Contribution of Corticospinal Tract Damage to Cortical Motor Reorganization after a Single Clinical Attack of Multiple Sclerosis

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The objectives of this study were to assess whether cortical motor reorganization in the early phase of multiple sclerosis (MS) is correlated with the clinical presentation and with specific damage to the corticospinal tract. Twenty patients with clinically isolated syndrome (CIS) and serial MR findings indicative of MS were selected. In 10 patients the CIS was hemiparesis (group H), and in 10 patients the CIS was optic neuritis (group ON). There were no significant differences in age, disease duration, total T2 lesion load (LL), and total T1 LL between group H and group ON. Ten age-matched healthy subjects served as controls (group C). All subjects were submitted to fMRI during a sequential finger-to-thumb opposition task of the right hand. Group H showed a significantly higher EDSS score and T1 LL calculated along the corticospinal tract than group ON. Group C showed, although at a lower level of significance (P < 0.001), higher activation of the contra lateral motor-related areas than group C. Multiple regression analysis showed that T2 and T1 LL along the corticospinal tract and time since clinical onset positively correlated with activation in motor areas in both cerebral hemispheres (P < 0.005). Total T2 LL positively correlated with activation in motor areas in the contralateral hemisphere (P < 0.005). Total T1 LL and EDSS did not show any significant correlation. More severe specific damage to the motor pathway in patients with previous hemiparesis may explain the significantly higher involvement of ipsilateral motor areas observed in group H than in group ON. Furthermore, the significant correlation between the time since clinical onset and activation in motor areas suggests that cortical reorganization develops gradually in concomitance with the subclinical accumulation of tissue damage.

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Key Words: fMRI; motor task; multiple sclerosis; clinically isolated syndrome; hemiparesis; optic neuritis; neuroplasticity.

INTRODUCTION

In patients with multiple sclerosis (MS), the ability of the brain to compensate for tissue damage or loss may contribute to the maintenance of normal performance despite scattered brain lesions. Adaptive functional changes in the cerebral cortex during a motor task have been described in patients with relapsing-remitting and both primary- and secondary-progressive MS (Lee et al., 2000; Reddy et al., 2000; Filippi et al., 2002).

The earliest clinical event in many patients with MS is a clinically isolated syndrome (CIS) suggestive of MS. In patients with CIS, the diagnosis of possible MS or MS can be made on the basis of magnetic resonance (MR) evidence of lesion dissemination in space and time (McDonald et al., 2001). We recently observed (Pantano et al., 2002) that cortical motor reorganization was already present in patients with a CIS suggestive of MS in whom a diagnosis of possible MS or MS was made on the basis of the criteria of McDonald et al. (2001).

The single clinical attack of these patients consisted of hemiparesis. Functional cortical changes have been interpreted as part of a process of reorganization in the motor cortex following loss of corticospinal fibers. Enlargement of activated motor-related areas was observed, however, when patients moved not only the previously paretic hand, but also the unaffected hand.

The relationship between the occurrence of motor deficit and reorganization of cortical motor areas is not yet fully understood since MS patients generally have multiple, scattered brain lesions even in the early phase of the disease. The brain lesion load on conventional MR in such patients is not, in fact, closely related to the presence and severity of clinical relapses (Smith et al., 1993).

We therefore decided to evaluate the pattern of motor activation in MS patients with a single clinical attack, paying particular attention to whether the motor system had or had not been involved. In particular, the aim of this study was to
evaluate whether cortical reorganization is closely associated with specific damage to the corticospinal tract; if so, it would ensue that changes in patterns of motor activation occur especially in patients who have experienced a motor deficit.

**SUBJECTS AND METHODS**

Subjects. Of a consecutive series of 70 subjects enrolled in a prospective study on patients with CIS and with positive MRI findings according to the criteria of Fazekas et al. (1988), we retrospectively selected 20 patients with a single clinical attack consisting either of hemiparesis (group H, n = 10) or optic neuritis (group ON, n = 10). Inclusion criteria were: (1) right-handedness; (2) no further clinical episode; (3) no sensory and/or motor deficit at the time of the fMRI study; and (4) no MR lesions in the spinal cord. Patients had a diagnosis of MS (n = 16) or of possible MS (n = 4) according to the recommendations of the international panel on the diagnosis of multiple sclerosis (McDonald et al., 2001).

There were 15 women and 5 men aged 21 to 51 years (mean 31 ± 8 years). None of them was treated with disease modifying agents. Time since clinical onset was 24 ± 17 months. They had no or only mild neurologic impairment, with a modified disability status scale (EDSS) score ranging between 0 and 2.5 (median = 1). Group H included 5 patients with right hemiparesis and 5 patients with left hemiparesis.

The control group for fMRI data consisted of 10 right-handed age-matched volunteers (group C). All subjects gave their written informed consent to participate in the study.

fMRI data acquisition. Morphologic and functional MRI data were acquired during the same imaging session using a 1.5-T magnet (Philips Gyroscan NT 15) with echoplanar 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 bicommissural (AC–PC) plane was assured by acquiring a multiplanar T1-weighted localizer at the beginning of each study; T2*-weighted echo planar images (64 × 64 matrix over a 24-cm field of view), consisting of 25 consecutive, 4-mm-thick axial sections, with TR/TE = 3000/50 ms, a 90° flip angle, and one excitation, were then acquired.

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

Motor task paradigm. During the fMRI acquisition, both patients and normal 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. "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 for controls. The rate of hand movement was not significantly different among group H, group ON, and group C (1.9 ± 0.2, 2.0 ± 0.2, and 2.1 ± 0.2 Hz, respectively).

Morphologic MRI acquisition and data analysis. After the fMRI study, a morphologic MRI protocol was performed, which included proton density (PD) 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 Gd-DTPA. For PD, 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, hyperintense T2 and hypointense T1 lesion load (LL) was calculated in each patient using the display program Dispunc (Plummer DL, University College of 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 T1-WI and corresponding to a region of high signal intensity on T2-WI. In addition, on both T2-WI and T1-WI, lesion load was calculated for lesions selectively located on the corticospinal tract both at the supratentorial and at the infratentorial level, as 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 fibers, lesion load values calculated along motor pathways in both hemispheres were summed.

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

Images were analyzed using a two-stage random-effect approach. At the first stage, the time series of functional MR images obtained from each participant was analyzed 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 modeled using a boxcar design, convolved with the hemodynamic response function chosen to represent the relationship between neuronal activation and blood flow changes.

Significance of signal changes related to hand movement was determined on a voxel-by-voxel basis using a t statistic, which was then transformed into a normal distribution. Regions of significant condition-associated signal changes were 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 location was expressed in terms of x, y, and z coordinates. MRI (Montreal Neurologic Institute) coordinates were converted to the Talairach space (Talairach and Tournoux, 1988) by using a linear transformation (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

The second stage of analysis included within-group analy-
Clinical and MR Data of 20 Patients with a Single Clinical Attack of Multiple Sclerosis Sorted According to Clinical Presentation

<table>
<thead>
<tr>
<th></th>
<th>Hemiparesis (n = 10)</th>
<th>Optic neuritis (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.9 ± 9</td>
<td>31.5 ± 7</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>24.3 ± 14</td>
<td>23.9 ± 20</td>
</tr>
<tr>
<td>EDSS</td>
<td>1.25 ± 0.8</td>
<td>0.45 ± 0.6</td>
</tr>
<tr>
<td>T2 LL (total, ml)</td>
<td>6.27 ± 3.4</td>
<td>7.19 ± 9.5</td>
</tr>
<tr>
<td>T1 LL (total, ml)</td>
<td>0.91 ± 0.9</td>
<td>0.88 ± 1.1</td>
</tr>
<tr>
<td>T2 LL (corticospinal tract, ml)</td>
<td>2.12 ± 1.4</td>
<td>1.19 ± 1.6</td>
</tr>
<tr>
<td>T1 LL (corticospinal tract, ml)</td>
<td>0.42 ± 0.5</td>
<td>0.09 ± 0.2</td>
</tr>
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* Statistically significant differences between groups by unpaired t test (P < 0.05).

RESULTS

No significant differences were found in age, disease duration, and T2 and T1 LL between group H and group ON. Group H showed a significantly higher EDSS score and T1 LL calculated along the corticospinal tract than group ON (P < 0.05 by unpaired t test). The difference in T2 LL along the corticospinal tract between the two groups did not reach statistical significance, although higher values were found in group H. The clinical and MR data of the MS patients sorted according to the clinical presentation are shown in Table 1.

The number of activated voxels in motor areas was not significantly different between patients with a previous right or left hemiparesis in agreement with the results of a previous study (Pantano et al., 2002). Therefore, in group analysis, patients were grouped independently of the side of previous hemiparesis to obtain the locations of significantly activated voxels in within- and between-group analysis.

DISCUSSION

Cortical reorganization of motor areas is a well-known phenomenon that has been reported in several diseases of the nervous system (Chollet et al., 1991; Weiller et al., 1992; Cao et al., 1992).
et al., 1998; Sabatini et al., 1994; Alkadhi et al., 2000; Yoshiura et al., 1997; Kew et al., 1993) including MS (Lee et al., 2000; Reddy et al., 2000; Filippi et al., 2002).

In patients with MS, however, it is not clear when, in the course of the disease, this phenomenon occurs and, above all, whether it is the consequence of the global, scattered tissue damage typical of MS or of more specific damage to the corticospinal tract.

In our previous study, we found that cortical reorganization was present in MS patients in the early phase of the disease (Pantano et al., 2002). However, the aforementioned question remained partially unresolved in that study since the patients studied were all CIS patients with a previous motor deficit. For this reason, we decided to study two groups of CIS patients who were matched for age, disease duration, and global tissue damage, but had a different involvement of the motor system, demonstrated by the clinical presentation and corticospinal tract involvement.

Our study shows changes in patterns of cortical activation during a simple motor task in patients with MS or possible MS who had suffered a single clinical episode. As expected, the extent of cortical reorganization was greater in patients with a previous hemiparesis and a higher lesion volume along the corticospinal tract than in patients with a previous optic neuritis and no clinical evidence of damage to the corticospinal tract.

In the group of patients with a previous hemiparesis, cortical motor reorganization was extensive and notably involved also the ipsilateral hemisphere. Motor-related areas in the ipsilateral hemisphere were significantly more active in patients in group H than in those in groups ON and C, as demonstrated by the statistical comparison of the three groups by ANOVA.

Interestingly, patients with a previous optic neuritis showed differences in the pattern of motor activation when compared with controls. Within-group analysis showed that some areas of the contralateral hemisphere, such as the left lateral premotor cortex, lentiform nucleus, and insula, were significantly more active in group ON, but not in group C.

These results suggest that recruitment of additional cortical areas of the sensory-motor network is confined to the contralateral hemisphere in patients with scattered white matter lesions and no previous symptom of motor deficit, but involves also the ipsilateral sensory-motor network in patients with a previous hemiparesis and a larger number of lesions specifically located along the corticospinal tract.

A marked involvement of the ipsilateral hemisphere in the execution of hand movement has been reported in MS patients with varying degrees of upper limb motor deficit and disability (Lee et al., 2000; Reddy et al., 2000). By contrast, increased ipsilateral activation in sensory-motor areas has not been observed in nondisabling relapsing-remitting MS
patients with no previous relapse affecting the functioning of the tested upper limb (Rocca et al., 2002).

In agreement with these data, our results strongly suggest that the involvement of the ipsilateral hemisphere during hand movement in MS patients is an adaptive mechanism apt to compensate for motor neuron loss or motor pathway disruption. This adaptive mechanism is not specific to MS since it has been repeatedly reported after brain damage of
various types (Chollet et al., 1991; Weiller et al., 1992; Cao et al., 1998; Sabatini et al., 1994; Yoshiura et al., 1997).

However, the evaluation of the effects of both structural damage and disease duration on functional changes is complex because the different aspects of white matter lesions, such as demyelination, gliosis, and axonal damage, which contribute to signal abnormalities on T2 and T1 images, may not be completely independent and usually increase over time.

Previous studies on MS patients have investigated the relationship between structural brain damage and functional cortical changes. A direct correlation between the extent of cortical reorganization and disease burden on T2 images has been described in some studies on MS patients (Lee et al., 2000; Rocca et al., 2002), while other data have highlighted the role of normal-appearing brain tissue damage in determining adaptive functional changes (Reddy et al., 2000; Filippi et al., 2002).

In our study, multiple regression analysis indicated that the type of clinical presentation, total T2 LL, both T2 and T1 LL along the corticospinal tract, and disease duration had an independent effect on patterns of motor activation, whereas total T1 LL and EDSS score did not correlate with functional changes.

Total T2 LL is a marker of overall disease burden indicating the extent of macroscopic tissue damage. Our results suggest that the functional activity in the contralateral primary–motor cortex during the right hand movement increases with increasing amount of scattered white matter lesions on T2 images. This finding can explain the occurrence of adaptive mechanisms in cortical motor areas observed in patients with ON who had never experienced a motor deficit.

Enlargement of motor activated areas was observed in group ON with respect to group C exclusively in the contralateral hemisphere and could represent an effect of overall damage accumulation.

Both T2 and T1 LL along the corticospinal tract positively correlated with activated foci in motor areas of both the cerebral hemispheres. This finding can explain the markedly more extended cortical activation in group H than in group ON owing to the significantly larger amount of T2 and T1 lesions specifically located along the corticospinal tract in patients with a previous hemiparesis. While hyperintense lesions on T2 images mainly reflect inflammation, demyelination, and gliosis, hypointense lesions on T1 images are associated with both extensive demyelination and loss of axons (van Walderveen et al., 1998; van Waesberge et al., 1999), even in the early stages of MS (Trapp et al., 1998). The specific involvement of the corticospinal tract could be compensated for by recruitment of larger components of neurons in primary and associative motor areas not only in the contralateral, but also in the ipsilateral hemisphere.

The amount of time that has elapsed since the clinical episode seems to be a critical factor for the cortical reorganization and involvement of the ipsilateral hemisphere. Disease duration positively correlated with activated foci in the ipsilateral sensory–motor (BA 1–4) and parietal cortex (BA 40) and in the contralateral parietal cortex (BA 40).

Anatomic connections between motor areas and parietal association areas are well documented (Godshalk et al., 1984; Petrides and Pandya, 1984; Cavada and Goldman-Rakic, 1989). A possible compensatory role of BA 40 has been suggested by a previous work (Pantano et al., 1996) that reported that stroke patients with a CT/MRI lesion of the parietal lobe showed a more severe motor deficit than patients with lesions in other cortical locations. Increased activation of BA 40 during hand movement was found in patients who had recovered from a striatocapsular stroke (Weiller et al., 1992), while a posterior shift of the center of activation in the contralateral sensory–motor cortex has been described in MS patients (Lee et al., 2000).

In our previous work (Pantano et al., 2002), a significant correlation between disease duration and increased activation of related motor areas in the ipsilateral hemisphere was observed in CIS patients with a previous single clinical episode of hemiparesis. We confirm now this correlation on a larger series of patients.

In one serial study on stroke patients, the involvement of the ipsilateral sensory–motor cortex during movements of the paretic hand decreased with time (Marshall et al., 2000). However, more recently, Calautti et al. (2001) reported that ipsilateral motor activation tended to increase over time and significantly correlated with recovery in stroke patients examined twice over several months. Lastly, transcranial magnetic stimulation (TMS) did not reveal the presence of ipsilateral motor evoked potentials in stroke patients during the acute phase, whereas ipsilateral motor evoked potentials were found 6 months later (Caramia et al., 2000).

The data obtained in stroke patients support our results suggesting that plastic changes in the ipsilateral hemisphere in MS patients do not occur immediately after damage to the corticospinal tract, but develop gradually over time along with tissue damage accumulation.

Extension of activation of motor areas may represent a compensatory mechanism that allows a normal motor function to be maintained despite a selective damage to the corticospinal tract. The question remains whether this compensatory mechanism could be exhausted by progressive accumulation of tissue damage. Longitudinal studies could investigate whether patients with extensive cortical motor activation exhibit lower ability to recover from additional damage to the corticospinal tract. In this respect, fMRI study in MS could assume prognostic relevance.

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