Effect of Corpus Callosum Damage on Ipsilateral Motor Activation in Patients with Multiple Sclerosis: A Functional and Anatomical Study

Delia Lenzi,* Antonella Conte, Caterina Mainero, Vittorio Frasca, Federica Fubelli, Porzia Totaro, Francesca Caramia, Maurizio Inghilleri, Carlo Pozzilli, and Patrizia Pantano

Department of Neurological Sciences, University of Rome "La Sapienza," Rome, Italy

Abstract: Functional MRI (fMRI) studies have shown increased activation of ipsilateral motor areas during hand movement in patients with multiple sclerosis (MS). We hypothesized that these changes could be due to disruption of transcallosal inhibitory pathways. We studied 18 patients with relapsing-remitting MS. Conventional T1- and T2-weighted images were acquired and lesion load (LL) measured. Diffusion tensor imaging (DTI) was performed to estimate fractional anisotropy (FA) and mean diffusivity (MD) in the body of the corpus callosum (CC). fMRI was obtained during a right-hand motor task. Patients were studied to evaluate transcallosal inhibition (TCI, latency and duration) and central conduction time (CCT). Eighteen normal subjects were studied with the same techniques. Patients showed increased MD ($P < 0.0005$) and reduced FA ($P < 0.0005$) in the body of the CC. Mean latency and duration of TCI were altered in 12 patients and absent in the others. Between-group analysis showed greater activation in patients in bilateral premotor, primary motor (M1), and middle cingulate cortices and in the ipsilateral supplementary motor area, insula, and thalamus. A multivariate analysis between activation patterns, structural MRI, and neurophysiological findings demonstrated positive correlations between T1-LL, MD in the body of CC, and activation of the ipsilateral motor cortex (iM1) in patients. Duration of TCI was negatively correlated with activation in the iM1. Our data suggest that functional changes in iM1 in patients with MS during a motor task partially represents a consequence of loss of transcallosal inhibitory fibers. *Hum Brain Mapp* 28:636–644, 2007. © 2006 Wiley-Liss, Inc.

Key words: fMRI; motor cortex; TMS; transcallosal inhibition; ipsilateral motor activation; corpus callosum; multiple sclerosis

INTRODUCTION

Several functional neuroimaging studies have shown altered cortical activation in patients with multiple sclerosis (MS) during motor tasks. In particular, a greater activation of the ipsilateral motor areas has been reported compared to healthy subjects [Lee et al., 2000; Pantano et al., 2002a,b; Reddy et al., 2000b, 2002; Rocca et al., 2004]. Nevertheless, the significance of such change has yet to be fully defined.

*Correspondence to: Dr. Delia Lenzi (c/o Prof. Patrizia Pantano), Department of Neurological Sciences, Section of Neuroradiology, University of Rome "La Sapienza," Viale dell'Università, 30 I-00185, Rome, Italy. E-mail: delia.lenzi@uniroma1.it

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The ipsilateral pattern of activation, and in particular the primary motor (M1) activation, could be compensatory to maintain performance, i.e., an expression of “plastic” changes that go from local synaptic reorganization to recruitment of existing parallel pathways from the ipsilateral hemisphere [Ziemann et al., 1999]. In humans, 8–10% of the pyramidal corticospinal tract fibers are uncrossed [Kandel et al., 2000].

On the other hand, overactivation of the ipsilateral motor cortex (iM1) in patients with MS could also be due to reduced inhibitory input from the contralateral M1 through the corpus callosum (CC) due to MS-induced white matter damage.

Interhemispheric transcallosal interactions between motor areas have been demonstrated in animals using direct electrical cortical stimulation [Asanuma and Okuda, 1962; Matsunami and Hamada, 1984] and more recently in humans using transcranial magnetic stimulation (TMS) [Ferbert et al., 1992; Hanajima et al., 2001]. In humans, according to lesion and anatomical studies [Huang et al., 2005; Pandya et al., 1971; Stancak et al., 2000, 2002] connections between the sensory-motor and premotor areas seem to be localized mainly in the body of the CC. Stimulation of one primary motor cortex may induce inhibitory and (or) facilitatory effects in contralateral motor cortex [Chen et al., 2003], although most authors agree that transcallosal connections have mainly inhibitory effects [Ferbert et al., 1992; Liepert et al., 2001; Meyer et al., 1998]. In healthy subjects, the transcallosal inhibitory pathway (TCI) between the primary motor cortices has been demonstrated by using TMS to one motor cortex to suppress tonic voluntary electromyographic activity in ipsilateral hand muscles [Ferbert et al., 1992; Meyer et al., 1998]. These data are supported by fMRI studies in healthy subjects [Allison et al., 2000; Nirkko et al., 2001; Stefanovic et al., 2004], which show a decrease in activation in the iM1 during sequential finger movement. Therefore, the loss of inhibitory fibers in the CC could result in reduced inhibition of iM1.

In patients with MS, atrophy and dysfunction of the CC are common findings, even in the early stages of disease, and have been demonstrated with conventional MRI [Pozzilli et al., 1991; Rao et al., 1989], diffusion tensor imaging (DTI) [Ciccarelli et al., 2003], MRS [Ranjeva et al., 2003], and TMS [Schmierer et al., 2002].

The aim of this study was to test, using fMRI and TMS, whether iM1 increased activation in patients with MS is due to reduced transcallosal inhibitory input from the contralateral M1. According to our hypothesis, the more severe the CC damage, the greater the activation in iM1.

SUBJECTS AND METHODS

We studied 18 patients (12 women, mean age: 36 years, standard deviation (SD): 8 years) with MS according to McDonald et al.'s [2001] criteria of relapsing-remitting type according to Lublin and Reingold [1996] referred to the outpatient Multiple Sclerosis Clinic at our institution.

Patients were selected according to the following criteria: right-handedness tested with the Edinburgh Handedness Inventory [Williams, 1986]; normal function of the right upper limb with no clinically evident motor or sensory impairment; no lesions in the spinal cord (in order not to alter neurophysiological results and interpretation); no concomitant therapy with antidepressant, psychoactive, corticosteroid, or muscle relaxant drugs; no clinical relapse for at least 3 months before study entry; no history of seizures or unexplained loss of consciousness or electroencephalographic abnormalities; and no other major medical illnesses.

Disability was evaluated with the Expanded Disability Status Scale (EDSS) [Kurtzke, 1983] and all study procedures were approved by the Ethical Committee of the Department of Neurological Sciences, University of Rome “La Sapienza.”

Eighteen right-handed sex- and age-matched healthy volunteers constituted the control group.

Conventional MRI

Data were acquired with a 1.5 T magnet scanner (Philips Gyroscan NT 15, Netherlands). All patients had conventional proton density and T2-weighted spin-echo images (TR 2000 ms; TE 20/90 ms; matrix 256 × 256 mm; field of view (FOV) 240 × 240 mm; 40 axial slices; slice thickness 4 mm; gap 0 mm), and T1-weighted images after the injection of a double dose (0.2 mmol/kg) of gadolinium-DTPA (TR 600 ms; TE 15 ms; matrix 256 × 256 mm; FOV 240 × 240 mm; 40 axial slices; slice thickness 4 mm; gap 0).

Hyperintense T2 and hypointense T1 lesion load (T2 LL, T1LL) was calculated in patients using the display program Dispunc (Plummer DL, University College, London, UK) with a semiautomated contouring technique [Grimaud et al., 1996].

Diffusion Protocol

The diffusion protocol consisted of acquisition of diffusion-weighted EPI spin-echo sequences (TR 3700 ms, TE 124 ms, matrix 128 × 128 mm, FOV 250 × 250 mm, b values: 0 and 1000 s/mm² applied along six noncollinear directions; 18 axial slices; slice thickness 6 mm; gap 0.6 mm).

The data were processed to determine the diffusion tensor on a pixel-by-pixel basis and fractional anisotropy (FA) and mean diffusivity (MD) were calculated [Basser et al., 1994; Pierpaoli et al., 1996]. Regions of interest (ROIs) of uniform size (3 × 3 pixels; 31.72 mm²) were drawn in the body of the CC on the FA maps, where fiber tracts can be easily visualized and subsequently copied onto MD maps. The ROI location was determined according to a tractography study, which indicated that frontal lobe fibers occupy the genu and a large part of the body of CC [Huang et al., 2005]. Inclusion of white matter lesions in the ROIs was avoided by inspecting the corresponding b0 weighted images. Within the body of the CC we chose the ROI that

had the mean FA with the smallest SD to avoid partial volume effect. An identical ROI with the same x–y coordinates was then positioned on MD maps. Statistical analysis was performed with SPSS 10.0 (Chicago, IL).

fMRI

Data acquisition

fMRI data were acquired with the same magnet scanner with echo-planar capabilities and a head volume radiofrequency coil. Each subject lay supine in the scanner with eyes closed. Head movements were minimized with foam padding and a restraining strap. T2*-weighted echo planar images (64×64 matrix over a 24-cm FOV), consisting of 25 consecutive, 4-mm thick axial sections, 0 gap, with TR/TE of 3000/50 ms, a 90° flip angle, and one excitation were acquired.

During fMRI scanning patients performed a repetitive index finger to thumb opposition movement with the right hand according to a block design consisting of 12 21-s epochs alternating between rest and activation, yielding a total scan time of 4 min and 12 s. Before image acquisition subjects were instructed to perform the motor task at a regular rate of 2 Hz. Throughout the fMRI study an external observer checked that participants performed correctly and recorded the actual rate of hand movement.

Data analysis

fMRI data were analyzed using dedicated software and General Linear Model statistics (SPM99) [Friston et al., 1995, 1996]. Images were realigned, normalized, and spatially smoothed using a Gaussian kernel of 8 mm. To obtain contrast images for each subject, individual data were modeled using a boxcar design, convolved with a hemodynamic response function chosen to represent the relationship between neuronal activation during right hand movement and blood flow changes.

The individual contrast images were then used in a second-level random effect analysis to assess differences in task-related blood oxygenation level-dependent (BOLD) responses between patients and controls (two-sample *t*-test). Clusters of voxels with a peak $Z > 3.1$ (cluster-level-corrected $P < 0.05$) were considered significant. 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. MNI (Montreal Neurologic Institute) coordinates were converted to the Talairach space [Talairach and Tournoux, 1988] using a linear transformation (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

Simple regression and multiple regression analyses were then performed considering fMRI data as the outcome variable (using contrast images from each patient) and clinical (EDSS, disease duration), radiological (T1-LL, T2-LL, MD, and FA in the body of the CC), and neurophysiological (transcallosal inhibition latency and duration) data

as predictors using SPM99. Clusters of voxels with a peak $Z > 3.2$ (cluster-level corrected $P < 0.05$) were considered significant. To test our hypothesis, we limited this analysis to a ROI that was fixed in shape and located in the iM1 (Right BA 4). This ROI was drawn on a T1 anatomical image template following anatomical landmarks [Pantano et al., 2002a; Reddy et al., 2000b].

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation was performed in 16 patients and 16 sex- and age-matched healthy control subjects. Two patients could not be tested because of technical problems. Consequently, we also excluded two controls.

Stimulation

TMS was delivered through a magnetic stimulator (Magstim, Whitland, South West Wales, UK) connected to a figure-eight coil placed over the motor area of the dominant hemisphere. Single magnetic pulses were delivered to the motor cortex to find the optimal position for evoking a motor-evoked potential (MEP) in the contralateral first dorsal interosseous (FDI) muscle (target muscle). This position was marked on the scalp and used throughout the experiment. Motor threshold (MTh) was calculated at rest using the lowest intensity able to evoke an MEP of more than 50 μ V in at least 5 of 10 consecutive trials in the FDI muscle. Target-muscle relaxation was monitored by means of electromyographic (EMG) acoustic and visual feed-back (Tektronic 5103N oscilloscope, Beaverton, OR).

The coil was held tangentially to the scalp with the handle pointing back and away from the midline at 45° . The induced current flow was posterior to anterior in the cortex perpendicular to the central sulcus. To evaluate CCT, TMS was also delivered with the coil positioned at the cervical level to elicit root-MEP. Stimulation intensity was set at 120% of MTh.

Among TMS methods to study inhibitory connections between motor areas, we chose transcallosal inhibition because it could be performed rapidly and our patients underwent clinical, radiological, and neurophysiological evaluations on the same day. This method has been applied in the assessment of MS patients [Boroojerdi et al., 1998; Schmierer et al., 2000].

We delivered TMS with the FDI muscle ipsilateral to the site of magnetic stimulation contracted. The patients were asked to exert a maximal tonic hand muscle contraction with the aid of EMG acoustic and visual (Tektronic 5103N oscilloscope) feedback. Stimulation intensity was set at 150% of MTh. Twenty trials were recorded at an interpulse interval of 1 min.

EMG recording

EMG activity was recorded through a pair of surface disk electrodes placed over the right and the left FDI muscle. EMG signals were recorded and filtered with a Digi-

TABLE I. Individual TCI latency and duration in multiple sclerosis (MS) patients

Patient no.	Transcallosal inhibition (TCI)		Transcallosal conduction time (ms)
	Latency (ms)	Duration (ms)	
1	39.9	18.1	20.9
2	42.8	23.9	21.8
3	38.4	24.0	18.9
4	37.7	18.8	16.7
5	31.9	12.0	12.1
6	37.0	13.0	16.6
7	—	—	—
8	42.8	17.7	22.3
9	51.0	13.0	28.4
10	—	—	—
11	—	—	—
12	46.2	19.0	26.8
13	54.2	20.0	32.2
14	—	—	—
15	52.2	27.1	29.5
16	57.2	16.0	34.4

timer D 160 (bandwidth 20 Hz to 1 kHz, sampling rate 2 kHz), full-wave-rectified, and averaged for the TCI paradigm, with a personal computer processed through a 1401 plus A/D laboratory interface (Cambridge Electronic Design, Cambridge, UK) and analyzed off-line. MEPs were recorded at rest.

Measurements and analysis

The size of MEP evoked by TMS was measured peak-to-peak. The latency of MEPs was measured from the onset of the stimulus artifact to the onset of the MEP. The central conduction time was calculated as the difference in latency between the scalp-MEP and root-MEP.

Onset and end latency of the TCI were taken at the initial and final intersections of the averaged signal with baseline indicating 80% of the background EMG level; the duration of EMG suppression between these two points was computed automatically [Inghilleri et al., 1993; Pascual-Leone et al., 2002; Schmierer et al., 2002]. Transcallosal conduction times were determined by subtracting the onset latency of the corticospinally mediated EMG response from the onset latency of TCI in the same FDI [Schmierer et al., 2002].

All results are expressed as mean $\pm$ SD. All the TMS variables studied were analyzed by *t*-test. *P*-values < 0.05 were considered statistically significant.

RESULTS

Clinical and Structural MRI

Patients had a mean $\pm$ SD disease duration of 7 ± 5 years and a median EDSS score of 1.5 (range 0–4.5). At the time of the study all patients but one were receiving interferon-beta for at least 3 months.

Patients had a mean T1-LL of 1671 mm^3 (SD $\pm 1816 \text{ mm}^3$) and a mean T2-LL of 10993 mm^3 (SD $\pm 8770 \text{ mm}^3$). None of them had gadolinium-enhancing lesions. DTI analysis showed that patients had increased MD in the CC body ($0.895 \pm 0.163 \times 10^{-3} \text{ mm}^2/\text{sec}$ vs. $0.756 \pm 0.092 \times 10^{-3} \text{ mm}^2/\text{sec}$, $P < 0.005$) and decreased FA in the CC body (0.645 ± 0.128 vs. 0.805 ± 0.043 , $P < 0.005$) with respect to controls.

TMS

None of the TMS test procedures caused any adverse events in either patients or control subjects. No significant difference was found in the rest-MTH between the two groups studied ($45 \pm 7\%$ vs. $49 \pm 10\%$ of the maximum stimulator output). Nor did MEP amplitude differ significantly in patients and control subjects (MEP amplitude: 1.03 ± 0.52 vs. $1.06 \pm 0.20 \text{ mV}$). Conversely, the MEP latency was significantly longer in patients than in healthy subjects (21.7 ± 1.29 vs. $20.2 \pm 0.82 \text{ ms}$; $P < 0.0001$).

CCT calculated in patients was significantly increased compared with control subjects (8.7 ± 1.29 vs. $5.8 \pm 0.48 \text{ ms}$; $P < 0.0001$).

Transcallosal inhibition (TCI) was absent in 4 out of 16 patients (Table I). In the remaining 12 patients latency and duration of TCI were significantly different with respect to controls (latency: 44.9 ± 7.87 vs. $36.4 \pm 1.45 \text{ ms}$, $P < 0.0001$; duration: 19.4 ± 5.39 vs. $25.2 \pm 1.78 \text{ ms}$, $P < 0.0001$). Also, transcallosal conduction time was significantly different with respect to controls (23.3 ± 6.8 vs. $16.0 \pm 1.5 \text{ ms}$, $P < 0.0001$) (Table I).

fMRI

Patients correctly performed the motor task during fMRI. Visual monitoring confirmed that all patients performed the simple motor task in the scanner at a constant

TABLE II. Areas significantly more activated in 18 patients with multiple sclerosis (MS) than in 18 healthy controls during a repetitive index finger to thumb opposition movement with the right hand

	Coordinates (x, y, z; mm)	Z
Right M1	32, -12, 44	3.49
Left M1	-50, -7, 28	3.16
Right PMC	59, 0, 37	3.27
Left PMC	-39, -12, 30	3.32
Right SMA	4, -9, 49	4.08
Right cingulate cortex	2, -15, 45	3.66
Left cingulate cortex	-8, -9, 43	3.51
Right insula	55, 12, 0	3.23
Right thalamus	14, -19, 16	3.42

M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area. Two-sample *t*-test, cluster level corrected $P < 0.05$.

Figure 1.

Between-group analysis (two sample *t*-test): statistical parametric maps showing more activated areas in 18 patients with MS than in 18 healthy subjects during right-hand movement (cluster-level corrected $P < 0.05$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

frequency in all sessions. No significant differences in movement rate were observed between patients and controls (1.80 ± 0.8 Hz vs. 1.78 ± 0.7 Hz). No mirror movements were noted in any of the patients.

Patients showed a significant increase of activation (two-sample *t*-test; cluster level-corrected $P < 0.05$) in bilateral premotor, primary motor, and cingulate cortices in the ipsilateral supplementary motor area, insula, and thalamus (Table II, Fig. 1). No brain foci were more active in controls than in patients.

Subsequent analyses were performed on 16 out of 18 patients due to TMS-associated technical problems (see above).

A simple regression analysis was performed between the contrast images created for each patient during right-hand movement and clinical (EDSS, disease duration), radiological MRI (T1-LL and T2-LL, MD, and FA in the body of the CC), and neurophysiological (TCI duration and latency) data.

A multiple regression analysis was then performed considering multisubject fMRI activity for right-hand movement as outcome variables and parameters that correlated on simple regression analysis (T1-LL, T2-LL, MD, and FA in the body of CC, and TCI duration) as covariates. (EDSS, disease duration, and TCI latency were excluded because

they were not significant at simple regression analysis). The results demonstrated that activation in iM1 positively correlated with T1-LL and MD in the body of the CC and negatively with duration of TCI (Table III, Fig. 2). The remaining correlations were all not significant.

DISCUSSION

Corpus Callosum: Structural and Neurophysiological Findings

We used DTI and TMS to estimate the integrity of the CC. DTI, as demonstrated in previous studies [Le Bihan, 2003; Pfefferbaum et al., 2003; Schulte et al., 2005], permits examination of the integrity of the microstructure of cerebral white matter by measuring the orientation displacement and distribution of water molecules. In agreement with previous studies on MS [Ciccarelli et al., 2003; Werring et al., 2001], DTI confirmed ultrastructural damage to the CC. In particular, we found increased MD and reduced FA values in a part of this structure, through which connections between sensory-motor and premotor areas pass [Pandya et al., 1971]. CC damage may be due both to direct inflammatory processes and to secondary Wallerian degeneration caused by diffuse hemispheric damage [Evangelou et al., 2000]. The disruption of myelin sheaths and axons can result in increased water motion that in turn leads to increased MD values and a change in the preferential direction of such motion that is responsible for decreased FA values [Pierpaoli and Basser, 1996; Pierpaoli et al., 1996]. DTI was calculated in the corpus of the CC in order to evaluate integrity of fibers connecting the motor cortices and permit correlation with fMRI and TMS data, which were confined as well to the motor system. A fiber-tracking technique would have been useful to place the ROIs on MD and FA maps precisely on the bundle connecting the two motor areas, but unfortunately at the time of the study this particular software was not yet available at our center.

Neurophysiology (TMS) in our patients confirmed damage to the CC. Transcallosal inhibition was absent in four patients, indicating that the left M1 was unable to inhibit the contralateral motor cortex when activated. This result

TABLE III. Multiple regression analysis

Variable	Ke	Z score (corrected at cluster level, $P < 0.05$)	Coordinates (iM1, BA 4) (<i>x, y, z</i> ; mm)
TCI duration (indir corr)	712	3.5	33, -23, 69
MD (CC body) (direct corr)	302	3.2	55, -9, 34
	388	3.3	33, -22, 69
T1 LL (direct corr)	1020	3.7	33, -20, 41

iM1, ipsilateral motor cortex; TCI, transcallosal inhibition; MD, mean diffusivity; CC, corpus callosum; LL lesion load.

Significant correlations between cluster of activations in the iM1 at fMRI during right-handed movement and MRI and TMS variables (cluster level corrected $P < 0.05$, SPM99).

Figure 2.

Results of the multiple regression analysis (SPM99), i.e., activity in the iM1 as outcome variable and T1-LL, T2-LL, MD, and FA in the body of the CC, transcallosal inhibition latency, and duration data as predictors. Three predictors and the correspondent clusters in the iM1 that are shown were found to be significantly correlated (cluster-level corrected $P < 0.05$): MD in the body of CC and T1-LL (directly) and TCI duration (inversely). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

can be explained by the presence of lesions visible (and therefore very consistent) at conventional MRI in the area immediately adjacent to the CC, where CC fibers are about to reach the motor cortices. In fact, no lesions were evident with conventional MRI on the body of the CC. We can reasonably exclude that the absence of TCI in four of the patients was due to technical problems because we recorded an MEP in the contralateral FDI muscle and stimulation intensity was consistently higher than motor threshold. In the remaining 12 patients TCI latency was significantly increased compared to controls. Increased latency is easily explained by demyelination of callosal fibers [Hoppner et al., 1999; Schmierer et al., 2002]. Patients also showed a significantly reduced TCI duration, which may be explained by a reduction of axon numbers, consistent with altered FA and MD values in the body of the CC. Two studies of TCI in patients with MS [Hoppner et al., 1999; Schmierer et al., 2002] reported increased TCI duration, suggesting, in their patients, a preponderance of local demyelination (leading to signal desynchronization) over axonal loss.

In conclusion, considering the data from TMS and DTI, the CC was affected both anatomically and functionally by the disease.

Corpus Callosum Damage and Activity in the Ipsilateral Sensory-Motor Cortex

Our fMRI data confirm previously reported results of an altered cortical activation pattern with motor tasks in MS patients compared to controls [Filippi et al., 2004; Lee et al., 2000; Pantano et al., 2002a,b, 2005; Reddy et al., 2000b; Rocca et al., 2004]. Differences between these two groups involve both hemispheres, with an increase of activation in patients in bilateral M1, premotor and cingulate cortices, in the ipsilateral insula and supplementary motor area and thalamus.

Our results support the hypothesis that the increased activation in iM1 in patients with MS is, at least in part, due to CC damage.

Mean diffusivity in the body of the CC correlated directly with activation in iM1: the greater the structural damage of the CC indexed by MD changes, the greater the activity in iM1. Duration of TCI (from contralateral to ipsilateral motor cortex) correlated inversely with iM1 activation. We assume that the duration of TCI is a parameter that reflects inhibition, i.e., the longer the duration of TCI after a single magnetic stimulation of contralateral M1, the greater the overall inhibition of iM1 during the fMRI motor task. This result confirms greater movement-induced iM1 activity when there is a reduction in TCI duration, hence in transcallosal inhibition.

Reddy et al. [2000a] studied fMRI motor activation in patients with agenesis of the CC and found no difference between patients and controls. However, in our study CC damage occurred after completion of normal brain development, when mature patterns of interhemispheric inhibition were established.

fMRI studies also in stroke patients have shown increased activation of ipsilateral/unaffected sensory-motor cortex with movement [Calautti and Baron, 2003; Cramer et al., 1997; Johansen-Berg et al., 2002; Ward et al., 2003]. Studies with TMS in stroke patients have reported hyperexcitability of the unaffected sensory-motor cortex [Cicinelli et al., 1997; Liepert et al., 2000; Traversa et al., 1997], which could be an expression of reduced TCI from the lesioned hemisphere. To explore the hypothesis that such hyperexcitability could be due to reduced transcallosal inhibition from the lesioned hemisphere, Shimizu et al. [2002] compared stroke patients with lesions caudal to the CC (sparing CC fibers) and those with cortical lesions involving CC fibers. They found a decrease of intracortical inhibition in the unaffected ipsilateral hemisphere in the latter group, suggesting that increased ipsilateral activation is due simply to the ischemic lesion also affecting CC fibers that are not critical to recovery.

However, a possible active role for an intact CC has also been considered in stroke patients [Calautti and Baron, 2003], the idea being that a reduction of inhibition to the unaffected/ipsilateral hemisphere facilitates recruitment of ipsilateral uncrossed motor output to maintain function. Patients with MS are indeed a good model because it enables study of the ipsilateral motor activity when the CC is damaged.

Diffuse Tissue Damage and Activity in the Ipsilateral Sensory-Motor Cortex

In order to mitigate against a false-positive correlation between iM1 activity and CC parameters due to a dependency of CC integrity on possible diffuse brain damage, we also included T1 and T2-LL in a multivariate analysis. Ciccarelli et al. [2003] reported a direct correlation between lesion load and DTI-assessed CC damage in MS patients. Evangelou et al. [2000] reported a similar finding in a post-mortem study on MS brains and concluded that the reduction in CC fibers was due to Wallerian degeneration of axons affected by remote MS lesions. Furthermore, several studies have reported a direct correlation between the iM1 activation and diffuse hemispheric tissue damage indexed by conventional and nonconventional MRI [Filippi et al., 2002; Lee et al., 2000; Pantano et al., 2000a,b; Reddy et al., 2000b].

The correlation between iM1 activity with MD and TCI despite inclusion of T1 and T2-LL in our multivariate analysis strengthens our hypothesis of a direct and independent role of CC damage on iM1 movement-induced increased activity in MS patients.

On the other hand, the fact that the T1-LL of the whole brain correlated with iM1-increased activation suggests that it is also an expression of cortical reorganization (i.e., recruitment of ipsilateral motor output), serving maintenance of normal motor behavior despite diffuse brain damage that presumably also affects other parts of the motor network—an idea reported by our group and others [Pantano et al., 2002b, 2005; Reddy et al., 2000b]. Central conduction time in our patients was increased above normal, suggesting that the motor system was indeed affected by the disease.

T2-LL did not show similar correlations probably because of lower relative specificity for axonal loss compared to T1-LL [Barkhof et al., 1998; Bitsch et al., 2001].

CONCLUSIONS

To conclude, our study suggests that damage to the CC leads to increased activation in the iM1. This conclusion is supported by a correlation of fMRI activity with neurophysiological and structural data. Thus, hyperactivation of iM1 seems to be a simple epiphenomenon of disease. However, a compensatory role of the ipsilateral primary motor cortex cannot be ruled out, since there is an independent effect of diffuse tissue damage on the level of activity in iM1. The T1 lesion load is a relative measure of damage in the motor system, which is very complex and diffused within the CNS.

MS appeared to be a good model to study the role of the CC damage in the activity of the iM1 but further studies are needed to address this complex issue. Of interest is clarification of what is meant by “compensation” and what may be a “bystander” result of pathology in a networked

system such as the brain. That is, supposing that there is indeed a clear-cut border between the two.

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