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Vicarious function within the human primary motor cortex?
A longitudinal fMRI stroke study

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Summary
While experimental studies in the monkey have shown that motor recovery after partial destruction of the hand motor cortex was based on adjacent motor reorganization, functional MRI (fMRI) studies with isolated primary motor cortical stroke have not yet been reported in humans. Based on experimental data, we designed a study to test if recovery after stroke within primary motor cortex (M1) was associated with reorganization within the surrounding motor cortex, i.e. the motor cortex was able to vicariate. Since motor recovery is time-dependent and might be inflected according to the tested task, the delay after stroke and two motor tasks were included in our design. We examined four patients with one ischaemic stroke limited to M1, and four sex- and age-matched healthy controls in a temporally balanced prospective longitudinal fMRI study over three sessions: <20 days, 4 months and 2 years after stroke. The paradigm included two motor tasks, finger tapping (FT) and finger extension (FE). Distinct patterns of motor activation were observed with time for FT and FE. At the first session, FT-related activation was lateralized in the ipsilateral hemisphere while FE-related activation was contralateral, involving bilateral cerebellar regions for both tasks. From 4 months, skilled motor recovery was associated with contralateral dorsal premotor and sensorimotor cortex and ipsilateral cerebellum motor-related activations, leading to lateralized motor patterns for both tasks. For the left recovered hand, FT and FE-related activations within M1 were more dorsal in patients than in controls. This dorsal shift progressively increased over 2 years, reflecting functional reorganization in the motor cortex adjacent to the lesion. In addition, patients showed a reverse representation of FT and FE within M1, corresponding to a greater dorsal shift for FT than for FE. This functional dissociation might reflect the structural subdivision of M1 with two distinct finger motor representations within M1. Recovery of FT, located within the lesioned depth of the rolandic sulcus in controls, might be related to the re-emergence of a new representation in the intact dorsal M1, while FE, located more dorsally, underwent minor reorganization. This is the first fMRI study of humans presenting with isolated M1 stroke comparable with experimental lesions in animals. Despite the small number of patients, our findings showing the re-emergence of a fingers motor task in the intact dorsal M1 instead of in ventral M1 are consistent with 'vicariation' models of stroke recovery.

Keywords: reorganization; fMRI; primary motor cortical stroke; cerebral infarction; vicariation

Abbreviations: BA = Brodmann area; BOLD = blood oxygenation level-dependent; CBF = cerebral blood flow; CBV = cerebral blood volume; FE = finger extension; fMRI = functional MRI; FT = finger tapping; MNI = Montreal Neurological Institute; NIHSS = National Institutes of Health Stroke Scale; M1 = primary motor cortex or BA4; PMd = dorsolateral premotor cortex or BA6; QCL = quadrangular cerebellar lobule; ROI = region of interest; SM1 = primary sensori-motor area; SMA = supplementary motor area; S1 = primary somatosensory cortex or BA3a, 3b, 1, and 2; TMS = transcranial magnetic stimulation

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Introduction

There is considerable evidence that motor recovery observed after lesions such as stroke, although highly variable, is based on functional reorganization (Chen *et al*., 2002; Rijntjes and Weiller, 2002). However, the underlying neurophysiological mechanisms that mediate reorganization of functional maps continue to be debated. Synaptogenesis, dendritric arborization, unmasking of silent synaptic connections and vicariation are the main neuroplasticity processes observed in primates and in rodents following focal cerebral injury (Bioulac *et al*., 1995; Jones *et al*., 1996; Xerri *et al*., 1998; Benton and Tranel, 2000; Kolb *et al*., 2000; Rossini *et al*., 2003).

In the early 19th century, the principle of recovery of function after brain injury was debated, with an ensuing controversy between the concepts of equivalence and redundancy supported by Flourens and the localizationist theory derived from Gall's scheme (Benton and Tranel, 2000). The general idea of reorganization was often expressed as vicarious functioning, i.e. the mobilization of a region connected to the damaged substrate—such as the homologous area in the opposite hemisphere or the immediately surrounding area—to assume responsibility for mediating the lost or impaired function (Soltman, 1876; Benton and Tranel, 2000; Finger *et al*., 2000). In view of the steadily increasing evidence for functional specialization of cerebral regions, this early concept regarding sparing and recovery was later viewed with scepticism (Benton and Tranel, 2000).

The complete motor recovery observed in monkeys, treated by motor re-education after serial destruction of bilateral precentral gyri led Ogden and Franz to hypothesize that the mechanisms underlying motor recovery were substitution and vicarious function by other brain regions (Ogden and Franz, 1917). In the 1950s, Glees and Coles (1950) reported that, following destruction of the thumb motor cortex area in macaques, the thumb representation reappeared in the non-affected part of the motor cortex—also suggesting a vicarious functioning. However, others have failed to observe any evidence of vicariation, possibly because the capacity for vicarious motor function in their studies may have been limited by the large size of the lesions considered.

Small focal ischaemic lesions of the simian motor cortex restricted to the partial destruction of the hand representation have led the issue of substitution and vicariation to be readdressed. Using microelectrode stimulation, Nudo *et al*. (1996*b*) observed that the topographic reorganization in squirrel monkeys depends on post-lesion training. In the absence of training, the intact hand area surrounding the infarct undergoes degenerative changes (Nudo and Milliken, 1996; Friel *et al*., 2000). In contrast, rehabilitative training of the impaired hand was associated with complete recovery and led to a displacement of the digit representation into former elbow and shoulder territories (Friel *et al*., 2000; Nudo *et al*., 2000, 2001*b*), suggesting that efficient motor recovery is based on reorganization of the hand area in the primary motor cortex (M1) adjacent to the lesion, and indeed on the vicarious capacity of M1 (Nudo *et al*., 2001*a*).

While it is assumed that primate models of stroke and recovery produce motor impairments comparable to those seen in human patients, functional MRI (fMRI) studies of patients presenting a pure primary motor cortical stroke have not, to our knowledge, yet been reported. The aim of this fMRI study was to test the hypothesis that the human motor cortex was capable of vicarious functioning, i.e. to test whether the recovery of motor function after restricted primary motor cortex stroke is associated with reorganization within the surrounding motor cortex (similar to what happens in monkeys and rodents).

Some issues have to be addressed regarding the current advances in anatomical and stroke recovery domains.

(i) Arguments based on cytoarchitecture and the quantitative distribution of transmitter-binding sites have led Brodmann area (BA) 4 in humans to be separated into two sub-areas: '4a anterior' or '4a dorso-rostral'; and '4p posterior' or '4p ventro-caudal' (Geyer *et al*., 1996). Despite an overlap, this structural subdivision of M1 may be related to a functional dissociation with two finger motor representations: one within M1a, with neurons responsive to joint manipulation and muscle stimulation; and one within M1p, responsive to cutaneous stimulation, and located within the depth of the rolandic sulcus (Geyer *et al*., 1996; Preuss and Kaas, 1996; Preuss *et al*., 1997). Whereas finger tapping (FT) and finger extension (FE) of the five fingers involve motor and proprioceptive sensory modalities, FT may more strongly involve the proprioceptive and discriminative sensory modalities than FE, leading to stronger activation of M1p with FT than with FE—the latter task requiring mainly motor strength and joint movements (Nudo *et al*., 1997). Such an anatomical–functional dissociation led us to assume that, after M1 lesion, the impairment of motor function may vary according to the type of task. In the hypothesis of such a dissociated recovery process in relation to motor function, partial damage to M1 resulting in graduated motor impairment may lead to the decoupling of processes underlying cortical reorganization and to distinct patterns of motor activation.

(ii) The role of the undamaged hemispheres in recovery after stroke lesion has been investigated in experimental neuroscience studies (Jones and Schallert, 1992; Jones *et al*., 1996) and in post-stroke studies using transcranial magnetic stimulation (TMS) (Netz *et al*., 1997; Schallert *et al*., 1997; Liepert *et al*., 2000*b*; Traversa *et al*., 2000; Rossini *et al*., 2003). Parallel to growth-promoting events in rats, hyperexcitability in motor regions has been observed in the unaffected hemisphere of stroke patients (Manganotti *et al*., 2002; Delvaux *et al*., 2003), reflecting functional involvement of this cortex in relation to plastic reorganization (Johansen-Berg *et al*., 2002*b*; Shimizu *et al*., 2002; Rossini *et al*., 2003). Therefore,

it is important that cortical remodelling after stroke is examined in both damaged and undamaged hemispheres.

(iii) The time course of recovery appears to be a key parameter in experimental studies as well as in clinical studies aimed at stroke recovery (Pantano *et al*., 1996; Schallert *et al*., 1997, 2000; Traversa *et al*., 2000; Binkofski *et al*., 2001; Delvaux *et al*., 2003; Ward *et al*., 2004). Furthermore, whereas most compensatory changes and motor recovery occur in the weeks to months after the injury (Binkofski *et al*., 2001; Delvaux *et al*., 2003), functional recovery in stroke patients is lasting longer than 2 years (Bach-y-Rita, 2000; Nudo *et al*., 2001*a*; Page *et al*., 2004).

In order to take into account both motor function type of task and time course, we designed a controlled prospective longitudinal fMRI study in patients presenting hand paresis due to a single acute infarction limited to primary motor right cortical cortex. These patients were compared with matched controls performing the two motor tasks over three sessions: the first 3 weeks, 4 months and 2 years after stroke. This completely temporally balanced experimental design allowing the closest comparison with animal experiments.

Material and methods

Subjects

We studied four right-handed patients (three males, one female, age range from 51 to 71 years) presenting with first-ever ischaemic stroke affecting a part of the hand area of the right primary motor cortex. Stroke topography and size were evaluated using diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) sequences performed at the first fMRI session (Fig. 1). Inclusion

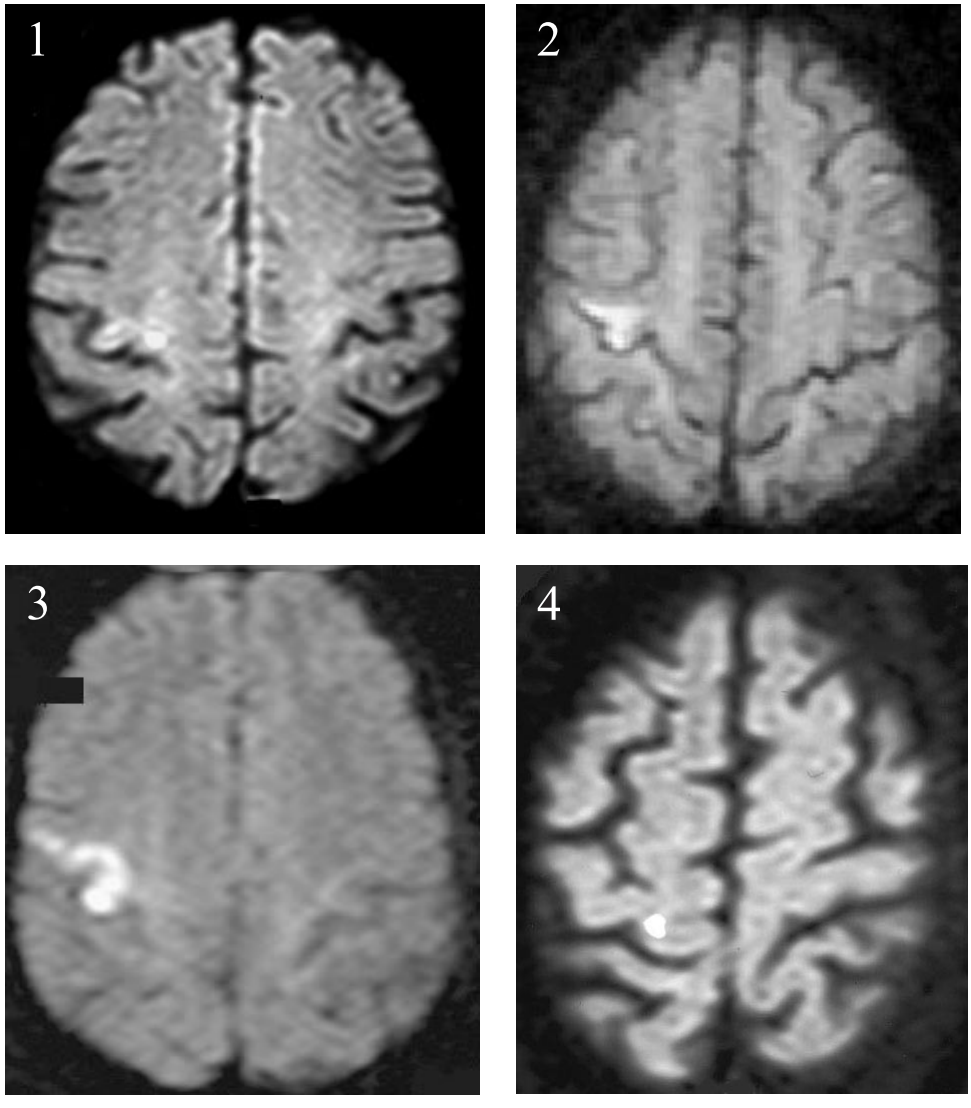

Fig. 1 Acute ischaemic stroke in the right primary motor area was revealed by diffusion weighted imaging, performed within 48 h after left hand paresia onset in the four patients. The *z* MNI coordinates (mm) of the MRI hypersignal are 45–60 (Patient 1), 45–55 (Patient 2), 15–50 (Patient 3) and 60–65 (Patient 4). Mean volume = 2.215 mm^3. Sections are arranged in radiological orientation (i.e. right side of brain to viewer's left).

criteria included: (i) right-handedness based on the Edinburgh Handedness Inventory Score (Oldfield, 1971); (ii) a single first-ever stroke within M1 area on the basis of MRI assessment; and (iii) severe hand paresis at admission [National Institutes of Health Stroke Scale (NIHSS) hand subscore = 2 (Lyden *et al*., 1994)], with persistent deficit, yet allowing the complete flexion and extension of all five fingers at the time of the first fMRI session. Patients with mild subjective sensory impairment were included, since transient sensory signs are often observed in pure motor strokes, despite the lack of any evidence of injury within the sensory cortex. These signs likely reflect the involvement of the direct primary sensorimotor connections (Mesulam, 2000*a*; Nudo *et al*., 2000).

MRI included DWI, FLAIR and T2 perfusion and angiography sequences for assessing acute stroke topography, old strokes, hemispheric perfusion asymmetry and cerebral or cervical artery occlusion. Exclusion criteria were infarction extending into subcortical or non-motor structures, leukoaraiosis, previous stroke on FLAIR or T2 imaging, decreased blood flow or delayed time to the peak signal in the affected hemisphere compared with the unaffected hemisphere, and stenosis or occlusion of the carotid or cerebral arteries. Patients who could not perform the first fMRI session within 20 days after stroke onset, or who presented with history of any neurological, psychiatric or malignant disorder, cognitive impairment, and non-motor associated neurological signs were excluded. All patients were admitted within 24 h following stroke onset to our Stroke Unit at University Hospital, Grenoble.

Serial neurological, neuropsychological and physiotherapeutic assessment (including NIHSS, neuropsychological evaluation, Fugl-Meyer scale (Fugl-Meyer *et al*., 1975), local motor scale, maximum FT rate and motor reaction time of the right hand using Trail-making A (Reitan, 1971), FE and FT tasks were performed at admission and during follow-up. The four patients received specific daily rehabilitative training during their hospitalization (10 days) and, subsequently, at home with 3-weekly physiotherapy by the second session (three patients). Three fMRI sessions were performed: within the first 3 weeks after stroke onset (session A), at 4 months ($\pm$3 weeks; session B) and at 2 years ($\pm$3 months; session C). Four normal subjects, matched for age ($\pm$5 years) and sex underwent the same fMRI protocols as the patients and thus also had three fMRI sessions. Given the small sample size of our study, the robustness of the hypothesis of a vicariant process has been tested. Thus, we included eight additional normal subjects for both motor tasks, resulting in a group of 12 normal controls for an extra session.

Patients and controls were recruited within the context of a longitudinal fMRI stroke study (CIRCE). Written consent according to the Declaration of Helsinki was obtained for all subjects. The study was performed in accordance with local Institutional Review Board (IRB) regulations.

Tasks

Subjects were trained to perform two self-paced tasks at a fixed rate with both hands: (i) finger tapping—sequential finger-to-thumb opposition (forefinger, middle finger, third finger, little finger, finger-to-thumb opposition); and (ii) flexion extension of the five fingers together, without movement of the wrist. Because patients had initially variable levels of performance, we chose a self-paced rate associated with a pre-session training at fixed amplitude and rate (0.66 Hz for FE and 1.3 Hz for FT) in order to promote the skill of the movement. The choice of a rate of 1.3 Hz was guided by previous studies, which have shown that the optimum signal in terms of intensity and variation was obtained between 1 and 1.5 Hz, the blood oxygenation level-dependent (BOLD) response decreasing dramatically below 1 Hz.

The delay after stroke was related to the patient's ability to perform correct FE and FT movements. Task training was performed with a metronome before the session, until the rate could be maintained around 1.3 Hz (80/min) for FT and 0.66 Hz (40/min) for FE. A block paradigm was used alternating two sequential conditions, i.e. motor task (30 s) and motor rest (30 s) repeated three times.

Four functional runs were performed at each session in the following order: right FT; left FT; right FE; and left FE. In order to avoid mirror movements, which could occur with long performance of task, the task duration was limited to 30 s and the total duration of each functional run to 3 min. Subjects read the instructions on a screen (which indicated when the subjects had to switch between control and task conditions) using a mirror placed in front of their eyes. During the fMRI session, performance, FT and FE rates, mirror movements, ipsilateral synkinesia, any other movement, errors in relation to the instructions were observed and noticed by a certified staff neurologist standing close to the patient. The runs were repeated when the task was incorrectly performed. All subjects performed in addition a fifth scan with a language task so that hemispheric predominance for language could be assessed.

fMRI

Experiments were performed at 1.5 Tesla (Gyroscan ACS-NT, Philips, Eindhoven, The Netherlands). First, scout images were acquired in the sagittal plane to locate anterior (AC) and posterior (PC) commissures. Secondly, the four functional runs were performed. A gradient-echo, echo-planar imaging sequence was applied. The following were the major MRI acquisition parameters: 32 axial slices parallel to the AC–PC line, 5 mm thick (no interslice gap), TR (repetition time) = 3000 ms, TE (echo time) = 45 ms, flip angle = 90°, acquisition matrix 64×64, FOV (field of view) = 256×256 mm^2 leading to a spatial resolution of $4 \times 4 \times 5$ mm^3. Thirdly, high-resolution T1-weighted, gradient-echo (fast field echo) anatomical images of the whole brain were acquired in the same orientation. The major acquisition parameters of this sequence were: 150 axial slices, slice thickness 1 mm (no interslice gap), TR = 22 ms, TE = 6 ms, flip angle = 30°, acquisition matrix 256×256, FOV = 256×256 mm^2.

Statistical analysis

Data processing was performed with a general linear model using the Statistical Parametric Mapping software (SPM 99, Wellcome Department of Cognitive Neurology, London, UK). Motion correction was first performed by realigning all the functional volumes on the first volume of the functional series and by co-registration on the anatomical volume. Anatomical and functional images were then normalized to a standard T1 image template based on the Montreal Neurological Institute (MNI) reference brain. Anatomical images were resampled to $1 \times 1 \times 1$ mm^3 voxels. Functional images were smoothed with a Gaussian kernel (full width at half maximum 8 mm). For each subject, anatomical images were transformed into Talairach space with a resolution of $1 \times 1 \times 1$ mm, and used to calculate a mean image for each group.

Data were first analysed individually and then, as a second step, across subjects using conjunction analyses based on a fixed effect model. The reason for using conjunction analyses was to establish

typical aspects of functional anatomy in a small number of subjects (Friston *et al*., 1999*a*) and not to infer about the population from which these subjects were selected (Friston *et al*., 1999*b*). Contrasts were assessed first individually and then for each group (patients and controls), for each task (FE and FT), for both hands, and per session. All group analysis were performed using conjunction analysis with $P < 0.05$ corrected for multiple comparisons and a 4 voxels extend threshold. The comparison between patients and controls groups was performed using a fixed effect analysis with 0.05 corrected P values.

For each group and each session, an anatomical mean image was obtained from the individual T1 images. Anatomical identification was performed first by superimposing functional maps of each group on the corresponding mean T1 image and then determining the accurate location of the activation foci according to the rolandic sulcus with the aid of the Talairach atlas using a non-linear transform of MNI to Talairach coordinates (Talairach and Tournoux, 1988) by means of appropriate converter software provided with SPM extensions (mni2tal.m; http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

To evaluate a possible vicarious process in M1, the geometric centre of mass of the sensorimotor cortex activation was determined and expressed in Talairach coordinates for each subject and each session in the following way. The region of interest (ROI) was functionally defined using MarsBaR ROI toolboxes (Brett *et al*., 2002), and the mean of the x,y,z coordinates of the ROI was computed using a home-made program (resulting in the geometric centre of mass) and then converted into x,y,z Talairach coordinates. Each of these coordinates was analysed using appropriate non-parametric tests (Wilcoxon signed ranks, Mann–-Whitney and Friedman tests) and plots with SPSS Graduate Pack 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Furthermore, the temporal evolution of each set of x,y,z coordinates was examined separately for each group, hand and task, using the Friedman two-way analysis of variance by ranks which is the non-parametric equivalent of a one-sample repeated measures design (Armitage and Berry, 1994; Wayne, 1999). In addition, we compared patients for each session with the extra session undertaken by the 12 controls.

To quantify the evolution of the intensity of the functional response with recovery, we measured the amplitude estimate at the location of the peak of activation for each subject, each task and each hand. This amplitude estimate corresponds to the coefficient of the task effect in the GLM (the so-called 'size effect' in SPM given by the β parameter). At each session, this amplitude was measured both in the contralateral M1 cluster and in the ipsilateral quadrangular cerebellar lobule (QCL) cluster. These amplitudes were compared between patients and controls, and plotted for both hands at each session using SPSS 11.0 software.

Results

Clinical and behavioural data

The four patients were included consecutively in the study from March 1999 to July 2003 out of the 1750 patients admitted to the stroke unit during this period. They were the only ones corresponding to the inclusion criteria. The characteristics and performances of patients and controls are summarized in Table 1. Three patients had partial damage of the M1 hand area. In the fourth patient, the ischaemic lesion extended from the hand area up to the facial area in M1, inducing initial facial paresis and dysarthria. Three patients had moderate hypertension, two had hypercholesterolaemia and one had diabetes mellitus. All four patients had severe left hand paresis at admission and showed incomplete recovery at the time of the first session. At that time, the maximum FT rate tended to be higher ($P = 0.07$) in controls than in patients. The amplitude of the FT and fine movements of the paretic hand were also qualitatively better in controls than in patients. Patients 2 and 4 sometimes had incomplete thumb-to-little finger opposition, and some mirror movements were observed at the end of the run in Patients 1 and 2. At the time of the second session, FT and FE rates were not significantly different between patients and controls. No ipsilateral proximal synkinesia was observed in any patients. Three patients had completely recovered (Rankin score = 0), while one patient (Patient 2) underwent good recovery but was still less handy with his left fingers (Rankin score = 1). However, he had resumed at his professional activity at 3 months, which required manual dexterity.

fMRI data

Brain activations related to the two motor tasks over the three sessions are presented for both hands in Tables 2–5.

Left FT and FE main effects for patients and controls (Fig. 2)

Controls left FT (Table 2)

Two clusters were activated over the three sessions. The first involved the right primary sensori-motor area (SM1) from the dorsolateral premotor cortex (PMd) to primary somatosensory cortex (S1). The second cluster corresponded to the left QCL. The highest activation in the M1 cluster was located within the ventral and caudal part of M1, the so-called M1p (Geyer *et al*., 1996).

Patients left FT (Table 2)

At the first session (A), patients activated the left ipsilateral PMd, marginally M1, S1, the bilateral QCL and on the right supplementary motor area (SMA). The reduction in k threshold to 2 voxels revealed a small cluster in the right M1. The hemispheric laterality index was −0.77. At the second session (B), motor activation was observed only into the usual contralateral right hemisphere, involving the right PMd and dorsal part of the M1, a small cluster in the left PMd (k = 2) and additionally the left posterior parietal cortex. In the same way, the left cerebellum alone was activated. At the 2-year session (C), lateralized activation was similarly observed, involving the right dorsal M1, PMd, S1, and bilateral SMA.

Controls left FE (Table 3)

Controls showed activation in right PMd, M1, and SM1 and in the left QCL over the three sessions.

Table 1 *Descriptive statistics of the four patients over the three sessions (A, B, C) and of the four controls at the time of the first session (A)*

	Session A	Session B	Session C	P_{ABC}	Controls	P_C
Edinburgh score (%)	100.0% (0)	–	–	–	100.0% (0)	1.00
Age (years)	61.25 (9.74): 51–72	–	–	–	60.0 (9.7): 50–71	0.59
NIHSS	2.25 (1.25): 1–4	0	0	0.04	0	–
Fugl-Meyer hand score/14	10.75 (1.89): 8–12	14.0 (0): 14–14	14.0 (0): 14–14	0.04	14.0 (0): 14–14	0.66
Mean trail–making A (s)	48.75 (13.67): 36–67	44.0 (10.98): 35–69	43.25 (14.80): 33–65	0.17	45.5 (17.21): 33–70	0.25
Mean trail–making B (s)	108.50 (42.75): 66–164	96.25 (24.66): 68–125	101.5 (31.29): 64–136	0.26	108.0 (48.64): 77–180	0.41
Right maximum FT rate (movements/min)	119.25 (14.36): 102–136	159.0 (21.5): 132–184	156.5 (13.7): 120–184	0.04	173.0 (34.78): 136–216	0.07
Left maximum FT rate (movements/min)	64.0 (7.3): 56.0–72.0	136.0 (19.8): 116–164	157.6 (12.0): 120–172	0.02	158.0 (33.28): 124–196	0.29
Delay from stroke (days)	9.5 (8.5): 1–21	120.75 (11.5): 120–134	786.75 (55.7): 733–854	–	–	–
Right FT rate in the magnet (movements/min)	74.0 (6.9): 72–84	68.5 (8.1): 64–80	74.0 (7.56): 64–80	0.63	78.00 (7.66): 68–84	0.45
Left FT rate in the magnet (movements/min)	63.50 (5.62): 56.0–68	68.0 (8.0): 64–80	72.0 (6.52): 64–80	0.09	78.00 (7.66): 68–84	0.19
Right FE rate in the magnet (movements/min)	37.5 (1.9): 36–40	42.75 (8.3): 36–54	37.0 (1.86): 35–39	0.31	38.50 (4.44): 34–44	0.26
Left FE rate in the magnet (movements/min)	37.0 (2.6): 34–40	42.75 (8.8): 36–56	35.75 (2.87): 32–38	0.09	38.25 (4.78): 33–44	0.9

$P_{ABC} = P$ values comparing the patients over the three sessions A, B and C, calculated using Friedman test. $P_C = P$ values comparing patients at the third session and controls using Wilcoxon test. Results shown as mean (SD): minimum–maximum.

Table 2 *MNI coordinates of significant cluster maxima in the conjunction analysis of the patients over the three sessions (A, B, C) and the controls during session C for the FT task of the left hand*

Anatomical area (BA)	Side	Patients A					Patients B					Patients C					Controls C				
		x	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*
Primary motor area (BA 4)	L																				
	R						36	−20	65	40	>8	36	−20	65	17	7.24	32	−20	50	*	7.19
Lateral premotor area (BA 6; 44)	L	−28	−12	65	11	6.69															
	R						24	−16	70	*	7.22	28	0	65	7	6.87					
SMA (BA 6)	R	4	0	70	4	6.25						0	−4	65	11	6.84					
Primary sensory area (BA 1 and 2)	L	−56	−28	40	6	5.42						56	−16	50	4	5.07	48	−32	60	40	>8
	R																				
Posterior parietal areas	L BA 7						−24	−48	65	24	7.34										
	L BA 40						−44	−36	55	7	5.89										
Cerebellum	L HV	−16	−56	−15	39	7.69											−20	−60	−15	19	>8
	R HV	24	−56	−20	7	5.29	52	12	−10	4	7.22										

$P < 0.05$ corrected, k ⩾ 4 voxels; *Secondary peaks; HV = hemispheric cerebellar lobule V; L = left hemisphere; R = right hemisphere.

Table 3 *MNI coordinates of significant cluster maxima in the group analysis of the patients over the three sessions (A, B, C) and controls during session C for the FE task of the left hand*

Anatomical area (BA)	Side	Patients A					Patients B					Patients C					Controls C				
		x	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*
M1 (BA 4)	R	36	−24	60	4	5.54	32	−16	65	32	>8	40	−20	65	44	>8	32	−20	55	*	5.61
Lateral premotor area (BA 6)	R	28	−16	70	8	6.01	24	−12	−70	*	>8	28	−16	−70	*	>8					
SMA (BA 6)	R	0	0	65	4	4.56															
Primary sensory area	R	40	−32	60	6	5.26						32	−24	45	*	5.25	36	−32	65	26	7.44
Cerebellum	L HV	−28	−56	−25	23	6.58	−12	−60	−15	4	5.70						−20	−52	−20	35	>8
	L HVII	−28	−64	−50	6	5.18															
	R HV	20	−56	−20	19	6.58															

$P < 0.05$ corrected, k ⩾ 4 voxels; *Secondary peaks; HV = hemispheric cerebellar lobule V; L = left hemisphere; R = right hemisphere.

Table 4 *MNI coordinates of significant cluster maxima in the conjunction analysis of the patients over the three sessions (A, B, C) and the controls during session C for the FT task of the right hand*

Anatomical area (BA)	Side	Patients A					Patients B					Patients C					Controls C				
		x	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*
Primary motor area (BA 4)	L	−40	−20	65	77	>8	−48	−16	60	49	>8	−40	−20	65	47	>8	−40	−24	60	*	>8
Lateral premotor area (BA 6; 44)	L	−40	−16	65	*	>8	−40	−16	65	*	>8	−32	−4	60	*	5.40	32	−20	70	*	7.51
SMA (BA 6)	L	−12	−4	65	18	5.93						−4	0	60	29	7.11					
Cingulum (BA 32)	L						−8	8	45	13	5.75										
Primary sensory area	L	−52	−20	60	*	>8	−48	−32	60	5	6.18	−44	−24	50	*	7.38	−48	−36	60	90	>8
Posterior parietal areas (BA 40; 5)	L BA 40											−52	−40	60	6	>8					
	L BA 7																−44	−44	65	*	5.80
Cerebellum	R HV	20	−56	−20	45	>8	20	−56	−20	43	>8	20	−60	−20	12	6.36	16	−52	−20	48	>8

$P < 0.05$ corrected, k ⩾ 4 voxels; *Secondary peaks; HV = hemispheric cerebellar lobule V; L = left hemisphere; R = right hemisphere.

Table 5 *MNI coordinates of significant cluster maxima in the conjunction analysis of the patients over the three sessions (A, B, C) and the controls C during session C for the FE task of the right hand*

Anatomical area (BA)	Side	Patients A					Patients B					Patients C					Controls C				
		x	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*
M1 (BA 4)	L	−52	−20	60	77	>8	−40	−20	65	48	>8	−40	−24	55	47	>8	−40	−20	65	50	>8
Lateral premotor area (BA 6; 44)	L	−36	−20	70	*	>8	−36	−20	70	*	>8	−40	−20	70	*	>8	−32	−12	65	*	5.14
SMA proper (BA 6)	L	−8	−4	55	3	5.38	−4	−4	60	5	5.24										
Primary sensory area	L	−44	−24	55	*	>8	−52	−20	55	*	6.97	−48	−24	55	*	>8	−40	−24	55	*	>8
Cerebellum	R HV	16	−52	−20	47	6.91	20	−52	−20	45	7.05	20	−52	−20	45	>8	24	−56	−20	48	>8

$P < 0.05$ corrected, k ⩾ 4 voxels; *Secondary peaks; HV = hemispheric cerebellar lobule V; L = left hemisphere; R = right hemisphere.

Patients left FE (Table 3)

At the first session (A), patients showed contralateral activation in right dorsal M1, PMd, S1, and bilaterally in SMA and cerebellum. An additional small activation was detected in the left PMd for k = 1 (Fig. 2). At the second session (B), activation was limited to the right dorsal M1 extending to PMd and to the left QCL. At 2 years (session C), activation was observed in the PMd, the right dorsal M1, the S1 and in the SMA. The hemispheric laterality index was equal to 1.00.

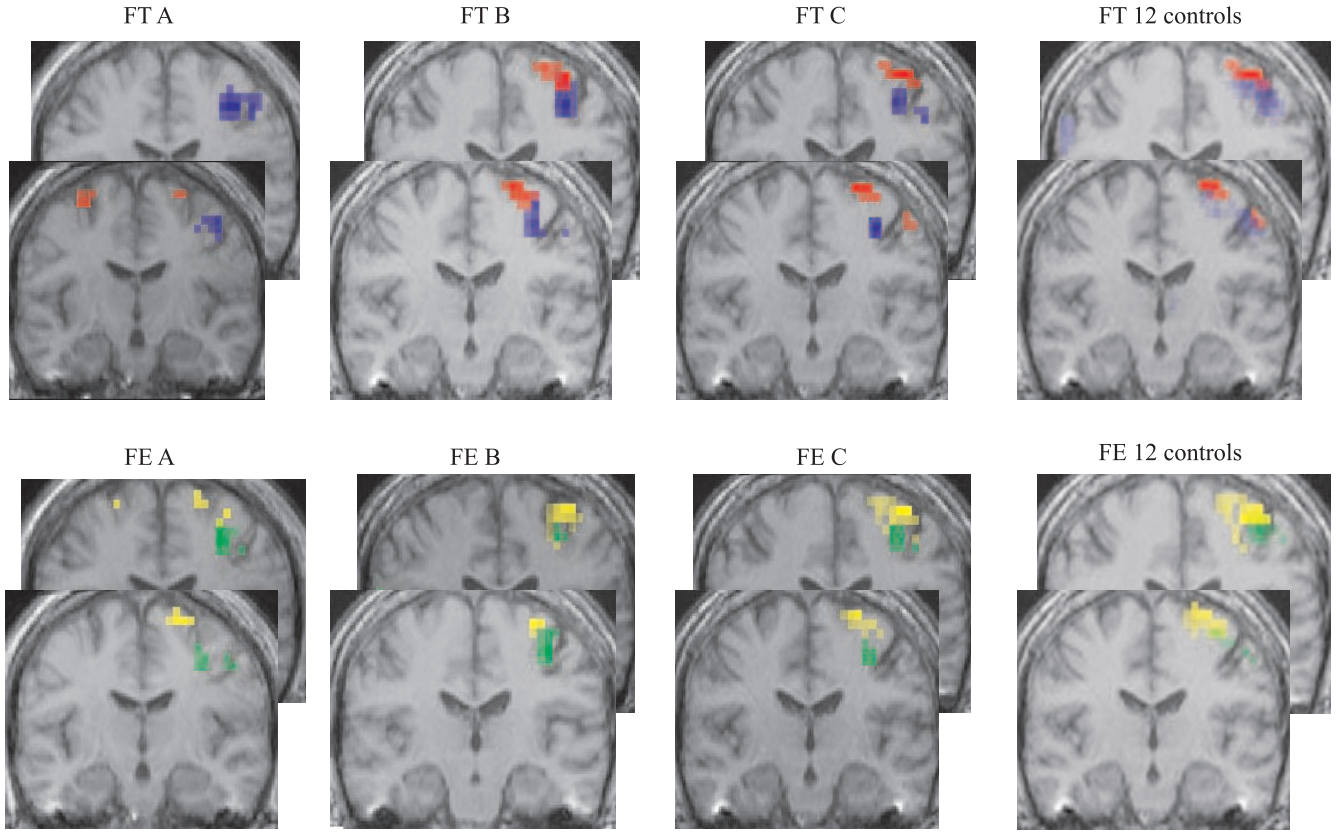

Fig. 2 Representative coronal sections from patient and control maps showing FT and FE-related activations for the left hand over time. (A) First session at 10 days after stroke. (B) Second session at 4 months after stroke. (C) Third session at 2 years after stroke. 12 controls = patients' third session and single session for 12 normal controls). MNI coordinates (mm) $y = -16$ in the lower row and $y = -20$ in the upper row for FT and FE. Red areas represent FT-related activation in patients; blue areas represent FT-related activation in controls; yellow areas represent FE-related activation in patients; green areas represent FE-related activation in controls. All voxels are significant at $P < 0.05$ corrected for multiple comparisons. Sections are arranged in neurological orientation (i.e. right side of brain to viewer's right). See Tables 2 and 3 for exact coordinates of voxels.

Right FT and FE

The FT and the FE led to the usual motor activation patterns in the controls and the patients groups (see Tables 4 and 5). Each group displayed PMd to SM1 and left QCL activations, plus a small cluster in the left posterior parietal cortex during the right FE.

Comparison of the paretic hand of patients with their matched controls at the chronic stage (session C)

The comparison of left FT in patients with controls at 2 years (patients C—controls C) revealed right PMd–dorsal M1 and SMA activations, as shown in Table 6 and Fig. 3. The reverse (controls C—patients C) displayed only S1 activation. For the left FE, the contrast (patients C—controls C) showed the same right PMd-dorsal M1 activation as for FT (more a small cluster in the left posterior parietal cortex), while the reverse (controls C—patients C) did not lead to any activation. The comparison of controls and patients did not induce activation for the right hand.

Left FT and FE of the 12 subjects control group

Both FT and FE tasks activated the M1 from right PMd to SM1, the left SMA and the left QCL. The right QCL was activated for FT alone. The peak of activation was more dorsal and rostral for FE than for FT. Compared with this control group, patients' FT and FE related motor activations were more dorsal and rostral (Fig. 2).

Motor centres of activation

When the mean x,y,z Talairach coordinates of the four patients and their four matched controls were analysed separately for FT and FE and for each hand, there were significant differences between patients and controls in the mean x and z Talairach coordinates for the left FT ($P = 0.028$ for x and $P < 0.001$ for z), but not for the left FE ($P = 0.319$ for x and $P = 0.089$ for z). For left FT, the mean x was lower and the mean z was higher in the patients than in the controls, corresponding to a dorsal shift of the motor centres of activation. No such significant difference was found for the right hand.

Table 6 *MNI coordinates of significant cluster maxima in the group comparison analysis of the patients with the controls during the third sessions (C) for FT and FE of the left hand*

Anatomical area (BA)	Side	Left FT					Left FE				
		x	*y*	*z*	k	*Z*	*x*	*y*	*z*	k	*Z*
Patients–controls											
M1 (BA 4)	R	32	−20	70	14	>8	32	−20	70	14	>8
SMA proper	R	4	0	70	6	6.10					
	L	−4	−16	70	5	5.70					
Superior parietal lobule (BA 5; 7)	L						−48	−40	65	6	4.88
Controls–patients											
Primary sensory area	R						44	−32	55	9	5.38

*$P < 0.05$ corrected, k ⩾ 4 voxels.

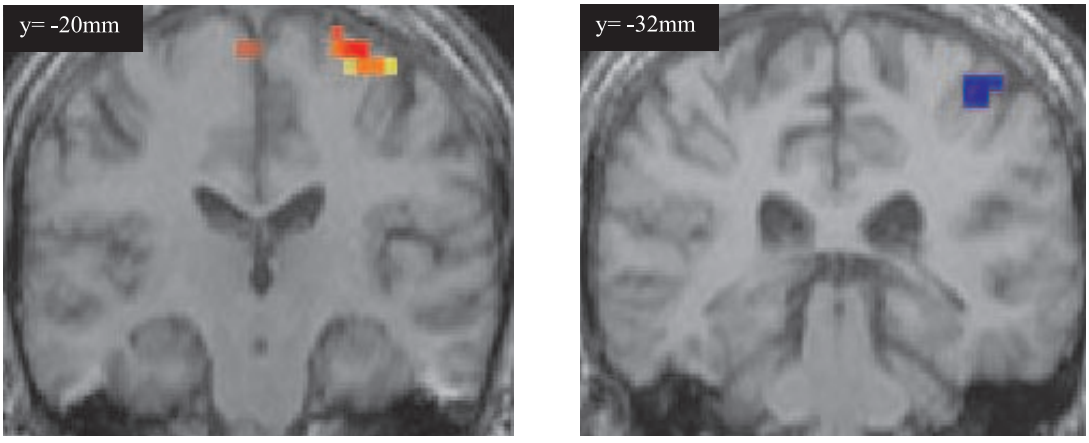

Fig. 3 Coronal sections (MNI coordinates) showing the comparison between patients and controls at 2 years after stroke of left finger tapping (FT) and flexion extension (FE). The contrast 'patients–controls' for FT is marked in red and the reverse in blue, indicating that FT-related activation is more dorsal and rostral in patients than in controls. The contrast 'patients—controls' for FE is marked in yellow, while the reverse, which did not induce activation at this threshold, is not displayed. Notice that patients' FT-related activation is located rostrally to FE. All voxels are significant at $P < 0.05$ corrected for multiple comparisons. Sections are arranged in neurological orientation (i.e. right side of brain to viewer's right).

In the patients' group (Fig. 4), there was a significant temporal evolution for *z* coordinate over the three sessions for left FT only ($P = 0.014$), which remained significant between the two last sessions ($P = 0.046$). No significant temporal evolution was observed for left FE ($P = 0.779$). The specific displacement over two years of the FT-related motor centres of activation in *z* coordinates is displayed in Fig. 4. Furthermore, when comparing the left FT of the patients for each session against the 12 controls, the mean *z* remained significantly higher in the patients for the three sessions (session 1 $P = 0.042$; session 2 $P = 0.042$; session 3 $P = 0.002$), while *z* did not vary for FE. The mean *x* and *y* were not significantly different between groups, whatever the session or the task.

The effect size

The effect size measured in the contralateral motor cortex (M1) for each hand and each task showed an initial decrease for the FT of the left hand compared either to the controls' left hand ($P = 0.05$) or to the right unaffected patients' hand ($P = 0.04$). No such differences were observed for the FE task. Furthermore, the effect size first increased significantly for both hands from the first to the second session ($P = 0.05$) and then decreased until the third session (Fig. 5). No such difference was observed in the cerebellum.

Discussion

In agreement with our primary hypothesis, the recovery after partial lesion of M1 at the chronic stage was associated with the canonical motor lateralized activations for both FT and FE tasks. Our results provide, for the first time in patients, evidence that efficient long-term motor recovery after stroke within M1 area is associated with reorganization within the surrounding motor cortex. However, the time course and the type of motor task in the recovery process have to be addressed.

Study design

Experimental design

The self-paced tasks can be questioned because they may induce variability in the performance (Sadato *et al.*, 1997*a*).

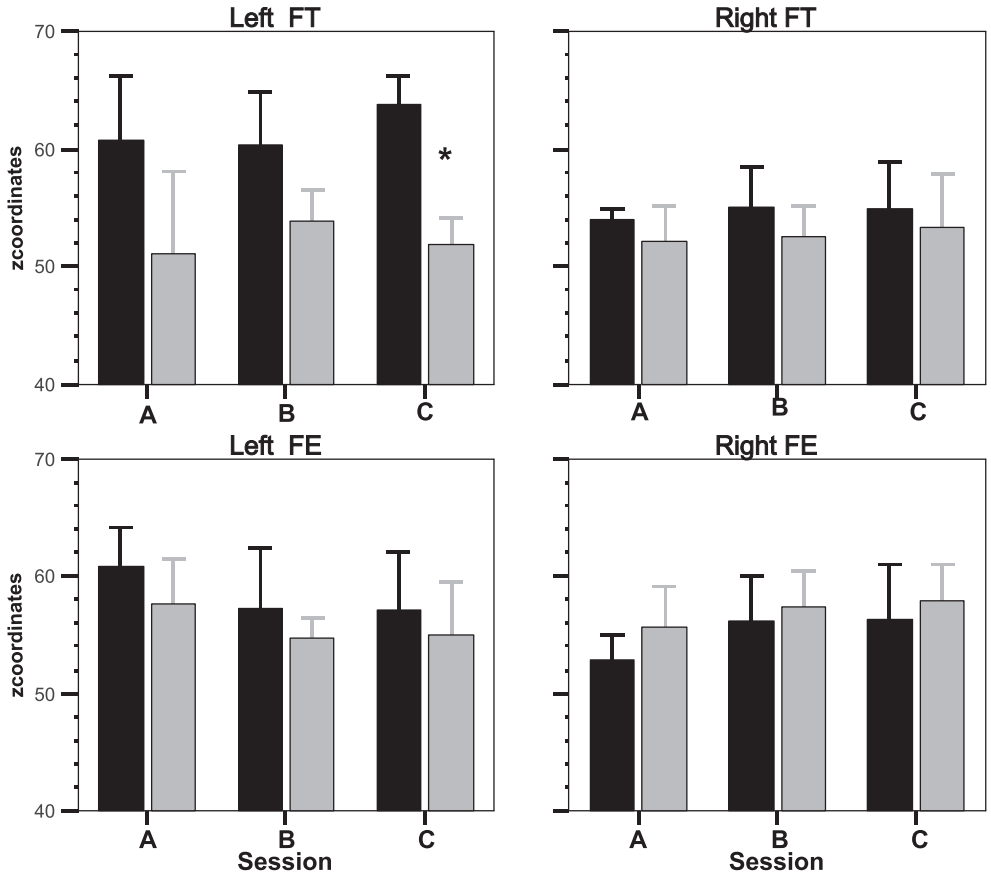

Fig. 4 Mean *z* Talairach coordinates of the centres of mass (in mm) and standard deviation for each task (FT and FE) and each hand in patients (black bars) and in controls (grey bars) over the three sessions (A, B and C). The first graph highlights the dorsal shift for left FT with a significant difference between patients and controls for the third session.

However, when patients perform a determined paced motor task, they may not control other aspects of the task such as amplitude, force and precision, possibly resulting in a correct rate but heterogeneous real performance. Yet, these performance parameters may modulate motor brain activation (Waldvogel *et al*., 1999; Ehrsson *et al*., 2000, 2001; Grafton *et al*., 2000). To promote the high quality of the performance of the movement, we chose a self-paced rate associated with pre-session training until each patient was able to perform correct FE and FT movements at a minimum rate of 1 Hz for FT (Jenkins *et al*., 1994; Petersen *et al*., 1998). Studies have shown that SM1 and SMA proper were equally activated either between regular and irregular cueing tasks (Toma *et al*., 2003) or between the self-paced and externally triggered movement conditions (Cunnington *et al*., 2002), indicating that the patterns of motor-related activation we see in our study are not related to the timing aspects of movement. According to data from Sadato *et al*. (1997*a*), we assumed that small variations of rate from 1.0 to 1.5 Hz do not induce significant variations of size and percentage of signal change in contralateral M1. Moreover, our results were not altered when adding the actual FT rate as a nuisance variable in the model. Furthermore, for handling the other potential confounding of task-related, learning-related and age effects, we used a completely temporally balanced experimental design (Petersson *et al*., 1999).

The role of the side of stroke

Usually, non-dominant hand movements have different cortical organization than dominant hand movements, the former being more bilaterally organized in right-handed subjects (Kim *et al*., 1993) and in chronic stroke patients (Zemke *et al*., 2003). Since our study included only right-handed patients with a right-sided stroke, ipsilateral motor-related activations may not be inferred from our results.

Contralateral and ipsilateral hemispheric motor-related activations at the subacute stage of recovery

At this period, we observed a dissociation of the motor-related activation according to the type of the task. The pattern of activation for the left FT task was characterized by the activation of the ipsilateral PMd, M1 and S1, associated to contralateral activation of SMA and bilateral QCL activation. In parallel, the effect size in the contralateral M1 was significantly decreased, corroborating the inability of the damaged

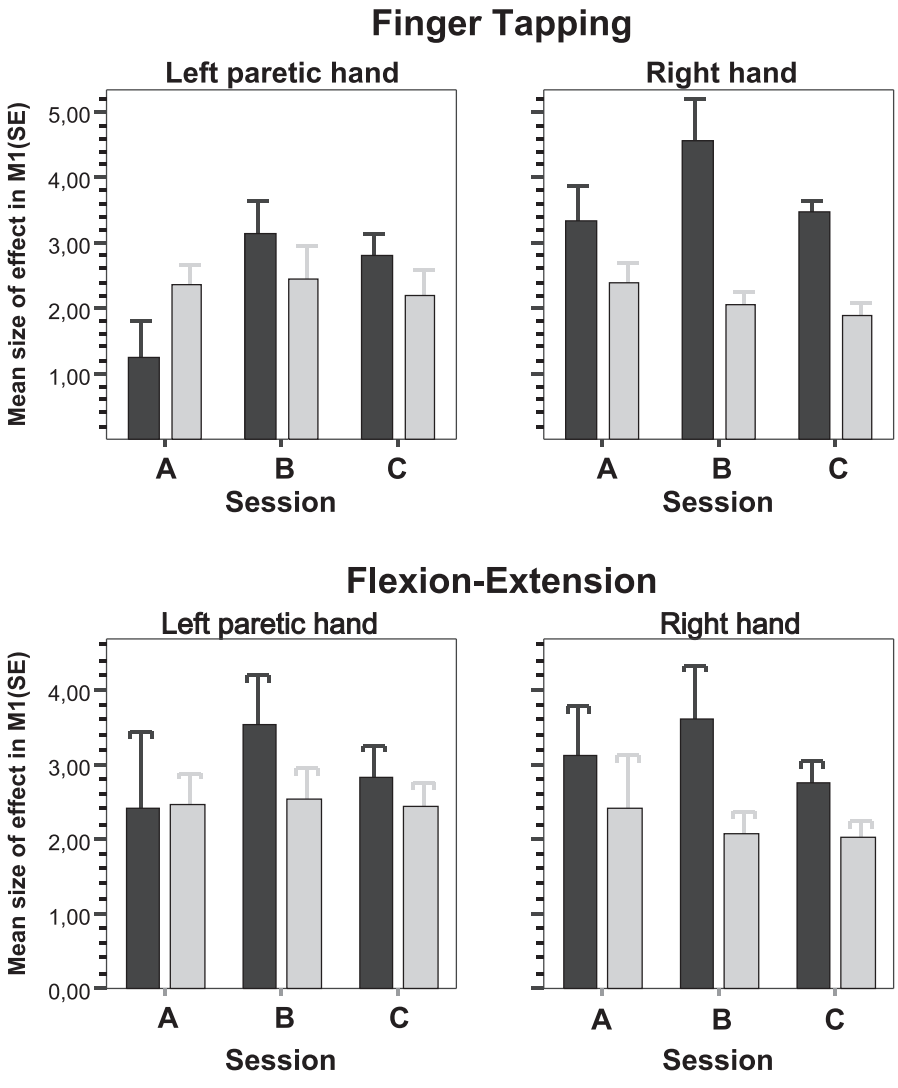

Fig. 5 Mean effect size at the maxima of the contralateral M1 cluster for the FT and FE tasks (dark bars represent patients and grey bars controls), showing: (i) the decreased effect size at the first session for the left FT in patients compared with the right FT and to the left FT of controls; and (ii) the increased effect size for the right FT and FE in patients compared with the controls over the three sessions.

M1 cortex alone to provide an efficient motor performance for FT. Unlike the FT, the left FE task induced a lateralized pattern of activation involving contralateral right PMd, M1 and S1. Furthermore, the effect size in contralateral M1 did not show significant decrease relative either to the controls or to the healthy hand.

The decreased contralateral BOLD signal in the damaged M1 may reflect changes in resting perfusion as it was shown that the magnitude of the BOLD response can be affected by the cerebral blood flow (CBF) increase in response to acetazolamide administration (Brown *et al*., 2003). Similarly, near exhaustion of cerebrovascular reserve (Bruhn *et al*., 1994), an usual condition in acute stroke, may produce a ceiling effect on the CBF response and affect the BOLD response (Cohen *et al*., 2002; Brown *et al*., 2003). By the time of the first session, the perfusion maps in our patients did not show differences larger than 20% between symmetric regions of both hemispheres, when determining the relative CBF and cerebral blood volume (CBV), either within or around the damaged area. The coupling of BOLD with neural activity remains to be examined, although we cannot exclude the possibility that BOLD signal decrease is related to changes of relative CBF/CBV within the injured area. This could not be detected in relation to its limited reliability to the low spatial resolution of perfusion MRI that may under diagnose ischaemia (Kiselev, 2001), or to abnormal cerebrovascular reactivity (Brown *et al*., 2003) usually associated to large infarcts and large artery occlusion (Yamamoto *et al*., 2004). However, our patients had small local cortical infarcts and CBF variations, which could not explain the increased BOLD signal in the undamaged motor cortex.

In healthy subjects, the focal inhibition of M1 obtained with TMS was mirrored by an fMRI BOLD signal decrease (Hamzei *et al*., 2002). After an acute stroke, a decreased

cortical excitability has been shown using TMS in the affected hemisphere (Wassermann *et al*., 2000) with a progressive tendency towards normality 3 months after stroke (Traversa *et al*., 2000). Thus, the BOLD signal decrease in the damaged cortex observed in our study is consistent with decreased cortical excitability in M1. Moreover, experimental data after motor cortex lesion in rodents have shown an initial atrophy of the dendritic fields of the pyramidal neurons in layer V in the adjacent motor cortex, followed by regrowth and expansion of these dendritic fields over several months (Kolb and Whishaw, 2000). Meanwhile, Dijkhuizen *et al*. (2001) carried out an fMRI stroke study in rats and showed that the forelimb impairment was associated with the loss of stimulus induced activation in the ipsilesional sensorimotor cortex at 3 days after stroke, with significant activation detected in the contralesional hemisphere. However, local tissue and perfusion were only moderately affected and cerebrovascular reactivity was preserved in the motor areas. At 14 days after stroke, bilateral activation was detected. Similarly, the decreased motor-related activation in the damaged hemisphere observed in our study might be correlated to dendritic dysfunction, while subsequent increased activation might reflect functional motor recovery as a result of dendritic regrowth and synaptic restructuring.

Changes observed in the intact hemisphere

Significant motor–premotor activation was induced in the undamaged hemisphere by FT but not by FE, resulting in a negative laterality index (−0.77) for FT and a positive index for FE (1.00). In parallel, at the time of the first session, patients' motor performance was impaired for FT, but not for FE. When analysing individual data, the only patient who had predominant ipsilateral motor activation during left FE in the acute period had the most extended M1 lesion, in contrast to the other patients with infarction restricted to a limited part of the hand motor area. This is consistent with TMS studies (Wassermann *et al*., 2000) where the greater motor impairment and the greater the interhemispheric asymmetry suggest that more the function is impaired, the more it is assumed by the undamaged hemisphere. After SM1 lesions in rats, Jones *et al*. (1996) described pruning of dendritic overgrowth associated with synaptic restructuring in the intact cortex occurring around day 18 and persisting beyond 30 days. The adaptability of the neural structure might facilitate spontaneous recovery by rewiring the brain (Schallert *et al*., 1997). In combined TMS–fMRI studies, Foltys *et al*. (2003) showed that forceful activation of homologous muscles of the hand increased excitability of the ipsilateral corticospinal system, which may be mediated by transcallosal inhibition rather than ipsilateral uncrossed descending pathway (Kobayashi *et al*., 2003) as a consequence of a decrease in GABAergic inhibition (Chen *et al*., 2002). Thus, the ipsilateral activation of motor regions may be regarded as an increased utilization of neural resources in our patients for whom the correct execution of a motor hand task was highly demanding and induced paucity of activation in contralateral motor areas. Furthermore, several experimental and human fMRI, TMS and PET stroke studies have underlined the role of the premotor cortex in motor recovery (Aizawa *et al*., 1991; Chollet *et al*., 1991; Cicinelli *et al*., 1997; Liepert *et al*., 2000*a*; Wassermann *et al*., 2000; Nudo *et al*., 2001*b*; Shimizu *et al*., 2002; Rossini *et al*., 2003) and provided evidences of the functional significance of ipsilateral PMd activity, which could mediate an adaptative compensatory motor function (Johansen-Berg *et al*., 2002*a*). The effective aptitude of the ipsilateral PMd and M1 cortex to be responsible of the FT task performed by the left hand can be questioned, since the exact relationship between the measured fMRI signal and the underlying neural activity remains unclear (Logothetis *et al*., 2001). Moreover, the relative increased BOLD signal observed in our patients for the healthy right hand emphasizes the hyperexcitability of the unaffected motor cortex in relation to decreased transcallosal inhibition from the damaged motor cortex. We can speculate that the transient ipsilateral PMd activation observed in the intact hemisphere of our patients for the FT reflects short-term plasticity.

Functional dissociation between FT and FE

Ipsilateral activation for FT and decreased effect size in the contralateral damaged M1 correlated with the impairment of patients' FT task performance at 10 days after stroke, while both the pattern of activation and the effect size tend towards normal for correctly performed FE. FT and FE differ by the higher sensory component involved in the FT, but also by the load or the complexity of this task. In this context, the functional dissociation between FT and FE might be related to the anatomic stroke topography. In our patients, the ischaemic lesion affected the depth of the rolandic sulcus, devoted to motor tasks involving sensory modalities such as FT compared with FE (Geyer *et al*., 1996; Preuss and Kaas, 1996; Preuss *et al*., 1997). Moreover, FT involving complex finger movements possibly implies a higher subjective level of attention to movement than FE (Binkofski *et al*., 2002). Our findings, showing an anatomical–clinical correlation between the dissociated performance of FT and FE, and the damage of the ventral part of M1, emphasizes the hypothesis of a dynamic organization of the motor systems rather than a somatotopic output organization developed by Sanes and Donoghue (1997). Their findings indicate that the connectional substrate for reorganization was already present in M1 at the acute stage, allowing new maps to emerge when the balance of excitatory and inhibitory synaptic connections is changed.

Cerebral reorganization at the chronic stage of recovery: a vicariant process?

At the chronic phase, i.e. over 4 months after stroke, our patients showed a lateralized pattern of motor activation involving contralateral PMd, M1, and SMA for both FT and FE.

Other longitudinal stroke studies in patients who regain most of their motor abilities have shown initial ipsilateral motor cortical activations associated with the recruitment of motor-connected regions such as prefrontal and parietal regions followed by more lateralized patterns of activations several months after stroke (Nelles *et al*., 1999; Marshall *et al*., 2000; Calautti *et al*., 2001*a*, *b*; Loubinoux *et al*., 2003; Ward *et al*., 2003). The more lateralized activation is maintained over time, the better the recovery (Rossini *et al*., 2003). Other studies have reported either a ventral expansion of M1 activation into the face area (Weiller *et al*., 1992) or a posterior shift (Pineiro *et al*., 2001; Calautti *et al*., 2003) in patients with one lacunar stroke. These plastic changes may correspond to the recruitment of parallel projections from the intact pyramidal tract. They are usually considered to reflect the large redundancy in cortical connections (Rijntjes and Weiller, 2002)—an assumption which is close to the concept of vicariance. Another study reported one patient with several chronic stroke lesions, of which one was restricted to the precentral gyrus from PMd to M1 (Cramer *et al*., 2000). In this study, FT-related brain activations were observed only in contralateral postcentral gyrus. However, the comparison with our results is limited due to the PMd damage and the association of other cerebral infarcts, which might have led to iterative modifications of cerebral networks.

As described above, M1 is subdivided into dorso-rostral and ventro-caudal fields, where neurons responsive to joint manipulation and muscle stimulation are located more rostrally (M1a) than neurons responsive to cutaneous stimulation located in the depth of the rolandic sulcus (M1p) (Geyer *et al*., 1996; Preuss and Kaas, 1996; Nudo *et al*., 1997; Preuss *et al*., 1997). After FT-related brain activation involved the ipsilateral motor area in the first few weeks, it further emerged in the contralateral (or ipsilesional) motor area. Our findings indicate that successful motor recovery process after limited lesion of the hand motor cortex is based on adjacent motor reorganization, suggesting a 'vicariation' (adaptive plasticity) model of recovery. The question about the vicariance is focused on the emergence of the representation of the FT in novel locations within the M1 motor area. Both FT and FE-related brain activations obtained for the recovered left hand at the chronic phase have shown a dorso-medial shift within M1 relative to the left hand of the controls. The robustness of these findings was reinforced when the sample size of the controls group was increased to 12 subjects (Fig. 2). The comparison of the motor centres of activation also evidenced a shift between the left hand of the patients and the controls, and between the left and right hands of the patients (Fig. 4). Interestingly, the left FT of the patients revealed a more dorsal motor activation than FE (Fig. 3), resulting in an inverted representation of FT and FE within M1. In addition, when examining the stroke topography of our patients, the lesion was located from 40 mm to 56 mm above the bicommissural plane with a median of 52 mm, in the ventro-caudal part of M1 (M1p) (Geyer *et al*., 1996). The ischaemic damage within M1p might have resulted in a dorso-caudal shift towards M1a, corresponding to a newly expanded representational territory of the finger movements towards the intact motor cortex. The emergence of a task-related motor representation in novel locations in the intact area 4a instead of the damaged area 4p, indicates a vicarious process within motor areas in accordance with experimental studies (Xerri *et al*., 1998; Nudo *et al*., 2000). Furthermore, we may assume that FT-related plasticity has been rewired by the recruitment of ipsilateral motor cortex inducing structural plasticity within the M1 hand area surrounding the lesion, i.e. within M1a. Meanwhile, FE movements, being mildly impaired, underwent only limited neural reorganization. Long-term plasticity changes including long-term potentiation, axonal regeneration and sprouting may result in the emergence of a new representation of the FT movements within M1a and in the restitution/re-emergence of the representation of the FE movements which were only transitorily impaired. The dissociated recovery strategies that occurred for the re-acquisition of pre-infarct FT and FT movements provide more evidence of a vicarious process within motor area.

Potential biases responsible of this shift have to be examined. Anatomical distortion secondary to infarct shrinkage could have modified activation maps, resulting in a misleading shift of activation between controls and patients. However, the small size of infarct (mean volume = 2.21 cm^3), and the relative greater shift of FT compared with FE do not support such a bias. Furthermore, infarct shrinkage should have reduced distances between the geometric centres of activation and the bi-commissural plane, leading to a ventral shift rather than to the observed dorsal shift. The role of increased attention to movement (Johansen-Berg and Matthews, 2002) and increased force (Cramer *et al*., 2002) by modulating cortical activity within M1 could also be confounders. However, the shift increased progressively over 2 years while the patients recovered and consequently need less effort.

A further point concerns the compensatory use of proximal musculature during the motor tasks, leading to the activation of dorsal motor cortex in relation to proximal arm somatotopy, which could look like a false dorsal shift. The absence of shoulder or elbow movements noticed by the observer close to the patient during the fMRI scans, the slowness of the FT and FE rate in the aim to obtain the best motor performance, and the bilateral extensive activations usually resulting from proximal movements allow us to rule out compensatory movements. However, the representation of joint movements of the fingers may have expanded in the dorsal M1 region at the expense of wrist/forearm representations, as has been demonstrated after training in squirrel monkeys (Nudo *et al*., 1996*a*, *b*) and in rats (Kleim *et al*., 1998).

Role of repetitive rehabilitative training

Repetitive rehabilitative training played a crucial role in the emergence of the modified representation of the hand movements within M1. Experimental studies have shown

that retention of hand representational area within M1 after cortical injury required repetitive use of the impaired hand, while the size of the hand representation had decreased in monkeys who did not receive rehabilitative training (Friel *et al*., 2000). Increased use of the impaired limb appears to have a modulatory effect on plasticity in the surrounding tissue (Nudo *et al*., 1996*b*; Johansson, 2000). However, repetitive motor training alone does not produce functional reorganization of cortical maps. Instead, motor skill acquisition appears to be a prerequisite factor in driving representational plasticity in the motor cortex (Nudo *et al*., 1997). However, the reorganization of cortical networks and motor skill re-acquisition may be compromised by the relative size of the lesion (Friel and Nudo, 1998). Our four patients, who presented with a restricted lesion of M1, followed daily post-stroke rehabilitation leading to motor skill re-acquisition. In these conditions, it is likely the existence of a vicariant process within M1 promoted by rehabilitative training could explain the post-stroke fMRI dorsal shift. The pre-session training was performed by all subjects in order to achieve a standard good result regarding the motor performance and to avoid learning effect-related activations.

Role of non-primary motor areas

A salient feature of our study was the FT and FE motor-related activation in the SMA proper at the post-acute and the chronic phase of recovery. The modulatory effect of SMA has been well-documented using functional imaging (Thaler *et al*., 1995; Rizzolatti *et al*., 1996; Sadato *et al*., 1997*b*; Ball *et al*., 1999; Cunnington *et al*., 2002; Toyokura *et al*., 2002). The SMA appears crucial in sequential performance of movements (Tanji, 1994), especially in the initiation of internally generated movements (Thaler *et al*., 1995). More recently, an fMRI study carried out in stroke patients has shown that post-acute motor-related activation of SMA correlated with a faster or better motor recovery (Loubinoux *et al*., 2003). Studies in primates had already raised the importance of the SMA in the re-acquisition of motor tasks after lesion of the motor cortex (Aizawa *et al*., 1991). The SMA proper, while receiving precentral and postcentral afferents, sends direct corticospinal efferences and projects to MI (Rizzolatti *et al*., 1996; Picard and Strick, 2001), suggesting that SMA might have supported the impaired motor function of M1 since the post-acute stage. Moreover, consistent with these data, our results indicate that motor-related activation of SMA may reflect an adaptative response to an increased demand related to the need to relearn motor tasks after stroke. The re-acquisition of a skilled performance at the chronic phase is highlighted by the recruitment of SMA for FT but not for FE when patients were compared with controls (Table 6). In parallel, the functional contribution of the ipsilesional PMd in motor recovery after lacunar stroke has been emphasized in a recent TMS study (Friedman *et al*., 2004).

The additional FT-related activations of parietal posterior areas we saw in our patients may reflect increased attentional load after stroke (Bremmer *et al*., 2001; Haslinger *et al*., 2002; Mesulam, 2000*b*). It also underscores the importance of the posterior parietal cortex in processing length and complexity of sequential finger movements (Ehrsson *et al*., 2000; Bremmer *et al*., 2001; Buccino *et al*., 2001), since FT-related posterior parietal activations were also found for the right hand in both patients and controls.

The present study describes, for the first time, the neural substrates of motor reorganization using fMRI in humans after one single unilateral ischaemic lesion limited to a part of M1. The small number of patients, related to the rarity of isolated ischaemic stroke involving only M1 in patients, is a limitation of this study. Therefore, if we were able to test the hypothesis of vicariation within the human motor cortex, our results might not be generalized as the usual mode of stroke recovery.

Our findings indicate that the impaired motor function was initially promoted, at least partly, by the premotor areas of the undamaged hemisphere. Then, as the patients recovered, skilled motor functions were completely assumed by the motor cortical areas adjacent to the lesion, leading to a dorsal shift of fMRI activation within the M1 cortex, in relation to plastic changes. Our results, consistent with previous experimental studies, suggest that the human primary motor cortex adjacent to a lesion is capable of vicarious function.

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