Evolution of Cortical Activation During Recovery From Corticospinal Tract Infarction

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Background and Purpose—Recovery from hemiparesis due to corticospinal tract infarction is well documented, but the mechanism of recovery is unknown. Functional MRI (fMRI) provides a means of identifying focal brain activity related to movement of a paretic hand. Although prior studies have suggested that supplementary motor regions in the ipsilesional and contralesional hemisphere play a role in recovery, little is known about the time course of cortical activation in these regions as recovery proceeds.

Methods—Eight patients with first-ever corticospinal tract lacunes causing hemiparesis had serial fMRIs within the first few days after stroke and at 3 to 6 months. Six healthy subjects were used as controls. Statistically significant voxels during a finger-thumb opposition task were identified with an automated image processing program. An index of ipsilateral versus contralateral activity was used to compare relative contributions of the 2 hemispheres to motor function in the acute and chronic phases after stroke.

Results—Controls showed expected activation in the contralateral sensorimotor cortex (SMC), premotor, and supplementary motor areas. Stroke patients differed from control patients in showing greater activation in the ipsilateral SMC, ipsilateral posterior parietal, and bilateral prefrontal regions. Compared with the nonparetic hand, the ratio of contralateral to ipsilateral SMC activity during movement of the paretic hand increased significantly over time as the paretic hand regained function.

Conclusions—The evolution of activation in the SMC from early contralesional activity to late ipsilesional activity suggests that a dynamic bihemispheric reorganization of motor networks occurs during recovery from hemiparesis. **(*Stroke*. 2000;31:656-661.)**

Key Words: lacunar infarction ■ magnetic resonance imaging ■ motor activity ■ rehabilitation

Stroke has a protean impact on disability worldwide,[1] yet many severe deficits at the time of stroke onset show remarkable recovery. Even in cases in which there is autopsy- or image-documented damage to the corticospinal tract, recovery from severe hemiparesis to near-normal function is possible.[2–4] Many lines of investigation have attempted to define the mechanisms for stroke recovery in the hope that understanding these mechanisms will improve our ability to enhance the recovery process. With the development of functional imaging methods, it has become possible to identify anatomic regions of the brain that show increased metabolic activity when a patient with recovered hemiparesis performs a motor task such as repetitive finger-thumb opposition.[5,6] In normal subjects, such motor tasks are associated with activation primarily in the contralateral sensorimotor cortex.[7] The contralateral premotor cortex, ipsilateral somatosensory cortex, and bilateral supplementary motor areas also appear to participate in hand and finger motor tasks, particularly when the task increases in complexity.[7–11] Recent functional activation MRI (fMRI) studies involving recovered stroke patients have identified additional regions of activation during finger motor tasks, including the ipsilateral sensorimotor and premotor cortex.[12,13] The presence of activity in these regions has suggested that ipsilateral motor pathways may assume functions that the contralateral motor pathways served prior to stroke. What remained uncertain is the role the unaffected hemisphere plays in the generation of movement of the paretic hand in the acute phase, and whether the relative contribution of the ipsilateral and contralateral hemispheres changes over time.

To address the time course of activation of motor regions in the ipsilateral and contralateral hemisphere, we performed serial fMRI imaging on 8 acute stroke patients with hemiparesis caused by lacunar infarctions in the corticospinal tract. By comparing the brain activity associated with movement of the paretic hand versus the nonparetic hand at different time points after stroke, we sought to determine how the relative contribution of each hemisphere might evolve over time. Six nonstroke volunteers served as a control group.

Received September 20, 1999; final revision received November 22, 1999; accepted December 8, 1999.

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Demographic and Clinical Features of Patients and Control Subjects

Patient No./Sex/ Age, y	Infarct Location	Day	Hand	Strength	Mvt Rate	SMC LI
1/M/50	L pons	1	P	1	0	0.00
			NP	5	15	0.71
2/M/72	L pons	6	P	0	0	−0.06
			NP	5	10	0.60
		90	P	5	15	−0.20
			NP	5	17	0.50
3/F/63	L pons	1	P	4	13	0.36
			NP	5	22	0.60
		90	P	5	21	0.82
			NP	5	22	0.57
4/M/67	L corona radiata	1	P	4	M	0.20
			NP	5	M	1.00
		90	P	5	M	0.50
			NP	5	M	1.00
5/M/65	L striato-capsular	2	P	0	0	−1.00
			NP	5	19	0.67
		90	P	5	10	0.04
			NP	5	13	0.71
6/F/69	R striato-capsular	1	P	0	0	0.00
			NP	5	18	0.13
		180	P	5	17	0.53
			NP	5	22	0.20
7/F/69	L striato-capsular	8	P	0	0	−0.38
			NP	5	15	−0.38
		90	P	5	15	−0.14
			NP	5	19	−0.71
8/F/66	L internal capsule	1	P	0	0	0.60
			NP	5	12	1.00
		180	P	5	15	0.71
			NP	5	17	0.82
9/F/20	Control	...	D	5	36	1.00
		...	N	5	32	0.85
10/M/34	Control	...	D	5	23	0.75
		...	N	5	25	0.21
11/M/36	Control	...	D	5	26	1.00
			N	5	21	1.00
12/M/29	Control	...	D	5	15	0.75
			N	5	17	0.76
13/M/32	Control	...	D	5	32	0.43
			N	5	35	1.00
14/F/30	Control	...	D	5	27	0.04
			N	5	24	0.52

Day indicates poststroke day; P, paretic hand; NP, nonparetic hand; D, dominant hand; N, nondominant hand; Strength, Medical Research Council motor strength; Mvt Rate, number of sequential finger-thumb repetitions in 30 seconds; and M, missing data.

Subjects and Methods

Subjects

Eight consecutive patients with first-ever corticospinal tract stroke causing hemiparesis were enrolled in the study. Patients were recruited from the inpatient service of the Columbia–Presbyterian Stroke Unit. Six healthy subjects were enrolled as a control group. Informed consent was obtained from all patients and subjects as approved by the Institutional Review Board. All stroke patients had to have significant hand weakness at onset, including marked impairment of individuated finger movements. Varying degrees of face and leg weakness and dysarthria were allowed. All strokes were identified by high-resolution MRI as small, subcortical, white matter infarcts involving the corticospinal tract. Three patients had paramedian pontine infarcts and 5 had infarcts in the posterior limb of the internal capsule with variable extension into adjacent corona radiata.

MRI Image Acquisition and Processing

Functional imaging was performed on a commercial, 1.5-T scanner (Signa, GE Medical Systems) equipped with a prototype 30.5-cm internal diameter 3-axis local gradient head coil and an elliptical end-capped quadrature radiofrequency coil. The system enabled whole-brain echo-planar imaging. Foam padding and tape across the patients' foreheads limited head motion during scanning. Image acquisition was done using a gradient-echo EPI sequence based on the blood oxygen level–dependent (BOLD) technique.[14] The following image parameters were used for acquisition: 20-cm field of view, 64×64 image matrix, 3000-ms TR, 80-ms TE, 90° flip angle, and 7-mm thickness, with 0 gap spacing. Three sequential 30-second "activation" periods were interspersed between four 30-second "rest" periods (sequence order B-A-B-A-B-A-B, where B is the baseline rest period and A the activation period). The total scan time for each run was 3 minutes 30 seconds. Raw image data were reconstructed offline, sorted into volumes, and analyzed by using a Silicon Graphics work station with the MEDx 3.0 program software (Sensor Systems, Inc). Motion correction was applied with the Woods algorithm.[15] The data were analyzed based on a correlation function to a "boxcar" waveform with 6-second delay for hemodynamic response that matched the time course of the rest and activation periods. Significant voxels were identified by applying a threshold of $Z \geq 3.0$ ($P < 0.001$) to the correlation map. The z map output thus represented the spatial extent of focal brain activation that correlated significantly with the time course of the task. All voxels that met the criterion were overlayed onto one of the coregistered T2* images, thus providing a statistical activation map with exact coregistration onto an anatomic image.

For each patient, regions of interest (ROIs) were drawn onto the background T2*-weighted image without knowledge of the activation patterns, using standard sulcal landmarks identified from a 3-dimensional sectional anatomy atlas.[16] The ROI template generated for each patient was then overlayed onto the statistical activation map with the T2* background, and the number of activated voxels (z score >3.0) was counted for each region. The number of activated voxels in the ROI thus represented the spatial extent of activation in

a given ROI.[17] The following ROIs were defined: primary sensorimotor cortex (SMC), encompassing the posterior precentral and anterior postcentral gyri on the lateral convexity, Brodman's area 4 and 3; premotor cortex, encompassing the precentral gyrus, Brodman's area 6; prefrontal cortex, encompassing the posterior middle and inferior frontal gyri, Brodman's area 8 and 9; the supplementary motor area, encompassing the paracentral lobule anterior to the central sulcus and the posterior portion of the parasagittal superior frontal gyrus, Brodman's area 4 and 6 medially; the posterior parietal region, encompassing the angular and supramarginal gyri, Brodman's area 39 and 40; anterior cingulate gyrus, Brodman's area 24; posterior cingulate gyrus, Brodman's area 23; and insular cortex. ROIs were drawn for the basal ganglia, thalamus, and cerebellum, but these regions were eliminated from final analysis because they extended outside the field of view on several patient scans.

Group Statistical Analysis

A "laterality index" (LI) was calculated to compare relative activity in the ipsilateral versus contralateral SMC for each time point after stroke. The LI was defined as $(C-I)/(C+I)$, where C and I represented the total number of activated voxels (z score >3.0) in the region contralateral or ipsilateral to the finger movement, respectively. Thus, the LI for each ROI could range from 1.0 (all activity in the contralateral hemisphere), to -1.0 (all activity in the ipsilateral hemisphere). The LI was calculated for the paretic and nonparetic hands in the acute and chronic phases and for the control subjects.

Our primary hypothesis was that the relative activity of the contralateral versus ipsilateral sensorimotor cortex would change over time. We therefore calculated the change in LI from the acute to the chronic time point for the paretic hand for each patient and compared those changes to the change in LI for the nonparetic hands in the patients over the same time course. A Mann-Whitney U test was used to compare the group differences. Control subjects were used for comparison with the nonparetic hands of stroke patients.

Motor Activation Task

Each patient and control subject was trained on a sequential finger-thumb opposition task for each hand. Instructions were to touch sequentially the first through fifth fingertip to the thumb tip as rapidly and accurately as possible during the 30-second activation periods, and to rest during the intervening rest periods. All subjects were instructed to keep all other body parts still. In those patients in the acute stroke phase who were unable to move the fingers of the paretic hand, the instructions were to attempt to move the fingers during the activation periods and to rest during the rest periods, as they did with the nonparetic hand. Direct observation was made by an investigator inside the MRI scanning room to assess for mirror hand movements during fMRI acquisition.

Results

Clinical Data

The stroke group included 4 men and 4 women of mean age 65.1 (SD 6.7) years, all with typical risk factors for lacunar stroke such as hypertension, cigarette smoking history, or diabetes mellitus.[18] The control subjects were healthy volunteers, 4 men and 2 women, of mean age 30.2 (SD 5.4) years. In 6 patients the paresis involved the dominant hand; in 2 the nondominant hand was affected. Finger movements were markedly impaired in all stroke patients at their entry into the study. In 5 patients there was complete hand plegia (MRC=0); in 1 patient there was a flicker of movement in the fingers (MRC=1); in 2 there was mild to moderate interosseus weakness (MRC=4-) but marked slowing of individual finger movements. Demographic and clinical features of the 8 patients and their motor status at each time point are listed in the Table.

Associated ("mirror") movements of the opposite side of the body were seen in 6 of 7 patients during attempted sequential finger-thumb opposition of the paretic hand in the acute phase. These movements included intermittent flexion (of a few millimeters) of the nonparetic fingers and, in 2 patients, slight rhythmic movements of the opposite foot. The movements occurred despite instructions to keep all other body parts still during the motor task. Mirror movements were rare in the chronic recovered phase.

All 8 patients were imaged within the first week after stroke onset, at a time when their hemiparesis was at its worst. In 6 of the 8, the first fMRI was done within 48 hours after stroke onset; in the remaining 2 the first fMRI scan was done at 1 week after onset. Seven patients had follow-up images at 3 to 6 months. Interosseus and finger flexion strength was fully recovered at 3 to 6 months in all 7 patients examined at that time. Over the course of the recovery period, mean rate of finger-thumb opposition was seen to increase in the paretic hand of all stroke patients and in the nonparetic hand in 4 of 7 stroke patients.

Imaging Data

fMRI in control subjects was associated with activation in the contralateral SMC, premotor cortex, posterior parietal region, and the ipsilateral cerebellum. Lesser activation was seen in both supplementary motor areas, the ipsilateral SMC, ipsilateral premotor cortex, and ipsilateral posterior parietal region. Almost no activation was seen in the prefrontal, anterior, or posterior cingulate, or in the insula. There was no difference in regional activation for the dominant versus the nondominant hand. Among the stroke patients, the finger-thumb opposition task of the paretic hand in the acute period was associated with regional activation similar to that of control subjects, but in addition bilateral prefrontal and ipsilateral posterior parietal was seen to be activated. Lesser activation was noted in some patients in the anterior cingulate and insula bilaterally. In the chronic phase, 3 to 6 months after stroke, finger-thumb opposition of the recovered paretic hand was associated with a relative increase in activity in the contralateral SMC compared with the ipsilateral SMC, and a relative decrease in the prefrontal and the ipsilateral posterior parietal regions. Figure 1 demonstrates typical activation patterns in the acute and chronic recovered phases of the paretic hand, and in controls. Motor performance of the nonparetic hand of stroke patients activated regions similar to those of the control subjects, but, as in the paretic hand activation, prefrontal activation was present.

Group Analysis

In the stroke patients, the laterality index in the SMC increased over time in for the paretic hand but did not change for the nonparetic hand. This difference was statistically significant ($P=0.013$; see Figure 2). In the acute period after stroke in the paretic hand, the amount of task-related activity was slightly higher in the ipsilateral than the contralateral SMC, resulting in an average SMC laterality index score of -0.04. The nonparetic hand in the acute phase, in contrast, had an average SMC LI of 0.52. In the chronic period of recovery the average SMC LI for the paretic hand was 0.32

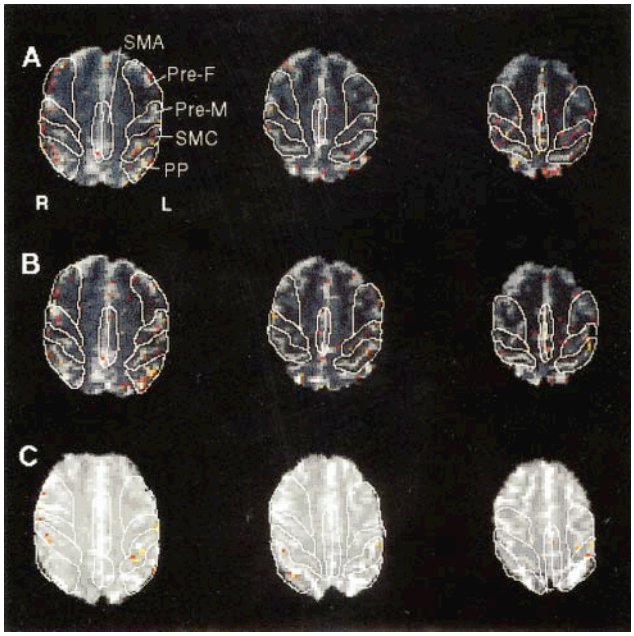

Figure 1. Activation pattern related to repetitive finger-thumb opposition. Colored voxels are statistically correlated with a *z* score of >3.0 ($P<0.001$; see text). A, activation pattern of a stroke patients performing the task 24 hours after stroke onset. B, activation of the same patient performing the motor task 3 months after stroke. C, control subject activation pattern.

and for the nonparetic hand 0.44. The mean LI for the control subjects was approximately 0.7 for both the dominant and nondominant hands.

Discussion

Our study demonstrated that the interhemispheral balance of motor-related activation for a recovering paretic hand evolved over time after corticospinal tract infarction. As time after stroke onset increased and the paretic hand regained function, a higher ratio of contralateral (ipsilesional) to ipsilateral (contralesional) activity was seen in the primary sensorimotor cortex during sequential finger-thumb opposition movements. The laterality index for the recovered paretic hand that we observed in the chronic phase in our study was concordant with the LI reported in a recent fMRI study of chronic recovered hemiparesis.[12] Our study is the first to demonstrate an evolution of the laterality index from the acute phase up to the point of recovery, however. Because all our stroke patients had small lesions restricted to the deep white matter, changes in cortical activation we observed could more confidently be attributed to compensatory metabolic adjustments in the cortex rather than to alteration the BOLD response as a consequence of peri-infarct–related edema, luxury perfusion, or altered vasoreactivity.

The regions of activation we observed in control subjects performing the finger-thumb opposition task were similar to those described in previous studies, with the exception of greater activation in the posterior parietal regions bilaterally. Our motor task involved internally paced, complex finger movements which have been shown to be associated with activation in the ipsilateral SMC and parietal cortex.[7,11,19] Imaging data in our stroke patients differed from those of our controls in showing greater activation in the ipsilateral SMC, ipsilateral posterior parietal cortex, and the prefrontal cortex, particularly in the acute phase. We do not feel that the ipsilateral SMC activation seen with movement of the paretic hand was due to mirror movements alone; the activation in the ipsilateral SMC was still present in the chronic phase of recovery when only rare mirror movements were observed. Although it is possible that some differences in activation pattern between control subjects and stroke patients were due to the mean age difference between the groups, there are no data to suggest that the nature of compensatory mechanisms in motor recovery are different across adult age groups. In either case, our use of the stroke patients' nonparetic hand

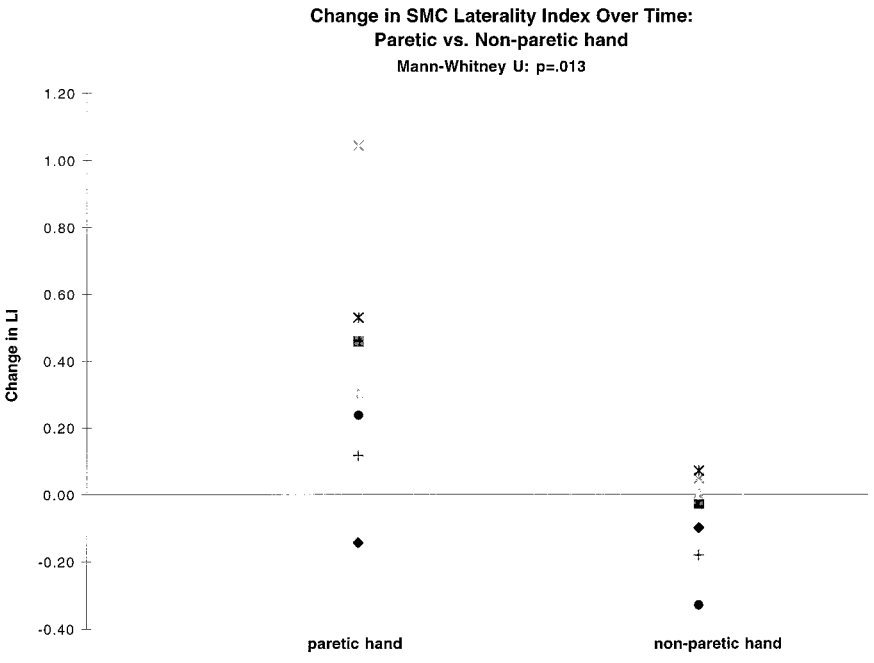

Figure 2. Change in SMC Laterality Index over time from the acute paretic to the chronic recovered phase. The paretic hand is compared with the nonparetic hand. Positive values indicate an increased LI from the acute to the chronic phase, negative values indicate a decreased LI, and a value of 0 indicates no change.

movement as a comparison for motor activation helped to control for potentially confounding demographic factors.

One current debate regarding the mechanism of stroke recovery concerns whether the contralesional hemisphere plays an active role in the recovery of hemiparesis or whether activated voxels in the nonstroke hemisphere appear only as an epiphenomenon of ischemic injury. Ipsilateral increases in blood flow velocity during movement of the paretic hand have been shown as early as 36 hours after stroke onset by transcranial Doppler.[20] Focal ipsilateral CBF increases have been shown in response to passive movement of a paretic limb 19 hours after stroke onset by positron emission tomography imaging.[21] One conclusion drawn from such data is that the role of the contralesional hemisphere is to provide ipsilateral motor pathways originating in the contralesional SMC. Ipsilateral motor pathways are said to account for a small but demonstrable portion of total descending pathways in the brain.[22] These uncrossed motor pathways have been detected in normal individuals by transcranial magnetic stimulation[23] but appear to be much more easily detectable after stroke.[24] Task-related activity was present in the contralesional hemisphere in our study, particularly in the acute phase.

The role of the ipsilesional hemisphere in stroke recovery is also of interest in our study. Our increase in the laterality index over time represented a combination of a reduction in contralesional activity and an increase in ipsilesional activity. Because infarction to the cortical spinal tract in the brain should prevent axonal conduction through the lesion, recovery of the primary descending pathway is unlikely to explain the increase in ipsilesional SMC activity. We cannot exclude the possibility that there was partial, temporary damage to the white matter tract, which permitted surviving axons to conduct impulses after the effects of the acute injury had resolved. Axonal conduction has been shown to be relatively resistant to ischemic injury.[25] Ipsilateral and contralateral pathways originating in the hemisphere containing the stroke have been shown to produce evoked responses by transcranial magnetic stimulation.[26]

We propose, however, that a poststroke motor network was present within 24 hours of infarction which included the ipsilesional SMC but did not require directly descending corticospinal pathways. Evidence that such a mechanism is possible includes studies in which monkeys that had undergone transection of the corticospinal tract in the brain stem still demonstrated motor responses to electrical brain stimulation of the ipsilesional SMC.[27] The corticospinal tract therefore appears to have the potential to be bypassed via alternative motor pathways. Instead of descending directly from the primary motor cortex, motor impulses generated by the ipsilesional SMC may descend via cortico-cortical connections to the supplementary motor or premotor regions, which have been shown to descend through the anterior limb or anterior portion of the posterior limb of the internal capsule.[3] Furthermore, activity in the ipsilesional SMC during movement of the paretic limb need not originate in the SMC. SMC activity could be induced, for example, by signals from anatomically connected regions such as the contralesional SMC, prefrontal cortex, ipsilateral posterior parietal cortex, or the anterior cingulate cortex,[28] all of which show activation in our study during finger-thumb opposition of the paretic hand. Our observation that ipsilesional SMC activity is present in some patients even when finger movement is not achieved suggests that the SMC may be included in a motor-planning network in the acute phase but does not necessarily act as a controller of movement itself. There is also accumulating psychophysical evidence that prefrontal regions are involved with motor learning.[29] The presence of prefrontal activity, particularly in the acute phase in our stroke patients, suggests that motor recovery may be a motor-learning process (J.W. Krakauer, MD, Z. Pine, MD, C. Ghez, MD, unpublished data, 1999), such that a greater difficulty of finger-thumb opposition for hemiparetic patients requires the use of additional motor regions to maintain a repetitive sequential motor pattern, unlike in the control subjects, in whom prefrontal activity is absent and for whom the task is easier.

Finally, our observation that improvement occurred in the motor function of the "unaffected" hand during the recovery period of the paretic hand suggests that an infarct in one hemisphere may alter the task-related motor network of the nonparetic hand. Impairment and recovery of motor function in the "nonparetic" hand has been previously reported in stroke patients.[30] According to one model of cortical reorganization, pathway injury in white matter tracts induces a blockade of inhibitory circuits, which results in an unmasking of lateral excitatory projections in surrounding areas of the cortex.[31] If the unmasking included cortical regions normally requiring inhibition during targeted, complex movements of the contralateral limb, the effectiveness of those movements might be impaired. The presence of prefrontal activation during finger-thumb opposition of the nonparetic hand, along with the lower laterality index for this hand compared with controls, suggests that the task-related motor network for the nonparetic hand was altered by the stroke in the opposite hemisphere. Furthermore, the presence of mirror movements we observed during movement of the paretic hand may represent transcallosal disinhibition,[19] which lends additional support to bihemispheral network reorganization as a consequence of unihemispheral stroke. Further study is needed to determine whether the task-related motor networks for the paretic hand and the nonparetic hand are interdependent from the onset of stroke and whether the altered networks correlate with motor function as recovery proceeds.

Acknowledgments

This work was made possible with the support of NIH grant 1K08NS01758 and the Doris and Stanley Tananbaum Foundation.

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