IC/BG	14	4+	1	4.1/4.6	30
6	24	F	R	L IC/IC	6	5	1	3.6/4.1	30
7	51	M	R	L IC	10	4	1	4.1/5.1	28
8	53	M	L	R CR	32	4	1	3.9/4.6	28
9	45	M	L	R CR	7	4	2	1.3/4.5	29
10	37	M	R	L Th	6	4+	1	3.9/6.2	30
11	60	M	R	L IC	8	4	2	3.5/4.4	29
12	54	M	L	R IC	6	4	1	2.8/5.0	29
Mean ± SD	46.6 ± 9.1	9 M/3 F	5 L/7 R		10.0 ± 7.0			3.3 ± 0.8/4.7 ± 0.5	28.8 ± 1.3

[a]Mean frequency of finger tappings with maximal speed averaged over three consecutive 5-second trials.
MRC = Medical Research Council; mRS = modified Rankin Scale; MMSE = Mini Mental State Examination (maximum: 30); IC = internal capsule; CR = corona radiata; BG = basal ganglia; Th = thalamus; SD = standard deviation.

0.01) and were usually close to the performance for unimanual movements of the affected hand.

Functional Imaging Data

Figure 2 demonstrates the regions activated by visually paced movements of the right and left hand in healthy subjects and movements of the affected and nonaffected hand in patients (all normalized as having left-sided lesions) relative to the low-level baseline (resting in the scanner). In healthy subjects, right or left hand fist closures increased neural activity in a network comprising contralateral M1 (including the primary somatosensory cortex), contralateral SMA, bilateral lateral PMC, and visual cortex ($p < 0.05$, corrected; see Fig 2). In patients, movements of the unaffected hand yielded similar activations as movements of the right or left hand in healthy subjects (see Fig 2B). Movements of the stroke-affected hand were associated with more widespread activation clusters in the lesioned hemispheres extending into frontal and parietal areas (see Fig 2A). Importantly, and in contrast with the healthy control group, movements of the affected hand were also associated with significant neural activity in the ipsilateral (ie, contralesional) hemisphere with clusters of activation around the central sulcus, precentral gyrus, and the inferior parietal cortex (see Fig 2).

F2

Changes of the Intrinsic Connectivity and Correlation with Motor Behavior

We first analyzed the impact of stroke on the intrinsic connectivity among cortical motor areas. In this context, "intrinsic connectivity" refers to the neural coupling between the areas in absence of the specific influence of the task. Note that intrinsic connectivity (which is not equivalent to baseline connectivity because of its mathematical nature, but rather represents the task-independent component) should not be influenced or even driven by task-related activity. Rather, the latter will be independently modeled in addition to it. Positive coupling parameters (Fig 3, green arrows) indicate a promotion of neural activity, whereas negative coupling parameters (see Fig 3, red arrows) indicate an inhibition of the target area. The coupling rates (measured in Hertz) also implicitly capture the influence of putative subcortical relay structures, such as the basal ganglia or the cerebellum.

F3

Figure 3A demonstrates that, in healthy subjects, the intrinsic coupling of neural activity among motor areas was symmetrically organized. The coupling parameters show that neural activity within the hemispheres was positively coupled, whereas the interhemispheric coupling among both M1 and both SMAs indicated a predominantly inhibitory influence of these areas that was balanced in either direction. Figure 3B depicts those connections in the motor network of the stroke patients that showed a significant difference in neural coupling compared with the healthy control group ($p < 0.05$, Bonferroni corrected). The data demonstrated a significant reduction in the neural coupling among SMA and M1 in the lesioned hemisphere. Furthermore, interhemispheric connections also showed significant changes in the patient group: Although M1

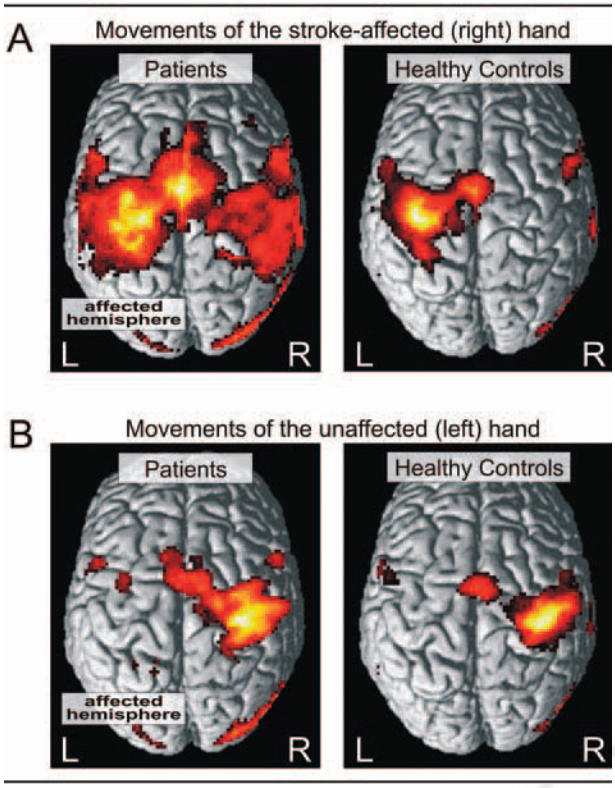


Fig 2. Neural activity during movements of the left or right hand in healthy subjects and in stroke patients with left-sided subcortical lesions ($p < 0.05$*, corrected on the cluster level). Activation clusters were surface rendered onto a canonical brain shown from above. In stroke patients, movements of the impaired hand were associated with significant activations also in ipsilateral (ie, contralesional) motor areas, which were absent in the healthy control subjects (A).*

activity in healthy subjects was intrinsically suppressed by SMA of the respective other hemisphere (negative coupling parameters), these influences were basically absent for ipsilesional M1 in stroke patients (see Fig 3B). Similarly, the intrinsically negative interhemispheric interaction between both SMA regions seen in healthy subjects was significantly reduced in stroke patients. The coupling parameters of the remaining connections were not significantly different between the two groups (see Fig 3B, gray arrows).

To test whether these changes in the intrinsic motor network correlated with the behavioral impairments of the patients, we performed a correlation analysis of the coupling parameters and the movement frequency of the paretic hand during scanning. The only intrinsic coupling parameter significantly correlating with the hand movement frequency, that is, the only pathway whose connectivity closely followed the behavioral performance of the patients, was the input from ipsilesional SMA into ipsilesional M1 (see Fig 3C). The stronger the intrinsic coupling between SMA and M1, the better the performance of the stroke-affected hand during unimanual (Pearson's $r = 0.78$; $p < 0.01$) or bimanual ($r = 0.60$; $p < 0.05$) hand movements in the scanner. Correlating the coupling parameters with behavioral parameters independent from the fMRI task (as listed in the Table) demonstrated a further significant correlation of ipsilesional SMA-M1 coupling with maximal finger-tapping frequency of the affected hand ($r = 0.59$; $p < 0.01$). All other measures (age, sex, side of lesion, time of stroke onset, modified Rankin Scale, MMST) were not significantly correlated.

Changes of Neural Coupling Induced by Unimanual Movements

In the next step, we analyzed the specific impact of unimanual and bimanual hand movements on the motor network. When healthy subjects performed unimanual (left or right) movements, neural coupling between SMA and the contralateral motor cortex was enhanced, whereas activity of ipsilateral M1 was significantly reduced by ipsilateral PMC, contralateral SMA, and also contralateral M1 ($p < 0.05$, corrected; Fig 4A). In contrast, when stroke patients moved their paretic hand, the unaffected, (ie, contralesional) motor cortex showed an additional negative influence on the neural activity of ipsilesional M1, which was not present in healthy control subjects (see Fig 4B). The coupling parameters of this increased inhibition were significantly correlated with the motor performance of the paretic hand at the individual level of the patients; that is, the stronger the inhibition exerted by contralesional M1 on ipsilesional M1, the lower the frequency of the performed hand movements (Pearson's $r = 0.74$; $p < 0.01$; see Fig 4C). Furthermore, testing for correlations with other behavioral measures (see the Table) showed a significant correlation of this coupling parameter with maximum finger-tapping frequency at the affected hand (Pearson's $r = 0.58$; $p < 0.05$). Also, *bilateral* hand performance significantly correlated with M1-M1 coupling during *unimanual* movements of the affected hand ($r = 0.73$; $p < 0.01$). All other measures (see the Table) were not significantly correlated. Movements of the patients' unaffected hands was not associated with any significant changes in neural coupling as compared with the healthy control subjects.

When healthy subjects moved both hands in-phase, activity in both M1 cortices was promoted by increased coupling with ipsilateral and contralateral SMA. Moreover, the negative intrinsic coupling between both M1 regions was inverted into a bilateral positive, that is, promoting, influence (Fig 5A). When the patients moved both hands in-phase, the neural positively modulated coupling between ipsilesional M1 and contralesional M1 was significantly reduced compared with healthy control subjects (see Fig 5B). Furthermore, in comparison with healthy control subjects, ipsilesional SMA exerted a significantly smaller positive driving in-

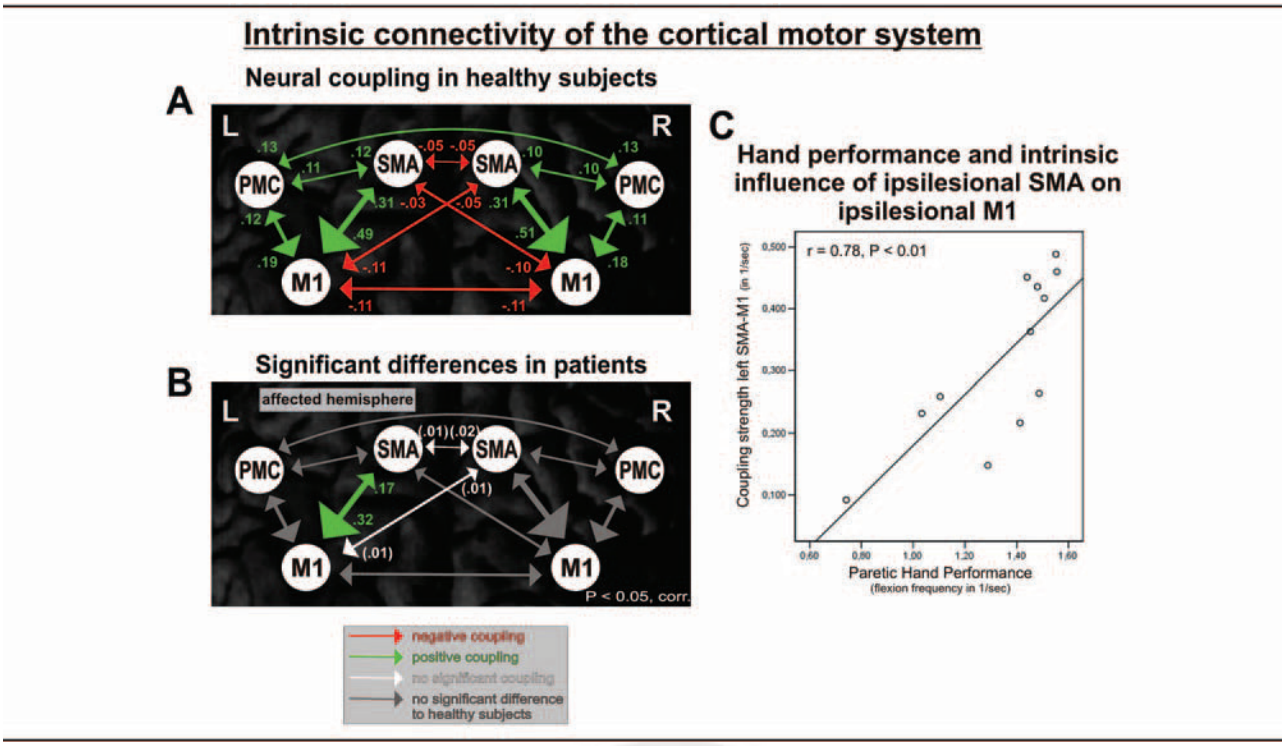


Fig 3. Intrinsic connectivity among motor regions. Coupling parameters (rate constants in 1/sec) indicate connection strength (changes in activation per second), which is also coded in the size and color of the arrows *representing effective connectivity. Positive* (green arrows) *values represent facilitatory activity; negative* (red arrows) *values represent inhibitory influences on neuronal activity. The greater the absolute value (reflecting the rate constant of the observed influence in 1/sec), the more predominant the effect one area has over another. (A) Intrinsic coupling parameters in healthy subjects ($n = 12$; $p < 0.05$ Bonferroni corrected). (B) Intrinsic coupling parameters in stroke patients significantly different from the healthy control group ($p < 0.05$, Bonferroni corrected).* Gray arrows *indicate no significant differences compared with control subjects.* White arrows *represent no significant coupling of activity. (C) Correlation between paretic hand performance and influence of ipsilesional supplementary motor area (SMA) on ipsilesional M1. PMC = premotor cortex.*

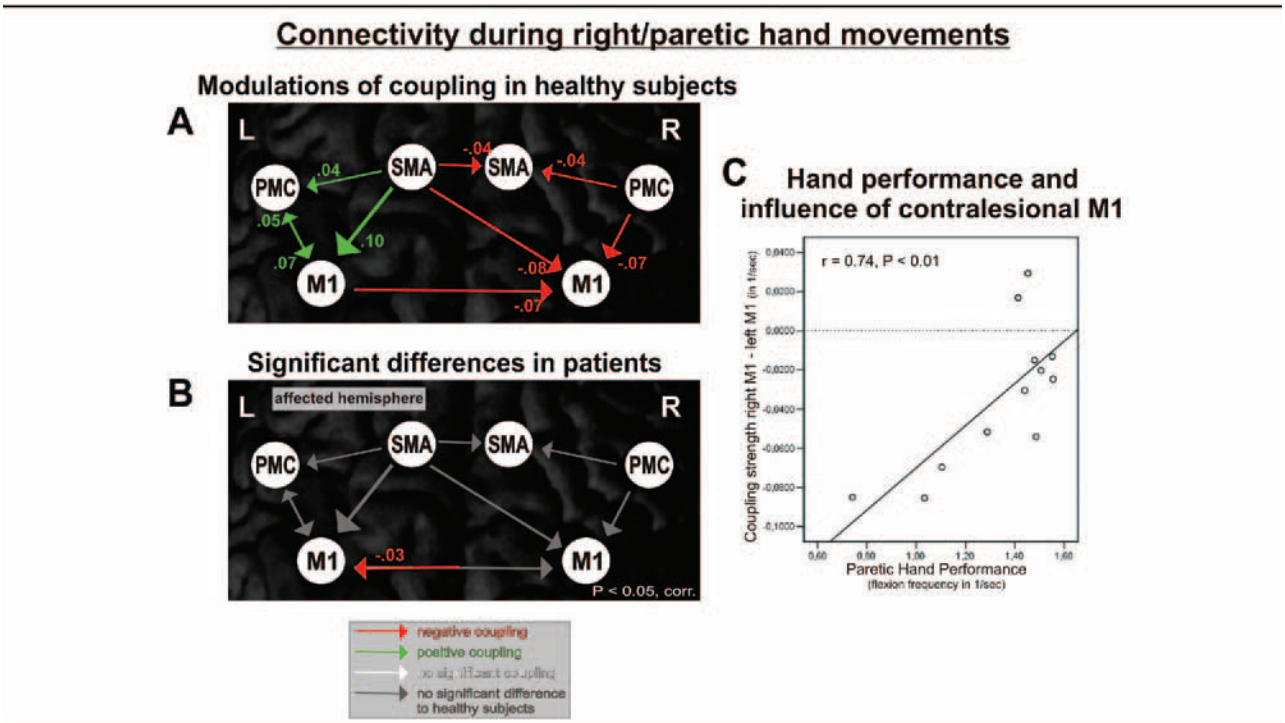
put on contralesional M1. The latter finding was correlated with the behavioral performance at the individual level: The impaired bilateral hand movements were matched by lower coupling strengths between ipsilesional SMA and contralesional M1 (Pearson's $r = 0.62$; $p < 0.05$; see Fig 5C). The reduced input from ipsilesional M1, however, was not significantly correlated with motor performance ($p = 0.68$). Also fMRI-independent parameters (see the Table) were not significantly correlated with either of the bilateral connectivity parameters ($p > 0.05$).

Discussion

We applied DCM to fMRI data during unilateral and bilateral hand movements to assess changes in effective connectivity within the cortical motor system evoked by unilateral subcortical stroke in the subacute phase. The data showed that a subcortical lesion affecting the motor system results in both intrahemispheric and interhemispheric disturbances in the cortical interactions of core motor areas. Earlier electrophysiological experiments already demonstrated abnormally high task-related inhibitory influences from the unaffected toward the affected M1 during the movement of the paretic hand in stroke patients.[1,2] Our results confirm but also extend these findings of disturbed M1-M1 interactions by showing at the same time changes in the interactions of other cortical motor areas in both hemispheres. Furthermore, the data suggest a functional relevance of these stroke-induced changes because of the strong correlations of different coupling parameters with the behavioral performance measures at the affected hand.

Concept of Dynamic Causal Modeling

DCM is a hypotheses-driven approach that relies on a priori assumptions on relevant regions and connections. DCM thus cannot be used as an exploratory tool to test which areas in the brain interact with a particular area of interest, as would be possible using, for example, Granger causality models[10] or psychophysical interaction[6,11] analyses. Furthermore, a high anatomical-functional precision in the location of the ROIs is essential for DCM analyses. We therefore did not include regions in the prefrontal cortex because their definition is often difficult at single subject level



COLOR

Fig 4. Modulation of coupling parameters caused by unimanual hand movements. (A) Coupling parameters for right hand movements in healthy subjects. (B) Coupling parameters for movements of the paretic (right) hand in stroke patients significantly different from healthy control subjects. (C) Correlation between paretic hand performance and interhemispheric inhibition exerted from contralesional M1 on ipsilesional M1. Red arrows *indicate negative coupling;* green arrows *indicate positive coupling;* gray arrows *indicate no significant differences compared with control subjects. PMC = premotor cortex; SMA = supplementary motor area.*

because of interindividual variability. Also, blood level oxygen dependent times series extraction from subcortical structures such as the basal ganglia was not possible in our study of subcortical stroke patients (see the Table and Fig 6).

F6

Furthermore, the numbers of ROIs included in DCM is limited to about eight regions to circumvent the problem of a dramatic increase of the number of free parameters, which require more stringent shrinkage priors to ensure system stability, and hence result in a reduction of the conditional precision for any of the estimated parameters. We tried to overcome this problem by focusing our analysis to core regions of the cortical motor system in accordance with the network suggested by the group analysis (see Fig 1).

AQ: 3

Meeting these constraints, DCM represents a powerful approach in connectivity analyses. In contrast with correlation or coherence analyses, which all work on the level of observed blood level oxygen dependent responses or event-related potentials, DCM treats the brain as a deterministic system in which external inputs cause changes in neural activity that, in turn, lead to changes in the fMRI signal.[7,12] The approach employed by DCM is to explicitly model *neuronal* activity, which is then linked via a biophysically validated hemodynamic model[7] to the measured functional response (ie, a change in the blood level oxygen dependent response). DCM, therefore, is much closer related to changes in neural dynamics in both time and space than previous approaches used to estimate connectivity. For example, correlation or coherence analyses suffer from insensitivity to directional and timing information of neural connectivity.[13] Other techniques of effective connectivity, such as structural equation modeling, assume that interactions are instantaneous, ignoring effects of timing,[12] and/or assume that the system is driven by unknown stochastic effects instead of the known experimental stimuli as in DCM.[7]

Changes in Cortical Activity Caused by Subcortical Stroke

Several neuroimaging experiments reported changes in cortical activation patterns during movement of the (contralesional) affected hand.[14–16] In the first weeks after stroke onset, movements of the paretic hand typically lead to a widespread recruitment of brain regions, which normalize to physiological levels of activity during recovery of motor function.[17] Movement-related overactivation has also been frequently described in contralesional motor areas.[14] Consistent with these

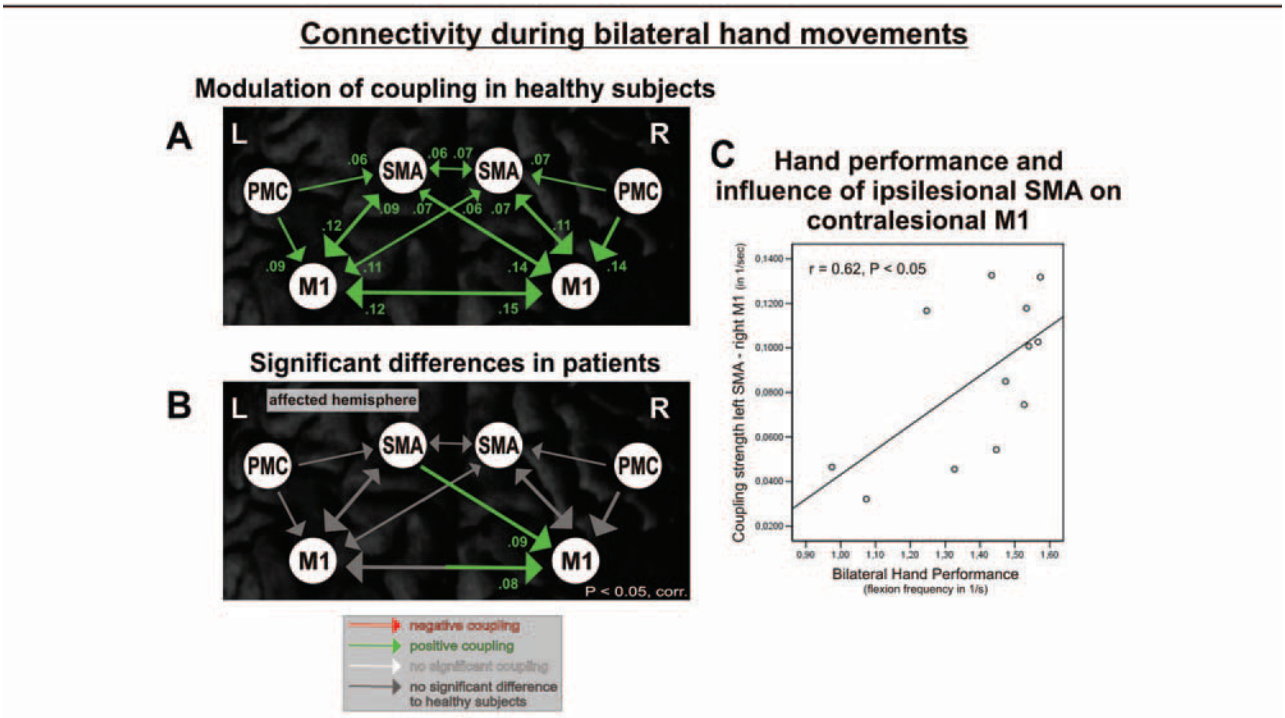


Fig 5. Modulation of coupling parameters caused by bilateral in-phase hand movements. (A) Coupling parameters in healthy subjects. (B) Coupling parameters in stroke patients significantly different compared with healthy subjects. (C) Correlation between bilateral movement performance and interhemispheric influence exerted from ipsilesional supplementary motor area (SMA) on contralesional M1. Note that the flexion frequency represents the performance of the affected hand only during bilateral movements. Green arrows *indicate positive coupling;* gray arrows *indicate no significant differences compared with control subjects. PMC = premotor cortex.*

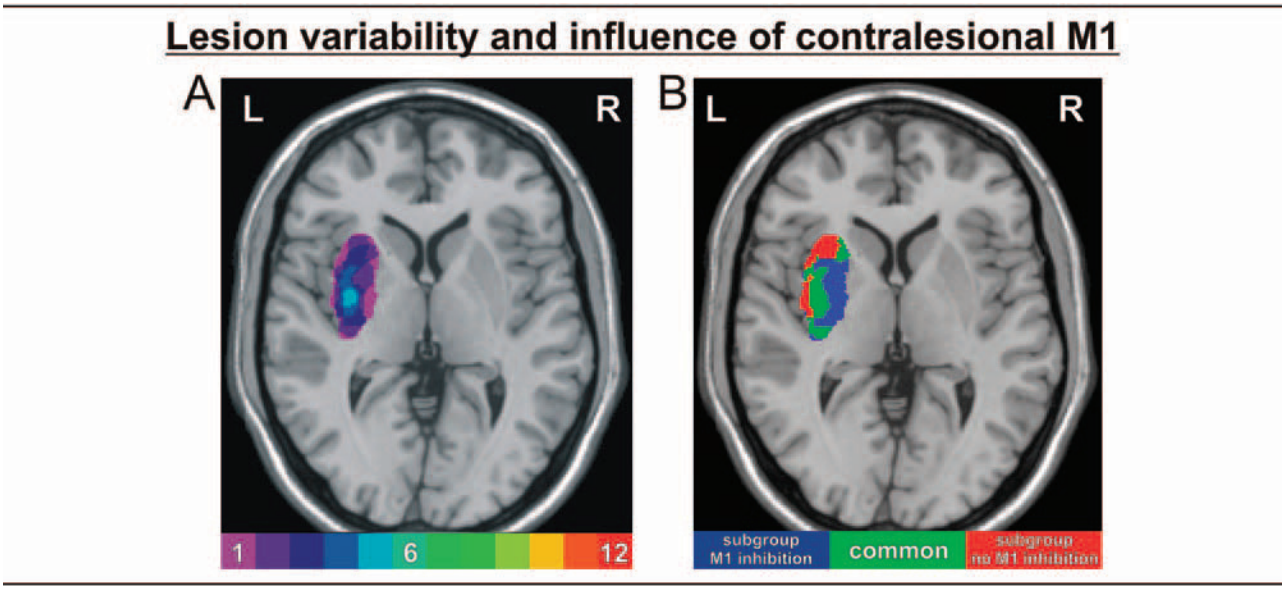
prior data, we found increased activity in the contralesional motor cortex when patients moved their paretic hand compared with healthy control subjects (see Fig 2A). This increased contralesional activity in stroke patients stimulated the discussion on the role of the unaffected hemisphere in motor recovery after stroke.[14,18]

Contralesional Overactivity: Beneficial or Detrimental?

It has been argued that the increase in neural activity in motor areas of the unaffected hemisphere represents compensatory strategies to support motor function of the lesioned hemisphere.[14,18,19] We here show that not only task-related activity of contralesional areas but also the intrinsic inhibitory influence between both SMA regions, which is observed in healthy subjects, was strongly reduced in stroke subjects. This task-independent disinhibition among SMA regions might therefore facilitate interhemispheric interactions that control hand movements. A similar role has been suggested for the PMC in a study showing that disruption of PMC activity in the contralesional hemisphere by means of rapid TMS impairs motor performance in stroke patients but not in healthy control subjects.[20]

However, in contrast with the hypothesis of a compensatory role of contralesional motor areas, recent TMS experiments suggested that contralesional M1 overactivity may inhibit, rather than facilitate, activity of ipsilesional M1.[1,2] Indeed, reducing excitability of the contralesional M1 by means of low-frequency rapid TMS can result in improved motor performance of the paretic hand in stroke patients,[21,22] which indicates that contralesional M1 overactivity may contribute to the motor disability after stroke.[1,2] Our results speak in favor of the latter hypothesis because movements of the stroke-affected hand led to a significantly increased inhibitory influence from M1 of the unaffected hemisphere to M1 of the affected hemisphere, which was not found when healthy subjects moved their right or left hand and which furthermore significantly correlated with the motor deficit of the paretic hand in our group of stroke patients (see Fig 4C). Whether other behavioral measures such as dynamometry or the 9-hole pegboard test also correlate with pathological changes in neural coupling remains to be elucidated in future studies.

The summary maps of all individual lesions demonstrated a considerable variability in lesion size and location. In our sample of stroke patients, the strongest lesion overlap was found in the regions of the basal ganglia (see Fig 6A). Relating these anatomical data with the magnitude of inhibitory modulation originat-



COLOR

Fig 6. Lesion distribution and relation to dynamic causal modeling (DCM) coupling parameters. (A) Summary map of all individual lesions demonstrate considerable variability (coded in a spectral color sequence) in lesion size and location. The strongest overlap was found in the regions of the basal ganglia. (B) Patient data were divided into two subgroups according to the magnitude of the inhibitory modulation originating from contralesional M1 as assessed with DCM (see Fig 4). The first subgroup contained those six subjects with the strongest inhibitory coupling parameters (mean coupling rate, −0.06Hz, blue); the other group contained those six subjects with the weakest coupling parameters (mean coupling rate, −0.00Hz, red). Plotting the lesion extents of these two groups demonstrated that abnormally increased negative M1-M1 coupling parameters were often associated with lesions in medial putamen and globus pallidus (red: weak/no pathological inhibitory M1-M1 coupling; blue: strong inhibitory M1-M1 coupling; green: overlapping zone).

AQ: 6

ing from contralesional M1 illustrated that especially those patients with lesions in more medial parts of the corpus striatum and globus pallidus showed an abnormally high negative M1-M1 coupling. This finding suggests that the observed pathological adaptation processes may result from lesions to these parts of the basal ganglia, which are known to be highly connected to M1 and SMA.[23,24] An important caveat of this conclusion is the relatively small sample size and the considerable variability in individual lesion location in our group of subjects. However, this observation needs further investigation.

Note that the patients studied were mostly subacute, and that at testing time they had experienced substantial motor recovery (subjects' power was equal to or greater than a Medical Research Council score of 4). Therefore, changes in more severely affected patients may differ from these findings. Furthermore, approaches such as diffusion tensor imaging[25] might help to disentangle the putative fiber tracts affected by the stroke lesions, probably contributing to the effects observed.

Reduced Performance of the Unaffected Hand at Bilateral Movements

In stroke patients, behavioral performance for bilateral movements was hampered at both hands, a finding that is consistent with other studies examining bimanual coordination in stroke patients.[27,28] Our data suggest that the origin of the bimanual deficit after stroke may be found in the reduction of promoting activity from the ipsilesional motor areas to contralesional M1 (see Figs 5B, C). The SMA has been shown to be crucially involved in the coordination of bimanual movements.[29] Furthermore, our data demonstrated that the promoting influence of ipsilesional SMA on contralesional M1 significantly correlated with bimanual performance in stroke patients. These observations raise the hypothesis that the reduction in motor performance for bilateral hand movements results from a disturbed interhemispheric interaction among M1 and SMA in both hemispheres rather than just being a reflection of motor adaptation to the performance of the paretic hand. Alternatively, the modulation of SMA influence on contralesional M1 could be a part of a synchrony network that includes the regions mentioned, but correlates with the adaptive strategy to default to the rate of the slower hand, therefore correlating with hand performance. These data do not allow differentiation between these alternative explanations.

Furthermore, bilateral arm training in unilateral stroke patients may significantly improve motor function of the affected arm compared with unilateral training.[30,31] These findings are compatible with our

data showing that interhemispheric modulation among both M1 (and also among other areas) is positively coupled during bilateral arm movements, implying a relative facilitation of neural activity in the lesioned motor cortex (see Fig 5).

Therapeutic Implications and Conclusions

Our results indicate that pathological intrahemispheric and interhemispheric interactions among key motor regions constitute an important pathophysiological aspect of contralesional and bilateral motor disability after subcortical stroke. In extension to the previously described imbalance of interhemispheric M1-M1 inhibition, our data show that a dysfunctional interaction between SMA and M1 may also contribute to motor disability. This is consistent with the general concept that successful control of M1 by ipsilateral higher level motor control structures is important for motor performance.

Therefore, therapeutic concepts aiming at a reduction of the pathologically enhanced overactivation only in contralesional M1 may be insufficient to overcome motor impairment because dysfunction of M1 also results from the loss of driving input exerted by ipsilesional SMA (see Fig 3B). Thus, additional enhancement of ipsilesional SMA activity, for example, by means of high-frequency transcranial magnetic or direct current stimulation,[22] might help to ameliorate the M1 dysfunction in the affected hemisphere.

The results of this study demonstrate that combining fMRI with DCM allows assessment of stroke-caused disturbances within sensorimotor brain networks. Investigating changes in cortical connectivity caused by brain lesions may therefore help to further our understanding of the pathophysiology of motor impairment at an individual level. Such an approach may enable monitoring physiological recovery based on cortical reorganization and designing new treatment regimens (eg, physiotherapy, TMS or pharmacological modulation)[32–35] that assist motor recovery.

References

1. Duque J, Hummel F, Celnik P, et al. Transcallosal inhibition in chronic subcortical stroke. Neuroimage 2005;28:940–946.
2. Murase N, Duque J, Mazzocchio R, et al. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 2004;55:400–409.
3. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006;5:708–712.
4. Chollet F, DiPiero V, Wise RJ, et al. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol 1991;29:63–71.
5. Marshall RS, Perera GM, Lazar RM, et al. Evolution of cortical activation during recovery from corticospinal tract infarction. Stroke 2000;31:656–661.
6. Friston KJ, Buechel C, Fink GR, et al. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 1997;6:218–229.
7. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. Neuroimage 2003;19:1273–1302.
8. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the state of patients for the clinician. J Psychol Res 1975;12:189–198.
9. Kiebel S, Holmes A. The General Linear Model. In: Frackowiak RS, Friston K, Frith CD, et al., eds. Human brain function. 2nd ed. San Diego: Elsevier Academic Press, 2004:725–761.
10. Roebroeck A, Formisano E, Goebel R. Mapping directed influence over the brain using Granger causality and fMRI. Neuroimage 2005;25:230–242.
11. Stephan KE, Marshall JC, Friston KJ, et al. Lateralized cognitive processes and lateralized task control in the human brain. Science 2003;301:384–386.
12. Penny WD, Stephan KE, Mechelli A, et al. Modelling functional integration: a comparison of structural equation and dynamic causal models. Neuroimage 2004;23(suppl 1):S264–S274.
13. Lahaye PJ, Poline JB, Flandin G, et al. Functional connectivity: studying nonlinear, delayed interactions between BOLD signals. Neuroimage 2003;20:962–974.
14. Ward NS, Cohen LG. Mechanisms underlying recovery of motor function after stroke. Arch Neurol 2004;61:1844–1848.
15. Nelles G, Spiekermann G, Jueptner M, et al. Evolution of functional reorganization in hemiplegic stroke: a serial positron emission tomographic activation study. Ann Neurol 1999;46:901–909.
16. Calautti C, Leroy F, Guincestre JY, Baron JC. Dynamics of motor network over-activation after striatocapsual stroke. A longitudinal PET study using a fixed performance paradigm. Stroke 2001;32:2534–2542.
17. Ward NS, Brown MM, Thompson AJ, et al. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 2003;126:2476–2496.
18. 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 2005;129:791–808.
19. Strens LH, Fogelson N, Shanahan P, et al. The ipsilateral human motor cortex can functionally compensate for acute contralateral motor cortex dysfunction. Curr Biol 2003;13:1201–1205.
20. Johansen-Berg H, Rushworth MF, Bogdanovic MD, et al. The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci U S A 2002;99:14518–14523.
21. Mansur CG, Fregni F, Boggio PS, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005;64:1802–1804.
22. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005;128:490–499.
23. Kaneda K, Nambu A, Tokuno H, et al. Differential processing patterns of motor information via striatopallidal and striatonigral projections. J Neurophysiol 2002;88:1420–1432.
24. Nambu A, Kaneda K, Tokuno H, et al. Organization of corticostriatal motor inputs in monkey putamen. J Neurophysiol 2002;88:1830–1842.
25. Johansen-Berg H, Behrens TE. Just pretty pictures? What diffusion tractography can add in clinical neuroscience. Curr Opin Neurol 2006;19:379–385.
26. Kim YH, Jang SH, Chang Y, et al. Bilateral primary sensorimotor cortex activation of post-stroke mirror movements: an fMRI study. Neuroreport 2003;14:1329–1332.
27. Lewis GN, Byblow WD. Bimanual coordination dynamics in poststroke hemiparetics. J Mot Behav 2004;36:174–188.

AQ: 4

28. Rose DK, Winstein CJ. The co-ordination of bimanual rapid aiming movements following stroke. Clin Rehabil 2005;19: 452–462.
29. Sadato N, Yonekura Y, Waki A, et al. Role of the supplementary motor area and the right premotor cortex in the coordination of bimanual finger movements. J Neurosci 1997;17: 9667–9674.
30. Stewart KC, Cauraugh JH, Summers JJ. Bilateral movement training and stroke rehabilitation: a systematic review and meta-analysis. J Neurol Sci 2006;244:89–95.
31. Summers JJ, Kagerer FA, Garry MI, et al. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: a TMS study. J Neurol Sci 2007;252: 76–82.
32. Loubinoux I, Tombari D, Pariente J, et al. Modulation of behavior and cortical motor activity in healthy subjects by a chronic administration of a serotonin enhancer. Neuroimage 2005;27:299–313.
33. Pariente J, Loubinoux I, Carel C, et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Ann Neurol 2001;50:718–729.
34. Tardy J, Pariente J, Leger A, et al. Methylphenidate modulates cerebral post-stroke reorganization. Neuroimage 2006;33: 913–922.
35. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 2006;5:708–712.