Simple and Complex Movement-Associated Functional MRI Changes in Patients at Presentation With Clinically Isolated Syndromes Suggestive of Multiple Sclerosis

Massimo Filippi,^{1*} Maria A. Rocca,¹ Domenico M. Mezzapesa,¹
Angelo Ghezzi,² Andrea Falini,³ Vittorio Martinelli,⁴ Giuseppe Scotti,³
and Giancarlo Comi⁴

¹Neuroimaging Research Unit, Scientific Institute and University Ospedale San Raffaele, Milan, Italy

²Multiple Sclerosis Center, Ospedale di Gallarate, Gallarate, Italy

³Department of Neuroradiology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy

⁴Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy

Abstract: Using functional magnetic resonance imaging (fMRI), we investigated whether movement-associated functional changes of the brain are present in patients who are, most likely, at the earliest stage of multiple sclerosis (MS). Functional MRI exams were obtained from 16 patients at presentation with clinically isolated syndromes (CIS) suggestive of MS and 15 sex- and age-matched healthy volunteers during the performance of three simple and one more complex motor tasks with fully normal functioning extremities. fMRI analysis was performed using statistical parametric mapping (SPM99). Compared to healthy volunteers, CIS patients had increased activations of the contralateral primary sensorimotor cortex (SMC), secondary somatosensory cortex (SII), and inferior frontal gyrus (IFG), when performing a simple motor task with the dominant hand. The increased recruitment of the contralateral primary SMC was also found during the performance of the same motor task with the non-dominant hand and with the dominant foot. In this latter case, an anterior shift of the center of activation of this region was detected. During the performance of a complex motor task with the dominant upper and lower limbs, CIS patients had an increased recruitment of a widespread network (including the frontal lobe, the insula, the thalamus), usually considered to function in motor, sensory, and multimodal integration processing. The comparison of brain activations during the performance of simple vs. complex motor tasks showed that the movement-associated somatotopic organization of the cerebral and cerebellar cortices was retained in patients with CIS. Cortical reorganization occurs in patients at presentation with CIS highly suggestive of MS. Local synaptic reorganization, recruitment of parallel existing pathways, and reorganization of distant sites are all likely to contribute to the observed functional changes. *Hum. Brain Mapp.* 21:108–117, 2004. © 2003 Wiley-Liss, Inc.

Key words: multiple sclerosis; clinically isolated syndromes; functional magnetic resonance imaging; cortical reorganization; motor tasks

INTRODUCTION

Using functional magnetic resonance imaging (fMRI), widespread cortical reorganization has been shown to occur in patients with established MS [Filippi et al., 2002a,b; Lee et al., 2000; Reddy et al., 2000a,b; Rocca et al., 2002a,b] and a relapsing remitting (RR) [Filippi et al., 2002a; Lee et al., 2000; Reddy et al., 2000a,b; Rocca et al., 2002a], a secondary progressive (SP) [Lee et al., 2000; Reddy et al., 2000a], and a primary progressive [Filippi et al., 2002b; Rocca et al., 2002b] course of the disease. There is also increasing evidence that brain plasticity in MS has the potential to limit the clinical consequences of the structural brain damage associated with

*Correspondence to: Dr. Massimo Filippi, Neuroimaging Research Unit Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Via Olgettina, 60, 20132 Milan, Italy.
E-mail: m.filippi@hsr.it

Received for publication 24 February 2003; Accepted 6 November 2003

DOI 10.1002/hbm.10160

the disease [Filippi et al., 2002b; Lee et al., 2000; Reddy et al., 2000a; Rocca et al., 2002a,b]. However, it is less clear how early in the course of the disease does this functional reorganization occur and which are the pathophysiological substrates underlying it.

Most frequently, the clinical onset of MS is an acute, remitting clinically isolated syndrome (CIS) involving the optic nerves, brainstem, or spinal cord [Noseworthy et al., 2000]. In about 50–70% of these patients, conventional MRI provides subclinical evidence of spatial dissemination of lesions at presentation [Barkhof et al., 1997; Brex et al., 2002; Filippi et al., 1994; O’Riordan et al., 1998], which recent ad-hoc International guidelines have integrated into a set of criteria to be used for establishing a diagnosis of the disease much earlier than that achievable when using clinical data in isolation [McDonald et al., 2001]. Although it is recognized that not all those individuals at presentation with CIS- and MRI-detected spatial dissemination of lesions will go on to develop a clinically definite MS, a recent long-term longitudinal study has shown that about 90% of such patients do so within 14 years from the clinical onset of the disease [Brex et al., 2002].

Against this background, we investigated, using fMRI and a general search method, whether movement-associated functional changes of the whole brain are present in patients who, to the best of our knowledge, are most likely to be at the earliest clinical stage of MS (i.e., patients at presentation with CIS and paraclinical evidence of spatial dissemination of lesions). To remove the potential confounding factors of performance differences and the presence of other clinical deficits that might impact motor functioning, previous fMRI work in MS has been generally limited to the assessment of simple motor tasks [Filippi et al., 2002a,b; Lee et al., 2000; Reddy et al., 2000a,b; Rocca et al., 2002a]. On the contrary, this is less of an issue in the patients we studied because of their complete normal motor functioning and the paucity of their MRI-detectable brain damage. As a consequence, these patients represent a unique opportunity to obtain “unbiased” fMRI activations following the performance of motor tasks with variable degrees of complexity, which, on turn, enabled us to provide additional insights into the pathophysiology of cortical plasticity in MS.

PATIENTS AND METHODS

Patients

We studied 16 consecutive right-handed patients (10 women, 6 men; mean age 31.7 years, range = 22–43 years) at presentation with CIS suggestive of MS and paraclinical evidence of dissemination in space [McDonald et al., 2001]. All patients were assessed within 3 months from the onset of the clinical symptomatology (mean = 34 days, range = 18–64 days). The presenting symptoms were optic neuritis in seven patients, an isolated brainstem syndrome in three, and an isolated spinal cord syndrome in six. All alternative neurological diagnoses were excluded by appropriate investigations [McDonald et al., 2001]. Oligoclonal

bands were found in the cerebrospinal fluid (CSF) of 13 patients. Before MR acquisition, but on the same day, each patient underwent a full neurological assessment performed by a single observer, blind to the MRI results. Disability was rated using the Expanded Disability Status Scale (EDSS) score [Kurtzke, 1983]. Twelve patients had an EDSS score [Kurtzke, 1983] of 0.0, and four had residual visual deficits, which resulted in an EDSS score of 1.0. None of the patients had been treated with corticosteroids within the previous month. Eight patients were treated with 1 g methylprednisolone iv/day for five days during the acute phase of the symptomatology. When fMRI was performed, all patients had no symptoms or signs of motor, sensory, or cerebellar impairment of the upper limbs and the right lower limb. None of the patients received any disease modifying treatment. Fifteen sex- and age-matched, right-handed healthy volunteers with no previous history of neurological dysfunction and a normal neurological exam served as controls (9 women, 6 men; mean age 33.6 years, range 21–45 years). Local Ethical Committee approval and written informed consent from all subjects were obtained prior to study initiation.

Functional Assessment

Motor functional assessment was performed for all the subjects on the same day of MRI acquisition. For the upper limbs, the nine-hole peg test (9-HPT) and the maximum finger tapping frequency were used [Herndon, 1997]. The maximum finger-tapping rate was observed for two 30-sec trial periods outside the magnet and the mean frequency to the nearest 0.5 Hz entered the analysis. For the right lower limbs, the maximum foot tapping frequency was used [Reddy et al., 2000b]. No difference was found in the performance of these tests between healthy volunteers and patients at presentation with CIS (Table I).

Experimental Design

Using a block design (ABAB), where epochs of activation were alternated with epochs of rest, all subjects performed four different tasks, each of them consisting of 60 measurements. Task 1 consisted of repetitive flexion-extension of the last four fingers of the right hand moving together. Task 2 was the same as task 1, but was performed with the left hand. Task 3 consisted of repetitive flexion-extension of the right foot, and task 4 was the simultaneous performance of tasks 1 and 3 in a phasic manner. Since the performance of this latter task implies attention, planning, and coordination, from now on we will define this task as “complex.” During scanning, all tasks were paced by a metronome at a 1-Hz frequency. Patients and controls were trained before performing the experiments. Subjects were instructed to keep their eyes closed during fMRI acquisition and were monitored visually during scanning to ensure accurate task performance and to assess for additional (e.g., mirror) movements. Tasks were performed equally well by all subjects.

TABLE I. Functional assessment of right upper and lower limbs and left upper limbs from patients at presentation with CIS suggestive of MS and healthy volunteers

	Healthy volunteers	CIS patients
Right upper limb		
Time to complete the nine-hole peg test (sec)	19.8 (3.2)	21.4 (3.2)
Maximum finger tapping rate (per sec)	3.6 (0.4)	3.4 (0.6)
Left upper limb		
Time to complete the nine-hole peg test (sec)	22.6 (2.7)	23.2 (2.5)
Maximum finger tapping rate (per sec)	3.0 (1.2)	3.0 (0.8)
Right lower limb		
Maximum foot tapping rate (per sec)	3.1 (0.3)	2.9 (0.8)

Values are expressed as mean (SD).

CIS, clinically isolated syndromes; MS, multiple sclerosis.

fMRI Acquisition

Brain MRI scans were obtained on a magnet operating at 1.5 Tesla (Vision, Siemens, Erlangen, Germany). Sagittal T1-weighted images were obtained to define the anterior-posterior commissural (AC-PC) plane. Functional MR images were acquired using a T2*-weighted echo-planar imaging (EPI) sequence (TR = 96, TE = 66, flip angle = 90, matrix size = 128 × 128, field of view (FOV) = 256 × 256 mm, interscan interval = 3 s). Twenty-four axial slices, parallel to the AC-PC plane, with a thickness of 5 mm, covering the whole brain were acquired during each measurement. Shimming was performed for the entire brain using an autoshim routine, which yielded satisfactory magnetic field homogeneity.

Structural MRI Acquisition and Analysis

Using the same magnet, a dual-echo turbo spin echo (TSE) sequence (TR = 3300, first echo TE = 16, second echo TE = 98, echo train length = 5, slice thickness = 5 mm, FOV = 192 × 256 mm, matrix size = 190 × 256) was also acquired from all the subjects. Lesions were identified on the proton-density (PD) weighted scans (T2-weighted images were always used to increase confidence in lesion identification) by two experienced observers blinded to the fMRI results and dual-echo lesion volumes were measured using a segmentation technique based on local thresholding, as previously described [Filippi et al., 2002a, 2002b; Rocca et al., 2002a,b].

fMRI Analysis

fMRI data were analyzed using the statistical parametric mapping (SPM99) software [Friston et al., 1995]. Prior to statistical analysis, all images were realigned to the first one to correct for subject motion, spatially normalized into SPM standard space, and smoothed with a 10-mm, 3D-Gaussian filter. Changes in blood oxygen level dependent (BOLD) contrast associated with the performance of the different motor tasks were assessed on a pixel-by-pixel basis, using the general linear model [Friston et al., 1995] and the theory of Gaussian fields [Worsley and Friston, 1997]. Specific effects were tested by applying appropriate linear contrasts.

Significant hemodynamic changes for each contrast were assessed using *t* statistical parametric maps (SPMt). The intragroup activations and the comparisons between groups were investigated using a random effect analysis [Friston et al., 1999], with a one-sample or a two-sample *t*-test performed as appropriate. This analysis is based on the height (or *Z* value) of the activated voxels. We report activations below a threshold of $P < 0.05$ corrected for multiple comparisons. Using cluster analysis on a patient-by-patient basis [Poilâne et al., 1997], we also evaluated the coordinates of the centers of activations and the percentage signal changes for those areas with significantly different relative activations at group analysis. Differences of these fMRI metrics between patients and healthy volunteers were assessed using a two-tailed Student *t* test for not-paired data. To assess the correlations of BOLD changes with dual-echo lesion volumes, these volumes were entered into the SPM design matrix, using basic models and linear regression analysis [Friston et al., 1999].

RESULTS

Structural MRI

All healthy volunteers had normal brain MRI dual-echo scans. By definition, all patients had paraclinical evidence of dissemination in space: in 13 of them this was demonstrated by MRI alone, in the remaining three by the combination of MRI findings and the presence of oligoclonal bands in the CSF (Table II) [McDonald et al., 2001]. In patients at presentation with CIS, the median T2-weighted lesion load was 3.1 ml (range = 0.3–12.4 ml).

Simple Task-Associated fMRI Activations: Between-Group Comparisons

During fMRI acquisition, all subjects performed the tasks correctly and no additional movements were noted.

Task 1

Compared to healthy volunteers, patients at presentation with CIS had more significant activations of the contralateral

TABLE II. Magnetic resonance imaging and cerebrospinal fluid findings from patients at presentation with CIS suggestive of MS demonstrating the spatial dissemination of the disease

Patient no.	Total T2 lesions (N)	IT lesions	IC lesions (n)	PV lesions (n)	GD lesions (n)	OB
1	2	1	0	1	0	P
2	6	0	0	3	0	P
3	13	0	0	12	0	P
4	14	1	1	9	0	P
5	18	1	2	8	0	A
6	20	2	1	11	0	A
7	6	0	1	3	1	P
8	12	1	0	2	1	P
9	78	8	1	19	0	P
10	35	5	1	16	0	P
11	54	6	1	29	0	P
12	6	1	1	1	0	P
13	3	1	0	1	1	P
14	57	1	1	27	0	A
15	16	1	1	9	0	P
16	17	1	1	7	0	P

IT, infratentorial; IC, iuxtacortical; PV, periventricular; GD, gadolinium-enhancing; OB, oligoclonal bands, P, present; A, absent.

primary sensorimotor cortex (SMC) (SPM space coordinates: $-34, -38, 38$; corrected $P = 0.004$), in a region corresponding to the location of the hand area [Indovina and Sanes, 2001; Yousry et al., 1996], of the contralateral ascending bank of the sylvian fissure (SPM space coordinates: $-58, -26, 18$; corrected $P = 0.002$), in a region corresponding to the secondary somatosensory cortex (SII) [Fink et al., 1997], and of the contralateral inferior frontal gyrus (IFG) (SPM space coordinates $-46, 10, 4$; corrected $P = 0.003$), in a region corresponding to Broca's area [Binkofski et al., 1999; Harrington et al., 2000; Haslinger et al., 2002; Stephan et al., 1995]. No difference in percentage signal changes and coordinates of the centers of activations of these three areas was found between patients and controls.

Task 2

Compared to healthy volunteers, patients had a more significant activation of the contralateral primary SMC (SPM space coordinates: $28, -28, 46$; corrected $P < 0.0001$), in a region corresponding to the location of the hand area. No difference in percentage signal change and coordinates of center of activation of this area was found between patients and controls.

Task 3

Compared to healthy volunteers, patients had a more significant activation of the contralateral primary SMC (SPM space coordinates: $-4, -24, 60$; corrected $P = 0.001$), in a region corresponding to the location of the foot area [Lotze et al., 2000]. Compared to controls, patients had also an increased percentage signal change (mean percentage signal

change [SD] = $1.82 [0.55]$ in patients vs. $1.40 [0.49]$ in controls; $P = 0.03$), and an anterior shift of the center of activation (SMC coordinates in y -plane [SD]: $-27 [9.9]$ in patients vs. $-37 [8.2]$ in controls; $P = 0.04$) of this region.

Complex Task-Associated fMRI Activations (Task 4)

Compared to healthy volunteers, patients had more significant activations of the contralateral primary SMC (SPM space coordinates: $-36, -34, 32$; corrected $P > 0.0001$), in a region corresponding to the location of the hand area [Indovina et al., 2001; Yousry et al., 1996], the contralateral SII (SPM space coordinates: $-56, -26, 18$; corrected $P = 0.02$), the contralateral insula (SPM space coordinates: $-42, 6, -12$; corrected $P < 0.0001$), the ipsilateral middle frontal gyrus (SPM space coordinates: $40, 20, 40$; corrected $P < 0.0001$), the ipsilateral inferior frontal gyrus (SPM space coordinates: $56, 14, 0$; corrected $P < 0.0001$), and the thalamus, bilaterally (SPM space coordinates: $8, -4, 14$, and $-16, -26, 10$; corrected $P < 0.0001$) (Fig. 1). Patients also had an increased percentage signal change of the hand region of the primary SMC (percentage signal change [SD] = $1.81 [0.57]$ in patients vs. $1.26 [0.32]$ in controls; $P = 0.02$). The center of activation of the contralateral insula was shifted on the x -plane in patients compared to controls (insula coordinates in the x -plane [SD]: $-37 [6.2]$ in patients vs. $-46 [1.15]$ in controls; $P = 0.005$).

Correlations Between Task-Associated fMRI Activations and t2 Lesion Load

In CIS patients, no correlations were found between the extent of fMRI activations, during the performance of the four different motor tasks, and dual-echo lesion loads.

Within-Group Comparisons of Complex vs. Simple Task-Associated fMRI Activations

Healthy volunteers

When task 4 was compared to task 1, the foot areas of the ipsilateral cerebellar hemisphere and the contralateral primary SMC were identified (Fig. 2A,C). A more significant activation of the supplementary motor area (SMA), bilaterally, was also detected (Fig. 2B). When task 4 was compared to task 3, the hand areas of the ipsilateral cerebellar hemisphere and the contralateral primary SMC were identified (Fig. 3A,C). A more significant activation of the SMA, bilaterally, was also detected (Fig. 3B).

Patients with CIS at presentation

When task 4 was compared to task 1, the foot areas of the ipsilateral cerebellar hemisphere and the contralateral primary SMC were identified (Fig. 2D,G). More significant activations of the SMA, bilaterally (Fig. 2F), and of the contralateral SII (Fig. 2E) were also detected. When task 4 was compared to task 3, the hand areas of the ipsilateral cerebellar hemisphere and the contralateral primary SMC were identified (Fig. 3D,F).

Figure 1.

Relative activations in right-handed patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis during the performance of a complex motor task (task 4). Two-sample *t* test vs. healthy volunteers, corrected $P < 0.05$. **A:** Contralateral

primary sensorimotor cortex and ipsilateral middle frontal gyrus. **B:** Contralateral secondary sensorimotor cortex and ipsilateral inferior frontal gyrus. **C:** Thalamus, bilaterally. **D:** Ipsilateral inferior frontal gyrus. **E:** Contralateral insula.

More significant activation of the SMA, bilaterally, and of the contralateral SII were also detected (Fig. 3E).

In Figure 4, the results of the within-group comparison of complex vs. simple task-associated fMRI activation in healthy volunteers and CIS patients have been overlaid on a high-resolution T1-weighted image normalized into standard SPM space, to show the cortical somatotopic localisation of the hand and the foot. An anterior shift of the center of activation of the foot area is clearly visible in CIS patients, thus confirming the results of the between-group comparisons (Task 3).

DISCUSSION

This study shows that marked changes in the patterns of movement-associated cortical activations during simple and complex motor tasks are detectable in patients at presentation with CIS suggestive of MS, thus suggesting that func-

tional reorganization of the cortex is an early event in the course of MS. Admittedly, the patients of this study can not be diagnosed as having established MS. Nevertheless, alternative diagnoses have been carefully excluded [McDonald et al., 2001] and all had clinical pictures suggestive of MS at presentation. They were also selected for having a dissemination in space at presentation, i.e., MRI and/or CSF findings consistent with a diagnosis of MS [McDonald et al., 2001]. As a consequence, we believe that all of them are at high risk to ultimately progress to a clinically definite form of the disease [Brex et al., 2002]. In addition, since all these patients had a fully normal functioning of their limbs, it can be excluded that the observed fMRI patterns of activations are attributable to confounding factors of performance differences and the presence of other clinical deficits that might impact motor functioning.

Figure 2.

Comparison of task 4 vs. task 1 in healthy subjects (A–C) and patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis (D–G) (paired *t* test for each group, corrected $P < 0.05$). The foot areas of the cerebellum (A,D) and of the primary sensorimotor cortex (C,G) were identified in both

groups. A significant activation of the supplementary motor area (B,F) was also detected in both groups. Compared to controls, patients had more significant activation of the contralateral secondary sensorimotor cortex (E).

During the performance of simple motor tasks, CIS patients had an increased activation of the contralateral primary SMC. This agrees with the results of a previous study of patients with RRMS and no clinical disability [Rocca et al., 2002a], whereas it disagrees with those found in patients with early MS according to McDonald's [2001] criteria [Pantano et al., 2002] and in patients with RRMS and SPMS with mild to moderate clinical impairment [Lee et al., 2000; Reddy et al., 2000a], where an increased activation of the ipsilateral primary SMC was shown. However, it is worth nothing that in one study [Pantano et al., 2002], patients were recruited for having a previous hemiparesis and, as a consequence, effects from performance difference cannot be ruled out completely. In addition, at the time of fMRI acquisition, these patients had a mean EDSS of 1.2 (vs. 0.2 in our series) and a mean disease duration of 24.3 months (vs. 34 days in our series). The same consideration applies to the other two studies [Lee et al., 2000; Reddy et al., 2000a], where patients had a mean EDSS of 4.5 and a mean disease duration of 14.5 years. Since our observation of an increased

recruitment of the contralateral SMC activation is robust (it was found during the performance of three different motor tasks with three different clinically-unaffected arms), the most tempting speculation to explain the discrepant results of these studies is to hypothesize that increased contralateral SMC activation occurs earlier in the course of the disease than ipsilateral SMC activation, which might have an important role in more advanced and disabling phases of the diseases, as a result of failure of contralateral SMC activation because of accumulating injury. We also found an anterior shift of the center of activation of the SMC following the motor performance with the right lower limb. This suggests an increased activity of modulatory pathways (for instance, from the frontal lobes), aimed at recruiting more cerebral neurons than those needed in normal individuals for the performance of the same task.

This study also showed that fMRI changes in patients with CIS suggestive of MS are not limited to the SMC, but also involve a more widespread sensorimotor network. During the performance of Task 1, we found an increased activation

Figure 3.

Comparison of task 4 vs. task 3 in healthy subjects (**A–C**) and in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis (**D–F**). Paired *t* test for each group, corrected $P < 0.05$. The hand areas of the cerebellum (**A,D**) and of the primary sensorimotor cortex (**C,F**) were identified in both

groups. A significant activation of the supplementary motor area (**B**) was also detected in both groups. Compared to controls, patients had a more significant activation of the contralateral secondary sensorimotor cortex (**E**).

of the SII and the IFG. SII is considered to function as a high-order processing areas for somatosensory perception [Karhu and Tesche, 1999], and its activation has been related to attention [Hamalainen et al., 2000], manual dexterity, and coordination [Disbrow et al., 2000]. The activation of the IFG has been observed with finger movement [Binkofski et al., 1999], movement imagination [Harrington et al., 2000], and motor learning [Stephan et al., 1995]. In addition, IFG activation is modulated by task complexity [Haslinger et al., 2002]. Thus, the increased activations of these areas in patients with CIS might be a reflection of their perception of the task as more difficult, thus leading to the recruitment of parallel existing pathways, which might be activated in nor-

mal individuals when actually performing complex motor tasks. Contrary to other studies of RRMS [Lee et al., 2000; Reddy et al., 2000a; Rocca et al., 2002a] and SPMS [Lee et al., 2000; Reddy et al., 2000a], we did not find an increased recruitment of the SMA. Considering again that our patients were in a much earlier phase of the disease than those studied previously [Lee et al., 2000; Reddy et al., 2000a; Rocca et al., 2002a], we interpret the lack of a demonstration of an increased SMA recruitment in the present study as an indication that increased SMA recruitment for performing simple motor tasks might be a later event in the course of the disease than increased contralateral SMC recruitment.

Figure 4.

Somatotopic localisation of the hand (**A**) and foot (**B**) areas in healthy subjects (in blue) and in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis (in red). Paired *t* test for each group, corrected $P < 0.05$. In patients, an anterior shift of the center of activation of the foot area is visible (**B**).

Nevertheless, when we compared the brain activations associated with the simple tasks vs. those associated with the more complex task, we found a complex task-associated increased activation of the SMA (in both the two groups of individuals), and of the SII in CIS patients, only.

The SMA is involved in movement programming and execution [Ohara et al., 2000; Weillke et al., 2001] and it modulates the activity of the primary SMC throughout its extensive connections with this area [Rouiller et al., 1994]. Furthermore, an increased activity of SMA has been showed to occur in healthy individuals with increasing task difficulty [Rao et al., 1993]. As a consequence, the increased activation of SMA and SII in patients with CIS might again represent the result of a recruitment of parallel existing pathways to improve the accuracy of the performance of complex motor tasks.

That fMRI changes in patients at presentation with CIS suggestive of MS are not limited to the SMC is even more clearly shown by the pattern of brain activations found with the performance of a more complex motor task (Task 4). Compared to normal individuals, patients showed an increased recruitment of a widespread network (including the frontal lobe, the insula, and the thalamus) usually considered to function in motor, sensory, and multimodal integration processing. An increased activation of frontal lobe areas suggests that, in patients with CIS, an increased attentional demand and motor programming are needed to perform a relatively complex motor task. The thalamus [Brooks, 1995; Parent et al., 1995] and the insula [Augustine, 1996; Mesu-

lam, 1998] also have extensive connections with the motor and somatosensory cortices and are involved in motor programming, execution, and control [Augustine, 1996; Mesulam, 1998; Parent et al., 1995]. In addition, the finding in CIS patients of a change in the coordinates of the center of activation of the insula suggests the recruitment of regions of this structure with different functional properties.

In conclusion, this study shows that cortical reorganization does occur in patients at presentation with CIS highly suggestive of MS. Since irreversible tissue loss is now considered to be a significant aspect of early MS [Brex et al., 2000; De Stefano et al., 2001; Iannucci et al., 2000; Rudick et al., 1999], it is likely that such a marked cortical reorganization is an equally early response of the human plastic brain to maintain a normal level of function. Interindividual variability in the efficiency of brain plasticity might yet be an additional factor contributing to the long-term clinical outcome of these patients [Brex et al., 2002].

ACKNOWLEDGMENT

This study was supported by the Fondazione Italiana Sclerosi Multipla (FISM 2002/R/28).

REFERENCES

- Augustine JR (1996): Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Brain Res Rev* 22:229–244 (review).

- Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Ader HJ, Losseff N, Valk J. (1997): Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069.
- Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H (1999): A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur J Neurosci* 11:3276–3286.
- Brex PA, Ciccarelli O, O’Riordan JI, Sailer M, Thompson AJ, Miller DH (2002): A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med* 346:158–164.
- Brex PA, Jenkins R, Fox NC, Crum WR, O’Riordan JI, Plant GT, Miller DH (2000): Detection of ventricular enlargement in patients at the earliest clinical stage of MS. *Neurology* 54:1689–1691.
- Brooks DJ (1995): The role of the basal ganglia in motor control: contributions from PET. *J Neurol Sci* 128:1–13 (review).
- De Stefano N, Narayanan S, Francis GS, Arnaoutelis R, Tartaglia MC, Antel JP, Matthews PM, Arnold DL (2001): Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability. *Arch Neurol* 58:65–70.
- Disbrow E, Roberts T, Krubitzer L (2000): Somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*: evidence for SII and PV. *J Comp Neurol* 418:1–21.
- Filippi M, Horsfield MA, Morrissey SP, MacManus DG, Rudge P, McDonald WI, Miller DH (1994): Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. *Neurology* 44:635–641.
- Filippi M, Rocca MA, Colombo B, Falini A, Codella M, Scotti G, Comi G (2002a): Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage* 15:559–567.
- Filippi M, Rocca MA, Falini A, Caputo D, Ghezzi A, Colombo B, Scotti G, Comi G (2002b): Correlations between structural CNS damage and functional MRI changes in primary progressive MS. *Neuroimage* 15:537–546.
- Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE (1997): Multiple nonprimary motor areas in the human cortex. *J Neurophysiol* 77:2164–2174.
- Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R (1995): Analysis of fMRI time-series revisited. *Neuroimage* 2:45–53.
- Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ. (1999): Multisubject fMRI studies and conjunction analyses. *Neuroimage* 10:385–396.
- Hamalainen H, Hiltunen J, Titievskaja I (2000): fMRI activations of SI and SII cortices during tactile stimulation depend on attention. *Neuroreport* 11:1673–1676.
- Harrington DL, Rao SM, Haaland KY, Bobholz JA, Mayer AR, Binderx JR, Cox RW (2000): Specialized neural systems underlying representations of sequential movements. *J Cogn Neurosci* 12:56–77.
- Haslinger B, Erhard P, Weilke F, Ceballos-Baumann AO, Bartenstein P, Graf von Einsiedel H, Schwaiger M, Conrad B, Boccker H (2002): The role of lateral premotor-cerebellar-parietal circuits in motor sequence control: a parametric fMRI study. *Brain Res Cogn Brain Res* 13:159–168.
- Herndon RM (1997): Handbook of neurologic rating scales. New York: Demos Vermande.
- Iannucci G, Tortorella C, Rovaris M, Sormani MP, Comi G, Filippi M (2000): Prognostic value of MR and MTI findings at presentation in patients with clinically isolated syndromes suggestive of MS. *AJNR Am J Neuroradiol* 21:1034–1038.
- Indovina I, Sanes JN (2001): On somatotopic representation centers for finger movements in human primary motor cortex and supplementary motor area. *Neuroimage* 13:1027–1034.
- Karhu J, Tesche CD (1999): Simultaneous early processing of sensory input in human primary (SI) and secondary (SII) somatosensory cortices. *J Neurophysiol* 81:2017–2025.
- Kurtzke JF (1983): Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33:1444–1452.
- Lee M, Reddy H, Johansen-Berg H, Pendlebury S, Jenkinson M, Smith S, Palace J, Matthews PM (2000): The motor cortex shows adaptive functional changes to brain injury from multiple sclerosis. *Ann Neurol* 47:606–613.
- Lotze M, Erb M, Flor H, Huelsmann E, Godde B, Grodd W (2000): fMRI evaluation of somatotopic representation in human primary motor cortex. *Neuroimage* 11:473–481.
- McDonald WI, Compston A, Edan G, et al. (2001): Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 50:121–127.
- Mesulam MM (1998): From sensation to cognition. *Brain* 121:1013–1052.
- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG (2000): Multiple sclerosis. *N Engl J Med* 343:938–952.
- Ohara S, Ikeda A, Kunieda T, Yazawa S, Baba K, Nagamine T, Taki W, Hashimoto N, Mibara T, Shibasaki H (2000): Movement-related change of electrocorticographic activity in human supplementary motor area proper. *Brain* 123:1203–1215.
- O’Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall Be, Rudge P, McDonald WI, Miller DH (1998): The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. *Brain* 121:495–503.
- Pantano P, Iannetti GD, Caramia F, Mainero C, Di Legge S, Bozzao L, Pozzilli C, Lenzi GL (2002): Cortical motor reorganization after a single clinical attack of multiple sclerosis. *Brain* 125:1607–1615.
- Parent A, Hazrati LN (1995): Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop [review]. *Brain Res Brain Res Rev* 20:91–127.
- Poline JB, Worsley KJ, Evans AC, Friston KJ (1997): Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage* 5:83–96.
- Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, Lisk LM, Morris GL, Mueller WM, Estkowski LD (1993): Functional magnetic resonance imaging of complex human movements. *Neurology* 43:2311–2318.
- Reddy H, Narayanan S, Arnoutelis R, Jenkinson M, Antel J, Matthews PM, Arnold DL (2000a): Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. *Brain* 123:2314–2320.
- Reddy H, Narayanan S, Matthews PM, Hoge RD, Pike GB, Duquette P, Antel J, Arnold DL (2000b): Relating axonal injury to functional recovery in MS. *Neurology* 54:236–239.
- Rocca MA, Falini A, Colombo B, Scotti G, Comi G, Filippi M (2002a): Adaptive functional changes in the cerebral cortex of patients with non-disabling MS correlate with the extent of brain structural damage. *Ann Neurol* 51:330–339.
- Rocca MA, Matthews PM, Caputo D, Ghezzi A, Falini A, Scotti G, Comi G, Filippi M (2002b): Evidence for widespread movement-associated functional MRI changes in patients with PPMS. *Neurology* 58:866–872.
- Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu HX, Wiesendanger M (1994): Transcallosal connections of the distal forelimb

- representations of the primary and supplementary motor cortical areas in macaque monkeys. *Exp Brain Res* 102:227–243.
- Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L (1999): Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. *Neurology* 53:1698–1704.
- Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann AO, Frith CD, Frackowiak RS (1995): Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J Neurophysiol* 73:373–386.
- Weilke F, Spiegel S, Boecker H, Von Einsiedel HG, Conrad B, Schwaiger M, Erhard P (2001): Time-resolved fMRI of activation patterns in M1 and SMA during complex voluntary movement. *J Neurophysiol* 85:1858–1863.
- Worsley KJ, Friston KJ (1995): Analysis of fMRI time-series revisited again. *Neuroimage* 2:173–181.
- Yousry TA, Schmid UD, Schmidt D, Hagen T, Jassoy A, Reiser MF (1996): The central sulcal vein: a landmark for identification of the central sulcus using functional magnetic resonance imaging. *J Neurosurg* 85:608–617.