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Dynamics of Motor Network Overactivation After Striatocapsular Stroke

A Longitudinal PET Study Using a Fixed-Performance Paradigm

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Background and Purpose—Although excessive brain activation during affected hand motion after stroke is well documented, its time course has been rarely studied, and when studied, this has either been with passive movement or with active but cognitively complex task and uncontrolled performance over time, complicating interpretation.

Methods—According to a prospective and longitudinal design, we studied 5 right-handed patients with right-sided hemiparesis due to first-ever left striatocapsular infarction. Three-dimensional PET H_2O^{15} studies were performed twice (≈7 and ≈31 weeks after stroke [PET1 and PET2, respectively]) during right thumb-to-index tapping executed at the same rate in both studies (1.26 Hz, auditory cued). With SPM96 software, significant group and individual overactivations ($P<0.05$, corrected for multiple comparisons) were computed by comparison with a group of 7 healthy age-matched right-handed control subjects performing the same task.

Results—Motor recovery was significant from PET1 to PET2. Both the group and individual analyses revealed striking overactivations at PET1, affecting notably the cortical hand area and the whole motor network bilaterally. These overactivations were less prominent at PET2 over both hemispheres, not only in terms of *Z* score but also in terms of spatial extent (almost reaching statistical significance in the affected hemisphere for the latter, $P=0.09$). However, new overactivations were found at PET2 in the left prefrontal areas, the putamen, and the premotor cortex.

Conclusions—This study is the first to document that to perform the same simple movement of the paretic fingers, the brain with subcortical infarction shows less overactivations at the late than at the early timepoint, especially on the affected side, suggesting reduced recruitment of affected-hemisphere motor networks. However, unaffected-hemisphere prefrontal, premotor, and putaminal overactivations, observed at PET2 only, may suggest late-appearing compensatory reorganization. **(*Stroke*. 2001;32:2534-2542.)**

Key Words: cerebral blood flow ■ motor activity ■ recovery of function ■ subcortical infarction ■ tomography, emission computed

Reorganization of the motor system after stroke such as assessed by functional neuroimaging has been the subject of considerable interest lately. Studies with PET or functional MRI (fMRI)[1–9] have used finger tasks known to normally elicit relevant activation of motor networks.[10–12] To facilitate comparison with control subjects, these investigations initially concerned only fully recovered patients, the assumption being that differences in activation patterns would tell us how the damaged brain has adapted to the lesion. Enhanced bilateral activation of motor pathways and recruitment of additional sensory and secondary motor structures not normally involved in the task have been reported after striatocapsular stroke.[1–3] In patients with sensorimotor cortex infarcts, the finding of strong perilesional activation[4] suggests reorganization/unmasking of sensorimotor maps similar to that described in monkeys after partial damage to the primary motor cortex.[13] However, most of these studies concerned patients investigated at a single timepoint after they reached full recovery, leaving open the possibility of potentially important dynamic changes in the pattern of excessive activation over time. To assess this issue, longitudinal studies in still recovering patients are necessary. Only 2 such studies, both involving subcortical strokes, have appeared in the literature so far.[8,9] In the study of Nelles et al,[8] in which 2 PET studies were performed in the acute-subacute stage, the activation paradigm consisted of passive movement of the paretic arm, which does not mimic the real-life situation of willed action. Interestingly, however, and despite the presence of motor deficit, a pattern of overactivations in motor and nonmotor areas similar to that found in earlier studies of recovered patients was observed. Regarding the time course, the results demonstrated decreases in activation

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in motor as well as in nonmotor areas mainly over the lesioned hemisphere, with only 1 area of mild activation increase in the affected-side premotor cortex. However, neither single-subject analyses nor direct comparisons with control subjects were carried out, whereas the comparison between the 2 PET studies may be affected by changes in the resting cerebral blood flow (rCBF) pattern. Marshall et al[9] studied patients in the acute (1 week) and chronic (3 to 6 months) stages using a complex self-paced motor task and reported early contralesional primary sensorimotor cortex (SM1) hyperactivity evolving to late ipsilesional hyperactivity. However, because the actual performance was not fixed (with some patients not even being able to perform the task at the first study), these changes from the acute to the chronic stage might merely represent differences in performance. In addition, the motor task used is known to be particularly difficult to perform and last to recover after stroke, and in addition, it might involve elaborate compensatory strategies (ie, cognitive). Finally, in most of the studies, the control subjects were not matched for age to the patients, which may complicate interpretation of the results.[14]

To study the temporal changes in brain overactivations after striatocapsular stroke and avoiding the above limitations, we designed a prospective longitudinal PET investigation of still-recovering patients. We used a simple motor task according to a fixed-performance paradigm and compared the data for patients with that for age-matched control subjects according to both group and individual analyses.

Subjects and Methods

Patients and Control Subjects

Patients

Enrollment was prospective and based on strict criteria as follows. Inclusion criteria consisted of right-handedness (based on the calculation of the laterality quotient [LQ] of the Edinburgh Inventory test[15]), age of 45 to 75 years, and first-ever subcortical ischemic stroke. Exclusion criteria consisted of complete recovery by 15 days after stroke onset; aphasia, cognitive impairment, neglect, or depression sufficient to impair full cooperation into the study; carotid artery occlusion or hemodynamically significant stenosis at ultrasound examination; previous clinical stroke or silent stroke at admission CT scan; and intake of drugs that may interfere with recovery, such as benzodiazepine, antidepressant, and anticonvulsants. The patients were studied twice with PET, with the first study planned 3 to 6 weeks after stroke or, if not possible at 6 weeks, as soon as they were able to perform the motor task at the frequency required (see later); the repeat study took place ≈2 to 8 months later, after clear recovery had occurred (see Results).

Control Subjects

The control group consisted of 7 right-handed healthy subjects matched for age to the patients (60.4±10.6 years, 3 women and 4 men, LQ 98.8±3.2, Mini-Mental Status Examination score 29.8±0.4). They were recruited through advertisement in the local newspaper. Enrollment was based on ≥8 years of school and lack of clinical, biological, or neuroradiological abnormality, as follows: normal somatic examination (in particular, no orthopedic or rheumatological problem affecting the arms, hands, or fingers), no cerebrovascular risk factors, smoking <10 cigarettes per day, no alcohol or coffee abuse, blood pressure within normal limits, no history or evidence of neurological disease, no current use of medication (except estrogen substitution therapy in postmenopausal women), lack of significant biological abnormality (including blood cell count, liver function tests, serum electrolytes, plasma glucose, cholesterol, and triglycerides), and lack of significant change at standard MRI (including T1- and T2-weighted scans) apart from would be considered part of normal aging.

All patients and normal volunteers gave written informed consent before participation, and the regional ethics committee approved the research protocol. The consent was obtained according to the Declaration of Helsinki.

Experimental Design

PET Paradigm

The patients were studied twice (PET1 and PET2, respectively). Each PET study consisted of 8 consecutive scans (H_2O^{15} injections) under 2 conditions, each replicated 4 times and performed in pseudorandom and balanced order: (1) affected-hand thumb-to-index (TI) tapping , at a frequency of 1.26 Hz, cued with a metronome, and (2) rest with eyes closed, metronome on at the same frequency ("rest"). This frequency was chosen because it has been shown in previous PET studies of normal subjects to induce optimal activation responses[11,16]; it is neither too rapid nor too slow, which otherwise induces complex activation patterns[17,18]; and a pilot clinical study showed that recovering hemiparetic patients were able to perform the TI tapping task at this rate (authors' unpublished observations, 1998). The task lasted a total of 1.75 minutes. Each normal subject underwent the same activation paradigm as the patients, except that the task was performed with both the right and the left hand, for a total of 12 H_2O^{15} injections, during a single PET session.

All subjects were instructed in the task before the experiment and trained to perform it adequately. Visual inspection during the task showed that both patients and healthy control subjects performed the task adequately in all runs, although at debriefing, the patients expressed that some effort was needed, especially for PET1. Total whole body radiation exposure was kept below 5 mSv for both groups.

In control subjects, and as described in detail elsewhere,[14] this task induced activation mainly of the SM1, parietal operculum and anterior cingulate cortex contralaterally, and the cerebellum ipsilaterally.

Clinical, Functional Scores, and Structural Imaging Data

Each patient was assessed on 3 occasions with quantitative scales: first within 8 days of stroke onset and subsequently on the days of the 2 PET studies. We used validated scales that evaluate the neurological deficit (with the European Stroke Scale [ESS][19]) and the functional status (with the Barthel Index [BI][20]). All patients had chronic-stage structural imaging to map the final infarct.

Data Acquisition

Patients and control subjects were scanned while lying supine with their eyes closed in a darkened and quiet room. The head was gently immobilized in a dedicated headrest. Head position was aligned transaxially to the orbitomeatal line with a laser beam. Measurements of regional distribution of radioactivity were performed with an ECAT HR+ (Siemens) PET camera with full volume acquisition allowing the reconstruction of 63 planes (thickness 2.4 mm, axial field-of-view 158 mm resolution ≈4.2 mm in all directions). Transmission scans were obtained with ^{68}Ge sources before emission scans. The duration of each scan was 90 seconds. About 6 mCi of H_2O^{15} was administered as a slow bolus in the left antecubital vein by means of an automated infusion pump. Each experimental condition was started ≈15 seconds before data acquisition and continued until scan completion. The interval between injections was 7 minutes; the position of the head was controlled just before each injection.

Data Analysis

Data Transformation

All calculations and image transformations were performed on UNIX SYSTEM workstations. First, the scans of each subject were realigned to each other (AIR 3.0[21]). For subsequent data analysis, the Statistical Parametric Mapping software (SPM96; Wellcome Department of Cognitive Neurology) implemented in the MATLAB environment was

TABLE 1. Clinical Data for the Patients

Patient	Sex	Age, y	Stroke Risk Factors	Symptoms in Acute Stage	Days From Stroke		Contralateral Synkinesia	
					PET1	PET2	PET1*	PET2*
1	M	51	Hyperlipemia, smoking	Right hemiparesis, hypoesthesia	119	348	−	−
2	M	72	Hypertension, obesity	Right hemiparesis	22	155	+	−
3	F	74	Hypertension	Right hemiparesis	30	209	−	−
4	M	45	Hypertension	Right hemiparesis	53	276	+	+
5	M	54	Hypertension	Right hemiparesis	37	92	−	+

*As assessed during the 2 PET studies (see Results).

used. The images were transformed into the standard space of the Montreal Neurological Institute MRI template,[22] which is based on the atlas of Talairach and Tournoux.[23] The images were smoothed using a 12-mm gaussian filter. Anatomic/cytoarchitectonic localization of the significant activations was based on the SPM96 MRI template and Talairach's coordinates (obtained from the coordinates listed by the SPM96 software according to the linear transforms proposed by A. Meyer-Lederberg [see spm@mailbox.ac.uk]). All of the coordinates listed in the sections that follow are Talairach's coordinates.

Statistical Parametric Mapping

The PET images from all patients (both studies) and control subjects were scaled to an overall CBF grand mean of 50 mL · 100 g^{-1} · min^{-1}. We used a gray matter threshold of 80% of the whole brain mean; and covariates were centered before inclusion in design matrix. ANCOVA, using global activity as a confounding covariate, was performed on a pixel-by-pixel basis. The results of *t* statistic [SPM (t)] were then transformed into a normal standard distribution [SPM (z)]. To compare the activations induced by the motor task between patients and control subjects, we performed factorial 2×2 analyses, that is, $[(\text{TI tapping}-\text{rest})_{\text{patient}}$ versus $(\text{TI tapping}-\text{rest})_{\text{control}}]$, both individually and for the whole group and for PET1 and PET2, separately. Only overactivations (ie, the [patients>control subjects] contrast) were considered. All statistical maps were thresholded at $Z>3.09$ voxel level ($P<0.001$, uncorrected for multiple comparisons) with the statistical significance set at $P<0.05$ (cluster level), corrected for multiple comparisons.

Results

Clinical Data

Five right-handed patients (age 59.2±13 years [mean±1 SD], 1 woman and 4 men, LQ 92.6±11.1) were enrolled (Table 1). Four had hypertension, and none had diabetes mellitus. They all had right hemiparesis from left striatocapsular infarction (Figure 1), as documented by chronic-stage structural imaging (MRI in patients 1, 3, and 5 and CT in patients 2 and 4 who had major contraindication to MR, ie, ferromagnetic orthopedic device). Structural imaging did not reveal evidence for significant chronic small vessel disease such as lacunes and leukoencephalopathy. Contralateral synkinesia (mirror movements) were observed in patients 2 and 4 at PET1 and in patients 4 and 5 at PET2 (Table 1). The clinical scores obtained 9±6 days after stroke ("Initial") and at PET1 (52±39 days) and PET2 (216±101 days) are shown in Table 2. There was a significant recovery of ESS and BI from Initial to PET1 and from PET1 to PET2 assessments, except for the BI (Initial to PET1) comparison.

PET Results

Because all 5 patients had right-sided hemiparesis, the motor task was right TI tapping in each case. The comparison with control subjects was therefore with right TI tapping.

Group Analysis

Significant overactivations in the patient group concerned (1), at PET1, in the bilateral SM1 (with caudal extension on the affected side) and inferior parietal lobule, the unaffected-hemisphere SMA proper, and the affected-hemisphere superior parietal lobule and insula, and (2), at PET2, the affected-side SM1 and the unaffected-side PM cortex (Table 3 and Figures 2 and 3).

Individual Analysis

PET1

Significant overactivations were observed in 4 of the 5 patients (patients 1, 2, 3, and 4) but with different patterns across subjects (Table 4 and Figure 4). Overactivation of the SM1 hand area was present bilaterally in patients 2 and 4, both of whom had mirror movements during the PET study, and in the affected hemisphere in patient 1, with caudal

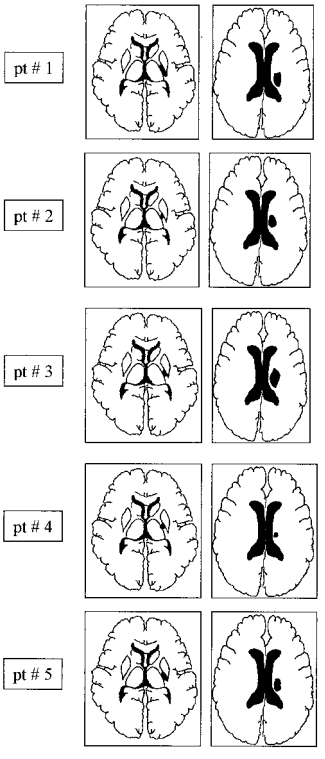

Figure 1. Localization of the subcortical infarct in each patient. This diagram is based on the structural neuroimaging obtained in each patient (MR for patients [pt #] 1, 3, and 5, CT scan for patients 2 and 4; see Subjects and Methods for details).

TABLE 2. ESS and BI for the Three Evaluations

	ESS			BI		
Patient	Initial	PET1	PET2	Initial	PET1	PET2
1	62	86	92	30	80	100
2	75	80	91	55	55	100
3	59	73	85	35	35	90
4	52	72	82	35	65	95
5	50	73	75	45	80	90
Mean±SD	60±10	77±6*	85±7†	40±109	63±17‡	95±5†

Normal value 100.
*$P<0.01$ vs Initial, paired *t* test.
†$P<0.02$ vs PET1, paired *t* test.
‡P=NS.

extension (also observed in patient 4). Regarding secondary motor areas, there was SMA proper overactivation bilaterally in patient 4 and on the unaffected side in patient 1. The superior parietal lobule (Brodmann's area 7) was overactivated bilaterally in patient 2 and on the unaffected and affected sides in patients 3 and 4, respectively. Likewise, area 40 was overactivated bilaterally in patient 4 and on the affected side in patient 1. Cerebellar overactivation was found in patients 1, 2, and 4. A complete list of the significant overactivations can be found in Table 4.

PET2

Compared with PET1, significant overactivations concerned fewer patients (patients 2, 3, and 4 only) and were less extensive (except in patient 2), especially on the affected side ($P=0.09$, comparing across the sample the volume of overactivations in the whole affected hemisphere between PET1 and PET2). This lesser extent of overactivations concerned all the motor-related areas, especially on the affected hemisphere, although individually, the situation varied. Bilateral SM1 hand area overactivation was still present in patients 2 and 4, although mirror movements had disappeared in the former; caudal extension was again observed in patient 4. Concerning secondary motor areas, the pattern of overactivations involved in patient 2 the SMA proper and PM cortex bilaterally (the latter not being noted at PET1), and in patient 3, the unaffected-hemisphere posterior parietal cortex and insula. Additional overactivations not present at PET1 concerned the prefrontal cortex of the affected hemisphere in patient 2 and of the unaffected hemisphere in patient 3, and the unaffected-side anterior putamen in patients 2 and 3.

TABLE 3. Results From the SPM Group Analysis of Overactivations in Patients Compared With Control Subjects

Anatomic Area	BA	*x, y, z*	Cluster	*Z*
PET1				
Motor cortex (hand area), L	4	−31 −23 50	3343	5.99
Inferior parietal lobule, L*	40	−41 −46 41		3.85
Postcentral gyrus (caudal) L*	4-1	−45 −21 32		3.54
Superior parietal lobule, L*	7	−24 −54 60		3.34
SMA proper, R	6	3 −13 50	465	5.22
Inferior parietal lobule, R	40	41 −32 46	791	4.49
Motor cortex (hand area), R*	4	32 −25 53		4.48
Insula, L		−40 10 6	286	4.04
PET2				
Motor cortex (hand area), L	4	−27 −27 55	370	4.25
PM cortex, R	4	27 −17 57	376	4.25

Shown are the overactivations found in the patient group at PET1 and PET2. Listed are the approximate Brodmann's areas (BA), when applicable, Talairach's *x, y, z* coordinates (see Subjects and Methods), cluster size (number of voxels with *Z* score >3.09), and peak *Z* scores.
Results at $P<0.05$, corrected for multiple comparisons, cutoff.
*Secondary peaks for each significant cluster.

Discussion

This study, which used a fixed-performance design, documents longitudinal changes in brain overactivation patterns during recovery from stroke. Although the sample consisted of only 5 patients, this size is comparable to that of previous similar studies[1–9]; furthermore, these patients were highly selected on a prospective basis and formed a highly homogeneous group with respect to clinical presentation as well as lesion location, side, and size. In addition, as shown by the sequential clinical scores, significant motor recovery occurred in each subject.

Based on a pilot clinical study, we elected to use a simple and cued motor task, which was effectively executed in all the patients and was fixed in both PET studies; that is, our design ensured that the task (1) could be performed by the patients,[24] (2) was the same at both PET studies, and (3) was the same as that performed by the control subjects. Thus, this was a highly controlled study, which in addition implemented individual analysis allowing the description of the findings in each patient as a function of time.

In this work, we identified significant overactivations by formally comparing the patients with age-matched control subjects and we used a stringent statistical cutoff in both the group and the individual analyses. Such a rigorous approach has not been used previously, giving additional weight to our findings. Both analyses documented significant overactivations in both hemispheres, which concerned the primary, secondary, and auxiliary motor-related areas as well as some non–motor-related areas. The salient finding from this study is that even though the task was fixed over time, the overactivations were not static but instead were dynamically changed, with essentially a decrease over the affected hemisphere.

In this work, because our interest was to study overactivations, the only analysis that was performed a priori was a comparison of the activation (ie, TI tapping versus rest) in the patients with that in the control subjects, separately for each PET study. Other types of analyses of our data set would, however, be possible; for example, it could be argued that a direct comparison of the activation between the 2 studies in the patients (ie, without reference to the control subjects) would be worthwhile. However, as mentioned in the introduction, this type of within-group analysis may be affected by changes in the regional CBF pattern from PET1 to PET2. Therefore, the following additional analyses had to be performed as well: (1) a comparison of the rest condition between patients and control subjects, for each PET study

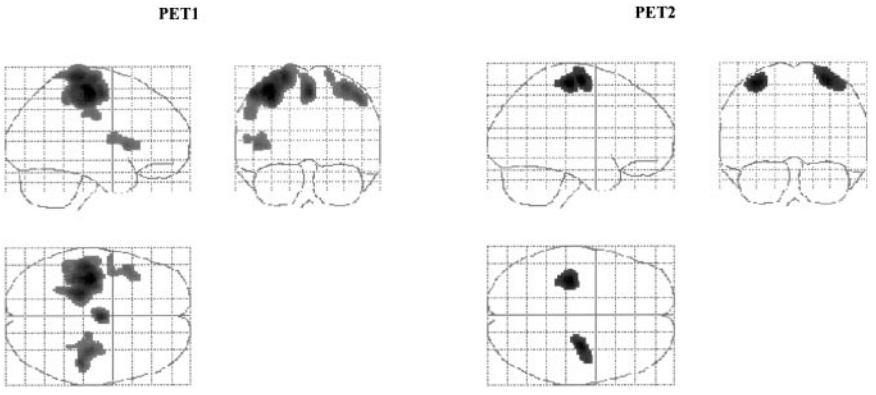

Figure 2. SPM96 group analysis of overactivations (ie, PET1 vs control subjects and PET2 vs control subjects). The images were obtained with ANCOVA, using global activity as confounding covariate, and performed on a pixel-by-pixels basis. The statistical significance is set at $P<0.05$, corrected for multiple comparisons (see Subjects and Methods for details). The data obtained are shown according to the "glass brain" display mode. The neurological convention is used (ie, right side of brain is shown on the right). See Table 3 for coordinates of the overactivations.

separately, and (2) a comparison of the rCBF pattern during TI tapping between patients and control subjects. The results from this set of additional analyses were entirely consistent with, and actually reinforced, the main finding from the overactivation analysis (ie, a global reduction in overactivations from PET1 to PET2 more marked for the affected than the unaffected hemisphere). First, the direct comparison of activations revealed a reduction in spatial extent of activated voxels over time that was more evident in the affected hemisphere (number of significantly more activated voxels in the affected and unaffected hemispheres was 546 and 214 voxels, respectively, in PET1 versus PET2 and 12 and 172 voxels, respectively, in the reverse comparison, using the $P<0.001$, uncorrected threshold). Second, consistent with our concerns, a comparison of the rest condition between PET sessions disclosed several hypometabolic clusters in the patients relative to control subjects, with some clear changes over time. Thus, at the $P<0.05$ corrected cutoff, the affected-side thalamus and some cortical regions (including SM1) were more hypometabolic at PET1 than at PET2, whereas the reverse was true for the contralateral cerebellum. Third, a direct comparison of the TI tapping condition between PET studies revealed clusters of significantly greater activity in the primary and secondary motor areas in the patients relative to the control subjects that were more extensive at PET1 than at PET2 (11 clusters for 9359 voxels and 10 clusters for 4728 voxels, respectively); furthermore, this difference in spatial extent of significant voxels from PET1 to PET2 was more evident for the affected than for the unaffected side. Interestingly, greater activity of the unaffected hemisphere PM cortex was present only at PET2, consistent with the overactivation analysis (see later).

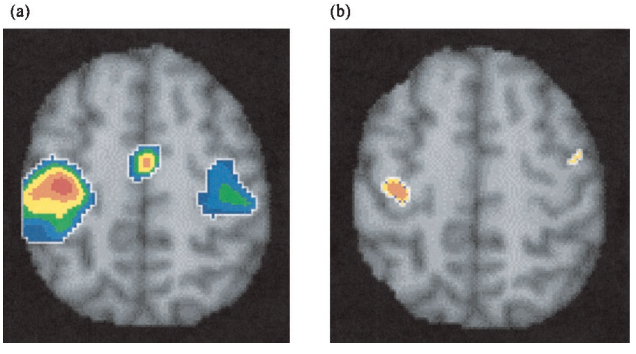

Figure 3. Group analysis of overactivations in the primary and secondary motor areas (ie, PET1 [a] and PET2 [b] versus control subjects). The significant voxels ($P<0.05$, corrected) are projected onto a rendering surface of a standard MRI template. The neurological convention is used. The data illustrate the dynamic changes of overactivations in both extent and spatial distribution from PET1 to PET2. Overactivations were found in the bilateral SM1 and SMA at PET1 (a) and in the affected-hemisphere SM1 and unaffected-hemisphere PM cortex at PET2 (b) (see Table 3 for area coordinates and cluster size).

Significant overactivation of the affected-hemisphere SM1 was found at both PET studies in the group analysis and in 3 and 2 patients, respectively, at PET1 and PET2 in the individual analysis. This finding is consistent with previous reports in subcortical stroke[1–3] and might represent overrecruitment of the deafferentated hand area, necessary to perform the task despite corticospinal tract lesion. These observations suggest that recovery takes place when the affected primary motor cortex is not only preserved structurally but also capable of enhanced workload and thus not completely deafferentated. During the 6-month interval between the 2 PET studies, there was a decrease in the amount of affected-hemisphere SM1 overactivation. This finding is novel, as previous longitudinal studies did not specifically assess overactivations; in addition, their results were discrepant, and they did not report individual analyses. Thus, Nelles et al[8] found a reduction in SM1 activation cluster size from PET1 to PET2 which would be consistent with our findings, whereas Marshall et al[9] reported the reverse pattern, a divergence that may be due to the non–fixed-performance paradigm used in the latter study, with some patients not even being able to perform the task at first study. Note, however, that the time frame of these 2 previous investigations differed from ours in that both performed their first study in the acute stage.

Another finding in the present study consisted in a caudal extension of the affected-hemisphere SM1 overactivation, which was found in 2 patients at PET1 and 1 at PET2, as well as in the group analysis at PET1. This suggests unmasking of silent connections[25] or recruitment of the SM1 cortex outside the boundaries of the zone activated in age-matched control subjects,[14] which would be consistent with the concept of cortical map reorganization. A similar finding was first reported by Weiller et al[3] in some of their patients studied in the chronic stage of recovery after striatocapsular stroke. In contrast to these authors, who used descriptive statistics, however, we document these complex changes here using

TABLE 4. Individual SPM Analysis of Overactivations

		PET1					PET2			
Patient	Anatomic Area	BA	*x, y, z*	Cluster	*Z*	Anatomic Area	BA	*x, y, z*	Cluster	*Z*
1	Occipital cortex, L	19	−22 −62 −9	406	5.87					
	Sensorimotor cortex (hand area), L*	1–4	−24 −30 63	1531	5.10					
	Sensorimotor cortex (caudal), L*	1–4	−27 −30 40		4.60					
	Inferior parietal lobule, L*	40	−43 −38 42		3.47					
	Cerebellum (vermis), R		3 −52 −14	299	4.96					
	Posterior cingulate cortex, L	31	−4 −30 42	519	4.95					
	SMA proper, R*	6	3 −17 48		4.61					
	Cerebellum (lateral), R		13 −32 −16	516	4.92					
	Pons, L*		−6 −23 −28		4.23					
	Pons, R*		4 −19 −21		3.92					
	Insula, central, L		−40 −5 10	352	4.59					
2	Cerebellum (vermis), R		6 −93 −21	553	6.01	Superior frontal gyrus, L	8	−27 39 37	720	6.05
	Superior parietal lobule, L	7	−15 −46 59	1717	5.62	Middle frontal gyrus, L*	9	−41 28 31		4.01
	Postcentral gyrus, L*	3	−29 −23 46		5.39	Middle frontal gyrus, L*	8	−43 18 41		3.63
	Motor cortex (hand area), L*	4	−13 −32 58		4.71	PM cortex, L*	6	−27 14 53		3.33
	Superior temporal gyrus, R	22	50 −36 7	319	5.15	Superior frontal gyrus, R	10	11 61 −4	345	5.48
	Sensorimotor cortex (hand area), R	1–4	22 −21 44	457	4.95	Inferior occipital gyrus, L	18	−6 −98 −5	456	5.22
	Superior parietal lobule, R*	7	24 −44 49		3.51	Middle occipital gyrus, R*	18	6 −96 18		3.73
	Pons, L		−10 −32 −25	487	4.70	Cuneus, R*	18	1 −98 12		3.59
	Cerebellum, L*		−1 −46 −15		4.04	Lingual gyrus, R*	17	4 −98 −8		3.44
	Mesencephalon/pons, R*		3 −38 −18		3.53	Motor cortex (hand area), L	4	−27 −25 55	1753	4.96
						SMA proper, R*	6	3 −3 66		4.45
						SMA proper, L*	6	−10 −11 71		4.19
						Superior parietal lobule, L*	7	−34 −60 49		3.87
						PM cortex, L*	6	−19 −19 69		3.72
						PM cortex, R*	6	17 1 63		3.71
						Mesencephalon, R		4 −34 −16	770	4.92
						Vermis, R*		4 −48 −3		4.89
						Medulla, R*		8 −34 −46		4.71
						Cerebellum, L*		−3 −48 −36		3.36
						Anterior putamen, R		20 22 1	394	4.46
						Thalamus, R*		17 −7 17		3.31
						Motor cortex (hand area), R		17 −25 69	273	4.01
3	Posterior cingulate cortex, R	30	18 −52 9	658	4.78	Anterior insula, R		43 12 0	1660	5.34
	Posterior cingulate cortex, R*	31	15 −32 16		3.09	Inferior frontal gyrus, R*	47	41 26 −4		5.25
	Middle temporal gyrus, L	39	−40 −67 28	437	4.24	Middle frontal gyrus, R*	10	31 43 13		3.96
	Precuneus, R	7	1 −62 42	311	4.24	Putamen, anterior, R*		32 14 −1		3.92
						Inferior parietal lobule, R	40	47 −52 27	837	5.07
						Parietal operculum (SII), R*	40	50 −23 13		3.61
4	Sensorimotor cortex (hand area), L	1–4	−29 −21 48	4884	7.00	PM cortex, R	6	54 −1 23	624	5.03
	Sensorimotor cortex (caudal), L*	1–4	−48 −21 32		6.60	Superior temporal gyrus, R*	22	59 −1 5		4.17
	Inferior parietal lobule, L*	40	−59 −38 22		4.75	Motor cortex (caudal), R*	4	59 −11 33		3.99
	Middle temporal gyrus, L*	21	−57 −48 8		4.60	Motor cortex, (hand area), L	4	−29 −21 50	807	4.86
	Paracentral lobule, L*	4	−8 −30 69		4.52	Motor cortex, (hand area), R	4	31 −30 54	1490	4.83
	Middle temporal gyrus, L*	22	−52 −36 3		4.14	Postcentral gyrus, R*	1–3	34 −29 46		4.69
	Superior parietal lobule, L	7	−31 −48 59		3.38	SMA proper, R*	6	6 −5 52		3.75
	Sensorimotor cortex (hand area), R	1–4	31 −30 53	2020	5.96					
	Inferior parietal lobule, R*	40	41 −30 46		5.13					
	SMA proper, R*	6	25 −13 48		3.67					
	Postcentral gyrus, R*	1–4	52 −25 34		3.60					
	Cerebellum (vermis), L		−1 −67 −35	654	5.90					
	Cingulate cortex, posterior, L	31	−8 −15 39	713	5.47					
	SMA proper, L*	6	−1 −11 48		5.13					
	Mesencephalon, R		11 −34 −13	466	5.06					

Each patient vs control group, with the $P<0.05$, corrected for multiple comparisons, cutoff. Shown are the overactivations found in each patient at PET1 and PET2. Of note is the lack of significant overactivation in patient 5 at both studies and in patient 1 at PET2. Same presentation as Table 3.

*Secondary peaks for each significant cluster.

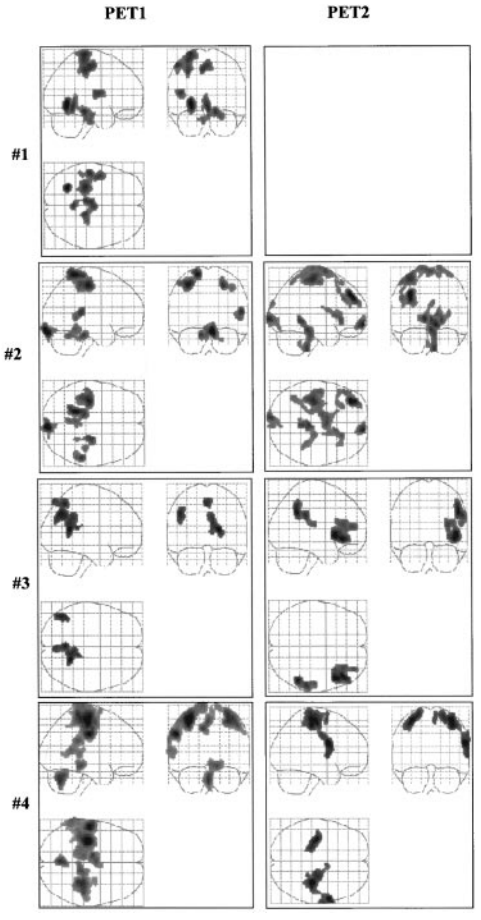

Figure 4. SPM96 individual analysis of the overactivations ($P<0.05$, corrected for multiple comparisons) at PET1 and PET2 in each patient. See Figure 2 for details. No significant overactivation was found in patients 1 (#1, at PET2) and 5 (#5, at both studies). See Results and Table 4 for a detailed description of the findings.

formal overactivation analysis with stringent statistical cutoff. A novel finding concerns the apparent change over time in this caudal extension, which was prominent at PET1 but found in only 1 subject at PET2. Although this observation would need confirmation, it may indicate a decreasing involvement of SM1 map reorganization with time.

Unaffected-hemisphere SM1 activation has been documented in previous studies of stroke recovery.[1–5,9] In our study, this overactivation decreased from PET1 to PET2 in the individual analysis (patients 2 and 4), whereas in the group analysis, it was present only at PET1. There are no comparable data in the literature to formally discuss these findings. Although unaffected-side SM1 overactivation might reflect recruitment of the uncrossed corticospinal tract, its relation with mirror movements is still a matter of debate.[1–5,26,27] In our study, mirror movements were documented in patients 2 and 4 at PET1 and in patients 4 and 5 at PET2, but although patients 2 and 4 did show corresponding overactivations, patient 5 did not, and in addition, patient 2 still showed this overactivation despite the fact that his mirror movements had vanished. Thus, if a relationship between unaffected hemisphere SM1 overactivation and mirror movements exists, it does not appear to be systematic. Further studies are required to resolve this issue.

We also found significant overactivation of the premotor and supplementary motor areas as well as the cerebellum, indicating an over-recruitment of other major components of the motor network apart from the SM1. These secondary motor areas are normally involved in simple as well as more complex motor tasks.[28] Interestingly, both the group and the individual analyses showed that overactivations in these areas were considerably less at PET2 than at PET1. This decrement was particularly evident for the cerebellum, an observation not mentioned in previous longitudinal studies.[8,9] Such temporal changes suggest that less recruitment of these secondary motor areas (ie, less "brain effort") was required at PET2 than at PET1 to perform the same task. Interestingly, in our study the patients mentioned that performing the task required more "effort" at PET1 than at PET2. Of note, however, there was at PET2 an increase in these overactivations in patient 2 and a new overactivation of the PM cortex in both the group and the individual analyses (patients 2 and 4) (see Figures 2, 3, and 4 and Tables 3 and 4). This finding concerning the PM cortex is consistent with 2 earlier reports.[6,8] In their longitudinal study, Nelles et al[8] observed an ipsilateral PM cortex activation at PET2 only during the execution of a passive motor task in still-recovering subcortical stroke patients. In a cross-sectional study, Seitz et al[6] reported a bilateral activation of the PM cortex in patients completely recovered from cortical infarcts. Both groups concluded that the PM cortex seemed to be critical for reorganization of the motor system during recovery of lost function not only for its role in selection and preparation of movement[29,30] but also because of its connections to SM1 and its contribution to the corticospinal tract.[31]

In our study, there also was a significant overactivation of ancillary motor-related areas such as the inferior and superior parietal cortex and the insula. Involvement of these areas during the execution of a motor task has been frequently reported in recovered stroke patients.[1–9] However, as with the more fundamental components of the motor network, there was less recruitment of these areas with elapsing time. Thus, in the group analysis, the BA 40, BA 7, and insula were overactivated at PET1 but not at PET2. With individual variability, a similar trend obtained in the individual analysis (Figure 4 and Table 4). Both of the earlier longitudinal studies mentioned[8,9] reported a bilateral activation of the posterior parietal cortex at both timepoints, which was less marked at the late point. These earlier findings would be consistent with our observations. Because activation of these areas in normal subjects occurs during execution of complex motor tasks,[28,32] their involvement in stroke patients might reflect the bringing into play of different strategies (eg, visuospatial) to carry out the task, even though the task used in our study was apparently simple. The lesser recruitment of these areas over time suggests that recourse to such strategies becomes less necessary with time, in parallel with motor recovery. In normal subjects, the bilateral activation of BA 40 has been related to transcallosal connections,[33] which may therefore be involved during motor recovery.

Overactivation of the prefrontal cortex was found at PET2 in patients 2 and 3 (bilaterally and unaffected hemisphere, respectively), as well as across the group (affected-

hemisphere only) by post hoc analysis, although with lower statistical significance ($z=3.57$ for BA 9, $z=3.41$ for BA 46). Consistent with these findings, several studies performed in the chronic stage of recovery also reported a bilateral[3] or affected-hemisphere[2,7] prefrontal activation not present in control subjects. Our finding is, however, more robust than these earlier reports, as we performed a direct statistical comparison and used age-matched control subjects.[14] Both previous longitudinal studies[8,9] also reported an activation of the prefrontal cortex (in the affected-hemisphere and bilaterally, respectively), but this was observed in the first study only. This discrepancy with our findings may, however, reflect differences between these reports and our investigation in both timing of the studies relative to stroke onset and motor activation paradigm (see earlier). Overactivation of the prefrontal cortex during motor recovery presumably reflects the engagement of executive processes to perform the task. Studies in monkeys suggest that the motor command originates from the prefrontal cortex,[34] and functional imaging in healthy subjects reports prefrontal activation in sequence learning tasks that require the involvement of attentional processes.[16,28] Interestingly, our data suggest that significant prefrontal overactivation emerges in the late phase of recovery, possibly reflecting a late compensatory mechanism, relaying early motor network over-recruitment.

Finally, another interesting finding was the overactivation of the unaffected-side anterior putamen at PET2 in patients 2 and 3. The physiological role of the basal ganglia in motor control remains uncertain.[35] Some authors reported basal ganglia activation during motor skill learning.[36] Of special interest in our study is the observation that overactivation of the putamen occurred in the same 2 patients who showed prefrontal overactivation. The prefrontal-striatum loop seems to be physiologically activated when the subject is learning a new motor task or is asked to pay attention to the performance of a prelearned task.[35]

In conclusion, thanks to our novel longitudinal, fixed-performance paradigm, we were able to document temporal changes in reorganization of the entire motor networks. Our findings show, first, that a highly significant overactivation of large motor-related areas is necessary at both timepoints to perform the task, even though this was considered a "simple" task. This suggests that the brain afflicted with a lesion of the corticospinal pathway at the level of the internal capsule must recruit these areas more than would be normally necessary to perform the same task. Second, while recovery was taking place, there was simultaneously a decrease in overactivations in primary, secondary, and ancillary motor areas and, at least in some subjects, new overactivations in the prefrontal and PM cortices as well as the striatum. Thus, the late excessive engagement of the latter areas may represent a sort of behavioral substitution (ie, the learning of new compensatory strategies). In other words, this individual variability in overactivation pattern despite relative homogeneity in infarct side, size, and location, as well as clinical symptoms, may reflect intersubject differences in cognitive processes during the motor task, such as attention, that may be involved in functional recovery.

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