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Cortical motor reorganization after a single clinical attack of multiple sclerosis

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Summary

In order to evaluate whether cortical motor reorganization occurs in the earliest phase of multiple sclerosis, we studied patients after a first clinical attack of hemiparesis. From a consecutive series of 70 patients enrolled in a study of patients with clinically isolated syndrome and serial MRI findings indicative of multiple sclerosis, we retrospectively selected 10 patients with hemiparesis as the onset symptom and no further clinical episode [mean age 32 ± 9 years, disease duration 24 ± 14 months, median Expanded Disability Status Score (EDSS) 1.25]. Ten age-matched, healthy subjects served as controls. Each subject was submitted to two functional MRI trials (one per hand) using a 1.5 T magnet during a sequential finger-to-thumb opposition task. Image analysis was performed using SPM99 software. Movements of both the 'affected' and the 'unaffected' hand activated significantly larger areas in patients than in controls in both the contralateral and ipsilateral cortical motor areas. Patients activated a greater number of foci than controls during both the right-hand and the left-hand movement. Most of these foci were located in cortical areas which were less or not at all activated in controls, such as the lateral premotor cortex [Brodmann area (BA) 6], the insula and the inferior parietal lobule (BA 40). Between-group analysis of patients versus controls showed significant ($P < 0.001$) foci in these areas, principally located in the ipsilateral hemisphere during right-hand movement and in both the cerebral hemispheres during left-hand movement. Time since clinical onset showed a significant positive correlation with the extent of activation in the ipsilateral motor areas ($P = 0.006$) during the right-hand movement and with the extent of activation in both the ipsilateral ($P = 0.02$) and contralateral ($P = 0.006$) motor areas during the left-hand movement. The T_1 lesion load along the motor pathway showed a significant positive correlation ($P = 0.007$) with the extent of activation in the contralateral motor areas during right-hand movement. Our study shows functional adaptive changes that involve both the symptomatic and asymptomatic hemisphere during a simple motor task in patients who had suffered a single clinical attack of hemiparesis. The extent of these changes increased with the time elapsed since disease onset and the severity of brain damage.

Keywords: fMRI; motor stimulation; multiple sclerosis; hemiparesis; neuroplasticity

Abbreviations: BA = Brodmann area; CIS = clinically isolated syndrome; fMRI = functional MRI; LL = lesion load; MNI = Montreal Neurological Institute; ROI = region of interest; SPM = statistical parametric mapping; T1WI = T_1-weighted spin-echo image; T2WI = T_2-weighted spin-echo image; TR = repetition time; TE = echo time

Introduction

Neuroplasticity is a fundamental property of the CNS throughout the lifespan and represents a mechanism to optimize behavioural gain. Patients with multiple sclerosis may show symptomatic recovery while accumulating tissue damage progressively. Accordingly, they often show a discrepancy between lesions on conventional MRI and clinical symptoms (Smith *et al*., 1993). It is conceivable that the ability of the brain to compensate for tissue impairment or loss may contribute to the maintenance of normal performance despite scattered brain lesions.

Two recent articles have shown adaptive functional changes, such as activation of the ipsilateral motor pathway and posterior extension of the contralateral primary motor area, in the cerebral cortex of multiple sclerosis patients in response to motor stimulation (Lee *et al*., 2000; Reddy *et al*., 2000). These studies, however, included patients with both

Table 1 *Clinical data of 10 patients with clinically isolated syndrome*

Patient	Age (years)	Side of hemiparesis	Months since onset	EDSS	T_1 lesion load (cm^3)	T_2 lesion load (cm^3)
1	38	Right	20	1	0.46	3.68
2	30	Right	18	2.5	1.04	9.47
3	27	Right	33	1.5	1.22	10.08
4	51	Right	23	1	3.12	10.19
5	41	Right	40	1	0.17	2.31
6	23	Left	36	1.5	1.50	4.90
7	21	Left	48	0	1.15	8.00
8	26	Left	8	0	0.53	3.98
9	29	Left	6	1.5	0.86	9.27
10	33	Left	11	2.5	0.31	1.79

relapsing–remitting and secondary progressive multiple sclerosis, with a disease duration which, in some cases, exceeded 20 years.

In patients with a long history of multiple sclerosis it is difficult to correlate functional changes in the motor cortex with clinical recovery from a single previous motor deficit because of the recurrent damage of the motor pathways and/or involvement of other neural systems. Moreover, it is difficult to establish exactly when, during the course of the disease, cortical reorganization takes place, whether it occurs immediately after a first, isolated motor deficit or whether repeated insults to the executive motor system and/or to connected neural pathways are needed to induce adaptive cortical changes.

The earliest clinical event in many patients with multiple sclerosis is a clinically isolated syndrome (CIS) suggestive of multiple sclerosis. In patients with CIS, the diagnosis of possible multiple sclerosis or multiple sclerosis can be made on the basis of MRI evidence of lesion dissemination in space and time (McDonald *et al*., 2001). We therefore focused on patients who had presented an isolated episode of transient hemiparesis and who showed serial MRI findings indicative of multiple sclerosis. The aim of this study was to evaluate patterns of brain activation during a motor task in these patients in order to assess whether cortical reorganization (i) is a phenomenon that occurs in the very early phase of the disease, (ii) is associated with clinical manifestations, i.e. changes in patterns of motor activation occur exclusively during the movement of the previously affected hand, and (iii) correlates with the severity of tissue loss, as measured by the T_1 hypointense lesion load.

Subjects and methods

Subjects

Out of a consecutive series of 70 patients enrolled in a study of patients with CIS and positive MRI findings according to the criteria of Fazekas and colleagues (Fazekas *et al*., 1988), we retrospectively selected patients who fulfilled the following criteria: (i) right-handedness; (ii) hemiparesis as the onset symptom; (iii) no further clinical episode; (iv) no sensory and/or motor deficit at the neurological examination; and (v) no MRI lesions in the spinal cord.

Ten women, aged between 21 and 51 years (mean 32 $\pm$ 9 years), were included in this study. At the time of the functional MRI (fMRI) study, nine of them had a diagnosis of multiple sclerosis and one of possible multiple sclerosis according to the recommendations of the International Panel on the Diagnosis of Multiple Sclerosis (McDonald *et al*., 2001). The mean time elapsed from the clinical episode to the fMRI study was 24 $\pm$ 14 months. The clinical and conventional MRI data of the 10 patients are summarized in Table 1. All the patients gave their written informed consent to participation in the study which was approved by The Ethical Committee of The University of Rome 'La Sapienza'.

The control group for fMRI data consisted of 10 right-handed volunteers (mean age 31 $\pm$ 8 years).

MRI data acquisition

Morphological and functional MRI data were acquired during the same imaging session using a 1.5 T magnet (Gyroscan NT 15; Philips, Eindhoven, The Netherlands) with echo-planar capabilities and a head volume radio-frequency coil. Each subject lay supine in the scanner with eyes closed. Head movements were minimized by using foam padding and a restraining strap.

Slice orientation parallel to the anterior–posterior commissural plane was ensured by acquiring a multiplanar T_1-weighted localizer at the beginning of each study. We then acquired T_2*-weighted echo-planar images (64 $\times$ 64 matrix over a 24 cm field of view), consisting of 25 consecutive, 4 mm thick axial sections, with repetition time/echo time (TR/TE) 3000/50 ms, a flip angle of 90° and one excitation.

Each functional study lasted 225 s, during which a total of 75 consecutive dynamics were acquired.

After the fMRI study, a morphological MRI protocol was performed which included proton density- and T_2-weighted spin-echo images (T2WI) (TR = 2000 ms, TE = 20/90 ms),

fluid-attenuated inversion-recovery (FLAIR) images (TR = 6000 ms, TE = 150 ms) and T_1-weighted spin-echo images (T1WI) (TR = 550 ms, TE = 12 ms) before and after injection of an intravenous bolus of 0.3 mmol/kg gadolinium–diethylenetriaminepentaacetic acid.

Motor task

During the fMRI acquisition, the patients and normal subjects performed a self-paced sequential finger opposition task in which the thumb repeatedly touched the other four fingers in sequential order. Two fMRI trials (one for each hand) were performed for each subject during the motor task. Seven periods of hand movement and seven periods of rest were alternated. 'Start' and 'stop' acoustic signals were given during the acquisition. Subjects were required to perform the task as quickly as possible with their hand opened widely. Correct execution of the task was confirmed by an operator who was present in the magnet room during the whole session and who recorded the rate of hand movements for patients and controls. The rate of hand movement was not significantly different either between the right and left hand in patients (2.0 ± 0.2 and 1.9 ± 0.1 Hz, respectively) or between patients and control subjects (1.9 ± 0.2 and 2.1 ± 0.2 Hz, respectively).

Functional MRI data analysis

fMRI data were analysed using statistical parametric mapping software (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London) according to the following procedure. Images were realigned, normalized and spatially smoothed using a Gaussian kernel of 8 mm.

Images were analysed using a two-stage random-effect approach. In the first stage, the time series of fMRIs obtained from each participant was analysed separately. The effects of the experimental paradigm were estimated on a voxel-by-voxel basis using the principles of the general linear model extended to allow the analysis of fMRI data as a time series (Friston *et al*., 1994, 1995). The data for each subject were modelled using a boxcar design, convolved with a haemodynamic response function chosen to represent the relationship between neuronal activation and blood flow changes. The boxcar had the same on/off frequency as the alternation frequency of the two conditions (hand movement and rest).

Signal changes that were significantly related to hand movement were obtained for each subject. Significance was determined on a voxel-by-voxel basis using a *t*-statistic, which was then transformed into a normal distribution. The resulting sets of spatially distributed *Z*-values constitute statistical parametric maps (SPM{*Z*}), which show regions of significant condition-associated signal changes. These regions were then displayed with a statistical threshold based on the amplitude ($Z > 5.1$, $P < 0.05$ corrected for multiple comparisons) and extent ($P < 0.05$) of the regions of activation (Friston *et al*., 1996). Within each region of statistical significance, local maxima of signal increase were determined (the voxels of maximum significance), and their locations were expressed in terms of *x*, *y* and *z* coordinates. MNI (Montreal Neurological Institute) coordinates were converted to Talairach space (Talairach and Tournoux, 1988) by using a linear transformation (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

The data were co-registered with a surface-rendered image of the brain to confirm the positions of activations on the sensorimotor strip relative to the central sulcus.

To determine the extent of significant activations in *a priori* locations of interest, we created regions of interest (ROIs) on the high-resolution T_1 image on the following structures: (i) sensorimotor cortex; (ii) inferior parietal lobule; (iii) lateral premotor cortex; (iv) supplementary motor area; (v) insula; (vi) basal ganglia; (vii) thalamus; (viii) vermis and (ix) cerebellar hemisphere. The main cerebral sulci and the schemes of the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) were used for ROI drawings.

For each subject, the number of significantly activated clustered voxels in each ROI was calculated at a corrected *P* value of <0.05. No activated voxels were present at this level of significance in the supplementary motor area, basal ganglia and thalamus in most subjects. The number of activated voxels in the parietal, sensorimotor and lateral premotor cortexes in both the contralateral and the ipsilateral hemisphere were summed for multiple regression with clinical parameters.

The second stage of analysis included within-group and between-group comparisons (one- and two-sample *t*-tests, respectively; SPM99). This analysis was conducted on the volume of interest represented by all the predefined ROIs, because of the *a priori* hypothesis that changes in activation in patients during hand movement should involve cortical motor areas and motor-related subcortical structures.

Within-group comparisons tested the null hypothesis that the mean of each group of observations was identical to zero. Clusters of voxels which had a peak *Z*-score of >3.7 (threshold $P < 0.0001$) were considered to show significant activation. Between-group comparisons tested the null hypothesis that the mean of the group of patients was identical to the mean of the controls. Clusters of voxels which had a peak *Z*-score of >3.1 (threshold $P < 0.001$) were considered to show significant differences.

On conventional MRIs, the hyperintense T_2 and hypointense T_1 lesion load (LL) was calculated in each patient using the display program Dispunc (D. L. Plummer, University College London, London, UK) with a semiautomated contouring technique (Grimaud *et al*., 1996). A hypointense lesion was defined as any region with lower signal intensity than the surrounding white matter visible on enhanced T1WI and corresponding to a region of high signal intensity on T2WI. In addition, on T1WI, the LL was calculated for lesions selectively located on the corticospinal tract, at both the supratentorial and the infratentorial level, as

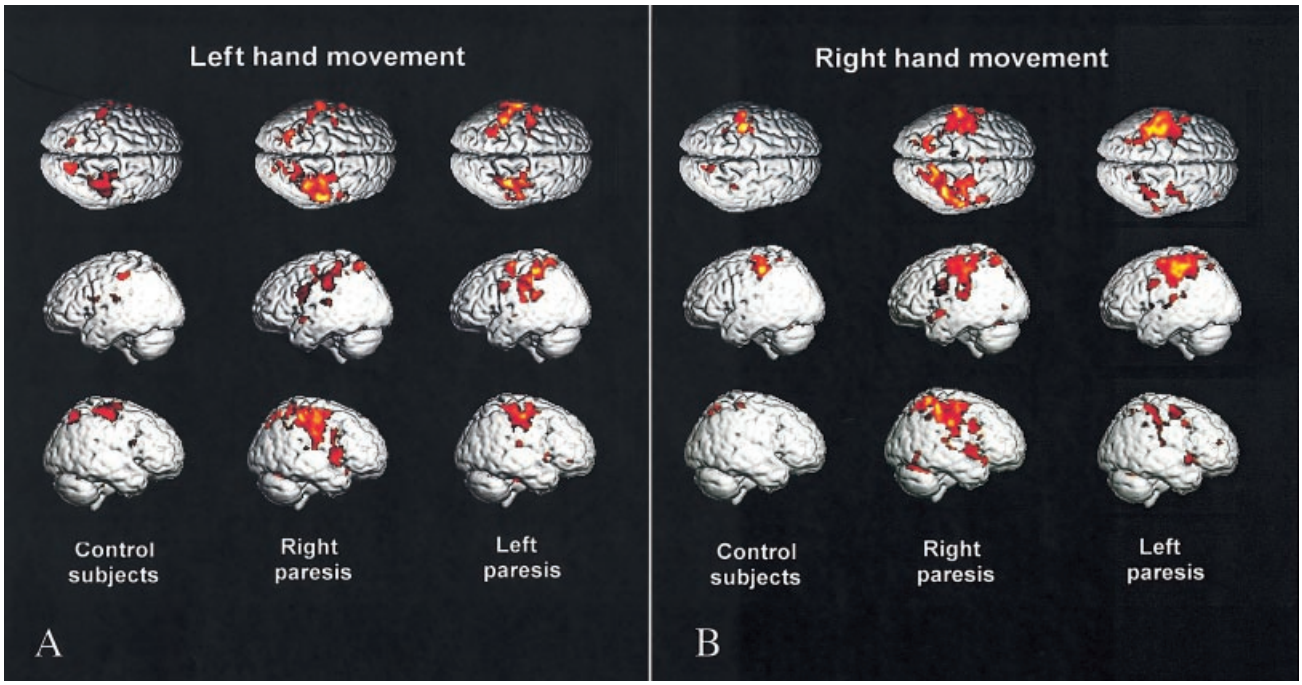

Fig. 1 Statistical parametric maps of the brain showing cortical activation during movement of the left hand (**A**) and right hand (**B**) in control subjects (n = 10) and 10 CIS patients with previous right (n = 5) or left hemiparesis (n = 5). During both right-hand and left-hand movement, patients with a previous right or left hemiparesis activated significantly larger cortical areas in the contralateral and ipsilateral cerebral hemisphere than control subjects.

outlined in the axial sections of the atlas of Talairach and Tournoux (1988). Since both hemispheres contribute to the execution of each hand movement, even if through a different contingent of fibres, mean T_1 LL values calculated along motor pathways in both hemispheres were used.

Results

In controls, both right-hand and left-hand movement activated the contralateral sensorimotor cortex and the ipsilateral cerebellum. However, a small pattern of activation in the ipsilateral sensorimotor cortex (five subjects) and contralateral cerebellum (three subjects) was occasionally observed during left-hand movement.

During both right-hand and left-hand movement, CIS patients with previous right or left hemiparesis activated significantly larger cortical areas in both the contralateral and the ipsilateral cerebral hemisphere than normal subjects (Fig. 1). Greater activation of the ipsilateral hemisphere with respect to controls was observed when patients moved both their 'affected' and their 'unaffected' hand, though this ipsilateral response was apparently wider for the movement of the affected hand. However, the number of activated voxels in predefined ROIs on motor structures was not significantly different between 'affected' and 'unaffected' hand movement (Table 2)

Therefore, in group analysis patients were grouped according to the side of hand movement (right or left hand) independently of the side of previous hemiparesis in order to obtain the locations of significantly activated voxels in within- and between-group analysis.

The results of within-group analysis are shown in Table 3. Patients activated a greater number of foci than controls during both the right-hand and the left-hand movement. Most of these foci were located in the ipsilateral hemisphere and in cortical areas which were less or not at all activated in controls, such as the lateral premotor cortex [Brodmann area (BA 6)], the insula and the inferior parietal lobule (BA 40).

Between-group analysis of patients versus controls during right-hand movement showed significant foci in the ipsilateral sensorimotor cortex (BA 1–4), lateral premotor cortex (BA 6), inferior parietal lobule (BA 40) and insula, and in the contralateral inferior parietal lobule (BA 40) ($P < 0.001$). Between-group analysis of patients versus controls during left-hand movement showed significant foci in the ipsilateral lateral premotor cortex (BA 6) and insula and in the contralateral inferior parietal lobule (BA 40) and insula ($P < 0.001$) (Table 4). No significant foci were present in the control versus patient between-group analysis.

In order to evaluate the relationships between clinical and conventional MRI parameters and the extent of activation, we used forward stepwise regression analysis. The dependent variables were the number of significantly activated voxels in predefined ROIs (sum of activated voxels in the inferior parietal, sensorimotor and lateral premotor cortex) in both the right and the left cerebral hemisphere during both the left-

Table 2 *Number of significantly activated voxels (mean ± standard error of the mean) in predefined ROIs during the movement of the 'affected' and 'unaffected' hand in 10 patients*

ROI	'Affected' hand	'Unaffected' hand	*P*
Contralateral primary motor	344 ± 106	306 ± 109	0.766
Ipsilateral primary motor	192 ± 95	97 ± 41	0.309
Contralateral premotor	272 ± 93	293 ± 91	0.758
Ipsilateral premotor	106 ± 48	105 ± 36	0.976
Contralateral parietal	178 ± 57	199 ± 78	0.828
Ipsilateral parietal	132 ± 55	60 ± 30	0.262
Contralateral insula	78 ± 45	73 ± 32	0.931
Ipsilateral insula	70 ± 39	63 ± 30	0.842
Contralateral cerebellum	216 ± 88	394 ± 146	0.098
Ipsilateral cerebellum	456 ± 179	394 ± 146	0.401
Vermis	175 ± 61	277 ± 108	0.177

Table 3 *Within-group analysis (one-sample* t*-test, SPM99): locations of significant activations in patients and controls during left-hand and right-hand movement*

Region	Right-hand movement				Left-hand movement			
	Controls		Patients		Controls		Patients	
	Talairach coordinates (*x*, *y*, *z*)	*Z*-score	Talairach coordinates (*x*, *y*, *z*)	*Z*-score	Talairach coordinates (*x*, *y*, *z*)	*Z*-score	Talairach coordinates (*x*, *y*, *z*)	*Z*-score
R sensorimotor (BA 1–4)	29, –19, 52	3.94	39, –15, 43	3.95	41, –25, 44	5.04	48, –19, 30	5.59
			31, –19, 55	3.94	31, –27, 51	4.71	50, –15, 41	4.78
					31, –21, 60	4.18	24, –19, 57	4.49
							25, –23, 50	4.10
L sensorimotor (BA 1–4)	–33, –17, 52	5.78	–34, –11, 55	4.87	–45, –31, 44	4.48	–55, –22, 32	4.90
			–48, –26, 34	4.62			–34, –40, 55	4.83
							–36, –9, 50	4.53
R inferior parietal lobule (BA 40)	40, –36, 49	4.59	41, –36, 42	4.29	40, –36, 47	4.90		
			45, –30, 39	4.19				
			24, –52, 46	4.18				
			36, –50, 52	4.17				
L inferior parietal lobule (BA 40)	–27, –40, 50	4.30	–43, –36, 45	4.89	–26, –44, 43	4.83	–43, –30, 33	4.90
	–40, –40, 55	4.22	–45, –34, 35	4.62	–36, –34, 42	4.81	–52, –25, 21	4.05
			–48, –32, 19	4.87			–27, –46, 52	4.90
							–20, –50, 50	4.65
R lateral premotor cortex (BA 6)			39, –7, 40	4.37			48, –1, 26	3.87
L lateral premotor cortex (BA 6)							–55, 4, 23	4.15
							–52, 1, 33	3.99
R insula			52, –22, 14	4.38			45, 1, 5	4.26
L insula			–54, –26, 12	4.31			–50, 10, 2	4.95
			–45, –25, 12	3.88			–47, –21, 13	4.34
R cerebellum	15, –63, –12	5.58	17, –60, –26	4.78			17, –58, –23	4.20
L cerebellum					–22, –52, –31	4.93	–17, –58, –26	5.19
Vermis	6, –67, –18	5.53	–3, –69, –20	5.39	–4, –67, –20	5.00	–6, –58,10	4.43
	8, –65, –25	5.11	1, –38, –7	5.26	8, –73, –20	4.93	–5, –69, –21	4.43
							10, –73, –21	4.20

BA = Brodmann area; R = right; L = left; *Z* = voxel level (uncorrected *P* value > 0.0001).

hand and the right-hand movements. The independent variables were age, time since clinical onset, Expanded Disability Status Score (EDSS), total T_2 LL, total T_1 LL and T_1 LL along the motor pathway.

Time since clinical onset was positively associated with the extent of activation in the ipsilateral motor areas ($b = 36.3 \pm 9.3$, $P = 0.006$) during the right-hand movement and with the extent of activation of in both the ipsilateral ($b = 14.2 \pm 4.9$, $P = 0.02$) and the contralateral ($b = 43.4 \pm 11.1$, $P = 0.006$) motor area during the left-hand movement. T_1 LL along the motor pathway was significantly associated with the extent of activation in the

Table 4 *Between-group analysis (two-sample* t*-test, SPM99): locations of differences in activation in patients versus controls during right-hand and left-hand movement*

Region	Right-hand movement		Left-hand movement	
	Talairach coordinates (x, y, z)	Z-score	Talairach coordinates (x, y, z)	Z-score
R sensorimotor (BA 1–4)	40, –15, 43	4.29		
	22, –25, 56	3.42		
L sensorimotor (BA 1–4)				
R inferior parietal lobule (BA 40)	41, –40, 24	3.56	32, –31, 30	3.41
L inferior parietal lobule (BA 40)	–35, –34, 28	3.83		
R lateral premotor cortex (BA 6)	38, –9, 38	4.02		
L lateral premotor cortex (BA 6)			–45, –10, 31	3.29
R insula	31, 24, 1	3.48	45, –20, 14	4.24
	36, 20, 4	3.34		
L insula			–33, 10, –6	3.84

BA = Brodmann area; R = right; L = left; Z = voxel level (uncorrected P value > 0.001).

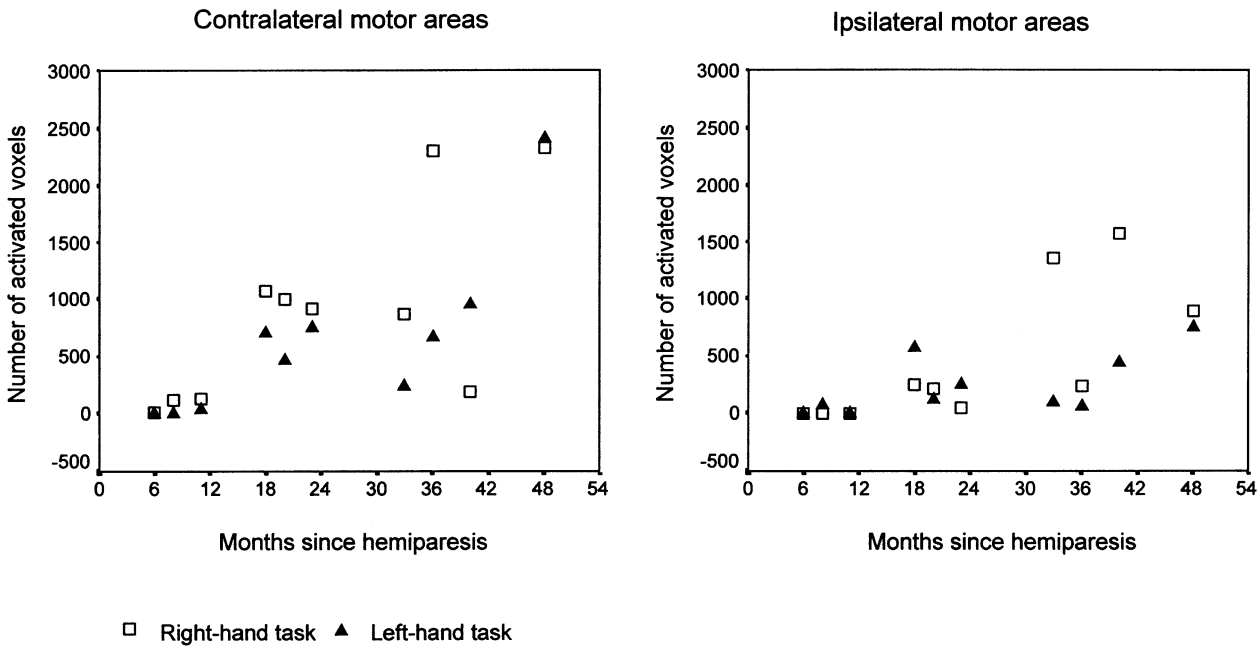

Fig. 2 Plots illustrating the relationships between time elapsed since the clinical onset of hemiparesis and the number of significantly activated voxels in the contralateral and ipsilateral hemispheres during right-hand and left-hand movement. Time since clinical onset was one of six independent variables entered in the stepwise regression model. See also text.

contralateral motor areas ($b = 1.3 \pm 0.3$, $P = 0.007$) during the right-hand movement. The other variables were not entered in the model as they were not significantly correlated. Plots illustrating the relationships between time since clinical onset and the extent of activation in both the cerebral hemisphere are shown in Fig. 2.

Discussion

Our study shows changes in patterns of cortical activation during a simple motor task in patients with multiple sclerosis or possible multiple sclerosis who had suffered a single clinical episode consisting of hemiparesis. Changes in cortical response involved both the symptomatic and asymptomatic hemisphere through two principal mechanisms involving the recruitment of ipsilateral corticospinal pathways and the extension of cortical areas normally dedicated to hand movement.

Cortical reorganization of motor areas has been reported repeatedly in studies that have used various neuroimaging techniques in various clinical conditions, such as in patients with stroke (Chollet *et al.*, 1991; Weiller *et al.*,

1992; Cao *et al*., 1998), developmental malformations (Sabatini *et al*., 1994; Alkadhi *et al*., 2000), brain tumours (Yoshiura *et al*., 1997) or lateral amyotrophic sclerosis (Kew *et al*., 1993).

The contribution of the ipsilateral motor pathway to the execution of movement after brain damage has been described in most of these studies, being interpreted as a vicarious function due to several mechanisms, such as the bilateral representation of motor function, the creation of new connections, the release of inhibition and synaptic sprouting. In our study, the involvement of the ipsilateral hemisphere was remarkable during both the right-hand and the left-hand movement. Between-group analysis showed that there was greater involvement of the ipsilateral motor pathway in patients than in controls during the right-handed task. This finding could be due to the more pronounced ipsilateral activation in physiological conditions during left-sided movements than during right-sided movements (Kim *et al*., 1993).

In both the ipsilateral and the contralateral hemisphere, we found enlargement of the activated areas in patients compared with controls. The reorganization of motor hand areas outside the usual boundaries involved the inferior parietal lobule (BA 40), the lateral premotor cortex (BA 6) and the insula, when compared with the foci detected in control subjects. Between-group analysis showed that these regions were significantly more active in patients than in controls. Activation of the lateral premotor cortex, inferior parietal lobule and insula has also been described in patients following recovery from striatocapsular motor stroke (Chollet *et al*., 1991; Weiller *et al*., 1992).

Experimental studies have reported that the total number of corticospinal neurones of the arm representations in the premotor areas equals or exceeds the total number of neurones of the arm representation in the primary motor cortex. The premotor areas collectively comprise more than 60% of the cortical areas in the frontal lobe that project to the spinal cord. These observations indicate that a substantial component of the corticospinal system originates in the premotor areas in the frontal lobe. Premotor areas have direct access to the spinal cord and consequently have the potential to influence the generation and control of movement (Martino and Strick, 1987; Dum and Strick, 1991).

Fibre connections between motor areas and parietal association areas are well documented (Godschalk *et al*., 1984; Petrides *et al*., 1984). In particular, the inferior parietal lobule (BA 40) projects to the premotor cortex (BA 6) (Cavada and Goldman-Rakic, 1989). Additionally, the insular cortex receives afferents from the somatosensory cortex and projects to the lateral premotor cortex (Augustine *et al*., 1996). The recruitment of these areas, therefore, may be substantial in the reorganization of motor function both by direct access of cortical neurones to the spinal cord and by the involvement of higher-order areas of the somatosensory cortex, which may have greater capacity for reorganization than the primary areas.

Our data show some differences from and analogies with results obtained in two recent studies on multiple sclerosis patients (Lee *et al*., 2000; Reddy *et al*., 2000). Our study confirms the remarkable participation of the ipsilateral motor areas in cortical reorganization. On the other hand, these previous fMRI studies reported a posterior shift in the centre of activation of the sensorimotor cortex in patients relative to controls. We did not find a posterior shift of the peak of activation in the sensorimotor cortex, but we observed a greater number of foci in the parietal cortex and additional foci in the premotor cortex and insula in patients relative to controls (Table 3).

Several differences between these previous studies and ours could explain, at least partially, these discrepant results. The previous studies included relapsing–remitting and secondary progressive multiple sclerosis patients, with greater disability (EDSS up to 7), a longer disease duration (up to 20 years) and various degrees of motor deficit of the upper limb. Moreover, both right- and left-handed patients were studied using a different motor task.

Interestingly, the extension of cortical activation to areas that are not dedicated to a given function in physiological conditions has been described in patients during the stimulation of other neural systems. Werring *et al*. (2000) reported that the stimulation of the recovered eye in patients after acute demyelinating optic neuritis induced extensive activation in cerebral areas which were not activated in controls, such as the insula–claustrum, the lateral temporal and posterior parietal cortices and the thalamus.

In our study, cortical functional changes in patients were observed not only when they were required to move their previously paretic hand but also when they moved the hand which had never suffered a motor deficit. The extent of motor activation was not significantly different between the 'affected' and the 'unaffected' hand movement. This finding suggests that cortical rearrangement is an adaptive mechanism designed to compensate for damage to the motor-related network, even at the subclinical level. Increased brain activity has been described in some subclinical conditions (e.g. in patients at risk of developing Alzheimer disease) when challenged with different types of cognitive tasks (Bookheimer *et al*., 2000), indicating that additional areas are recruited to achieve the goal. Expanding the area of neural tissue dedicated to a given task and increasing the number of neurones recruited in a given functional area may represent a basic compensatory mechanism which allows normal performance despite neural damage or loss.

The amount of time that has elapsed since the clinical episode seems to be a critical factor in cortical reorganization and the involvement of the ipsilateral hemisphere. The number of activated voxels in the cortical motor areas of both hemispheres during the left-hand movement and in the ipsilateral hemisphere during the right-hand movement increased significantly with time elapsed since clinical onset.

In previous studies on motor recovery after stroke, cortical functional changes were observed within a few months of

clinical onset (Chollet *et al*., 1991; Weiller *et al*., 1992; Cao *et al*., 1998). In one study on stroke patients (Marshall *et al*., 2000), the involvement of the ipsilateral sensorimotor cortex during movements of the paretic hand decreased with time. Further serial PET studies on stroke patients, however, showed decreased activation over time in the affected hemisphere and increased activation in the prefrontal, premotor and putaminal regions of the unaffected hemisphere, suggesting reduced recruitment of motor networks in the affected hemisphere and late-appearing compensatory reorganization in the ipsilateral hemisphere (Calautti *et al*., 2001). A bilateral increase in sensory and motor areas has also been found after a period of task-oriented arm training in hemiparetic stroke patients (Nelles *et al*., 2001).

Some discrepancies between studies on stroke patients and our results may reflect different mechanisms of cortical reorganization in these two diseases, to compensate either for a single motor-deficit episode or for more widespread and progressive, even subclinical, cerebral damage. The increase in cerebral activation with time observed in some studies on stroke patients supports our findings and suggests that neuroplasticity may develop gradually over time.

The hypothesis of cortical reorganization designed to compensate for progressive tissue damage is also supported by the positive correlation between the extent of cortical activation in the contralateral hemisphere during the right-hand movement and the amount of axonal damage of the corticospinal tract, as expressed by the averaged T_1 LL. Hypointense lesions on T1WI are markers of severe tissue destruction, since they are associated with both extensive demyelination and loss of axons (van Walderveen *et al*., 1998; van Waesberghe *et al*., 1999). Axonal transection is a consistent feature of the lesions in multiple sclerosis, and it seems to start at the onset of the disease (Trapp *et al*., 1998). Axonal destruction may cause pyramidal cell death by retrograde degeneration, which could be compensated for by vicarious or redundant neuronal pathways.

Our data indicate that cortical reorganization of motor areas is affected above all by the amount of selective damage to the corticospinal tract, and that total brain damage, as expressed by T_2 and T_1 LL, plays a minor role in this very early phase of the disease. A significant correlation between increased activation in the ipsilateral sensorimotor cortex and decreased *N*-acetylaspartate has, instead, been found in a more advanced phase of the disease (Reddy *et al*., 2000). In our study we did not, unfortunately, obtain MRI sequences for the evaluation of normal-appearing white matter. Further studies may elucidate the contribution of changes in normal-appearing white matter to cortical motor reorganization in the early phase of multiple sclerosis.

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