

Pilot Study of Functional MRI to Assess Cerebral Activation of Motor Function After Poststroke Hemiparesis

Y. Cao, PhD; L. D'Olhaberriague, MD, PhD; E.M. Vikingstad, BS;
S.R. Levine, MD; K.M.A. Welch, MD

Background and Purpose—Studies of cerebral activation of motor function after ischemic stroke may enhance our understanding of the underlying mechanisms of motor functional recovery, including the role of the noninfarcted hemisphere.

Methods—Eight right-handed recovering hemiparetic or hemiplegic patients were studied using functional MRI. Results were evaluated for each patient to consider individual variability in original functional organization, neuroanatomy, infarct size and extent, treatment, age, and sex. The results were also pooled as a group for comparison with a control group of eight right-handed normal subjects.

Results—In six of eight stroke patients, extended activation in ipsilateral sensorimotor cortex was observed during paretic hand movements. Bilateral activation of the primary sensorimotor cortex was recorded in three of these six patients; ipsilateral activation alone was recorded in the remaining three patients. Only two patients had mild synkinesia. Furthermore, in two male patients, the paretic hand movements activated extended areas of ipsilateral premotor and dorsolateral prefrontal cortex, when compared with normal subjects. In two patients with left frontal infarction, profound activation in the right supramarginal gyrus and in the right premotor cortex was observed during the ipsilateral paretic hand movements.

Conclusions—Synkinesia alone cannot explain the extent of ipsilateral activation in primary sensorimotor cortex. The explanation offered for our findings is that preexisting uncrossed motor neural pathways may be accessed or recruited to compensate for damage to the crossed motor pathways after ischemic stroke. (*Stroke*. 1998;29:112-122.)

Key Words: functional reorganization ■ magnetic resonance imaging ■ motor activity ■ stroke, ischemic

Motor function of limbs is predominantly represented in the contralateral primary motor cortex in right-handed healthy subjects. Therefore, damage of the primary motor cortex and other motor pathway components (eg, premotor cortex, supplementary motor areas, parietal cortex, and subcortical or brain stem) can cause contralateral hemiparesis or hemiplegia, a common neurological ailment in stroke.¹ Although poststroke hemiparesis is not a static phenomena, and partial or complete recovery of motor function after stroke is the rule more than the exception,² mechanisms and determinants of this recovery are poorly understood. The concept of brain function reorganization (plasticity)³ is useful to develop a conceptual approach to understand motor recovery after stroke. In recent years, new techniques (PET,⁴ transcranial magnetic stimulation,⁵ and fMRI⁶) have been developed that allow us to study the physiology and pathophysiology of the motor pathways. Until now, no complete study of motor recovery after stroke with fMRI has been reported. An fMRI

study of sensorimotor function in a group of young patients with perinatal unilateral brain injury showed approximately equally activated volumes in the uninjured hemisphere during contralateral and ipsilateral finger movements.⁶ In adults with motor loss due to striatocapsular infarction, PET identified increased ipsilateral motor cortex activation and recruitment of inferior parietal cortex and the anterior aspects of the insula.^{4,7} There are now a number of preliminary reports (in conference presentations) in patients with ischemic stroke that have documented activation of alternative motor patterns to normal using fMRI.⁸ They suggest that cortical motor control of function and pathways can be reorganized after focal ischemic stroke and that the nondamaged hemisphere probably plays a crucial role in recovery. We hypothesized that in the recovering hemiplegic or hemiparetic stroke patients the ipsilateral activation in the primary sensorimotor cortex of the noninfarcted hemisphere would be increased, in comparison with normal (control) subjects. To test this hypothesis, we have used

Received July 10, 1997; final revision received October 10, 1997; accepted October 31, 1997.

From the NMR Research Center, Department of Neurology, Henry Ford Health Sciences Center, Detroit, Mich, and the Department of Radiology (E.M.V.), The University of Chicago (Illinois).

Correspondence to Yue Cao, PhD, NMR Research Center, Department of Neurology, NMR Laboratory, Henry Ford Hospital & Health Sciences Center, 2799 W Grand Blvd, Detroit, MI 48202-2689.

E-mail yue@neurmis.neuro.hfh.edu

© 1998 American Heart Association, Inc.

Selected Abbreviations and Acronyms

AC	= anterior cingulate
AG	= angular gyrus
BOLD	= blood oxygenation level–dependent
fMRI	= functional magnetic resonance imaging
GRE	= gradient recalled echo
LED	= light-emitting diodes
MCA	= middle cerebral artery
NIHSS	= NIH Stroke Scale
paraCL	= paracentral lobule
PET	= positron emission tomography
SM	= sensorimotor
SMG	= supramarginal gyrus
SPL	= superior parietal lobe
TPA	= tissue plasminogen activator

an fMRI technique that is based on measurements of cerebral BOLD contrast to investigate activation of the cerebral motor cortex of hemiparetic patients recovering from focal ischemic stroke. We explored the individual differences in lesion size and location, and motor activation of cortical regions, as well as grouped results from these patients.

Materials and Methods

Subjects

We studied motor function of eight right-handed recovering hemiparetic or hemiplegic patients (mean age, 46 years; 2 men and 6 women) who suffered a single unilateral ischemic stroke and eight right-handed normal control subjects (mean age, 42 years; 4 men and 4 women). The protocol was approved by the Human Rights Committee of Henry Ford Hospital. Written, informed consent was obtained from all subjects before the study. The handedness of the subjects was assessed using the Edinburgh inventory.⁹

The criteria used to select patients were (1) Patients suffered a single unilateral ischemic stroke determined from CT and/or MRI images, causing hemiparesis or hemiplegia; (2) patients lost individual finger movement at the onset of the stroke; and (3) patients must have recovered to at least the point where they were capable of finger opposition of thumb to the index and middle finger. There was no time restriction on when the study was performed after the onset of stroke symptoms. Patients were excluded from the study because of (1) inability to obtain informed consent, (2) transient ischemic attack, (3) brain stem stroke, (4) prior cerebrovascular disease, (5) preexisting neurological or psychiatric disorders (ie, amyotrophic lateral sclerosis, multiple sclerosis, Parkinsonism, AIDS, and dementia), (6) severe to profound deafness and/or blindness, or (7) being nonambulatory.

The clinical presentation of the patients at the onset of the stroke and at the time of the study was evaluated by a team of neurologists (L.D., S.R.L., K.M.A.W.). The neurological abnormalities and motor disabilities of the patients were assessed by the total and the motor scores of the NIHSS.¹⁰ Overall recovery was also measured by the modified Rankin score.¹¹ Motor impairment of the paretic hands was further assessed by a specific finger opposition task in which the time required to perform 20 finger oppositions of each hand was recorded. The prolonged time for the paretic hand performance was used as an indicator of the motor impairment. Arterial territories and locations of the infarcts were determined from T2-weighted MR images; dimensions of the infarcts were measured on the cross-sectional MR images.

Imaging Protocol

All MRI experiments were performed with a 3.0 T scanner with a resonator head coil. A fast localizer scan was used to locate the motor cortex and to guide adjustments of the patient's position. A radio frequency spoiled gradient echo–pulse sequence was used to produce T2*-weighted images (128×64 matrix over a 24-cm field of view). Three axial sections of 10-mm thickness were acquired during 7

seconds with TR/TE=38/30 milliseconds, flip angle 25°, and one excitation, followed by a 0.4-second delay. The most superior slice was placed at 10 mm below the vertex. The insula gyrus, thalamus, and cerebellum were not imaged. Each functional study lasted approximately 4 minutes, in which a total of 90 images were acquired. The fMRI protocol consisted of 10 alternating periods of task performance and rest. Axial T2-weighted images of cranial anatomy of the whole head of each patient were acquired and used to identify the location and size of the infarct. Also, T1-weighted images were acquired at the same locations as the fMRI to overlap anatomically with the voxels studied for functional activity.

Motor Protocol

During the functional MRI scan, all stroke patients and normal control subjects performed a sequential finger opposition task in which the thumb repeatedly touched the associated four fingers in a sequential order. Patient 2, who could not touch all four fingers, performed a three-finger opposition task. This task performance occurred in periods of 24 seconds, interspaced with 24-second “rest” periods. The cycle of task performance and rest was repeated 5 times during each experiment. Two methods were used to instruct subjects to start and stop the finger movement. In the first, a series of LEDs was mounted about 1.5 feet anterior and inferior to the level of the subject's eyes as they lay in the magnet. The subject was instructed to perform finger opposition while the LEDs were lit. When the LEDs were off, the subject immediately ceased finger movement. In the second method, an MRI-compatible video display system was used. The subject wore mirrored goggles directed toward a display screen at one end of the magnet. Simple instructions, such as “stop moving and lie still” and “tap right fingers” were projected on the screen from a computer-controlled video projector. To ensure that the patients followed the start and stop signals, and that their finger-tapping speeds were similar to those recorded outside the magnet, their task performance relative to prompting was monitored by a staff member who was physically present with the patient throughout the study. If the patient failed to carry out the task with acceptable response times and speed, the scan was aborted. The staff explained the procedure to the patient again, and the experiment was repeated. If the patient still had trouble following instructions, the study was aborted again and the patient took no further part in the study. The experiments were repeated twice for each hand.

Data Analysis

Data analysis consisted of motion correction, statistical analysis of activated pixels, and calculation of activated volumes in specific anatomic regions. Motion correction was carried out by two-dimensional cross-correlation¹² to correct for possible in-plane translation and rotation of the head between serial images. Each image in the series was registered with the first baseline image by applying a range of test transformations consisting of planar translations and rotations. The first image was subtracted on a pixel-by-pixel basis from the transformed image. The transformation that yielded the minimum difference in magnitude between the paired images was selected as the optimal correction for the subject movement. A 0.125-degree rotation and 0.12-mm translation were used to test for minimum rotation and translation, respectively. If large movement of the head occurred, motion artifact could not be corrected (usually >1.5 mm translation) and the data were discarded. Such patients were later called back for another study. Three studies were repeated due to motion artifact.

Statistical analysis of activated pixels was based on combinations of temporal cross-correlation of the time course of the MR signals with a sine function¹³ and cluster size thresholding¹⁴ to justify multiple comparisons in an image. The pixels were thresholded at a level of cross-correlation coefficients ≥ 0.513 , which had one-tailed type I error of 0.0025 per pixel. A second threshold of a cluster size at ≥ 5 pixels was further applied, resulting in the estimated probability of false-positive of $P < .0006$ per pixel. Finally, activation images were overlaid on T1-weighted anatomic images for further analysis.

Localization of the activated pixels in specific anatomic regions was achieved by using the T1 weighted images and *Human Brain Anatomy in Computerized Images*.¹⁵ Specifically, the number of pixels in the

TABLE 1. Motor Activation of Right-Handed Normal Subjects (n=8)

	Right Hand		Left Hand		Pooled Data	
	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi
Sensorimotor	88.6±20.2	12.3±5.7	85.4±20.7	17.8±9.2	87.0±17.8	15.0±5.7
Frontal	23.3±11.6	9.6±5.8	8.4±4.0	4.9±3.5	15.8±6.6	7.3±3.1
AC, paraCL	5.3±2.7	7.8±2.7	2.3±1.1	0.8±0.8	3.8±1.6	4.3±1.6
SPL, SMG, AG	3.4±1.3	13.1±12.0	1.9±1.9	5.0±3.4	2.6±0.9	9.1±7.5
Total	163.3±37.9		126.3±21.0			

Contra (Ipsi); indicates activation was observed in the hemisphere contralateral (ipsilateral) to the hand. Values are number of pixels, mean±SEM.

regions of SM cortex, the remaining parts of frontal lobe (including superior, middle, and inferior frontal gyri), AC gyrus, paraCL, SPL, SMG, and AG, was computed over three MR slices and tabulated.

Correlation between the age and time required for the unaffected hand to perform 20 finger oppositions was examined using linear regression. Furthermore, the two methods used to assess motor deficits of the patients (the prolonged time for the paretic hand to perform 20 finger oppositions, and the summed score of NIHSS of the upper limb and hand) were tested for correlation (linear regression).

Results

Summary of Normal Subjects

Table 1 summarizes the fMRI results obtained from eight right-handed control subjects. In control subjects, activation obtained from sequential finger opposition primarily occurred in the contralateral SM cortex with minor ipsilateral activation for both hands. The mean±SEMs of the contralateral activation in the SM cortex were 88.6±20.2 and 85.4±20.7 pixels for the right and left hands, respectively, and for ipsilateral activation of SM cortex, 12.3±5.7 and 17.8±9.2 pixels for the right and left hands, respectively. Activation was also observed in contralateral and ipsilateral premotor cortex, AC gyrus, paraCL, SPL, SMG, and AG. The mean and standard error values of activated pixels in each specific region are given in Table 1. No significant differences in ipsilateral SM cortex activation (which might indicate use of uncrossed motor pathway) were found between the dominant and nondominant

hemispheres ($P=.64$, nonparametric Wilcoxon signed rank test). Therefore, we pooled data from both hemispheres (Table 1) to perform statistical comparisons with the patient group.

Individual Patient Results

Clinical presentations of the eight stroke patients at the onset of stroke as well as at the time of study are summarized in Table 2. Severity of stroke and motor deficit, measured at the same two time points by the total and the subgroup motor NIHSS scores, are given in Table 3. Overall recovery at the time of study, documented by the modified Rankin score, is also listed in Table 3. The time required to perform 20 finger oppositions of each hand and the prolonged time for paretic hand performance are given in Table 3. In the following section, a brief description of the clinical presentation and fMRI findings of each stroke patient will be given.

Patient 1, a 25-year-old woman, suffered her first ever ischemic stroke due to dissection of the left internal carotid artery (the only subject with extracranial artery involvement) that caused a solitary infarct (largest dimension 7.9 cm) in the left anterior cerebral artery territory (Table 2). The infarct extended from the superior frontal gyrus to the superior portion of the precentral gyrus, and to the paraCL, and partially spared the hand motor area (Fig 1). At stroke onset, she experienced right hemiplegia, right hemisensory loss, and a transcortical mixed aphasia. At the time of study (5 months

TABLE 2. Summary of Clinical Characteristics of Stroke Patients

Pt No.	Sex	Age, y	Side	Ischemic Infarct			Clinical Features			
				Topography	Artery Territories	Dim, cm	Onset	Time of Study	Synkinesia	
1	F	25	L	Frontal	ACA	7.9	R hemiplegia f-a-l+ transcortical mixed aphasia	R hemiparesis+ transcortical motor aphasia	None	
2	F	19	L	Frontoparietotemporal	MCAB	9.1	R hemiplegia f-a-l+ global aphasia	R hemiparesis+ motor aphasia	None	
3	F	41	L	Frontoparietal	MCAB	6.0	R hemiplegia f-a-l+ global aphasia	R hemiparesis f-a+ motor aphasia	Yes	
4	M	60	R	Frontoparietotemporal	MCA	12.0	L hemiplegia+ neglect+ gaze palsy	L S-M f-a	None	
5	F	51	R	Frontoparietotemporal	MCAB	5.5	L hemiplegia f-a-l+ neglect	L hemiparesis f-a	None	
6	F	70	R	Parietal	MCAB	5.0	L S-M f-a-l+ neglect	L S-M f-a-l	None	
7	M	64	R	Corona radiata	PB	2.4	L pure hemiparesis f-a-l	L pure hemiparesis f-a	Yes	
8	F	36	R	Striatocapsular	LSA	3.6	L hemiplegia	L S-M f-a-l	None	

Pt indicates patient; S-M, sensorimotor syndrome; f-a-l, face-arm-leg; Dim, largest dimension; MCAB, middle cerebral artery branch; PB, parietal branch; LSA, lenticulostriate arteries; and ACA, anterior cerebral artery.

TABLE 3. Measurements of Stroke Severity and Motor Deficits of Stroke Patients

Pt. No.	At Onset of Stroke				Time Interval, mo	At Time of Study							
	NIHSS Scores					NIHSS Scores				Rankin Scores	Time for 20 Finger Oppositions, s		Prolonged Time, s
	Total	LL	UL	Hand		Total	LL	UL	Hand		NH	PH	
1	15	4	3	1	5	4	1	1	0	2	23	34	11
2	24	4	4	2	14	11	3	2	1	3	30	80†	50
3	20	4	4	2	5	8	0	0	1	3	38	51	13
4	13	2	3	2	5	3	0	1	0	1	38	39	1
5	*	*	*	*	43	3	0	1	1	2	27	32	5
6	10	3	2	2	19	7	2	1	1	1	55	75	20
7	5	1	1	1	10	3	0	1	1	1	59	75	16
8	*	*	*	*	24	5	1	1	1	2	40	84	44

NIHSS, indicates NIH Stroke Scale; LL, lower limb; UL, upper limb; NP, normal hand; and PH, paretic hand.

*Patients 5 and 8 were evaluated at another hospital at stroke onset; therefore, the NIHSS scores were not available.

†Time was obtained from finger's open-close movements.

after the stroke), she had recovered sufficiently to perform finger opposition of her paretic hand at a rate of 2.4 Hz, compared with 3.5 Hz for her unaffected hand. She continued to suffer right hemiparesis and transcortical motor aphasia.

Her normal (left) hand activated the contralateral SM cortex and the lateral premotor cortex. Minor activation was also observed in the ipsilateral SM cortex and the contralateral SPL and SMG. The number of activated pixels in each region is listed in Table 4. Activation produced by her paretic (right) hand movements was primarily observed in the contralateral SM cortex, ipsilateral SMG, and lateral premotor cortex (Fig 1). A small volume in ipsilateral SM cortex was also activated. The location of activation in contralateral SM cortex during the paretic hand movements was shifted inferiorly, in comparison to that produced by her unaffected hand movements. The activated volume in the ipsilateral SMG (123 pixels) of this patient was profoundly enlarged when compared within the patient group (the mean of the number of activated pixels was 28, see Table 4) and when compared with the control group (the mean of 9 pixels, see Table 1).

Patient 2, a 19-year-old woman, suffered an ischemic infarct (largest dimension 9.1 cm) in the left hemisphere involving the frontal, anterior parietal, and temporal cortices (Table 2). This was caused by branch occlusion of the MCA. The infarct further extended into the posterior portion of the putamen and globus pallidus. At the onset of her stroke, she experienced right hemiplegia and global aphasia. At the time of the study (14 months after stroke onset), she suffered the most severe hand motor impairment among the patient group; she could only tap three fingers of the paretic hand and took the most prolonged time (50 seconds) to perform the task.

During her normal (left) hand movements, only the contralateral SM cortex was activated. However, the paretic (right) hand activated minimal volumes in the contralateral SM, AC, and paraCL. Instead, the ipsilateral motor cortex, premotor, SMG, and SPL were activated. A total number of 39 pixels was activated in SMG and SPL. This was four times the mean value of the control group.

Patient 3, a 41-year-old woman, suffered a first-ever ischemic stroke due to branch occlusion of the left MCA, resulting in an infarct of the left frontal and parietal cortices (largest dimension 6.0 cm) (Fig 2). At stroke onset, she experienced right hemiplegia and global aphasia (Table 2). Five months after the stroke, she regained her right hand movement, even though she continued to suffer right hemiparesis involving face and arm and motor aphasia. The residual impairment of the paretic (right) hand was further demonstrated by 13 seconds of prolonged performance time compared with the normal (left) hand (Table 3). She also developed minor synkinesia of the unaffected (left) hand. Her unaffected hand was twitching with a magnitude of less than 1 mm while the paretic hand performed a motor task.

The unaffected hand movements of this patient produced activation in the contralateral SM cortex, premotor cortex, and SPL. For the paretic hand movements, no activation was obtained in the contralateral hemisphere (infarct site); instead, ipsilateral SM and premotor cortex was markedly activated at a locus nearly identical to that activated by the unaffected hand movements (Fig 2).

Patient 4, a 60-year-old man, suffered the largest infarct within the group, due to right MCA occlusion. The infarct was located in the right frontal region, extending posteriorly to the parietal cortex and inferiorly to the temporal cortex (largest dimension 12.0 cm). The infarct spared the striatocapsular region and the hand area of the primary motor cortex. The patient was the only subject who had received acute thrombolytic therapy with tissue plasminogen activator (TPA). At the onset of the stroke, he experienced left hemiplegia, neglect, and gaze palsy. At the time of study (5 months after stroke onset), he had recovered the most completely within the patient group, even though he continued to suffer left sensorimotor deficit involving face and arm. Both of his hands had almost identical kinetic ability (38 and 39 seconds required for 20 finger oppositions of the normal and paretic hands, respectively); however, the magnitude of the paretic hand movements was less than the unaffected hand.

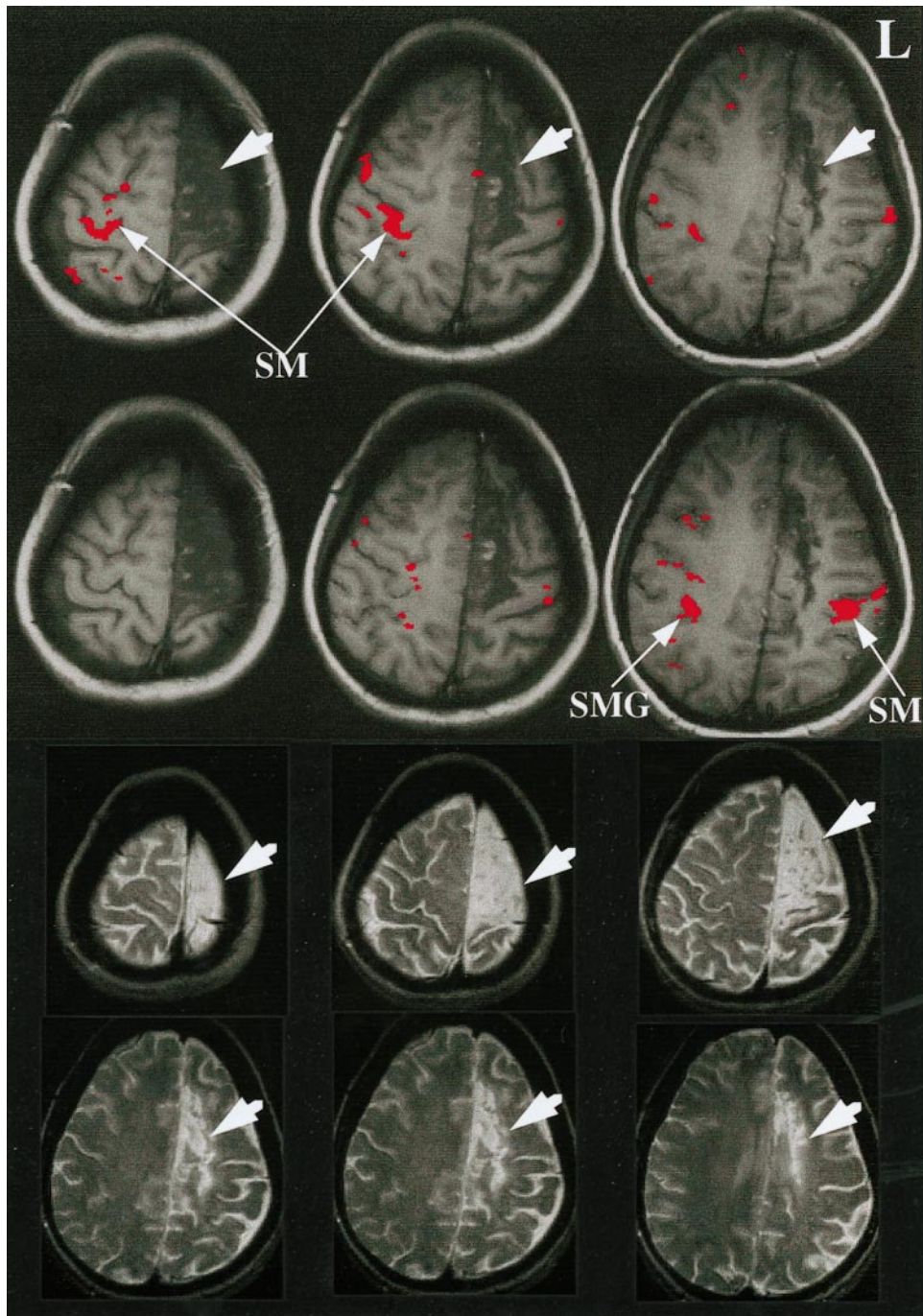


Figure 1. Patient 1 suffered an ischemic infarct, with hyperintensity in T2-weighted MR images (bottom two rows), in the left anterior cerebral artery territory. The infarct is denoted by arrow heads. Motor activation (red color) produced by movement of the unaffected (left) and paretic (right) hands is overlaid on T1-weighted MR images, and illustrated in the first and second rows of images, respectively. Note that the location of activation in the contralateral SM cortex during paretic hand movements was shifted inferiorly, compared with locations activated by unaffected hand movements. The right SMG region was profoundly activated during ipsilateral paretic hand movements. L indicates left.

This patient's unaffected (right) hand movements activated the contralateral SM cortex and bilateral SMA and AC gyrus. Activation from his paretic (left) hand was observed in contralateral SM cortex, bilateral SMG, contralateral AC gyrus, and ipsilateral lateral premotor cortex. The activated volumes in the ipsilateral lateral premotor and prefrontal regions were approximately 12-fold larger than the average value of the normal control group. No activation was observed in the

ipsilateral SM cortex during the paretic hand movements (Table 4).

Patient 5, a 51-year-old woman, suffered her first ischemic stroke due to branch occlusion of the right MCA, resulting in an infarct (largest dimension 5.5 cm) in the right frontoparieto-temporal cortex (Fig 3). She experienced left hemiplegia and neglect at stroke onset. At the time of the study (43 months after stroke onset), she continued to suffer left hemi-

TABLE 4. Motor Activation of Stroke Patients

Patient No.	Normal Hand Movement		Paretic Hand Movement	
	Contra Hemisphere	Ipsi Hemisphere	Contra Hemisphere	Ipsi Hemisphere
1				
Sensorimotor	249	11	204	85
Frontal	56	0	0	28
AC, paraCL	6	0	0	6
SPL, SMG, AG	6	0	0	123
2				
Sensorimotor	111	0	13	42
Frontal	0	0	0	9
AC, paraCL	0	0	11	0
SPL, SMG, AG	0	0	0	39
3				
Sensorimotor	153	0	0	31
Frontal	42	0	0	0
AC, paraCL	0	0	0	0
SPL, SMG, AG	32	5	0	25
4				
Sensorimotor	220	7	58	0
Frontal	0	20	33	89
AC, paraCL	28	25	30	0
SPL, SMG, AG	24	16	8	17
5				
Sensorimotor	122	0	16	110
Frontal	0	0	0	12
AC, paraCL	17	0	14	17
SPL, SMG, AG	0	0	6	10
6				
Sensorimotor	11	0	18	0
Frontal	0	6	0	0
AC, paraCL	0	0	8	0
SPL, SMG, AG	0	0	0	0
7				
Sensorimotor	180	7	61	89
Frontal	15	24	35	196
AC, paraCL	0	0	20	11
SPL, SMG, AG	0	0	0	12
8				
Sensorimotor	46	6	17	59
Frontal	0	0	9	6
AC, paraCL	0	0	8	0
SPL, SMG, AG	0	15	0	0
Sensorimotor (mean±SEM)	136±28.9	3.9±1.6	48.4±23.5	52.0±14.5
Frontal (mean±SEM)	14.1±7.9	6.3±3.5	9.6±5.4	42.5±24.3
AC, paraCL (mean±SEM)	6.4±3.7	3.1±3.1	11.4±3.6	4.3±2.3
SPL, SMG, AG (mean±SEM)	7.8±4.5	4.5±2.5	1.8±1.2	28.3±14.3
Total (mean±SEM)	182.5±41.8		198.1±56.8	

Values are number of pixels. Contra indicates contralateral and Ipsi ipsilateral.

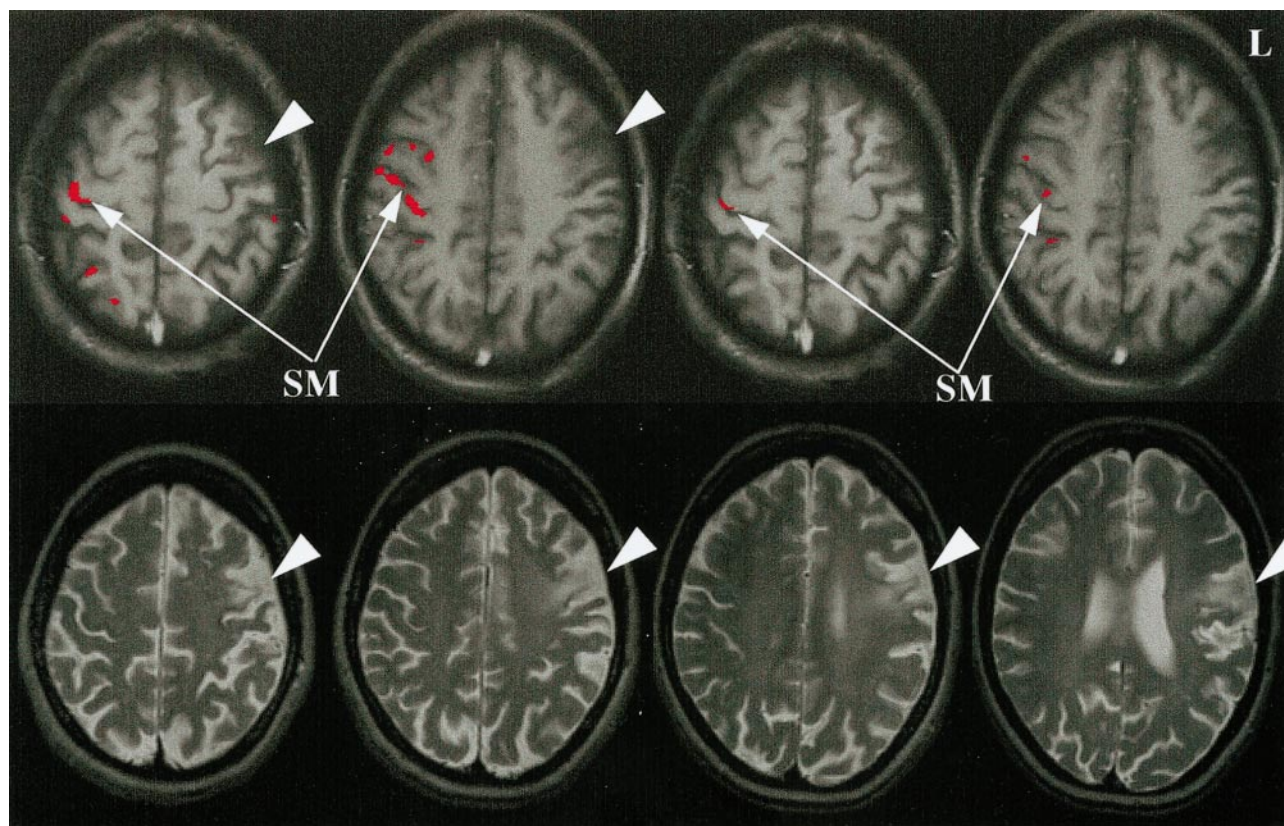


Figure 2. Patient 3 suffered an ischemic infarct, with hyperintensity in T2-weighted MR images (bottom row), in the left MCA territory. The infarct is denoted by arrow heads. Motor activation (red color) overlaid on T1-weighted MR images is shown in the top row of images. The left two images were obtained during unaffected (left) hand movements; the right two images represent activation during paretic (right) hand movements. Note that the ipsilateral activation produced by paretic hand movements was at a locus nearly identical to that activated by unaffected hand movements.

paralysis of face and arm. A minimally prolonged time (5 seconds) was required for her paretic (left) hand to perform the finger opposition task, in comparison to the unaffected hand. No synkinesia was observed.

This patient's unaffected (right) hand movements activated the contralateral SM cortex, SMA, and lateral premotor cortex. Her paretic (left) hand movements activated ipsilateral SM and premotor cortex, and bilateral SMA (Fig 3). The volume activated in the ipsilateral SM cortex was approximately 10-fold greater than the mean volume of the control group. Minimal activation was observed in the contralateral SM cortex (Table 4).

Patient 6, a 70-year-old woman, suffered an infarct (largest dimension 5.0 cm) in the right parietal cortex due to branch occlusion of the right MCA. At stroke onset, she experienced a left SM paralysis of face, arm, and leg and neglect. At the time of study (19 months after stroke onset), she continued to suffer SM deficits of left face, arm, and leg. Compared with the unaffected hand, her paretic hand required a prolonged time of 20 seconds to perform the finger opposition task, indicating moderate recovery.

During her unaffected hand movements, the contralateral SM cortex was activated. The paretic hand movements activated the contralateral motor cortex and AC gyrus. This patient is the only one in whom no ipsilateral activation was observed.

Patient 7, a 64-year-old man, suffered a solitary infarct (largest dimension 2.4 cm) in a region of the right corona radiata. At stroke onset, he experienced pure hemiparesis of the left face, arm, and leg. The severity of the stroke, documented by the total NIHSS score of 5, was the least of the group. By the time of the study (10 months after stroke onset), the patient developed minor synkinesia of the normal (right) hand. The motor deficits of the paretic hand were indicated by the longer time (16 seconds) required to perform the finger task, compared with the unaffected hand (Table 3).

The unaffected (right) hand movements activated contralateral SM cortex. The paretic hand movements produced bilateral activation in SM cortex, SMA, and lateral premotor cortex. The activated pixels in the ipsilateral SM cortex and the premotor region were 6 and 28 times, respectively, larger than those observed in normal control subjects (Tables 1 and 4).

Patient 8, a 36-year-old woman, suffered an ischemic stroke due to occlusion of lenticulostriate arteries. The infarct (largest dimension 5.0 cm) was located in the right striatocapsular region, extending inferiorly to the putamen and globus pallidus. She experienced left hemiplegia at the time of stroke onset. At the time of the study (24 months after stroke onset), she continued to experience left SM deficits in the face, arm, and leg. Based on the finger opposition task, the motor impairment of her paretic hand was next to the most severe within the patient group (Table 3).

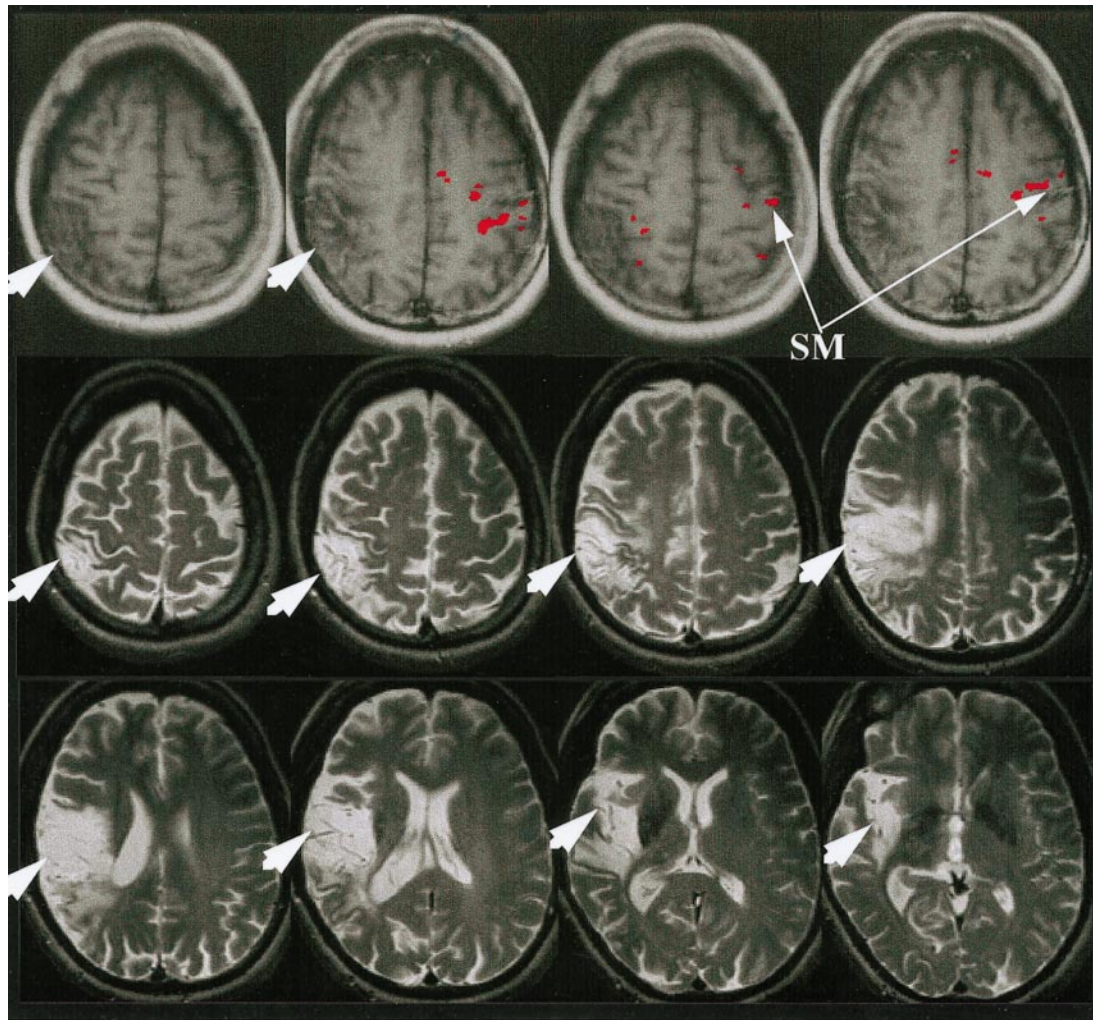


Figure 3. Patient 5 suffered an ischemic infarct, with hyperintensity in T2-weighted MR images (bottom two rows), in the right MCA territory. The infarct is denoted by arrow heads. Motor activation (red color) overlaid on T1-weighted MR images is shown in the top row of images. The left two images were obtained during unaffected (right) hand movements; the right two images represent activation during paretic (left) hand movements. No activation was observed in the contralateral SM cortex during paretic hand movements.

During unaffected (right) hand movements, the contralateral SM cortex was activated. During the paretic (left) hand movements, there was activation of bilateral SM cortex. Activation of the ipsilateral SM cortex (59 pixels) was at a locus nearly identical to that activated by the unaffected hand movement.

Group Results

In this study, the motor deficit of the patient's paretic hand was also assessed by the time required to perform 20 finger oppositions. The time required for the unaffected hand performance (Table 3) was significantly correlated with age ($r=.75$, $P=.032$, $n=8$, linear regression). The prolonged time required for the paretic hand to carry out the task as compared with the unaffected hand (Table 3) was significantly correlated with the summed NIHSS score for the upper limb and hand ($r=.74$, $P<.036$, $n=8$, linear regression). No correlation was found between the residual motor deficit of the paretic hand (either measured by the prolonged time for the finger opposition or by the summed NIHSS score of the upper limb and

hand) and the activated volumes in ipsilateral SM cortex among the six patients who had the increased ipsilateral activation ($r_s=-.543$, $P>.2$, Spearman rank correlation).

In the patient group, paretic hand movements produced the nearly identical number of total activated pixels (mean \pm SEM, 198 \pm 56 pixels) as did their unaffected hand movements (mean \pm SEM, 182 \pm 42 pixels). No significant difference in the total number of activated pixels was detected between the patient and control groups ($P>.45$, nonparametric Mann-Whitney U test). These data establish the bases for comparison of normal and paretic hands within the patient group as well as between patient and control groups, even though variability of effort required to perform the motor task existed between the two groups and between the two hands within the patient group.

During paretic hand movements, the volume of activated ipsilateral SM cortex was extensive in six of eight recovering stroke patients compared with control subjects. Bilateral activation of the primary SM cortex was recorded in three of these patients; ipsilateral activation alone was recorded in three

patients who suffered major cerebral infarctions with hemiplegia. Only two patients had mild synkinesia, which alone cannot be responsible for the increased ipsilateral activation in primary SM cortex. Furthermore, in two male patients, the paretic hand movements activated more extensive volumes of ipsilateral premotor and dorsolateral prefrontal cortex compared with control subjects. In two patients with left frontal infarction, profound activation was observed in the right SMG (Brodmann area 40) and in the right premotor cortex during the ipsilateral paretic hand movements. Even when one considers that only six patients had ipsilateral activation, in the total patient group the paretic hand produced a statistically significant increase in the number of activated pixels in the ipsilateral SM cortex (mean, 52 pixels) compared with that observed in the control group (mean, 15 pixels) ($P < .03$, Mann-Whitney U test).

Discussion

The technique of fMRI used in this study is based on BOLD contrast^{16–19} between rest and activated states of human brain. During activation of normal brain, oxygenation of cerebral blood increases because the increase of cerebral blood flow (29% to 50%)^{20,21} exceeds the increase in oxygen extraction (5%).²² Although in ischemic tissues the blood flow–metabolism couple is impaired,^{23–25} it remains normal in noninfarcted tissue.^{4,23,25} For example, PET studies of patients with striatocapsular infarction⁴ confirmed a cerebral blood flow increase during task performance in ipsilateral primary motor cortex, lateral prefrontal cortex, and insula. For the purpose of this fMRI study we focused on functional activation in the noninfarcted hemisphere and normal tissue regions in the damaged hemisphere.

Our study has shown different patterns of cortical motor activation in recovering hemiparetic patients, who suffered cortical lesions in the majority. The primary SM cortex in noninfarcted hemispheres of six of the eight recovering hemiparetic patients was activated during movements of the ipsilateral (paretic) hand. In three patients who suffered infarcts that spared the hand area of the primary motor cortex (two subcortical and one superior frontal), the paretic hand movements led to bilateral activation of the SM cortex. In three other patients with precentral gyrus infarction, only ipsilateral activation occurred during paretic hand movements. These activation patterns were significantly different from those observed in our normal control subjects. One possible explanation is that in some patients recovering from hemiparesis after unilateral ischemic stroke, functional motor pathways may reorganize in an attempt to recruit any prestroke link between the paretic hand and the primary motor cortex in the noninfarcted hemisphere via uncrossed corticospinal tracts or other indirect uncrossed pathways. In normal humans, uncrossed corticospinal tracts, comprising about 10% to 15% of all of the corticospinal fibers,²⁶ rarely participate in distal limb movements. This is supported by our observation in the control group of 20% or less ipsilateral activation in each hemisphere, as well as similar results from other activation studies.^{12,27–30} In normal nonhuman primates, the majority of primary motor cortex neurons subserved contralateral movement; only 7% to 8%

of neurons were associated with ipsilateral distal limb movement.³¹ Our findings are further supported by studies in patients with pyramidal tract infarcts^{4,32} and in young patients (mean age, 15 years) with hemiparesis who suffered perinatal unilateral brain injury.⁶ A PET study of individual motor patterns after striatocapsular stroke found that increased ipsilateral activation in primary SM cortex was observed only in patients with associated movements,³² so it could not be determined whether this ipsilateral activation reflected recruitment of uncrossed corticospinal pathways or was secondary to the associated movements. In the present study, however, increased ipsilateral primary sensorimotor activation could not be explained in this way, because four of the six patients with this finding had no associated movements. Furthermore, as observed in one (patient 3) of our two patients with synkinesia, the fact that there was exclusive ipsilateral activation during paretic hand movements indicates that the noninfarcted hemisphere must control both voluntary and associated movements. Therefore, other physiological explanations for ipsilateral activation, such as reorganization of functional motor pathways or recruitment of the preexisting uncrossed pathways, must be considered.

In two patients (patients 1 and 2) with the large left frontal infarcts, we observed extensive activation in the right SMG (Brodmann area 40) and right premotor cortex during ipsilateral paretic hand movements. Parietal lobe lesions are known to impair skilled movements and to affect performance of symbolic gestures, motor production, and ideation.^{33–35} Neuroimaging patterns of cerebral activation (eg, in premotor, SMA, and parietal regions) during both mental rehearsal of a motor task and its execution^{36,37} add further support that the posterior parietal cortex is an important component of motor pathways. Specific contributions of the parietal cortex in motor behavior were recently studied during the mental representation of hand movements after parietal cortex damage.³⁸ This study demonstrated that parietal cortex lesions selectively impaired capability of predicting the time necessary to perform differentiated finger movements and visually guided pointing gestures. Furthermore, Weiller et al³² have proposed an accessory motor system involving Brodmann area 40 and those anterior portions of the insula functionally connected to the motor network via direct projections to the inferior premotor cortex or the centromedian nucleus of the thalamus. One possible explanation for our finding of enhanced activation in the right SMG after left ischemic infarction is that ipsilateral nonprimary cortical motor areas and their efferent corticocortical pathways may compensate for disruption of the output of the contralateral primary motor cortex and for inefficiency of the ipsilateral primary motor cortex and the uncrossed corticospinal tracts. In a separate study, the posterior parietal cortex, particularly the right hemisphere, was activated in trial-and-error motor sequences.³⁹ Activation of the posterior parietal cortex was also observed during self-paced complex finger movements.⁴⁰ The specific contribution or possibly multiple roles of Brodmann area 40 in complex motor behavior remain to be determined, however. Because the right SMG area (Brodmann area 40) may also be part of a spatial attention network,^{41,42} the possibility cannot be ruled out that the right

SMG activation in our patients is due to enhanced attention required during paretic hand movements.

Problematic in all activation and task performance studies is how to control for the effort of subjects and the associated nonspecific cognitive components. The outcome of increased effort may be enlarged activation volumes and nonspecific cognitive components may recruit newly activated regions. In previous normal motor studies, the pace of movement was controlled because it is linearly proportional to the magnitude of activation.⁴³ However residual motor impairment in recovering hemiparetic patients may exaggerate the variability in effort if the speed of movements is controlled. Also, prolonged finger movements may cause fatigue and increased effort by hemiparetic patients, or even normal subjects. Because this may result in the use of proximal limb muscles in addition to hand muscles, this might explain expanded regions of motor cortex activation. We attempted to overcome this in our pilot study by using a self-paced, more automatic finger opposition task with comfortable performance time (24 s) for most patients.

A 3T magnet and GRE pulse sequence were used for this study. The approach to studying motor function with GRE pulse sequences has several limitations. First, the examined volume was limited to a 30-mm thick section of the brain rather than the entire head. Second, the GRE pulse sequence is more sensitive to motion than echo-planar imaging (EPI). Third, T_2^* -weighted images, acquired by either GRE or gradient-echo EPI techniques, are sensitive not only to tissue blood oxygenation changes but also to BOLD signals in venules and veins.⁴⁴ However, the percentage of BOLD signals arising from capillaries and brain tissue increases with magnetic field strength.^{45,46} In this respect, then, a 3T magnet is superior to a 1.5T scanner.

In summary, we have demonstrated that fMRI allows study of recovery of motor function after ischemic stroke in humans. We were able to investigate differences in motor activation of individual patients and to explore the group results. Our study suggests that BOLD contrast is sensitive to functional recovery and organization of motor pathways. In the future, fMRI may be a useful tool to monitor and study poststroke rehabilitation and may be important in aiding our understanding of the mechanisms of poststroke motor recovery.

Acknowledgments

This work was supported in part by NIH grant NS 23393 and an AHA Grant-in-Aid (96009160). The authors would like to thank Patricia Booker and Susan Ferrari for their assistance in helping to recruit patients, Dr Rima Dafer for patient referral, Dr Mike Boska for methodological advice in the NMR Laboratory, and Dr Jay Nelson for technical support.

References

1. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The pilot stroke data bank: design, methods, and baseline characteristics. *Stroke*. 1988;19:547-554.
2. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J. Measurement of motor recovery after stroke: outcome measures and sample size requirements. *Stroke*. 1992;23:1094-1098.
3. Hallett M. The plastic brain. *Ann Neurology*. 1995;38:4-5.
4. Weiller C, Chollet F, Friston KJ, Wise RJS, Frackowiak RSJ. Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Ann Neurol*. 1992;31:463-472.
5. Bridgers S. Magnetic cortical stimulation in stroke patients with hemiparesis. In: Chokroverty S, ed. *Magnetic Stimulation in Clinical Neurophysiology*. Boston, Mass: Butterworths; 1989:233-247.
6. Cao Y, Vikingstad EM, Huttenlocher PR, Towle VL, Levin DN. Functional magnetic resonance studies of the reorganization of the human hand sensorimotor area after unilateral brain injury in the perinatal period. *Proc Natl Acad Sci U S A*. 1994;91:9612-9616.
7. Chollet F, DiPiero V, Wise RJS, Brooks DJ, Dolan RJ, Frackowiak RSJ. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann Neurol*. 1991;29:63-71.
8. Cao Y, D'Olhaberriague D, Levine SR. Brain reorganization during motor recovery from stroke in humans. *Stroke*. 1996;27:194.
9. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia*. 1971;9:97-113.
10. Brott T, Adams HPJ, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, Rorick M, Moonaw CJ, Walker M. Measurement of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864-870.
11. Van Jign J. Measurement of outcome in stroke prevention trials. *Cerebrovasc Dis*. 1992;2(suppl 2):23-34.
12. Cao Y, Towle VL, Levin DN, Balter JM. Functional mapping of human motor cortical activation by conventional MRI at 1.5 T. *J Magn Reson Imaging*. 1993;3:869-875.
13. Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Reson Med*. 1993;30:161-165.
14. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med*. 1995;33:636-647.
15. Damasio H. *Human Brain Anatomy in Computerized Images*. New York, NY: Oxford University Press; 1995.
16. Ogawa S, Lee T, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med*. 1990;14:68-78.
17. Ogawa S, Tank DW, Menon R, Ellerman JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping using MRI. *Proc Natl Acad Sci U S A*. 1992;89:5951-5955.
18. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng H-M, Brady TJ, Rosen BR. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A*. 1992;89:5675-5679.
19. Bandettini PA, Wong EC, Hinks PS, Tikofsky RS, Hyde JS. Time course EPI of human brain function during task activation. *Magn Reson Med*. 1992;25:390-397.
20. Fox PT, Meizin FM, Allman JM, Van Essen DC, Raichle ME. Retinotopic organization of human visual cortex mapped with positron emission tomography. *J Neurosci*. 1987;7:913-922.
21. Deiber MP, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RSJ. Cortical areas and the selection of movement: a study with positron emission tomography. *Exp Brain Res*. 1991;84:393-402.
22. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A*. 1986;83:1140-1144.
23. Heiss W-D, Huber M, Fink GR, Herholz K, Pietrzyk U, Wagner R, Wienhard K. Progressive derangement of perinfarct viable tissue in ischemic stroke. *J Cereb Blood Flow Metab*. 1992;12:193-203.
24. Wise RJS, Bernardi S, Frackowiak RSJ, Legg NJ, Jones T. Serial observations on the pathophysiology of acute stroke. *Brain*. 1983;106:197-222.
25. Wise RJS, Rhodes CG, Gibbs JM et al. Disturbance of oxidative metabolism of glucose in recent human cerebral infarcts. *Ann Neurol*. 1983;14:627-637.
26. Nyberg-Hansen R, Rinvik E. Some comments on the pyramidal tract, with serial reference to its individual variations in man. *Acta Neurol Scand*. 1963;39:1-30.
27. Ramachandran VS. Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain. *Proc Natl Acad Sci U S A*. 1993;90:10413-10420.
28. Colebatch JG, Deiber M-P, Passingham RE, Friston KJ, Frackowiak RSJ. Regional cerebral blood flow during voluntary arm and hand movements in human subjects. *J Neurophysiol*. 1991;65:1392-1401.
29. Fox PT, Burton H, Raichle ME. Mapping human somatosensory cortex with positron emission tomography. *J Neurophysiol*. 1987;67:34-43.

30. Kim SG, Ashe J, Georgopoulos AP et al. Functional imaging of human motor cortex at high magnetic field. *J Neurophysiol.* 1993;69:297–302.
31. Tanji J, Okano K, Sato KC. Neuronal activity in cortical motor areas related to ipsilateral, contralateral and bilateral digit movements of the monkey. *J Neurophysiol.* 1988;60:325–343.
32. Weiller C, Ramsay SC, Wise RJS, Friston KJ, Frackowiak RSJ. Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. *Ann Neurol.* 1993;33:181–189.
33. Clark MA, Merians AS, Kothari A, Poizner H, Macauley B, Rothi LJG, Heilman KM. Spatial planning deficits in limb apraxia. *Brain.* 1994;117:1093–1106.
34. Jeannerod M. The formation of finger grip during prehension: a cortically mediated visuomotor pattern. *Behav Brain Res.* 1986;19:99–116.
35. Heilman KM, Rothi LJ, Valenstein E. Two forms of ideomotor apraxia. *Neurology.* 1982;32:342–346.
36. Decety J, Perani D, Jeannerod M, Bettinardi V, Tadary B, Woods R, Mazziotta JC, Fazio F. Mapping motor representations with positron emission tomography. *Nature.* 1994;371:600–602.
37. Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann AO, Frith CD, Frackowiak RSJ. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J Neurophysiol.* 1995;73:373–386.
38. Sirigu A, Duhamel J-R, Cohen L, Pillon B, Dubois B, Agid Y. The mental representation of hand movements after parietal cortex damage. *Science.* 1996;273:1564–1568.
39. Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RSJ, Passingham RE. Motor sequence learning: a study with positron emission tomography. *J Neurosci.* 1994;14:3775–3790.
40. Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, Lisk LM, Morris GL, Mueller WM, Estkowski LD, Wong EC, Haughton VM, Hyde JS. Functional magnetic resonance imaging of complex human movements. *Neurology.* 1993;43:2311–2318.
41. Gitelman DR, Alpert NM, Kosslyn S, Daffner K, Scinto L, Thompson W, Mesulam M-M. Functional imaging of human right hemispheric activation for exploratory movements. *Ann Neurol.* 1996;39:174–179.
42. Selemon LD, Goldman-Rakic PD. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. *Neurosci.* 1988;8:4049–4068.
43. Blinkberg M, Bonde C, Holm S, Svarer C, Anderson J, Paulson OB, Law I. Rate dependence of regional cerebral activation during performance of a repetitive motor task: a PET study. *J Cereb Blood Flow Metab.* 1996;16:794–803.
44. Boxerman JL, Bandettini PA, Kwong KK, Baker JR, Davis TL, Rose BR, Weisskoff RM. The intravascular contribution to fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo. *Magn Reson Med.* 1995;34:4–10.
45. Menon RS, Hu X, Adriany G, Andersen P, Ogawa S, Ugurbil K. Comparison of spin-echo EPI, asymmetric spin-echo EPI and conventional EPI applied to functional neuroimaging: the effect of flow crushing gradients on the BOLD signal. In: Proceedings of the Society for Magnetic Resonance. San Francisco, CA: 1994:622. Abstract.
46. Song AW, Wong EC, Jesmanowicz SG, Tan SG, Hyde JS. Diffusion weighted fMRI at 1.5 T and 3T. In: Proceedings of the Society of Magnetic Resonance. Nice, France: 1995:457. Abstract.