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Cortical functional reorganization and its relationship with brain structural damage in patients with benign multiple sclerosis

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Abstract

Background: Patients with multiple sclerosis (MS) who have a favourable clinical status several years after disease onset are classified as 'benign'. In many cases brain tissue damage does not differ between benign MS and the 'classical' MS forms.

Objective: To assess whether the favourable clinical course in benign MS could be explained by the presence of an efficient functional cortical reorganization.

Method: Twenty-five right-handed patients with benign MS (defined as having Expanded Disability Status Scale ≤ 3 and disease duration >15 years) underwent functional MRI during a simple motor task (right-hand tapping) to assess movement-associated brain activation. This was compared with that of 10 patients with relapsing–remitting MS and 10 normal controls. Benign MS patients also underwent conventional brain MRI and magnetization transfer imaging, which was compared with an identical examination obtained 1 year before. Quantitative structural magnetic resonance measures were baseline and changes over time in T2-lesion volume, magnetization transfer ratio in T2 lesions and normal-appearing brain and total brain volume.

Results: Movement-related activation was greater in patients with benign MS than in those with relapsing–remitting MS or normal controls, extensively involving bilateral regions of the sensorimotor network as well as basal ganglia, insula and cerebellum. Greater activation correlated with lower T2-lesion magnetization transfer ratio, and with decreasing brain volume and increasing T2 lesion volume.

Conclusions: The results suggest that bilateral brain networks, beyond those normally engaged in motor tasks, are recruited during a simple hand movement in patients with benign MS. This increased activation is probably the expression of an extensive, compensatory and tissue-damage related functional cortical reorganization. This can explain, at least in part, the favourable clinical expression of patients with benign MS.

Keywords

benign multiple sclerosis, brain atrophy, functional MRI, hand movement, magnetization transfer

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Introduction

Benign multiple sclerosis (B-MS) is characterized by a favourable clinical status several years after clinical onset, despite extensive brain tissue damage. Over the past decade, by using different magnetic resonance (MR) techniques, several studies have attempted to clarify this apparent paradox, reporting conflicting results.[1] Some studies have found brain damage to be

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relatively lower in patients with B-MS than in those with other MS forms in both white matter[2,3] and grey matter.[4,5] By contrast, other studies have failed to show these differences[6,7] and, if any, differences could be found in the less pronounced involvement of clinically eloquent brain areas in B-MS patients compared with patients with other MS forms.[8,9]

It is clear from these previous studies that the presence of a more favourable clinical status several years after clinical onset of disease in patients with B-MS is likely related to many factors. In this context, brain plasticity and the presence of effective compensatory mechanisms may play a relevant role. Functional cortical reorganization has been demonstrated during the performance of a simple motor task in the sensorimotor cortex of patients with MS,[10–15] and to be different across different MS stages[16–18] and associated with the level of hand disability[19] and brain injury.[10,11,13,18,19] As for B-MS, greater activation of the network involved in cognitive performance (Stroop test) was associated with damage of specific white matter structures, probably representing an adaptive response driven by it.[20] However, in a recent cross-sectional study, brain activation during a simple motor task was not clearly associated with the extent of structural brain damage in patients with B-MS.[18]

Against this background, we studied a cohort of patients with B-MS and assessed: the pattern of brain networks activated during a simple hand movement, as measured by functional MRI (fMRI); and the relationship between brain activation and MR measures of structural brain damage cross-sectionally and between two time points, with the aim of better clarifying whether functional brain reorganization may represent a mechanism leading to a non-disabling clinical evolution.

Subjects and methods

Subjects

We studied 25 patients with B-MS, defined as having Kurtzke's Expanded Disability Status Scale (EDSS) score ≤ 3 after at least 15 years from clinical onset of disease.[21] These patients were recruited from the MS Units of the University of Siena, the University of Florence, and Hospital of Empoli and had previously taken part in other studies on B-MS.[3,22,23]

In order to compare movement-related brain activation of patients with B-MS, a group of 10 relapsing–remitting MS (RRMS) patients, recruited from the MS Unit of the University of Siena, and a group of 10 normal controls, recruited from laboratory and hospital workers, were also included in the study. Patients who had had a relapse or corticosteroid treatment in the 3 months before fMRI scanning were excluded from the study. On the day of fMRI data acquisition, each patient had EDSS score measured. Normal controls had a normal neurological examination and no history of neurological dysfunction.

Before fMRI scanning, all study participants filled in the Edinburgh Handedness Inventory (EHI)[24] to assess the degree of handedness and performed the 9-Hole Peg Test (9-HPT) to assess hand function and dexterity. Patients showed no symptoms or clinical signs of upper limb impairment and were able to perform the simple motor task as well as the normal controls.

At the time of fMRI scanning, 11 of 25 patients with B-MS and eight of 10 patients with RRMS were on treatment with disease-modifying agents.

This study received approval from the Ethics Committee of the Faculty of Medicine of the University of Siena and informed written consent was obtained from all study participants.

MR examination

The same MR protocol was used for all study participants. Acquisitions were performed on a Philips Gyroscan (Philips Medical Systems, Best, The Netherlands) operating at 1.5 T and located at the NMR Centre of the University of Siena.

A dual-echo turbo spin-echo sequence (TR, TE1, TE2 = 2075/30/9 ms, 256×256 matrix, 1 signal average, field of view [FOV] = 250×250 mm, 50 contiguous 3-mm-thick slices) yielding T2-weighted and proton density images was acquired axially and parallel to the anterior commissure-posterior commissure (AC-PC) plane.

A magnetization transfer sequence was also performed, acquiring two axial T1-weighted gradient-echo images, one without and one with magnetization transfer saturation pulse (TR/TE = 35 ms/10, 256×256 matrix, 1 signal average, FOV = 250×250 mm), which yielded 50 contiguous 3-mm-thick axial slices, oriented to exactly match T2-weighted and proton density images. The magnetization transfer pulse was a 1.2 ms on-resonance, binomial pulse (radio-frequency strength = 20 μT) placed just before each slice-selective excitation.[25]

This conventional brain MRI and magnetization transfer imaging protocol had also been obtained from patients with B-MS a mean of 1.31 years (SD ± 0.18) before.

fMRI scanning was performed in patients with B-MS and RRMS and in normal controls. The fMRI paradigm consisted of a 'block design', with six periods of a 30 s visual cue for right-hand movement alternated with six periods of 30 s rest. This whole sequence was repeated four times in each scanning session (total scan time 24 min). Participants had to repetitively flex and

extend the fingers of their right hand with each flash of light (1 Hz frequency) coming from a red light-emitting diode placed, together with a metronome, at the person's feet. A wooden hand frame was used to restrict finger extension to 3 cm. To minimize learning effects during fMRI scanning, hand tapping was practised twice for 30 s before scanning. Participants were visually monitored during scanning to ensure full protocol compliance. fMRI images were obtained using a standard GE Echo Planar Imaging sequence (TE = 60 ms, TR = 3000 ms, FOV = 240 × 240 mm, matrix 64 × 64, voxel resolution = 3.75 × 3.75 × 6 mm^3). Twenty-one contiguous axial slices (120 volumes/slice) were acquired parallel to the AC-PC plane. At the end of fMRI acquisition, a high-resolution T1-weighted sequence (TE = 3 ms, TR = 20 ms, 50 contiguous 3-mm-thick axial slices parallel to the AC–PC plane) was also acquired to allow anatomical localization of fMRI data to standard space after registration.

Monthly quality assurance sessions and no major hardware upgrades were carried out on the MR scanner during the time of the study.

MR data analysis

Structural. Classification of T2 and T1 lesions was performed by a single observer, blinded to participants' identity, with a segmentation technique based on user-supervised local thresholding (Jim 3.0, Xinapse System, Leicester, UK). Hyperintense T2 lesions were outlined on proton density images, but information from T2-weighted images was also considered. Hypointense T1 lesions were defined as those lesions with signal intensity between that of the grey matter and the cerebrospinal fluid on T1-weighted images.[26] We computed lesion volume, after multiplying lesion area by slice thickness, for total lesions and for lesions located along the corticospinal tract (CST) of both hemispheres, using standard-space masks derived from the JHU White Matter Tractography Atlas, implemented in FMRIB's Software Library.

Brain parenchyma volumes were measured at the time of fMRI on T1-weighted GE images with SIENAx (part of FSL v. 4.1: www.fmrib.ox.ac.uk/fsl/), a method previously described[27] which allows estimation of global (normalized brain volume) and selective (normalized cortical volume)[28] brain volumes Percent brain volume change, as measured by the SIENA method[27] (also part of FSL), was also computed between the two time points.

For the analysis of magnetization transfer data, we used an in-house fully automated procedure[3] to compute the magnetization transfer ratio (MTr) in T2 lesions and normal-appearing brain tissue at the two time points.

Functional. fMRI data processing was carried out with FEAT (FMRIB Expert Analysis Tools, also part of FSL).

For the first-level (within-sequence) analysis the following pre-statistics processing was applied: motion correction using MCFLIRT[29]; non-brain removal using BET (Brain Extraction Tool)[30]; spatial smoothing using a Gaussian kernel of full width at half maximum (FWHM) 6.0 mm; grand-mean intensity normalization of the whole four-dimensional dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 75.0 s). Independent component analysis-based exploratory data analysis was carried out using MELODIC (multivariate exploratory linear optimized decomposition into independent components)[31] in order to investigate the possible presence of unexpected artefacts. Components representing patterns with known artefacts such as motion and high-frequency noise were identified by visual inspection and excluded from further analysis. Registration of fMRI data to high-resolution structural T1-weighted images and standard space was carried out using FLIRT.[29,32] Registration from high-resolution structural T1-weighted image to standard space was then further refined using FNIRT (FMRIB's Nonlinear Image Registration Tool).[33,34] Time-series (i.e. signal change in active vs rest blocks) statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction.[35]

In the second-level (within-subject) analysis, the four analysed sequences for each subject were combined using a fixed-effect model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects),[36,37] and thus an average activation map was created for each person.

Third-level (group) analysis was carried out using FLAME stage 1 with automatic outlier detection.[38] See the next section for third-level voxelwise statistical analyses.

Statistical analysis

Between-group comparisons of clinical–demographic and lesion volume features were performed, when appropriate, with the Mann–Whitney test, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) after correcting for age. The number of patients with B-MS and RRMS and T1 and T2 lesions along the CST were compared with Fisher's test. Data were considered significant at $p < 0.05$.

In all third-level voxelwise statistical analyses, Z (Gaussianized T) statistic images were thresholded using a cluster threshold of $p < 0.05$,[39,40] corrected for multiple comparisons across space. One-sample t-test was used for mean activation within each group. A three-group ANOVA followed by Bonferroni-corrected pairwise comparisons were used to assess between-group differences. Finally, correlation analysis between fMRI data and structural MR measures was performed in patients with B-MS. Age was used as a covariate in all voxelwise statistical models.

Anatomical location of the significant clusters was determined by reference to the Harvard-Oxford brain atlas, integrated into FSLView (also part of FSL).

Results

Table 1 shows clinical–demographic and lesion volume features of the three study groups at the time of fMRI scanning. Table 2 shows the other MR features of the patients with B-MS at the time of fMRI scanning and between the two time points.

Brain activation

All participants performed the fMRI protocol correctly and no additional movements (e.g. mirror movements) were noted during the task.

In patients with B-MS, brain activation was widespread and was found bilaterally in many regions (Figure 1A), including motor and non motor-related areas.

Movement-related activation was less widespread in normal controls (Figure 1B). Figure 1C shows movement-related brain activation in the group of patients with RRMS.

Patients with B-MS showed greater activation than normal controls in the primary sensorimotor cortex bilaterally, in the left central opercular cortex and

Table 2. Other MR features of patients with benign multiple sclerosis at the time of functional MRI and between the two time points

MR measure	Values
NBV, mean ± SD (cm^3)	1472 ± 72
NCV, mean ± SD (cm^3)	536 ± 46
T2-lesion MTr, mean ± SD	26.4 ± 2
NAWM MTr, mean ± SD	35 ± 1.1
Cortical MTr, mean ± SD	23 ± 0.6
T2 lesion volume change, mean ± SD (cm^3)	0.2 ± 0.7
PBVC, mean ± SD (%)	−0.6 ± 0.6
T2-lesion MTr change, mean ± SD	0.3±1.2
NAWM MTr change, mean ± SD	−0.07 ± 0.5
Cortical MTr change, mean ± SD	0.1 ± 0.7

MTr, magnetization transfer ratio; NAWM, normal-appearing white matter; NBV, normalized brain volume; NCV, normalized cortical volume; PBVC, percent brain volume change.

Table 1. Clinical–demographic and lesion volume features of patients with benign multiple sclerosis, relapsing–remitting multiple sclerosis and normal controls at the time of functional MRI

	B-MS ($n = 25$)	Normal controls ($n = 10$)	RRMS ($n = 10$)	p-value
Age, mean ± SD (years)	47.2 ± 6.3	29.6 ± 4.1	36.6 ± 6.1	<0.001*
Sex, males/females	3/22	6/4	3/7	0.01*
Disease duration, mean ± SD (years)	23.4 ± 5.2	–	4.6 ± 2.4	<0.001**
EDSS score, mean ± SD	1.4 ± 0.6	–	1.9 ± 1	0.21 (NS)**
Handedness (EHI) score, mean ± SD	96.5 ± 7.5	78.5 ± 8.2	83.2 ± 5.3	<0.001*
9-HPT, mean ± SD (s)	24.6 ± 4.2	21.4 ± 1.4	23 ± 1.5	0.95 (NS)^
T2 lesion volume (total), mean ± SD (cm^3)	12.1 ± 10.5	–	5.2 ± 5.5	0.07 (NS)^
T1 lesion volume (total), mean ± SD (cm^3)	6.1 ± 5.2	–	1.7 ± 2.3	0.05^
Patients with T2 lesions in the CST	23/25 (92%)	–	6/10 (60%)	0.04^^
T2 lesion volume (CST), mean ± SD (cm^3)	0.24 ± 0.26	–	0.06 ± 0.06	0.08 (NS)^
Patients with T1 lesions in the CST	15/25 (60%)	–	5/10 (50%)	0.71 (NS)^^
T1 lesion volume (CST), mean ± SD (cm^3)	0.06 ± 0.07	–	0.009 ± 0.01	0.06 (NS)^
T1/T2 lesion volume (total), mean ± SD (cm^3)	0.50 ± 0.15	–	0.30 ± 0.13	0.03^
T1/T2 lesion volume (CST), mean± SD (cm^3)	0.25 ± 0.29	–	0.11 ± 0.14	0.20 (NS)^

*Analysis of variance (ANOVA); **Mann–Whitney test; ^Analysis of covariance (ANCOVA) corrected for age; ^^ Fisher's test.
9-HPT, 9-hole peg test; B-MS, benign multiple sclerosis; CST, corticospinal tract; EDSS, expanded disability status scale; EHI, Edinburgh handedness inventory; RRMS, relapsing–remitting multiple sclerosis.

temporal pole and in the right frontal pole and inferior frontal gyrus, pars opercularis (Table 3). No brain regions showed lower activation in patients with B-MS compared with normal controls.

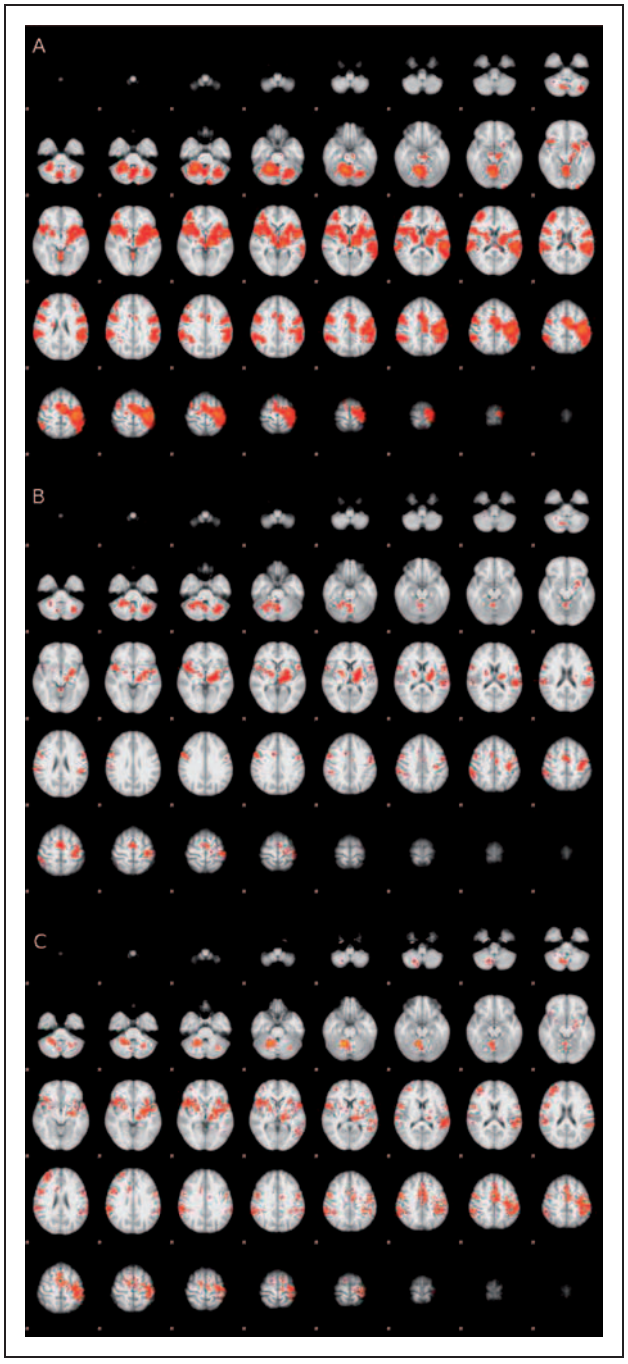

Figure 1. Red-yellow shows brain areas where activated ($p < 0.05$, cluster corrected for multiple comparisons) during right-hand tapping in patients with benign multiple sclerosis (A), normal controls (B) and patients with relapsing–remitting multiple sclerosis (C), overlaid on the MNI standard brain. Yellow shows voxels with highest *Z*-max.

Compared with patients with RRMS, patients with B-MS showed greater activation in the inferior temporal gyrus, central opercular cortex and lingual gyrus of the right hemisphere (Table 4). Patients with B-MS showed less brain activation compared with patients with RRMS in the frontal medial cortex (−2, 50, −20 mm; *Z*-max = 3.73) and anterior division of the cingulate gyrus (6, 34, −6 mm; *Z*-max = 3.63).

Brain regions where patients with RRMS had greater activation than normal controls were located in the left primary sensorimotor cortex and in the right precentral gyrus and frontal pole (Table 5). There were no brain regions where normal controls showed greater activation than patients with RRMS. Because patients with B-MS were significantly ($p < 0.001$) older than normal controls and patients with RRMS, sex was different between patients with B-MS and normal controls ($p = 0.01$) and EHI scores were significantly higher in patients with B-MS than in normal controls and patients with RRMS ($p < 0.001$),

Table 3. Brain areas where patients with benign multiple sclerosis showed greater activation than normal controls

Brain region (local maxima)	Side	MNI *X*, *Y*, *Z* (mm)	*Z*-max
Postcentral gyrus	R	46, −22, 54	3.72
Precentral gyrus	L	−18, −20, 76	3.58
Postcentral gyrus	L	−16, −30, 76	3.49
Precentral gyrus	R	54, −8, 50	3.39
Central opercular cortex	L	−58, 0, 4	3.39
Precentral gyrus	M	0, −14, 66	3.37
Temporal pole	L	−56, 16, −6	3.27
Frontal pole	R	32, 46, 20	3.05
Inferior frontal gyrus, pars opercularis	R	52, 18, 2	2.98

Brain regions are ordered by decreasing values of *Z*-max. L, left; M, middle; R, right.

Table 4. Brain areas where patients with benign multiple sclerosis showed greater activation than patients with relapsing–remitting multiple sclerosis

Brain region (local maxima)	Side	MNI *X*, *Y*, *Z* (mm)	*Z*-max
Inferior temporal gyrus	R	58, −42, −26	3.39
Central opercular cortex	R	42, 8, 12	3.35
Lingual gyrus	R	8, −62, −4	3.35

Brain regions are ordered by decreasing values of *Z*-max. R, right.

we also ran the comparison analyses after controlling for age, sex and EHI scores. After these corrections, the pattern of differences in movement-associated brain activation of patients with B-MS compared with normal controls and patients with RRMS did not change.

Table 5. Brain areas patients with relapsing–remitting multiple sclerosis showed greater activation than normal controls

Brain region (local maxima)	Side	MNI *X*, *Y*, *Z* (mm)	*Z*-max
Postcentral gyrus	L	−30, −36, 70	4.28
Precentral gyrus	L	−26, −26, 74	4.16
Precentral gyrus	R	14, −24, 70	3.79
Frontal pole	R	32, 58, −12	3.06

Brain regions are ordered by decreasing values of *Z*-max. L, left; R, right.

Table 6. Brain regions (local maxima) of patients with benign multiple sclerosis where greater movement-associated activation is correlated with lower T2-lesion magnetization transfer ratio at the time of functional MRI (A) and with higher T2-lesion volume change (B) and lower percent brain volume change (C) between the two time points

Brain region (local maxima)	Side	MNI *X*, *Y*, *Z* (mm)	*Z*-max
A			
Supplementary motor cortex	L	−4, −8, 62	14.2
Postcentral gyrus	L	−28, −30, 66	11.4
Parietal operculum cortex	L	−42, −38, 18	7.62
Precentral gyrus	L	−56, 8, 16	5.28
Frontal pole	R	40, 42, 28	2.86
B			
Postcentral gyrus	L	−38, −30, 50	7.23
Cerebellum	R	6, −58, −12	6.65
Temporal pole	L	−54, 6, −4	5.87
Superior temporal gyrus	L	−64, −38, 12	5.36
Temporal pole	R	48, 10, −8	5.19
Brainstem	L	−10, −24, −12	4.82
Thalamus	L	−8, −22, 12	4.67
Inferior temporal gyrus	R	62, −50, −14	4.23
C			
Postcentral gyrus	L	−30, −26, 68	7.13
Parietal operculum cortex	L	−38, −28, 24	5.47
Planum temporale	L	−58, −26, 8	4.95

Brain regions are ordered by decreasing values of *Z*-max. L, left; R, right.

Correlations between structural and functional MR data in patients with B-MS

In patients with B-MS, greater activation in many brain regions was correlated with lower T2-lesion MTr at the time of fMRI scanning (Table 6A), and with increasing T2 lesion volume change and decreasing percent brain volume change (Table 6B and 6C) between the two time points.

No significant correlations of movement-related brain activation were found with other MTr and brain volume measures.

Discussion

The mechanisms responsible for preservation of functional capacity several years after the clinical onset of MS are poorly understood. It is common knowledge that the human brain is capable of reacting to injury, whatever the nature of the injury. The presence of brain functional plasticity in the brains of patients with MS has been recognized not only during an acute relapse, but also in clinically stable patients[41] and seems to show variability across the different stages of disease.[16,18,42] In the present study, we used a simple motor task (right-hand tapping) to assess the presence of cerebral cortical reorganization in a patient population such as B-MS, characterized by the absence of clinical disability despite longstanding disease. This task represents a simple and easy-to-interpret model for assessing the brain's strategies to maintain an important function such as manual function and dexterity in a complex disease such as MS[17] and, being ideal for probing one of the most clinically 'eloquent' cortical regions in MS brains, has been extensively used in the literature of MS for different purposes.[10,13,18,19,43–46] By using this task, patients with B-MS showed, when compared with normal controls and patients with RRMS, increased activation not only of the 'classical' motor network such as the contralateral primary sensorimotor cortex but also of ipsilateral primary sensorimotor cortex and additional areas that are normally recruited during complex motor or non-motor tasks. These findings suggest that patients with B-MS extensively recruit different brain networks even to perform a simple motor task, thus explaining, at least in part, their preservation of functional capacity with the presence of a cortical functional reorganization.

Previous fMRI studies on MS have emphasized the relevance of the association between the amount of T2 and T1 lesions along the CST and the recruitment of larger cortical sensorimotor regions in both hemispheres.[47,48] In the present study, we specifically assessed tissue damage in the CST, as expressed by the presence of T1- and T2-visible lesions, in patients

with B-MS and RRMS. In general, there were no clear differences in macroscopic tissue damage of the CST between the two patient groups. Thus, the results of the higher brain activation during a simple motor task found here in patients with B-MS compared to those with RRMS could not be fully explained by the presence of more tissue damage along the CST in patients with B-MS. However, while the number of patients with T2 lesions along the CST was higher for B-MS than RRMS, this difference did not translate into an increased number of patients with B-MS and T1 lesions in the same white matter tract (see Table 1). This finding might be in line with recent studies suggesting that a possible explanation for preservation of neurological functions in patients with B-MS could lie in the presence of less pronounced destructive tissue damage.[3,49] However, it is unlikely that this is the only mechanism explaining the favourable clinical course of patients with B-MS. The higher functional reorganization found for patients with B-MS compared with RRMS also in areas not directly connected to the CST supports this hypothesis.

While in our study patients with B-MS showed no areas of lower brain activation in comparison to normal controls, they did show less activation than patients with RRMS in the anterior cingulate and frontal medial cortex. Anterior cingulate and frontal medial cortex normally exert a modulatory ('higher-order') effect on motor function, by facilitating the execution of the appropriate responses and/or suppressing the inappropriate ones[50] as well as by implementing performance adjustments in goal-directed behaviors.[51] Thus, previous data have shown during a similar motor task higher activation in the anterior cingulate of patients with RRMS and secondary progressive MS compared with normal controls[44] and of patients with secondary progressive MS compared with those with RRMS,[16] as if a simple motor task was perceived as more difficult with worsening of the clinical status. In this context, it is conceivable that in our study, patients with B-MS had lower activation in those brain areas because they perceived the task as less difficult or less complex than patients with RRMS.

We also found significant correlations in our cohort of patients with B-MS between movement-associated brain activation and different MR structural measures of focal (T2-lesion MTr and T2-lesion volume change) and global (brain atrophy) tissue damage. This finding adds to a recent fMRI study on B-MS[18] in which, during a similar motor task, higher brain activation was found in patients with B-MS compared with normal controls and patients with secondary progressive MS, although an association between higher brain activation and focal and global tissue damage was not clearly seen. Given that low MTr and brain atrophy can be considered as markers of myelin[52,53] and neuroaxonal[54] damage, it is conceivable that functional brain organization in B-MS is able to potentially limit the impact of brain tissue damage. Moreover, the fact that brain areas in which activity was associated with focal and global MR measures of tissue damage are different, suggests that separate but interacting networks contribute to a widespread functional cortical response to brain injury from patients with B-MS.

It has recently been suggested that cognitive impairment can be significant in patients with B-MS and it has been recognized that an adequate assessment of the cognitive status is an important requisite to correctly identify patients with B-MS.[22,55] In light of this, we identified and excluded from our B-MS group those patients ($n = 4$) with cognitive impairment, as previously defined.[22,23] In cognitively preserved patients with B-MS, the pattern of movement-related brain activation and the difference with respect to patients with RRMS and normal controls were consistent with the findings obtained from the whole cohort of patients with B-MS (data not shown).

Our study is not without limitations. First, the presence of different ages and sex might have influenced the comparison of movement-related brain activation between patients with B-MS and normal controls. However, the use of these variables as covariates in the voxelwise comparison analyses should have corrected for this. Moreover, in a previous study[44] no differences in age-related activation changes between patients with MS and normal controls were found. Second, the availability of only cross-sectional fMRI data may have limited the interpretation of the temporal dynamics of the relationship between structural and functional changes in B-MS brains. Third, we compared patients with B-MS with another MS patient group such as RRMS, who had similar clinical disability but much shorter disease duration. There is not an ideal MS form to compare to B-MS as, for example, a secondary progressive group would have similar disease duration, but different clinical disability. However, a recent fMRI study showed increased brain activation in patients with B-MS compared with patients with secondary progressive MS,[18] supporting the view of the presence of a particularly pronounced cortical functional reorganization in B-MS.

In conclusion, by investigating brain networks activated during a simple hand movement in patients with B-MS, we showed the recruitment of several bilateral brain areas, beyond those normally engaged in motor tasks. This activation was more widespread than in normal controls and, to a lesser extent, in patients with RRMS and was related to focal and diffuse structural brain damage. All together, these data help to

explain the favourable clinical expression of disease in patients with B-MS.

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Conflict of interest statement

None declared.

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