Motor Imagery After Subcortical Stroke
A Functional Magnetic Resonance Imaging Study

Nikhil Sharma, MRCP(UK), PhD; Lucy H. Simmons, BSc; P. Simon Jones, MSc;
Diana J. Day, MSc; T. Adrian Carpenter, PhD; Valerie M. Pomeroy, PhD;
Elizabeth A. Warburton, DM; Jean-Claude Baron, MD, FRCP, FMedSci

Background and Purpose—In recovered subcortical stroke, the pattern of motor network activation during motor execution can appear normal or not, depending on the task. Whether this applies to other aspects of motor function is unknown. We used functional MRI to assess motor imagery (MI), a promising new approach to improve motor function after stroke, and contrasted it to motor execution.

Methods—Twenty well-recovered patients with hemiparetic subcortical stroke (14 males; mean age, 66.5 years) and 17 aged-matched control subjects were studied. Extensive behavioral screening excluded 8 patients and 4 control subjects due to impaired MI abilities. Subjects performed MI and motor execution of a paced finger–thumb opposition sequence using a functional MRI paradigm that monitored compliance. Activation within the primary motor cortex (BA4a and 4p), dorsal premotor, and supplementary motor areas was examined.

Results—The pattern of activation during affected-hand motor execution was not different from control subjects. Affected-hand MI activation was also largely similar to control subjects, including involvement of BA4, but with important differences: (1) unlike control subjects and the nonaffected hand, activation in BA4a and dorsal premotor was not lower during MI as compared with motor execution; (2) the hemispheric balance of BA4p activation was significantly less lateralized than control subjects; and (3) ipsilesional BA4p activation positively correlated with motor performance.

Conclusions—In well-recovered subcortical stroke, the motor system, including ipsilesional BA4, is activated during MI despite the lesion. It, however, remains disorganized in proportion to residual motor impairment. Thus, components of movement upstream from execution appear differentially affected after stroke and could be targeted by rehabilitation in more severely affected patients. (*Stroke*. 2009;40:1315-1324.)

Key Words: functional imaging ■ motor imagery ■ motor recovery ■ stroke

Incomplete recovery of the hand after stroke interferes with activities of daily living and limits independence. Yet the human brain is able to undergo marked reorganization, driving improvements in function.[1,2] Understanding the neural substrates that underlie these changes is important in providing neuroscience-based rehabilitation.

Previous functional imaging studies, which focused largely on motor execution (ME), have improved our understanding of how the motor system adapts after stroke. These studies report correlates of the recovery of motor function that include overactivation of the cortical motor areas[3] and alterations in the hemispheric balance.[2,4–6]. Importantly, the primary motor cortex (BA4, specifically BA4p) has emerged as a crucial node in the recovery of motor function after stroke.[7,8] It is unknown whether these changes are related to motor output itself or to aspects of movement that are more upstream (ie, nonexecutive).[9]

Although partly task-dependent,[10–13] it is widely agreed that patients with stroke who have recovered nearly normal motor function have essentially normal cortical activation patterns during movement.[1,2] Yet in such patients, recent studies[11] suggest that nonexecutive aspects of movement can remain disrupted. Why these nonexecutive disturbances have not been highlighted by functional MRI (fMRI) studies of executed movement is unclear, but one possibility is that the poor temporal resolution of the blood-oxygen level-dependent signal favors the more dominant executive activation. Understanding this form of plasticity not highlighted by ME could provide a specific target for novel insights into cortical reorganization after stroke.

Motor imagery (MI) shares many cognitive aspects of movement with, but does not involve, actual execution.[9] MI can be defined as the internal reactivation of a first-person motor program that is governed by the principles of central

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motor control without any overt motor output.[9] In healthy volunteers, MI shares many neural substrates with ME.[14–16] Across these fMRI studies, BA4 is activated during MI, albeit at a reduced level[14] and with some differences in topography.[16] Whether ipsilesional BA4 is involved during MI after stroke is unknown. Clarifying this issue would significantly strengthen or weaken the rationale for MI as a form of rehabilitation[14] given BA4's role in motor learning.[17]

A recent Phase 2 trial suggested MI is beneficial in partially recovered patients with chronic stroke.[18] Although MI as a rehabilitation technique is primarily intended for patients who are unable to move their affected limb, aiming to improve motor function until some movement has returned and active movement techniques can take over, it is important as a first step to elucidate the fMRI activation pattern of MI in patients who have recovered executive movement, because the latter can serve as a reference or control, especially because near-normal activation of ipsilesional BA4 is then expected.[1,2]

Although stroke does not appear to impair the capacity to perform MI,[19,20] the situation may in fact depend on the site and extent of the lesion. In some patients, there is disruption of both the accuracy and the temporal coupling (ie, restriction by the principles of "motor control") of MI,[21] so-called "chaotic motor imagery."[14,16] Including such subjects in fMRI studies would produce incongruent results.

In this study, we therefore test 2 hypotheses: (1) that MI will involve BA4 in near fully recovered patients with subcortical hemiparetic stroke despite their residual lesion; and (2) that MI demonstrates disorganization of the cortical motor network that is not highlighted by ME. To address the latter, we analyze not only the activation patterns, but also the laterality index (LI),[5] which expresses the hemispheric balance and is a sensitive index in well-recovered patients with stroke.[4,5] Attention is given to the subdivisions of BA4, namely BA4a and BA4p, because they subtend different aspects of motor function.[16,22] In addition, stringent behavioral selection of the subjects for their capacity to perform MI is used to exclude any patient unable to perform adequately.

Methods

Subjects
Twenty patients (6 female; mean age, 66±8.8 years) with first-ever subcortical stroke (nadir hand power ≤2/5 Medical Research Council scale) were prospectively recruited. Exclusion criteria consisted of: carotid artery stenosis/occlusion, persistent language deficit, neglect/inattention, significant renal/liver disease, treatment with selective serotonin reuptake inhibitors/benzodiazepines, visual impairment, depression, left-handedness, significant small vessel disease on routine CT, and contraindications to MRI. Seventeen age-matched control subjects (9 males) aged >40 years (mean, 57.6±8.5 years) were recruited through local advertisement. Control subjects had no history of medical disorders and were not taking regular medication.

All subjects were right-handed (assessed by the Edinburgh scale[23]), gave written consent in accordance with the Declaration of Helsinki, and the protocol was approved by the regional ethics committee.

Behavioral Battery
All subjects were assessed with a behavioral battery termed chaotic motor-imagery assessment and excluded if they failed. This battery comprises 3 components, the combination and sequence of which is crucial in preserving the underlying cognitive assumptions. Chaotic

motor imagery is defined as an inability to perform MI accurately or, if having preserved accuracy, the demonstration of temporal uncoupling.[14] For MI tasks, subjects were instructed (1) to perform first-person MI; (2) not to view the scene from the third person; and (3) not to count or assign numbers or tones to each finger.

Component 1: Hand Rotation
Subjects were presented with 96 picture cards of hands—4 different views, 12 rotations (30° steps), left and right[24]—with their hands resting on their lap and asked to respond whether the presented picture was of a left or right hand. This task aims to provide an objective measure of an individual's implicit ability to perform MI; it is widely accepted to activate the MI network.[25] Subjects were excluded if they scored below 75%.

Component 2: Pseudo-Functional Magnetic Resonance Imaging Paradigm
The subjects were taught an auditory-paced (1 Hz) finger–thumb opposition sequence (2, 3, 4, 5; 2, 3, …) using ME, which alternated with periods of rest in a block design similar to the fMRI paradigm. Once executed performance was perfect, it was repeated using MI of the same finger sequence. To monitor compliance, the block-length was varied pseudorandomly and the subject asked to confirm finger position within the sequence at the end of each pseudoblock by touching the appropriate "stop" finger.

Component 3: Alternative Cognitive Strategies
A subject may correctly perform Component 2 by using an alternative cognitive strategy such as counting. To detect this confound, a task based on Fitt's law (ie, speed/accuracy tradeoff) was adapted.[21] Subjects were asked to perform the same auditory-paced finger-opposition sequence (2, 3, 4, 5; 2, 3…) of the right hand using ME, but the rate was gradually increased, initially 40 beats/min and increasing by 10 beats/min every 5 seconds. When the subject was no longer able to perform the task accurately, they said "stop" (confirmed visually by the investigator) triggering and recording the time, which was repeated 3 times and defined as the "break point."

The procedure was repeated using MI. Subjects were excluded if their mean break point was greater for MI compared with ME, because the cognitive strategy used did not obey the principles of motor control and thus by definition was not MI.[9]

Motor Scores
Patients with stroke who passed the chaotic motor-imagery assessment went on to undergo a detailed motor battery within 24 hours of the fMRI, including the National Institutes of Health Stroke Scale, Action Research Arm Test, Motricity Index, and documentation of maximum thumb–index finger taps over 15 seconds. Mirror synkinesia were also recorded.

Vasomotor Reactivity
Patients with stroke underwent transcranial Doppler to assess vasomotor reactivity with 30 seconds of breathholding.[26]

Functional Magnetic Resonance Imaging

Motor (Imagery) Paradigm
The fMRI was a block design with pseudorandom block length of the auditory-paced (1 Hz) finger–thumb opposition sequence (2, 3, 4, 5; 2, 3, …) alternating either MI or ME with rest for each hand. To monitor compliance during the MI task, the block length was covertly varied as stated previously. Subjects were instructed to keep their eyes closed throughout. Finger movements during scanning were monitored using individually calibrated, highly sensitive bilateral fiberoptic gloves (Fifth Dimension Technologies, SA) worn throughout the session; the signal was continuously monitored in the control room for noncompliance, ie, overt movement, and recorded on a personal computer. Like in Component 3 of the chaotic motor-imagery assessment, the subject confirmed their finger position within the sequence at end of each MI block by touching the appropriate "stop" finger (monitored in the control room through the fiberoptic gloves).

Table 1. Chaotic MI Assessment: Control Group

Subject	Age, years	Hand Rotation, Percent Correct	Pseudo-fMRI	Break Point MI−ME, %	MIS Right	MIS Left
C1	72	91	√	−50	7	7
C2	41	97	√	0	6	5
C3	45	91	√	−28	6	4
C4	70	93	√	−5	5	5
C5	60	94	√	−9	6	6
C6	65	88	√	−30	7	7
C7	54	86	√	−24	5	4
C8	52	94	√	−25	6	6
C9	62	99	√	−25	4	4
C10	50	90	√	−69	7	7
C11	50	100	√	−43	4	3
C12	60	100	√	−44	5	4
C13	53	95	√	−18	5	4
C14†	64	95	√	+32	n/p	n/p
C15†	63	88	√	+15	n/p	n/p
C16*	62	73	n/p	n/p	n/p	n/p
C17*	57	67	n/p	n/p	n/p	n/p

*Excluded due to poor hand rotation.
†Excluded due to incompatible break point.
n/p indicates not performed.

The sessions were counterbalanced (ie, right/affected versus left/nonaffected); however, because activation patterns during MI may be unduly influenced if preceded immediately by ME,[27] ME was performed after MI. At debriefing, subjects rated the difficulty of MI performance on a 7-point scale, Motor Imagery Score (MIS)—the easier the task, the higher the score.[28] The MIS were compared between groups using the Mann-Whitney test.

Data Acquisition
A 3-T Brucker system was used to acquire both T2-weighted and proton-density anatomic images and T2*-weighted MRI transverse echoplanar images ($64 \times 64 \times 23$; field of view $20 \times 20 \times 115$; 23 slices, TR=1.5 seconds, TE 30 ms; voxel size $4 \times 4 \times 4$ mm). To allow the subject to respond (ie, finger position) during the MI sessions, the total number of volumes acquired varied during each session; these volumes were identified and removed from further analysis for a total of 60 volumes acquired for each condition.

Image Processing
Each task acquisition was processed separately using Statistical Parametric Mapping software (SPM5; www.fil.ion.ucl.ac.uk/spm) after the first 12 volumes were discarded to allow for T1 equilibration effects. Images were corrected for slice-timing and then realigned and "unwarped." No subject moved more than 2 mm. The images were transformed into the standard space of the Montreal Neurological Institute MRI template, which is in Talairach and Tournoux space. Due to the small subcortical infarcts studied (Supplemental Figure I, available online at http://stroke.ahajournals.org), the lesions were not masked during normalization. The images were smoothed using a 12-mm Gaussian filter as required by random field theory.

Regions of Interest and Masks
Based on our hypotheses, all analyses concerned only the cortical motor areas, ie, dorsal premotor (PMd), supplementary motor area (SMA), BA4a, and BA4p. The regions of interest (ROIs) used were based on Eickhoff's probabilistic cytoarchitectonic maps.[29] The probability given for each voxel directly reflects the overlap among 10 postmortem brains and thus is in increments of 10%. Few voxels overlap in all 10 subjects, meaning for BA4, only a small percentage of voxels exceed 60% probability.

The voxel-based analysis was performed within the mask made by the summation of BA4a, BA4p, and BA6 (includes PMd and SMA) ROIs.[29] Cytoarchitectonic maximum probability maps, ie, where voxels are assigned to one cortical area, were used to produce a continuous nonoverlapping binary parcellation of the motor system. BA6 ROI was split according to anatomic constraints into SMA and PMd using the superior frontal sulcus as used in the Anatomical Automatic Labeling (AAL) atlas. Ventral Premotor Cortex (PMv) was removed to leave PMd by removing areas below the superior frontal gyrus (z=+54 mm) as implemented in previous studies[4,30] based on prior work.[31] These ROIs were used for the LI analysis.

Voxel-Based Mapping
Single-subject fixed-effect analysis generated a contrast image for each task, which was then used for second-level (random effect) analysis in a factorial design.

Contrasts were performed within the previously mentioned mask ($P<0.05$ family-wise error–corrected). Contrasts assessed were (1) task versus rest for each task and hand (and interaction); (2) between-group comparison for each task and hand; (3) within-group comparison of MI versus ME for each hand; and (4) between-group comparison of MI versus ME for each hand. The coordinates were labeled using the probabilistic cytoarchitectonic maps.[29]

Before processing, the images were flipped for patients with a nondominant hemisphere stroke (n=4) so that the affected hemisphere is the left. To compensate, 4 control subjects were randomly selected and their images flipped. Because the majority of subjects used their right hand, it is still referred to as right-hand tasks.

Weighted Laterality Index
We examined the weighted LI for BA4a (wLI_{BA4a}), BA4p (wLI_{BA4p}), and PMd (wLI_{PMd}) as it has been well established that hemispheric activation balance can be more sensitive to subtle

Table 2.   Chaotic MI Assessment: Patients With Stroke

Subject	Hand Rotation, Percent Correct	Pseudo-fMRI	Break Point MI−ME, %	MIS Affected	MIS Nonaffected
S1	82	√	−24	2	4
S2	91	√	−14	6	6
S3	93	√	−1	5	6
S4	89	√	−42	4	4
S5	95	√	−67	5	4
S6	93	√	−26	2	4
S7	85	√	−20	4	4
S8	100	√	−21	4	3
S9	93	√	−15	6	6
S10	94	√	−6	6	6
S11	77	√	−19	6	7
S12	98	√	−69	7	7
S13†	80	√	+11	n/p	n/p
S14†	88	NC	NC	n/p	n/p
S15†	90	√	+32	n/p	n/p
S16*	64	n/p	n/p	n/p	n/p
S17†	89	√	+17	n/p	n/p
S18*	59	n/p	n/p	n/p	n/p
S19†	83	√	+260	n/p	n/p
S20†	99	√	+12	n/p	n/p

*Excluded due to poor hand rotation.
†Excluded due to incompatible break point.
n/p indicates not performed.
NC indicates not completed due to excess movement.

alterations in activation patterns than voxel-based mapping and can show important correlations with residual clinical deficit.[2–6] This was performed using a previously described method, which normalizes for intersubject variations in global fMRI signal and reduces the chances of floor or ceiling LIs.[4] The basic formula that underlies the calculation is:

$$wLI = \left(\sum t_{LH} - \sum t_{RH}\right) / \left(\sum t_{LH} + \sum t_{RH}\right)$$

$\sum t_{RH}$ = sum of the t-value within the ROI in the right hemisphere; and

$\sum t_{LH}$ = sum of the t-value within the ROI in the left hemisphere.

The wLI would be +1 in exclusively left-hemisphere activations and −1 if exclusively right-sided. Wilcoxon tests were used to compare wLI within groups, Mann-Whitney for between-group comparisons, and Spearman for correlations with motor scores. A priori we hypothesize that the wLI for the affected hand tasks would positively correlate with motor scores.[4,6,32]

Results

The behavioral assessment results are shown in Tables 1 and 2 and the patients demographics in Table 3. Four control subjects and 8 patients with stroke were excluded because of chaotic motor imagery. The remaining subjects performed adequately on the chaotic motor-imagery assessment and there was no difference between the stroke group and control subjects. Representative T2-weighted scans are shown in Supplemental Figure; some had mild small vessel disease. The transcranial Doppler-assessed vasomotor reactivity was normal in all with a temporal window. Motor scores (Table 4)

documented a high level of performance on all motor scores, although most patients did exhibit some degree of upper-limb impairment.

Functional Magnetic Resonance Imaging

All patients performed the ME and MI fMRI paradigm without errors or evidence of noncompliance. There was no significant difference in MIS between groups and no significant effect of MIS when entered into the fMRI model for any contrast.

Activation Maps

The regions activated for the right hand of control subjects and affected hand of patients during ME and MI are shown in Table 5 (peak voxels), and the clusters are overlaid on a standard MRI in Figure 1.

During ME in the control subjects, there was activation of the contralateral BA4a and 4p, SMA, and PMd and to a lesser extent of similar ipsilateral areas. The pattern was similar for the affected hand of patients. During MI, the magnitude of activation was less overall than during ME in both control subjects and patients. In control subjects, the activation involved similar areas as ME, whereas in patients, the activation pattern of BA4 and PMd was clearly more bilateral than in either control subjects or during ME (Table 5; Figure 1). There was no interaction between task×hand for either group.

Table 3.   Patients With Stroke: Clinical Data

Patient	Age, years	Sex	Affected Hand	Site of Lesion	Stroke Syndrome	PMH	Medication
S1	58	F	L	R SC	R Lac	Smoker	Asp, statin
S2	70	F	R	L Pons	L Lac	HT, chol	Diuret, ACE(I), Asp, ß-blocker
S3	80	M	L	R IC	R PACS	Nil	Asp, statin
S4	46	M	R	L SC	L PACS	Chol, smoker, FH	Asp, ACE(I), statin
S5	56	M	R	L SC	L Lac	Chol, smoker, FH	Asp, PPI, statin
S6	66	M	L	R IC	R Lac	Chol, smoker, HT	Asp, statin, ACE(I), diuret
S7	70	M	R	L SC	L Lac	Smoker	Asp
S8	66	F	R	L IC	L Lac	Chol, HT	Asp, Ca2 blocker
S9	73	F	L	R.Thal.H	R Lac	HT	Diuret, ACE(I), Ca2 blocker
S10	74	M	R	L SC	L Lac	Chol	Asp, statin
S11	70	M	R	L SC	L Lac	Chol, Smoker, HT	Asp, statin
S12	81	M	R	L.SC	L Lac	Nil	Asp, ß-blocker, Ca2 blocker
S13	73	M	R	L SC	L Lac	Chol, HT, AF	AgII, clopdl, statin
S14	63	F	R	L SC	L Lac	DM	Asp, statin, gliclizide
S15	62	M	R	L SC	L Lac	FH, HT	Asp, statin, ACE(I)
S16	80	M	R	Nil*	L Lac	DM,AF	Asp, statin, metformin
S17	62	M	L	R IC	R Lac	Smoker, Chol, HT	Asp, statin
S18	61	F	L	R IC	R Lac	Chol, DM, FH	Aspirin, statin
S19	65	M	R	L Thal	L Lac	Chol	Aspirin, statin
S20	60	M	R	L IC	L Lac	Smoker, Chol, HT	Asp, statin, diuret

*CT performed <3 hours.

F indicates female; M, male; L, left; R, right; FH, positive family history; HT, hypertension; Chol, hypercholesterolemia; DM, diabetes mellitus; AF, atrial fibrillation; Lac, lacunar syndrome; PACS, partial anterior circulation syndrome; IC, internal capsule; SC, subcortical; Thal.H, thalamic hemorrhage. Asp, aspirin; AgII, angiotensin II receptor antagonist; Clopdl, clopidogrel; diuret, thiazide diuretic.

The findings for the left hand of control subjects and the nonaffected hand of patients were similar to those for the right hand in control subjects (Supplemental Table I, available online at http://stroke.ahajournals.org).

Direct Comparison Between Patients and Control Subjects

Directly contrasting control subjects with patients showed no significant difference for either task or hand despite the appar-

Table 4.   Patients With Stroke: Motor Scores

Patient	TSS, days	TIT Ratio	NIHSS/42	ARAT/57	Motricity Index (arm)/100	Motricity (arm+leg+trunk)/300
S1	9	0.71	1	57	100	300
S2	132	0.78	0	57	77	269
S3	217	0.65	2	57	92	268
S4	132	0.68	1	57	100	300
S5	703	1.20	1	57	100	300
S6	182	0.79	1	57	100	292
S7	7	0.67	4	57	93	269
S8	7	0.94	0	57	100	300
S9	291	0.73	1	57	84	284
S10	7	1.09	0	57	100	300
S11	173	0.56	1	49	84	268
S12	198	1.16	0	57	100	300

Only patients with stroke who passed the chaotic MI assessment went on to undergo a detailed battery of motor scores, including ARAT (Action Research Arm Test), NIHSS (National Institutes of Health Stroke Score, motricity index, TIT (maximum thumb–index taps in 15 seconds. Mean time since stroke (TSS) was 171 days. The subjects showed a high level of performance on all motor scores; median NIHSS score 1, median ARAT of 57, mean motricity score (arm+leg+trunk) of 287; motricity (arm) 94; mean thumb–index tapping (maximum no. of taps in 15 seconds) affected/nonaffected ratio (TIT ratio) 0.83. No subject exhibited mirror synkinesia.

Table 5. Voxel-Based SPM Analysis

Task	Cluster	T-Value	x	y	z	Location		Task	Cluster	T-Value	x	y	z	Location	
Right hand in control group															
Executed movement	6950	11.41	−34	−12	52	L	PMd (60%)	Motor imagery	4603	7.74	−30	−10	56	L	PMd (50%)
		11.19	−44	−18	54	L	BA4a (60%)			7.24	−6	4	56	L	SMA (70%)
		9.09	−4	0	54	L	SMA (80%)			6.96	40	0	52	R	PMd (60%)
		6.94	38	−28	52	R	BA4p (90%)			6.71	−32	−12	48	L	BA4a (50%)
		6.83	44	−16	56	R	PMd (50%)			6.25	−36	−30	48	L	BA4p (60%)
		6.69	40	−24	52	R	BA4a (50%)			6.21	−36	−10	44	L	PMd (40%)
		6.18	−52	−10	36	L	BA4p (70%)			5.29	38	−28	52	R	BA4p (90%)
		4.88	14	−6	56	R	SMA (40%)			5.13	−48	−14	38	L	BA4p (70%)
Affected hand in stroke group															
Executed movement	1308	7.46	−44	−18	54	L	BA4a (60%)	Motor imagery	2953	6.94	36	−6	52	R	PMd (50%)
		7.02	−42	−6	56	L	PMd (80%)			6.2	−4	8	54	R	SMA (70%)
	1087	6.15	−2	−2	56	L	SMA (80%)			5.85	42	−12	48	R	PMd (50%)
	468	5.94	42	−10	56	R	SMA (60%)			5.07	−30	−6	58	L	PMd (50%)
		4.28	30	−34	52	R	BA4p (60%)			4.87	−24	−6	62	L	PMd (50%)
		4.18	38	−28	52	R	BA4p (90%)			4.45	−42	−8	44	L	BA4a (40%)
		4.09	50	−14	46	R	BA4a (50%)			4.1	54	−4	34	R	BA4a (50%)
										3.99	54	−10	34	R	BA4p (70%)

ently lower t-value in the stroke group (Table 5). To ensure that this result was not secondary to the conservative threshold used, the percent signal change within the ipsilesional BA4a, BA4p, and PMd ROIs during both tasks was contrasted, and again no significant difference was found (data not shown).

Direct Comparison Between Motor Imagery and Motor Execution

In control subjects, the direct ME>MI contrast for the right hand revealed a single cluster (183 voxels; Figure 1C) with peaks within both PMd and BA4a (PMd: T=4.98, x=−44, y=−22, z=64, probability 60%; BA4a: T=4.69, x=−44, y=−16, z=52, probability 50%). In contrast, this analysis disclosed no significant voxels when applied to the affected hand of patients (Figure 1F). There were no significant findings with the reverse contrast in either group.

Regarding the left hand of control subjects and the nonaffected hand of patients, the results of these contrasts were almost identical to the right hand of control subjects (data not shown).

Direct Comparison of Motor Execution>Motor Imagery Between Patients and Control Subjects

Comparing [ME>MI] for the control subjects over [ME>MI] for the patients revealed a single cluster (15 voxels) in PMd (T=4.23, x=−32, y=−14, z=52, probability 50%). There were no significant findings for the reverse contrast.

Weighted Laterality Index and Clinical Correlations

In keeping with the voxel-based analysis suggesting more bilateral activation during MI of the affected hand in patients than in control subjects, there was a significant reduction in the wLI_{BA4p} in the former (median [range], 0.35 [−0.96 to 0.78] and 0.52 [−0.06 to 0.99], respectively; $P<0.05$, Mann-Whitney; Figure 2A) with a similar trend for wLI_{PMd} (0.17 [−0.48 to 0.52] and 0.40 [−0.08 to 0.76], respectively; $P=0.084$, Mann-Whitney) and no significant difference for wLI_{BA4a} (0.12 [−0.33 to 0.78] and 0.37 [−0.29 to 0.91], respectively).

There was a significant positive correlation between the wLI_{BA4p} during MI of the affected hand and the motricity (arm) scores (rho=0.610; $P<0.05$), ie, the better the recovery, the more physiological the activation balance (Figure 2B). To explore the nature of this shift, a correlation analysis for was performed on the percent signal change data, which showed a significant positive correlation (rho=0.656, $P<0.05$) between this motor score and ipsilesional BA4p such that the better the recovery, the greater the activation within this region (Figure 2C).

In contrast, there was no significant difference between patients and control subjects for any ROI during ME of the affected hand nor for MI or ME of the nonaffected hand (data not shown).

Discussion

In this sample of well-recovered patients with subcortical stroke, we found that MI of the affected hand not only
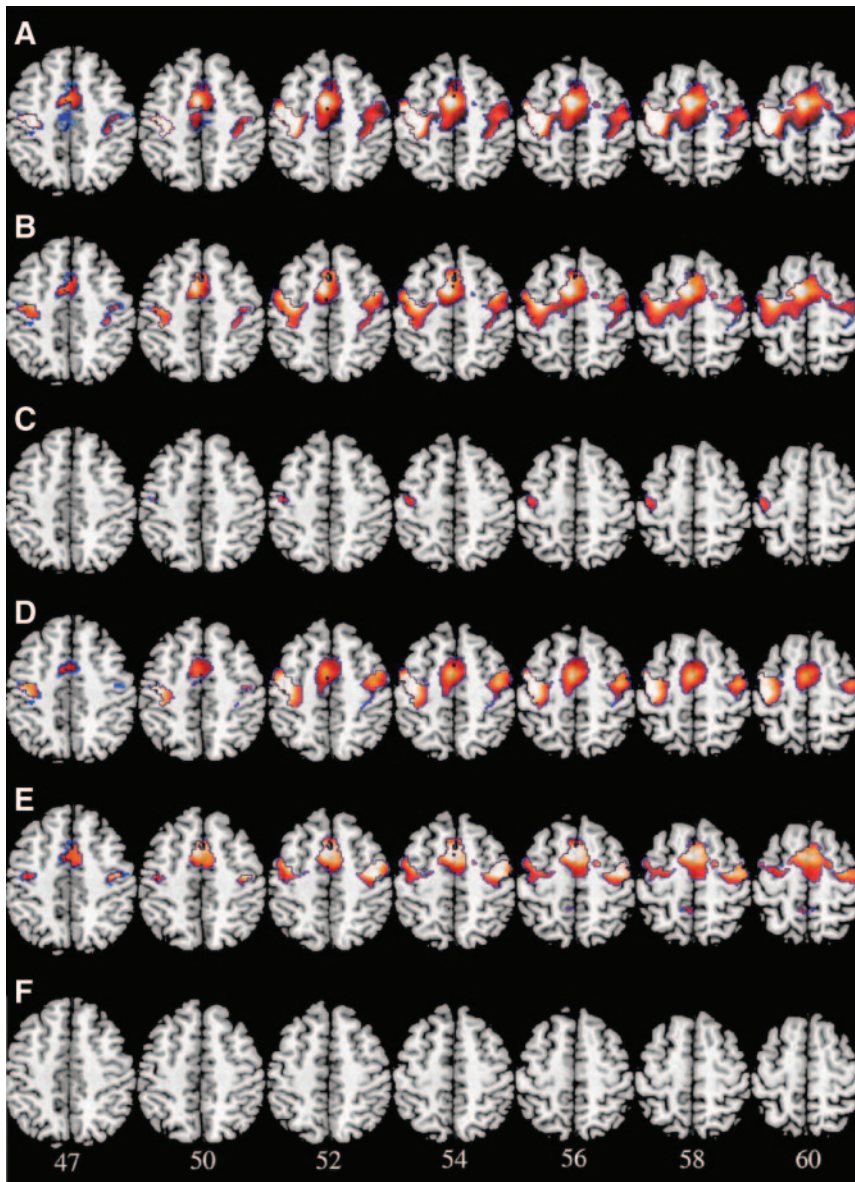
Figure 1. Voxel-based analysis for control subjects (A–C) and patients (D–F). A, right-hand ME; (B) right-hand MI; (C) right-hand ME>MI; (D) affected-hand ME; (E) affected-hand MI; (F) affected-hand ME>MI.

activated cortical motor areas, including BA4, but also highlighted disorganization of the motor network, notably more bilateral involvement of BA4p with a similar trend for PMd. This is in contrast to ME, which was associated with essentially normal activation patterns, although the presence of subtle differences escaping our extensive analysis cannot be excluded. For BA4p, the degree of hemispheric imbalance was less pronounced with better motor recovery, which was mediated largely by increased activation of ipsilesional BA4p. Thus, the cortical motor network can remain significantly disorganized during MI, although the activation pattern during the same but executed movement is unremarkable.

Including 4 patients whose nondominant hand was affected may have introduced a bias not fully compensated by image "flipping" of 4 control subjects. We therefore repeated the wLI analysis removing these subjects. For the remaining 8 patients with stroke, the difference between wLI_{BA4p} during MI persisted (Mann-Whitney $P=0.036$) as did the correlation with the motricity (arm) index ($P=0.008$, rho=0.846).

Driven by our hypothesis (see the beginning of this article), we used a cortical motor network mask including BA4, SMA and PMd. However, because other areas are known to be involved in MI,[14] we also performed post hoc whole-brain analysis (family-wise error $P<0.05$) of MI of the affected hand. In keeping with reports in normal volunteers,[14] this demonstrated activation of the bilateral superior and inferior parietal lobe, globus pallidus, and BA44. The ventral aspect of BA6 (ie, PMv) was not activated, contrary to motor imagery tasks involving a visual focus.[25,33]

We have shown that appropriate screening for MI abilities is important in proof-of-principle studies with small subject numbers, particularly because those excluded did not appear clinically distinct. Previous behavioral studies excluded subjects based on lesion location,[19,20] which our data suggest is not optimal. We used fiberoptic gloves during the fMRI session, rather than electromyography, because they allowed real-time monitoring for subtle movement and for subjects' responses.[16] The only previous study to examine the neural
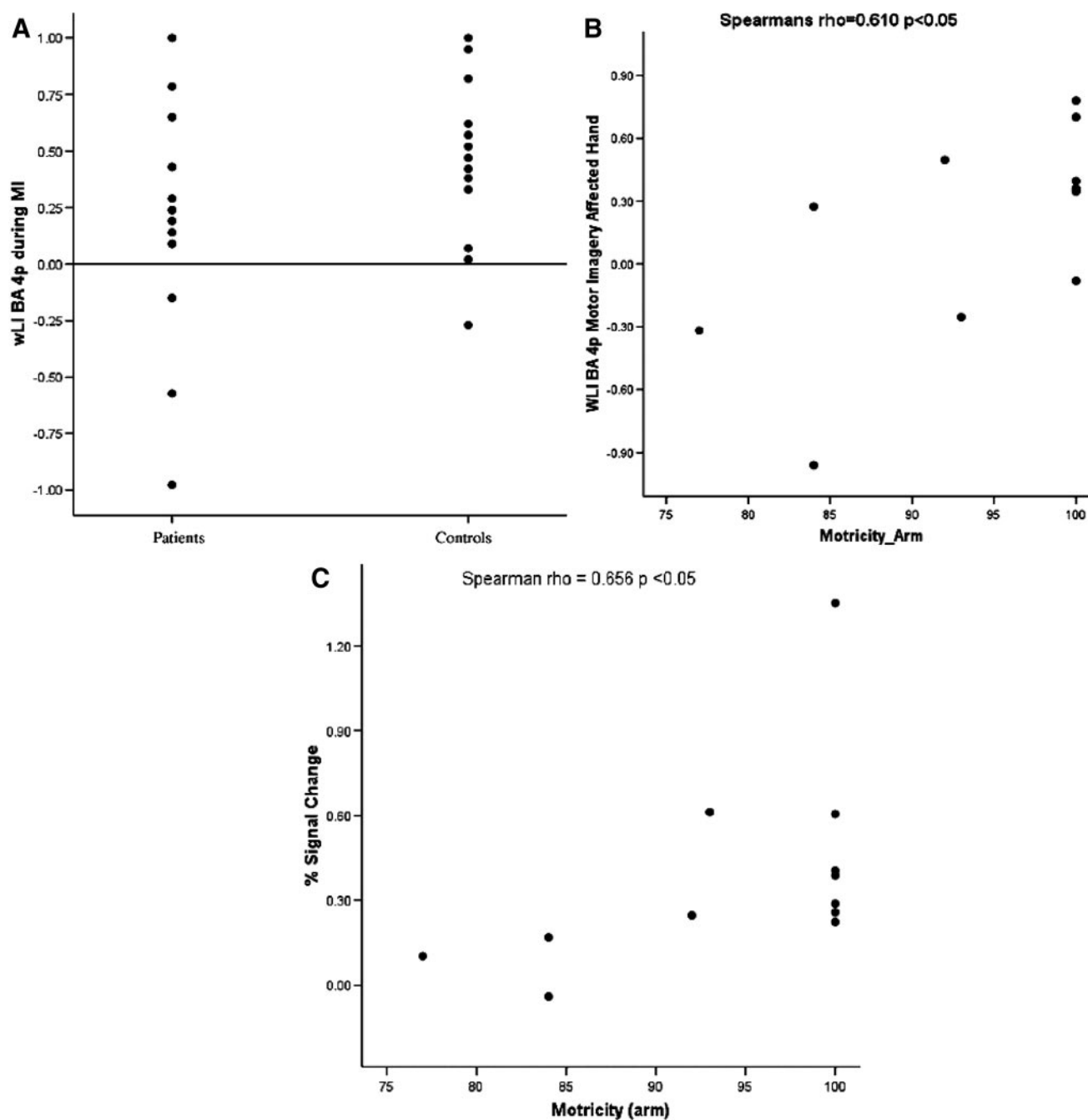
Figure 2. A, Individual wLI$_{BA4p}$ results in control subjects and patients. B, Correlation (Spearman's) between wLI$_{BA4p}$ versus motricity (arm) score. C, Correlation (Spearman's) between percent signal change in ipsilesional BA4p versus motricity (arm) score.

substrates of MI in stroke[34] reported on just 7 patients who all had cortical lesions (including BA4), whereas no MI screening or monitoring was used, making the results difficult to interpret.

We found that BA4 is involved during MI in patients with stroke. This is in keeping with this previous study,[34] despite its just-mentioned limitations. Because BA4 is an important node in motor learning, this finding strengthens the rationale for applying MI training to more severely affected patients with stroke. In keeping with this idea, a recent Phase 2 study of MI training on 32 partially recovered patients with chronic stroke showed encouraging results.[18]

Our finding of reduced BA4 activation during MI relative to ME for both the control group and the nonaffected hand of patients is consistent with studies in healthy volunteers.[14,16] Yet no such difference was found for the affected hand. Several explanations for this negative result are unlikely. For instance, it could be related to differences in task difficulty and/or MI performance, but if this was true, there should be similar results for the nonaffected hand, and these differences should be reflected in the chaotic motor-imagery assessment or MIS, which was not the case. A second possibility would be that BA4 activation was reduced during ME, but given the extensive analysis, this should have been picked up as a

difference to control subjects. So the most plausible explanation is that it is BA4 function during MI that is at fault. This in turn raises 2 questions: What is the role of BA4 during MI? Why does it appear to behave differently after stroke?

It has been suggested that during MI, the executive component of BA4 is suppressed by premotor areas.[35] Accordingly, patients with spinal cord injury demonstrate overactivation of BA4 during MI,[28] presumably because BA4 no longer requires suppression, although this finding was not replicated in a recent study.[36] The lack of significant findings with the ME task goes some way against this interpretation. In contrast, the function of BA4 during MI may be nonexecutive,[14] an increasingly recognized notion. For instance, direct cellular recording[37] taken during MI in primates, suggests that BA4 is involved in the storage of spatial information.

In keeping with our hypothesis, BA4 hemispheric balance was impaired during MI of the affected hand, whereas it appeared preserved during ME. Hemispheric imbalance during ME consistently correlates with motor recovery[1–4] and can be influenced by rehabilitation.[6] Hence, our finding that the wLI_{BA4p} during MI correlates with motor recovery is in keeping with the wider literature. Furthermore, the wLI behaved as it does in ME in more severely affected patients, ie, the better the recovery, the more physiological the balance. Note, however, that no previous study of ME had examined BA4a and BA4p separately. In our sample of well-recovered patients, the wLI_{BA4p} during ME of the affected hand appeared intact, further emphasizing that hemispheric balance and activation patterns can be influenced by the motor task.[12]

Our data further suggest that it is ipsilesional BA4p activation that modulated the shift in hemispheric balance during MI, ie, better recovery was associated with increased recruitment of ipsilesional BA4p. This is in contrast to findings with ME that show greater activation of contralesional BA4 with poorer recovery.[4] Each subdivision of BA4 has a distinctive cytoarchitecture and receptor density[22] and is likely to perform distinct functions. In contrast to BA4a, BA4p is modulated by attention.[22,38] Our findings may therefore represent an increased attention to MI of the affected hand after stroke,[7,22,38] If so, however, one would expect the reverse correlation, ie, the poorer the recovery, the greater the BA4p activation. A more plausible explanation is that BA4p is involved in encoding spatial components of movement "upstream" from execution that could be specifically targeted during rehabilitation. The integrity of the cortico-spinal tract can modulate BA4p during ME,[8] but whether this is a direct result of the executive process or a consequence of increased demand on spatial encoding in the presence of a lesion remains unclear.

What of BA4a? It is conceivable that modulating BA4a, not BA4p, during rehabilitation is the most important to motor recovery, which should be addressed in future work. Finally, our results also suggest that the cortical disorganization during MI may also extend to PMd, which is important for MI-based rehabilitation because PMd is of functional relevance after stroke.[32,39]

To conclude, our results indicate that ipsilesional BA4 is involved during MI in well-recovered patients with subcortical stroke, and this is encouraging with respect to the potential effects of MI training. Studies specifically assessing patients who are unable to move their affected limbs are required to determine whether our findings also apply to the early stage of stroke recovery.

Sources of Funding

Disclosures

None.

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