A longitudinal fMRI study on motor activity in patients with multiple sclerosis

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Using functional MRI (fMRI), patients with multiple sclerosis showed a greater extent of motor activation than controls. Although functional changes are often interpreted as adaptive and as a contributing factor in limiting the clinical deficit, no longitudinal studies have yet been performed for multiple sclerosis. Sixteen patients with multiple sclerosis, two patients with possible multiple sclerosis and nine age-matched controls underwent two fMRI studies with a time interval of 15–26 months. The motor task consisted of a self-paced sequential finger opposition movement with the right hand. Patients with multiple sclerosis exhibited greater bilateral activation than controls in both fMRI studies. At follow-up, patients showed a reduction in functional activity in the ipsilateral sensorimotor cortex and in the contralateral cerebellum. No significant differences between the two fMRI studies were observed in controls. Activation changes in ipsilateral motor areas correlated inversely with age, extent and progression of T1 lesion load, and occurrence of a new relapse. This study may help the understanding of the evolution of brain plastic changes in multiple sclerosis indicating that, in younger patients with a less structural brain damage and benign clinical course, the brain reorganizes its functional activity towards a more lateralized pattern of brain activation. The tendency towards a normalization of brain functional activity is hampered in older patients and in those developing relapses or new irreversible brain damage.

Keywords: multiple sclerosis; fMRI; motor activity; longitudinal study

Abbreviations: BA = Brodmann area; EDSS = expanded disability status scale; fMRI = functional MRI; L = left; LL = lesion load; MR = magnetic resonance; R = right


Introduction

A number of functional MRI (fMRI) studies have demonstrated that, in almost all the clinical phenotypes of multiple sclerosis, patients showed greater motor activation than healthy controls. This correlated with the tissue damage revealed by conventional (Lee et al., 2000; Pantano et al., 2002a,b) or non-conventional MRI (Filippi et al., 2002; Reddy et al., 2000a; Rocca et al., 2003).

Brain functional changes may represent a compensatory function designed to maintain a normal performance despite scattered brain lesions. Indeed, patients with multiple sclerosis may show recovery from symptoms while progressively accumulating tissue damage and they often show a discrepancy between lesions on conventional magnetic resonance (MR) and clinical symptoms (Smith et al., 1993). This discrepancy may partially be explained by diffuse abnormality in normal appearing brain tissue as seen on non-conventional MRI (Miller et al., 2003).

Cortical motor reorganization is not specific to multiple sclerosis, since it has been described in various diseases including tumours (Roux et al., 2000), vascular malformations (Schlosser et al., 1997) and stroke. Longitudinal fMRI studies on motor activity in stroke patients have suggested that cortical reorganization is a dynamic phenomenon that evolves with time and may correlate with clinical outcome (Calautti and Baron, 2003).

Dynamic cortical changes paralleling the clinical course have also been described in a multiple sclerosis patient who completely recovered from right hemiplegia (Reddy et al., 2000b). No other longitudinal fMRI studies have explored possible changes in the pattern of motor activation over time in multiple sclerosis.
The knowledge of how brain reorganization evolves in response to disease evolution may shed light on the role of brain plasticity in multiple sclerosis and the potentialities of medical or physical therapies in modulating it. The aim of this study was to evaluate longitudinal changes in motor-related brain activation in patients with early multiple sclerosis and their relationship with clinical and conventional MRI features.

**Material and methods**

**Subjects**

Patients were recruited from the Multiple Sclerosis Service at the Department of Neurological Sciences, University of Rome ‘La Sapienza’, Italy. Inclusion criteria were: (i) a single clinical episode; (ii) positive MR findings according to Fazekas’s criteria (Fazekas et al., 1988); (iii) no sensory and/or motor deficit at the neurological examination; (iv) no treatment with immunomodulatory or immunosuppressive drugs; (v) time elapsed since the end of steroid treatment, if any, of not less than 2 months; and (vi) no MR lesions in the spinal cord.

Eighteen patients who met these inclusion criteria were included in the study. They had been the object of previous fMRI studies (Pantano et al., 2002a,b). All patients had suffered from a single clinical attack consisting either of hemiparesis (n = 9; five right hemiparesis and four left hemiparesis) or optic neuritis (n = 9), and they had had a diagnosis of multiple sclerosis (n = 16) or of possible multiple sclerosis (n = 2) according to the recommendations of the international panel on the diagnosis of multiple sclerosis (McDonald et al., 2001). All patients underwent conventional neurological examination and were scored on the expanded disability status scale (EDSS) (Kurtzke, 1983).

Nine healthy gender and age-matched volunteers constituted the control group. They had no history of neurological or psychiatric disease and were free of any medication.

All patients and controls underwent a second fMRI study (fMRI2) with the same modalities within a time interval of 15–25 months (median: patients = 19; controls = 18) since the first fMRI study (fMRI1).

All patients and controls were right-handed and gave their written consent in accordance with the declaration of Helsinki. The study was approved by the Local Ethical Committee of the University of Rome ‘La Sapienza’.

**fMRI data acquisition**

Morphological MRI and fMRI data were acquired during the same imaging session using a 1.5 T magnet (Philips Gyroscan NT 15 Philips, the Netherlands) with echo planar capabilities and a head volume radio frequency coil. Each subject lay supine in the scanner with the spinal cord.

The thumb repeatedly touched the other four fingers in a sequential order with the right hand. Seven periods of hand movement and seven periods of rest were alternated (each period lasting for 15 s). ‘Start’ and ‘stop’ acoustic signals were given during the acquisition. Subjects were required to perform the task as quickly as possible, opening their hand wide. Correct execution of the task was confirmed by an operator who was present in the magnet room throughout the session and who recorded the rate of hand movements both for patients and controls.

**Motor task paradigm**

During fMRI acquisition, both patients and healthy subjects performed a self-paced sequential finger opposition task in which the thumb repeatedly touched the other four fingers in a sequential order with the right hand. Seven periods of hand movement and seven periods of rest were alternated (each period lasting for 15 s). ‘Start’ and ‘stop’ acoustic signals were given during the acquisition. Subjects were required to perform the task as quickly as possible, opening their hand wide. Correct execution of the task was confirmed by an operator who was present in the magnet room throughout the session and who recorded the rate of hand movements both for patients and controls.

**fMRI data analysis**

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

At the first stage, the time series of functional MR images 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 regarding each subject were modelled using a boxcar design, convolved with the haemodynamic response function chosen to represent the relationship between neuronal activation and blood flow changes.

Four contrast images were created for each subject: (i) task-related activation at fMR1; (ii) task-related activation at fMR1; (iii) task-related activity increase between the two fMRI studies (fMR1 < fMR2); and (iv) task-related activity decrease between the two fMRI studies (fMR1 > fMR2).

These contrast images were then used for a second level random effect analysis, according to a 2 × 2 design with time (fMRI1 and fMRI2) and group (patients and controls) as factors. We assessed main effects, interactions and simple main effects using subject-specific contrasts as the response variable and one or two sample t-tests. Clusters of voxels (corrected P < 0.05) that had a peak Z score >3.7 were considered to show significant changes.

We also performed a within-group multiple regression analysis to look at the effects of age, disease progression and related measures on the extent of activations by including 11 clinical and radiological variables (see Results). Clusters of voxels (corrected P < 0.05) which had a peak Z score >2.4 were considered to be significantly correlated.

Within each region of statistical significance, local maxima of signal increase were determined (the voxels of maximum significance) and their location was expressed in terms of x, y, and z coordinates. Montreal Neurological Institute (MNI) coordinates were converted to the Talairach space (Talairach and Tournoux, 1988) using a linear transformation (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

**Morphological MRI acquisition and data analysis**

After the fMRI study, we performed a morphological MRI protocol that included proton density and T2-weighted spin-echo images (T2-WI) (TR = 2000 ms; TE = 20/90 ms), and T1-weighted spin-echo images (T1-WI) (TR = 550 ms; TE = 12 ms) before and after injection of an intravenous bolus of 0.3 mmol/kg gadolinium
diethyltriamine pentacetic acid (Gd-DTPA). For proton density, T2-WI and T1-WI, 40 contiguous axial slices were acquired with 4-mm thickness, 256 × 256 matrix and 24-cm field of view.

On conventional MR images, hypointense T2 and hypointense T1 lesion load (LL) were calculated in each patient using the display program Dispunc (D.L. Plummer, University College London, London, UK) with a semi-automated contouring technique (Grimaud et al., 1996).

Results
Clinical data
Patients comprised 14 females and four males aged from 21 to 51 years (mean ± SD = 31 ± 8 years). Controls comprised seven females and two males aged from 24 to 50 years (mean ± SD = 31 ± 8). EDSS score at the time of fMRI ranged from 0 to 2.5 (median = 1.0; mean ± SD = 0.81 ± 0.75).

Patients underwent a second fMRI study 15–26 months later (mean ± SD = 19.8 ± 3.4 months).

No mirror movements were noted during right-hand movement in any of the patients at either fMRI study. The rate of hand movement did not differ significantly between patients and controls and between fMRI1 and fMRI2 (patients: fMRI1 = 1.98 ± 0.18 Hz; fMRI2 = 2.00 ± 0.19 Hz.; controls: fMRI1 = 2.02 ± 0.20 Hz.; fMRI2 = 2.01 ± 0.18 Hz.). There were no significant differences in the rate of right hand movements between patients who had had a right hemiparesis and those who had had a left hemiparesis.

Five patients had presented a new clinical event in the interval time between the two fMRI studies and begun interferon-beta (IFNß) therapy. Relapses consisted of optic neuritis (n = 2), hypoaesthesia in both legs (n = 1), diplopia with mild ataxia (n = 1) and left upper limb hypoaesthesia (n = 1). Six patients had a subclinical progression of the disease (appearance of new T2 hyperintense lesions without a new clinical event). The remaining seven patients were in a stationary phase. The EDSS score at the time of fMRI2 ranged from 0 to 2.5 (median = 1.0; mean ± SD = 1.22 ± 0.75).

Clinical and conventional MR data of the 18 patients at the time of the two fMRI studies are shown in Table 1. No significant differences were observed in EDSS, T1 and T2 lesion load between time 1 and time 2.

Changes in motor-related brain activation as a function of time
Foci of significant activation during right-hand movement at both the first and the second fMRI studies in nine control subjects and 18 patients with multiple sclerosis are shown in Tables 2 and 3, respectively. Motor activation was significantly greater in patients than in controls at both fMRI studies in primary and secondary sensori-motor areas \((P < 0.05\) corrected for multiple comparisons, two-sample t-test). Task-related differences between patients and controls at the time of the first fMRI are not reported explicitly in the current study since we have described them previously (Pantano et al., 2002a,b). At the time of the follow-up study, patients showed greater activation than controls in the lentiform nucleus, thalamus and insula bilaterally, in the ipsilateral premotor and superior parietal cortices.

Patients with multiple sclerosis showed significant task-related activity changes between the two fMRI studies (fMRI1 and fMRI2). Functional changes consisted of a decreased motor activity (fMRI1 > fMRI2) in the left cerebellar hemisphere \((x, y, z\) coordinates = −22, −56, −10; \(Z = 4.44, corrected \ P < 0.05\)) and in the right sensorimotor cortex \((x, y, z\) coordinates = 18, −27, 48; \(Z = 3.74, corrected \ P < 0.05\) (Fig. 1).

No focus of increased motor activity was observed at follow-up (fMRI1 < fMRI2) in the group of 18 multiple sclerosis patients. No significant differences between the two fMRI studies performed with a time interval of 20.0 ± 2.1 months were observed in the group of nine healthy subjects.

Table 1 Clinical and conventional MR data of the 18 patients with multiple sclerosis at the time of the two fMRI studies

<table>
<thead>
<tr>
<th></th>
<th>fMRI1</th>
<th>fMRI2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS</td>
<td>0.81 ± 0.75(0–2.5)</td>
<td>1.22 ± 0.75(0–2.5)</td>
</tr>
<tr>
<td>Number of patients with a second clinical event</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>T2 LL (ml)</td>
<td>7.29 ± 7.1(0.73–33.3)</td>
<td>7.55 ± 6.7(0.91–28.9)</td>
</tr>
<tr>
<td>T1 LL (ml)</td>
<td>1.03 ± 0.9(0.15–3.24)</td>
<td>1.09 ± 1.2(0.07–4.81)</td>
</tr>
<tr>
<td>Number of T2 hyperintense lesions</td>
<td>41 ± 35(7–120)</td>
<td>43 ± 36(7–120)</td>
</tr>
<tr>
<td>Number of patients with new T2 lesions</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

EDSS, T2 and T1 lesion load, and the number of T2 hyperintense lesions are expressed as mean ± SD (range).

Relationship between time-dependent changes in motor activation and clinical and conventional MRI findings
We tested which of the various clinical and conventional MR features in 18 patients with multiple sclerosis correlated significantly with changes in the brain in motor activity between the two fMRI studies. The following clinical and radiological variables were included in the multiple regression analysis: (i) age; (ii) EDSS score at fMRI1; (iii) disease duration; (iv) type of clinical syndrome at presentation; (v) occurrence of a relapse; (vi) time interval between fMRI1 and fMRI2;
Cluster level) during right-hand movement in 18 patients with multiple sclerosis at baseline and at follow-up

sorimotor (BA 1–4) cortex, indicating that the younger the patients, the greater the decrease in motor activation in these areas at follow-up.

The occurrence of a new relapse correlated significantly with activation foci in the ipsilateral sensorimotor cortex (BA 1–4) and in the supplementary motor area (BA 6), indicating that the decrease in motor activation in these areas was smaller in patients with a worse clinical course.

T1 lesion load at baseline correlated significantly with activation foci located in the ipsilateral parietal cortex (BA 7) and in the contralateral sensorimotor cortex (BA 1–4) and in the supplementary motor area (BA 6).

Table 2 Within group analysis (one-sample t-test, SPM99). Location of significant activations (P < 0.05 corrected at the cluster level) during right-hand movement in nine control subjects at baseline and at follow-up.

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Talairach coordinates (x, y, z)</td>
<td>Z</td>
</tr>
<tr>
<td>L sensorimotor cortex (BA 1–4)</td>
<td>−33, −17, 52</td>
<td>5.78</td>
</tr>
<tr>
<td>L inferior parietal lobule (BA 40)</td>
<td>−27, −40, 50</td>
<td>4.30</td>
</tr>
<tr>
<td>L lateral premotor cortex (BA 6)</td>
<td>−40, −40, 55</td>
<td>4.22</td>
</tr>
<tr>
<td>L supplementary motor area (BA 6)</td>
<td>−59, −9, 27</td>
<td>4.01</td>
</tr>
<tr>
<td>R sensorimotor cortex (BA 1–4)</td>
<td>−47, 2, 45</td>
<td>3.46</td>
</tr>
<tr>
<td>R supplementary motor area (BA 6)</td>
<td>−2, 0, 60</td>
<td>4.36</td>
</tr>
<tr>
<td>R inferior parietal lobule (BA 40)</td>
<td>29, −19, 52</td>
<td>3.94</td>
</tr>
<tr>
<td>R lateral premotor cortex (BA 6)</td>
<td>40, −36, 49</td>
<td>4.59</td>
</tr>
<tr>
<td>R supplementary motor area (BA 6)</td>
<td>3, 0, 55</td>
<td>4.46</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>15, −63, −12</td>
<td>5.58</td>
</tr>
<tr>
<td>Vermis</td>
<td>6, −67, −18</td>
<td>5.53</td>
</tr>
<tr>
<td></td>
<td>8, −65, −25</td>
<td>5.11</td>
</tr>
</tbody>
</table>

Z = voxel level.

Table 3 Within group analysis (one-sample t-test, SPM99). Location of significant activations (P < 0.05 corrected at the cluster level) during right-hand movement in 18 patients with multiple sclerosis at baseline and at follow-up.

<table>
<thead>
<tr>
<th>Brain area</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Talairach coordinates (x, y, z)</td>
<td>Z</td>
</tr>
<tr>
<td>L sensorimotor cortex (BA 1–4)</td>
<td>−44, −19, 43</td>
<td>5.80</td>
</tr>
<tr>
<td>L inferior parietal lobule (BA 40)</td>
<td>−46, −32, 52</td>
<td>5.24</td>
</tr>
<tr>
<td>L lateral premotor cortex (BA 6)</td>
<td>−34, −5, −55</td>
<td>5.14</td>
</tr>
<tr>
<td>L supplementary motor area (BA 6)</td>
<td>−2, −1, 55</td>
<td>4.27</td>
</tr>
<tr>
<td>L insula</td>
<td>−12, −12, −1</td>
<td>5.22</td>
</tr>
<tr>
<td>L thalamus</td>
<td>−72, −11, 13</td>
<td>4.72</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>−55, 12, 3</td>
<td>4.69</td>
</tr>
<tr>
<td>R thalamus</td>
<td>−18, −55, −17</td>
<td>5.17</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>42, 0, 52</td>
<td>4.06</td>
</tr>
<tr>
<td>R supplementary motor area (BA 6)</td>
<td>−32, −48, 54</td>
<td>5.23</td>
</tr>
<tr>
<td>R lateral premotor cortex (BA 6)</td>
<td>−30, −7, 57</td>
<td>5.08</td>
</tr>
<tr>
<td>R superior parietal lobule (BA 7)</td>
<td>57, 8, 36</td>
<td>4.81</td>
</tr>
<tr>
<td>R thalamus</td>
<td>12, −7, 13</td>
<td>4.17</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>57, −19, −4</td>
<td>4.78</td>
</tr>
<tr>
<td>Vermis</td>
<td>47, 4, −1</td>
<td>3.91</td>
</tr>
<tr>
<td></td>
<td>18, −55, −17</td>
<td>6.59</td>
</tr>
<tr>
<td></td>
<td>−2, −67, −10</td>
<td>5.89</td>
</tr>
</tbody>
</table>

Z = voxel level.

(vii) T2 LL and (viii) T1 LL at fMRI1; (ix) T2LL and (x) T1LL changes between fMRI1 and fMRI2; and (xi) number of new T2 hyperintense lesions at fMRI2.

Age, occurrence of a new relapse, T1 LL at fMRI1 and T1LL changes between fMRI1 and fMRI2 were inversely correlated with decreased activity in different motor areas, mainly located in the ipsilateral hemisphere (Table 4).

Age correlated significantly with activation foci located in the ipsilateral premotor [Brodmann area (BA 6)] and sensorimotor (BA 1–4) cortex, indicating that the younger the
(BA 1–4), indicating that the decrease in motor activation in these areas was smaller in patients with a higher T1 lesion load at baseline.

T1 lesion load changes correlated significantly with activation foci in the ipsilateral sensorimotor (BA 1–4) and parietal cortex (BA 40), showing that the decrease in motor activation was smaller in patients with a greater increase in T1 lesion load between the two fMRI studies.

**Discussion**

Motor activity in patients with multiple sclerosis was significantly reduced in the follow-up fMRI study compared with the first fMRI study, which had been performed 15–26 months earlier. No significant longitudinal differences were observed in controls in the same time interval.

Some caution must be used in longitudinal fMRI studies because the blood oxygenation level-dependent (BOLD) contrast, which reflects a complex interaction between blood flow, blood volume and haemoglobin oxygenation (Ogawa et al., 1990; Kwong et al., 1992), may be modified by various physiological and environmental factors (Levin et al., 2001; Laurienti et al., 2003). This could affect the reliability of fMRI data obtained across different sessions. However, a good reproducibility has been demonstrated in multiple cerebral areas specific to the motor system in healthy subjects (Mattay et al., 1996; Yetkin et al., 1996), particularly after a time interval of some months (Loubinoux et al., 2001).

None of our control subjects demonstrated an increase or a decrease in task-related activation between the two fMRI sessions. Conversely, patients with multiple sclerosis exhibited a significantly reduced activity in the ipsilateral sensorimotor cortex and in the contralateral cerebellum.

At follow-up, however, our patients still showed a higher degree of activation in motor areas of both the cerebral hemispheres than controls, confirming our previous data.

![Fig. 1](https://example.com/fig1.png)
that microscopic damage exists even in the so-called ‘normal appearing white matter’ of patients with multiple sclerosis (Fernando et al., 2004) does not exclude disease progression at an ultrastructural level, as demonstrated with more sophisticated MR techniques (Caramia et al., 2002).

Given the heterogeneity of the sample studied in terms of both clinical manifestations and MRI features, we were interested in assessing which factors could determine the observed pattern of reduced brain motor activity over time.

Multiple regression analysis indicated that age, occurrence of a new relapse, T1 LL at baseline and T1 LL changes between the two fMRI studies had an independent effect upon changes in motor activation patterns. All these factors were inversely correlated with motor areas mostly located in the ipsilateral hemisphere.

Age is known to influence motor recovery after brain damage: experimental and clinical data suggest that younger subjects have a greater ability to recover motor function and are likely to benefit substantially from treatments that facilitate plasticity-mediated recovery (Goldstein and Bullman, 1999; Gwak et al., 2004; Katz et al., 2004; Stein, 2004). Ipsilateral sensorimotor cortex has been found to be more activated in older than in younger healthy subjects during a motor task, suggesting that a recruitment of motor cortical units accompanies aging (Hutchinson et al., 2002).

The greater activation of the ipsilateral motor cortex is one of the most important effects of neuroplasticity in patients with multiple sclerosis (Lee et al., 2000; Pantano et al., 2002a; Reddy et al., 2000b). The role of this increased motor activation and, in particular, that of the ipsilateral motor pathway in patients with multiple sclerosis is not completely clear. Increased ipsilateral activation may have a vicarious function owing to a variety of mechanisms such as bilateral representation of motor function, creation of new connections, release of inhibition and synaptic sprouting.

What is still unknown is the evolution of these functional changes over time in patients with multiple sclerosis. To our knowledge, only one previous report has described longitudinal fMRI changes in a single multiple sclerosis patient studied with serial magnetic resonance spectroscopy (MRS) and fMRI while recovering from an acute relapse of hemiplegia (Reddy et al., 2000b). The clinical improvement paralleled the recovery of N-acetylaspartate and progressive reduction in abnormally increased fMRI motor activation.

None of our patients was in an acute phase at the time of each fMRI study. All the patients had recovered from a single clinical event at the time of the first fMRI and few had suffered a new relapse in the time between the two fMRI studies. Only five patients had presented a new clinical event at least 4 months before the second fMRI study. The rate of clinical conversion in our sample of patients with a single clinical event and MR findings suggestive of multiple sclerosis is in agreement with the rate of ∼30% in 18 months reported by the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) group (CHAMPS, 2002).

In six patients, we observed the appearance of new T2 lesions during the follow-up period despite the absence of new symptoms. In the remaining seven patients, the disease was in an apparent phase of stability. However, the knowledge changes over time in patients with multiple sclerosis is not completely clear. Increased ipsilateral activation may have a vicarious function owing to a variety of mechanisms such as bilateral representation of motor function, creation of new connections, release of inhibition and synaptic sprouting.

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in patients with multiple sclerosis. However, T1 LL specifically located along the corticospinal tract correlated positively with activated foci in the ipsilateral premotor cortex. Therefore, the total amount of axonal damage does not seem to influence the initial level of motor activity, but it can influence the subsequent reorganization of the motor network. The tendency of brain motor activity to return towards a more lateralized activation pattern seems to be affected by the amount of axonal damage and by how much this damage increases over time.

The decrease in motor activation in the ipsilateral sensorimotor cortex we observed over time in patients with multiple sclerosis is consistent with results reported in stroke patients. Indeed, longitudinal studies have shown a general trend towards a reduction in motor activation and a focusing on the damaged hemisphere, i.e. in contralateral motor areas after a cerebrovascular lesion (Marshall et al., 2000; Feydy et al., 2002). Moreover, a task-related brain activation decrease over time has been found to correlate with motor recovery (Ward et al., 2003).

Our results suggest that brain functional changes in multiple sclerosis are a dynamic phenomenon dependent on age, clinical course and brain tissue damage. The altered pattern of brain activation in patients with multiple sclerosis may partially be reversed during non-active periods of disease, especially in the ipsilateral hemisphere, focusing on a contralateral activation pattern. Conversely, the persistence of increased motor activation in patients with multiple sclerosis is associated with either clinical or subclinical disease progression.

In this study, we present longitudinal fMRI changes in a cohort of 18 patients with multiple sclerosis observed over a long period of time. Previous studies have demonstrated acute fMRI changes in multiple sclerosis in response to drugs (Parry et al., 2003; Mainero et al., 2004) and motor training (Morgen et al., 2004). Our data may represent a useful reference for further studies aimed at investigating the effects of treatments on cerebral plasticity in multiple sclerosis in the long term.

Acknowledgements

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