Corpus Callosum Damage and Cognitive Dysfunction in Benign MS

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Abstract: Corpus callosum (CC), the largest compact white matter fiber bundle of the human brain involved in interhemispheric transfer, is frequently damaged in the course of multiple sclerosis (MS). Cognitive impairment is one of the factors affecting quality of life of patients with benign MS (BMS). The aim of this study was to investigate the relationship between the cognitive profile of BMS patients and the extent of tissue damage in the CC. Brain conventional and DT MRI scans were acquired from 54 BMS patients and 21 healthy controls. Neuropsychological tests (NPT) exploring memory, attention, and frontal lobe cognitive domains were administered to the patients. DT tractography was used to calculate the mean diffusivity (MD) and fractional anisotropy (FA) of the CC normal appearing white matter (NAWM). An index of CC atrophy was also estimated. Nine (17%) BMS patients fulfilled criteria for cognitive impairment. Compared with controls, BMS had significantly different CC diffusivity and volumetry ($P < 0.001$). Compared with cognitively preserved patients, those with CI had significantly higher CC lesion volume (LV) ($P = 0.02$) and NAWM MD ($P = 0.02$). The scores obtained at PASAT were significantly correlated with CC T2 LV, and NAWM FA and MD (r values ranging from -0.31 to 0.66 , P values ranging from 0.04 to <0.001). Cognitive impairment in BMS is associated with the extent of CC damage in terms of both focal lesions and diffuse fiber bundle injury. MRI assessment of topographical distribution of tissue damage may represent a rewarding strategy for understanding the subtle clinical deficits of patients with BMS. *Hum Brain Mapp* 30:2656–2666, 2009. ©2008 Wiley-Liss, Inc.

Key words: benign multiple sclerosis; cognitive impairment; corpus callosum; diffusion tensor magnetic resonance imaging; tractography; voxel-based analysis

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INTRODUCTION

Cognitive dysfunction has been described in up to 45% of patients classified as having the benign form of multiple sclerosis (BMS) [Amato et al., 2006], and can be one of the major factors affecting their quality of life [Rao et al., 1991]. Despite several scales have been applied to assess MS-related disability [Kurtzke, 1983; Ravnborg et al., 1997; Rudick et al., 1997; Sharrack and Hughes, 1999], the most commonly used, i.e., the Expanded Disability Status Scale

(EDSS) [Kurtzke, 1983], has a relatively low reproducibility, is poorly responsive to disease-related changes, and is heavily weighted toward locomotor disability [Amato and Portaccio, 2007]. During the last few years, more comprehensive scales (e.g., the Multiple Sclerosis Functional Composite [MSFC], which also include an assessment of cognitive impairment [Rudick et al., 1997]), have been developed and proposed. In spite of this, the definition of BMS is still based on the development of a low locomotor disability (e.g., EDSS ≤ 3) after a relatively long disease duration (e.g., ≥ 15 years) [Lublin and Reingold, 1996; Hawkins and McDonnell, 1999; Pittock et al., 2004; Ramsaransing et al., 2001]. More recently, epidemiological [Pittock et al., 2004; Sayao et al., 2007] and imaging [Pittock et al., 2007; Strasser-Fuchs et al., 2008] studies have suggested that such a definition of BMS might not be adequate to identify patients with a “real” benign course at long-term, and prompted a better characterization of the clinical and radiological profiles of patients with this clinical phenotype of the disease.

In this study, we selectively investigated the presence and extent of corpus callosum (CC) damage, in terms of focal lesions, intrinsic lesion damage, diffuse tissue changes, and irreversible tissue loss in a relatively large sample of patients with BMS. The CC was selected because it is the largest compact white matter (WM) fiber bundle of the brain, which connects cortical and subcortical regions of the two hemispheres, thus allowing interhemispheric transfer of auditory, sensory, and motor information that is central for maintaining normal cognitive performances [Hines et al., 1992]. Previous magnetic resonance imaging (MRI) studies have shown consistently that the CC is one of the sites most frequently hit by demyelinating lesions [Gean-Marton et al., 1991; Simon et al., 1986] and that CC atrophy is a common finding in MS [Barkhof et al., 1998; Martola et al., 2007; Pelletier et al., 2001]. In addition, a histopathologic study has detected a significant loss of axons and density of fibers in the CC of patients with relapsing-remitting (RR) and secondary progressive (SP) MS [Evangelou et al., 2000]. Only a few studies, however, have investigated the association between CC damage and cognitive impairment in MS, and the majority of these studies focused on the relationship between CC atrophy and the performance of tasks requiring interhemispheric transfer [Gadea et al., 2002; Edwards et al., 2001; Pelletier et al., 2001]. The demonstration of a relation between CC damage and cognitive impairment in MS is in line with the hypothesis that cognitive dysfunction in MS is likely to result from a multiple disconnection syndrome [Calabrese and Penner, 2007]. Additionally, the performance of the majority of neuropsychological tests requires a preservation of cognitive networks and of their connections, and the CC, because of its crucial role in interhemispheric transfer of different stimuli, is likely to play a crucial role in this. The association between intrinsic CC damage, estimated by using diffusion-tensor (DT) MRI tractography, and cognitive impairment in MS has been

addressed so far only by Lin et al. [2008], who limited their neuropsychological assessment to the Paced Auditory Serial Addition Test (PASAT).

To achieve a complete picture of CC damage, we used a multiparametric MRI approach. Diffusivity characteristics and volumetry changes [Pagani et al., 2007] of the entire structure were measured using DT MRI and tractography analysis. The distribution of the abnormalities found was defined in the different portions of the CC, using a voxel-based (VB) analysis. The relationship between the cognitive profile of BMS patients and the various components of tissue damage in the CC was also investigated in an attempt to improve our understanding of the mechanisms related to cognitive impairment in these patients.

PATIENTS AND METHODS

Patients

Patients were selected consecutively from the outpatient MS clinics populations of the participating centers. To be included, they had to be relapse- and steroid-free for at least one month prior to study entry. All patients underwent a complete neurological examination, with rating of the Expanded Disability Status Scale (EDSS) score [Kurtzke, 1983]. This was done by a single observer, who was unaware of MRI results, on the same day of the MRI session. Criteria for a diagnosis of BMS were an EDSS score equal to or less than 3.0 and disease duration equal to or longer than 15 years. All patients had to be unaffected by visual deficits or upper limb impairment that may interfere with their performance on the neuropsychological tests and be right-handed [Oldfield, 1971]. Other inclusion criteria were the absence of history of drug and alcohol abuse. Twenty-one healthy individuals with no history of neurological signs and normal neurological examination served as controls.

Within 48 h from MRI acquisition, BMS patients underwent an extensive battery of neuropsychological tests exploring the following domains: (a) attention and information processing: PASAT (3” version) [Gronwall, 1977], trail making test [Bowie and Harvey, 2006], attentive matrices test [Spinnler and Tognoni, 1981]; (b) verbal and visual-spatial memory: Digit span test, short story test, corsi span test, word list test, rey-osterrieth complex figure [ROCF] test—Recall task [Caffarra et al., 2002]; (c) abstract reasoning (Raven test) [Basso et al., 1987]; (d) executive functions: Token test [Spinnler and Tognoni, 1981], verbal fluency test [Spinnler and Tognoni, 1981], Wisconsin card sorting Test (WCST) [Heaton, 1981]; (e) spatial cognition (ROCF test—Copy task) (RCT) [Caffarra et al., 2002]. For each patient, the results from all neuropsychological tests were scored using a standardized method based upon a comparison with the percentile distribution of values from normal controls [Spinnler and Tognoni, 1981]. This set of neuropsychological tests is frequently used in the assessment of cognitive impairment in MS [Comi et al., 1995;

1999; Mesaros et al., 2008; Rocca et al., in press], because it provides a comprehensive picture of all cognitive domains potentially affected by MS. The individual test scores ranged from 0 to 4, where grade 4 means a normal performance. Only those patients with score 0 in at least 3 tests were considered affected by cognitive impairment [Amato 2006, 2008; Camp et al., 1999; Comi, 1995]. Local Ethical Committee approval and written informed consent from each subject were obtained prior to study initiation.

MRI Acquisition

Brain MRI scans were obtained using a 1.5 T scanner (Vision, Siemens, Erlangen, Germany). The following sequences were collected during a single session: (1) dual-echo (DE) turbo spin-echo (repetition time [TR] = 3300 ms, echo time [TE] = 16/98, echo train length = 5, 24 axial slices, slice thickness = 5 mm, matrix size = 256×256 , field of view [FOV] = 250×250 mm²), (2) pulsed-gradient echo-planar (PGSE) (inter-echo spacing = 0.8 ms, TR = 4500 ms, TE = 123 ms, 10 contiguous, slice thickness = 5 mm, matrix size = 128×128 matrix, FOV = 250×250 mm², number of averages = 8), with diffusion gradients applied in 8 noncollinear directions. The duration and maximum amplitude of the diffusion gradients were respectively 25 ms and 21 mT/m, giving a maximum b factor in each direction of 1044 s/mm². DE slices were positioned to run parallel to a line that joins the most inferoanterior and inferoposterior parts of the CC [Miller et al., 1991]. PGSE scans had the same orientation as the DE scans, with the second-last caudal slice positioned to match exactly the central slices of the DE set.

MR Data Postprocessing

All postprocessing was performed by an observer who was blinded to subjects' identity on an independent computer workstation (Sun Sparcstation, Sun Microsystems, Mountain View, CA, USA). Total T2-hyperintense lesion volume (LV) was assessed using a semiautomated segmentation technique [www.xinapse.com] and lesion maps were produced, as previously described [Ceccarelli et al., 2008].

Diffusion-weighted images were first corrected for distortion induced by eddy currents, then the DT was estimated by linear regression [Basser et al., 1994], and fractional anisotropy (FA) and mean diffusivity (MD) maps calculated [Basser and Pierpaoli, 1996]. Using the VTK CISC Registration Toolkit [Hartkens et al., 2002], the rigid transformation needed to correct for position between the b = 0 images (T2-weighted, but not diffusion-weighted) and T2-weighted images, as well as the affine transformation between the T2-weighted scan and the Montreal Neurological Institute (MNI) atlas [Maziotta et al., 2001] were calculated. The two consecutive transformations were then applied to the FA and MD images.

An FA atlas was created from healthy subjects' data and, using DT MRI tractography, probability maps of the CC were produced as described in details elsewhere [Pagani et al., 2005, 2007]. The nonlinear transformation [Rohde et al., 2003] between single-subject's FA map and the atlas was then calculated, as well as the determinant of the Jacobian of the transformation. This scalar index summarizes the point-wise volume changes produced by the deformation: values less than unity reflect atrophy, whereas values greater than unity reflect hypertrophy [Pagani et al., 2007].

In BMS patients, to obtain a measure of normal appearing (NA) WM damage, T2-visible lesions of the CC were excluded from MD and FA maps. Then, the CC probability map from controls was applied to non-linearly transformed patients' maps, and average MD, FA, and Jacobian determinant (JD) values were obtained. CC T2 LV and CC lesion average MD and FA were also calculated. MD, FA, lesion, and JD maps, already transformed into the atlas space, were smoothed with a 8 mm FWHM Gaussian kernel, before performing VB analysis of CC damage, using statistical parametric mapping (SPM2) [www.fil.ion.ucl.ac.uk/spm].

Statistical Analysis

Using SPSS for Windows (version 13.0), a nonparametric Mann-Whitney Test was used to compare demographic, conventional, and DT MRI-derived metrics between BMS patients and controls, as well as between BMS patients with and without cognitive impairment. Univariate correlations between clinical, neuropsychological, and MRI-derived metrics were assessed using the Spearman Rank Correlation Coefficient (SRCC).

Using SPM2, an analysis of covariance (ANCOVA) was used to compare CC DT MRI-derived metrics between the studied groups at a VB level. Age and sex were included as nuisance covariates. A multivariate analysis was used to assess the correlation between CC DT MRI-derived metrics and clinical/MRI variables, with age and sex as nuisance covariates. To limit the analysis to the region of interest, CC probability map was applied as explicit mask. We considered a threshold of $P < 0.05$ as significant, after correction for multiple comparisons with the family-wise error approach.

RESULTS

Clinical and Neuropsychological Findings in BMS Patients

We studied 21 healthy individuals (women/men: 11/10; mean age: 45.7 [range: 25–66] years) and 54 patients with BMS (34 women; mean age [range] = 46.4 [35–63] years; mean disease duration [range] = 22.5 [15–39] years; median EDSS score [range] = 1.5 [0.0–3.0]). Thirty-six were not receiving any disease-modifying treatment, 13 were

being treated with interferon β -1a and 5 with glatiramer acetate.

Sixteen (30%) patients had abnormal performances in the WCST (30%), 11 (20%) in the ROCF test—recall task, 9 (17%) in the PASAT (17%), and 8 (15%) in the RCT. The executive domain was the one with the highest number of patients having at least one abnormal test (30%). Memory was affected in 20%, attention in 17%, and spatial cognition in 15% of the patients. Nine patients (17%) were classified as being affected by cognitive impairment. There was no statistically significant difference in age, disease duration, and EDSS score between cognitively impaired (CI) and cognitively preserved (CP) patients, while a slight male predominance was found in the former group ($P = 0.04$). Additionally, there was no difference in EDSS score between patients who failed in one, two or three tests.

Brain and CC T2 LV

All controls had normal brain MRI scans. In BMS patients, median brain T2 LV was 11.8 ml (range = 0.4–36.3 ml). Although brain T2 LV was higher in CI patients (median = 20.3 ml; range = 5.9–32.9 ml) than in CP ones (median = 11.2 ml; range 0.4–36.3 ml), this difference did not reach statistical significance ($P = 0.06$). There was no difference in T2 LV between patients who failed in one, two or three tests.

Fifty-three patients (98%) had lesions located in the CC (median CC LV = 3.9 ml; range = 0.0–10.1 ml). CC T2 LV was significantly higher in CI (median = 5.7 ml; range = 2.6–10.1 ml) than in CP (median = 3.8; range 0.0–8.5 ml) patients ($P = 0.02$).

DT MRI-Derived Metrics of the CC

In Table I, DT MRI metrics from the CC of BMS patients and controls are shown. Compared with controls, patients had significantly higher CC average MD and lower CC average FA and JD. The comparison between CI and CP patients showed a significant increase of CC average NAWM MD in the former group ($P = 0.02$), whereas no difference was found for the remaining metrics (Table II).

TABLE I. Diffusion-tensor MRI-derived metrics of the corpus callosum from patients with benign MS and healthy controls

	BMS	Healthy controls	<i>P</i>
Average NAWM MD (SD)	1.05 (0.08)	0.93 (0.04)	<0.001
Average NAWM FA (SD)	0.46 (0.04)	0.52 (0.02)	<0.001
Mean JD (SD)	0.91 (0.04)	0.97 (0.04)	<0.001

Average MD is expressed in units of $\text{mm}^2/\text{s} \times 10^{-3}$, FA is dimensionless index. BMS, benign multiple sclerosis; NAWM, normal-appearing white matter; MD, mean diffusivity; SD, standard deviation; FA, fractional anisotropy; JD, Jacobian determinant.

TABLE II. Diffusion-tensor MRI-derived metrics of the corpus callosum from benign MS patients with and without cognitive impairment

	CI BMS	CP BMS	<i>P</i>
Average NAWM MD (SD)	0.82 (0.05)	0.78 (0.04)	0.02
Average NAWM FA (SD)	0.44 (0.06)	0.47 (0.03)	0.16
Mean JD (SD)	0.89 (0.03)	0.90 (0.04)	0.45
Average lesion FA	0.34 (0.04)	0.35 (0.06)	0.64
Average lesion MD	1.25 (0.13)	1.21 (0.14)	0.38

Average MD of the diffusivity histogram is expressed in units of $\text{mm}^2/\text{s} \times 10^{-3}$, FA is dimensionless index. CI, cognitively impaired; BMS, benign multiple sclerosis; CP, cognitively preserved; NAWM, normal-appearing white matter; MD, mean diffusivity; SD, standard deviation; FA, fractional anisotropy; JD, Jacobian determinant.

In patients, brain and CC T2 LV were significantly correlated with DT MRI measures of NAWM damage of the CC (Table III). CC JD (atrophy) was also significantly correlated with CC average NAWM FA ($r = 0.41$, $P = 0.002$) and average NAWM MD ($r = -0.56$, $P < 0.001$).

Voxel-Based Analysis

Compared with controls, BMS patients showed a widespread increase of CC MD, which was more pronounced in the genu (Fig. 1). Compared with CP patients, CI ones had significant clusters of increased MD in the right CC body (SPM space coordinates: 20, 20, 18; cluster size = 99; $t = 4.98$; $P < 0.05$), left CC splenium (SPM space coordinates: -18, -32, 20; cluster size = 15; $t = 4.76$; $P < 0.05$), and left CC genu (SPM space coordinates: -2, 34, -4; cluster size = 21; $t = 4.43$; $P < 0.05$) (see Fig. 1). Compared with controls, BMS patients had diffusively decreased CC FA values (see Fig. 2), but no difference was found between CI and CP BMS patients.

In BMS, significant clusters of reduced CC volume were found in the splenium, bilaterally (SPM space coordinates for the right splenium: 18, -30, -2, cluster size = 701; $t = 7.08$; left splenium: -14, 28, 0, cluster size = 701; $t = 6.87$; $P < 0.05$) and the right genu (SPM space coordinates: 14, 48, -20; cluster size = 47; $t = 5.67$; $P < 0.05$) (see Fig. 3).

TABLE III. Correlations of brain and corpus callosum T2 lesion volumes with diffusion tensor MRI-derived metrics

	T2 LV (<i>P</i> value)	CC T2 LV (<i>P</i> value)
CC average NAWM MD	$r = 0.64$ (<0.001)	$r = 0.56$ (<0.001)
CC average NAWM FA	$r = -0.50$ (<0.001)	$r = -0.50$ (<0.001)
CC mean JD	$r = -0.44$ (0.001)	$r = -0.59$ (0.001)

LV, lesion volume; CC, corpus callosum; NAWM, normal-appearing white matter; MD, mean diffusivity; FA, fractional anisotropy; JD, Jacobian determinant.

Figure 1.

Statistical parametric mapping analysis (color-coded for t values) of corpus callosum regions with increased mean diffusivity (MD): **A:** Benign multiple sclerosis (BMS) patients vs. healthy controls; **B:** BMS patients with vs. without cognitive impairment ($P < 0.05$, corrected for multiple comparisons).

No difference in atrophy was detected between CI and CP patients.

The comparison of T2-visible lesion distribution between CI and CP BMS patients showed that the former group had a significantly higher frequency of lesion occurrence in the left and right splenium and in the right body of the CC ($P < 0.05$). Between-groups differences in lesions location did not correspond to between-groups differences in MD abnormalities (see Fig. 4).

CC DT MRI-derived changes were significantly correlated with brain (for FA r values ranging from -0.59 to -0.75 ; for MD $r = 0.81$; all $P < 0.05$ corrected for multiple comparisons) and CC T2 LV (for FA r values ranging from

-0.54 to -0.69 ; for MD r values ranging from 0.60 to 0.79 ; all $P < 0.05$ corrected for multiple comparisons).

Correlation Between DT MRI-Derived Metrics and Neuropsychological Data

In BMS patients, there was a significant correlation between PASAT scores and the majority of CC DT MRI metrics (Table IV). WCST scores correlated with CC average NAWM FA ($r = 0.34$, $P = 0.04$). A significant correlation was also found between PASAT scores and FA changes derived from the VB analysis (see Fig. 5) (r values ranging from 0.57 to 0.66 ; $P < 0.05$ corrected for multiple

Figure 2.

Statistical parametric mapping analysis of corpus callosum regions with decreased fractional anisotropy (FA) values in benign multiple sclerosis patients vs. healthy controls ($P < 0.05$, corrected for multiple comparisons). Clusters are shown in yellow over the FA atlas.

Figure 3.

Statistical parametric mapping (SPM) analysis (color-coded for t values) of corpus callosum regions with significant lower Jacobian determinants in benign multiple sclerosis patients vs. healthy controls. The splenium, bilaterally (**A**, **B**) and the right genu (**B**) were identified ($P < 0.05$, corrected for multiple comparisons).

Figure 4.

T2 lesion probability maps (red) and areas with significantly increased mean diffusivity (blue) in cognitively-impaired vs. cognitively-preserved benign multiple sclerosis patients, overlaid on the fractional anisotropy atlas.

TABLE IV. Correlations between the paced auditory serial attention test scores and MRI-derived metrics

	<i>r</i>	<i>P</i>
T2 LV	−0.32	0.03
CC T2 LV	−0.31	0.04
CC average lesion FA	0.40	0.006
CC average NAWM FA	0.50	<0.001
CC average NAWM MD	−0.47	0.001

LV, lesion volume; CC, corpus callosum; FA, fractional anisotropy; NAWM, normal-appearing white matter; MD, mean diffusivity.

comparisons). MD values in a few, preferentially left-sided CC clusters were also correlated with the performances of PASAT (see Fig. 5) (*r* values ranging from −0.59 to −0.66; *P* < 0.05 corrected for multiple comparisons).

DISCUSSION

In this study, we investigated the relation of the overall amount of CC damage and the topographic distribution of such a damage with cognitive performance in a relatively large cohort of patients with BMS. To do this, we combined DT MRI tractography (including a recently developed method, which allows to obtain estimates of volume changes of WM fiber bundles) [Pagani et al., 2007] and VB analysis of DT MRI-derived maps and T2-weighted images, in an attempt to achieve a comprehensive *in vivo*

assessment of CC damage. To limit the cerebrospinal fluid contamination of average DT MRI-derived metrics and to obtain a good intersubject anatomical overlap in the VB analysis, a nonlinear transformation was used to compensate for major morphological differences secondary to atrophy. In particular, the nonlinear registration algorithm applied here uses basis functions that have a local influence, to achieve a better compensation for small and local differences. In addition, to achieve an optimal overlap of the same WM fiber bundles across subjects, we used FA maps to drive the transformation.

The definition of BMS in our study is in line with that used by the majority of recent published studies, i.e., EDSS score less than or equal to 3.0 after at least 15 years of disease duration [Amato et al., 2006; 2008; Ceccarelli et al., 2008; De Stefano et al., 2006; Mesaros et al., 2008; Rocca et al., in press] and is in agreement with that proposed by the National Multiple Sclerosis Society Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis, which, albeit does not recommend a cut-off for the EDSS score, suggests that “the patient (should) remains fully functional in all neurological systems 15 years after disease onset” [Lublin and Reingold, 1996]. It is worth noting that other studies used different criteria to define BMS patients, such as an EDSS score less than or equal to 3.0 [Hawkins and McDonnell., 1999; Ramsaransing et al., 2001; Sayao et al., 2007; Strasser-Fuchs et al., 2008] or 2.0 [Pittock et al., 2004] after at least 10 years of disease duration. However, a long-term follow up study suggested that appropriate and reliable criteria to identify those MS patients who

Figure 5.

A: Statistical parametric mapping (SPM) regions where corpus callosum (CC) fractional anisotropy (FA) values were significantly correlated with the scores obtained at the paced auditory serial attention test (PASAT) (*P* < 0.05, corrected for multiple comparisons). **B:** SPM regions where CC mean diffusivity values were significantly correlated with PASAT (*P* < 0.05, corrected for multiple comparisons). Clusters are shown in yellow over the FA atlas.

remain with mild disability over the long term have yet to be determined [Sayao et al., 2007]. This is also in agreement with the results of two recent studies, which confirmed the need to redefine BMS and suggested an EDSS score equal or less than 2.0 after 20 years of disease duration as a new way to diagnose BMS [De Stefano et al., 2006; Mesaros et al., 2008].

The analysis of the cognitive profile of our patients demonstrated that only 17% of BMS patients had cognitive impairment, with a predominant involvement of memory and executive skills, in agreement with the pattern usually described in patients with MS [Rao et al., 1991]. It is worth noting that the frequency of cognitive impairment in our patients was lower than that reported in early RRMS [Amato et al., 1995; Lin et al., 2008], primary progressive (PP) MS [Camp et al., 1999], and SPMS [Comi et al., 1995]. Such a frequency was also lower than the one reported in a recent, large-scale study of 163 patients with BMS [Amato et al., 2006]. Although the use of different batteries of neuropsychological tests and the use of stringent criteria to define cognitive impairment in our study might be among the factors contributing to explain such a discrepancy and might prevent a head-to-head comparison with the study by Amato et al. [2006], other differences should be mentioned. These include the fact that, contrary to our results, which showed similar locomotor disability between CI and CP BMS patients, Amato et al. [2006] found significantly higher EDSS scores in patients with cognitive impairment, suggesting the presence of subtle clinical differences between the two study populations, which might in turn account for the lesser extent of cognitive impairment in our cohort. This notion is also supported by the similarity between our results and those of a recent study in BMS, where the frequency of CI patients was 23% [Amato et al., 2008], and where these patients had an EDSS score similar to those of CP patients.

The analysis of the whole brain T2 LV demonstrated an increased lesion burden in CI compared with CP patients, although this difference was not statistically significant. However, CC T2 LV was significantly higher in CI patients. That the extent of focal lesions in the CC might be higher in CI BMS patients is in line with a recent study of patients with RRMS [Lin et al., 2008]. In the present study, we also defined the topographical distribution, at a voxel-based level, of CC lesions. This latter analysis showed that CI BMS patients had a significantly higher frequency of lesion occurrence in the splenium and in the right body of CC. Taking together, these results support the notion that T2-visible lesions located in the CC might serve as a marker of cognitive dysfunction in BMS.

Contrary to previous magnetization transfer (MT) MRI studies [Filippi et al., 2000; Rovaris et al., 1998], which have shown that the severity of intrinsic lesion damage may have a role in MS-related cognitive impairment, the present study did not reveal any difference between CI and CP BMS patients in this respect. Our results are in line with those of a recent study in BMS patients, which

showed that MT ratio (MTR) values of T2- and T1-weighted lesions were similar in patients with and without cognitive impairment [Amato et al., 2008]. This may be interpreted by assuming that the progressive accumulation of damage inside lesions does not have a further impact on clinical manifestations, when a given threshold of tissue damage is overcome. This hypothesis is also supported by the observation that, in patients with MS, the MTR of the internal capsule is also not related to the severity of motor deficits [Pendlebury et al., 2000].

In agreement with previous studies in patients with different disease clinical phenotypes [Ciccarelli et al., 2003; Coombs et al., 2004; Filippi et al., 2001; Ge et al., 2004; Lin et al., 2008; Oh et al., 2004], including those with BMS [Ceccarelli et al., 2008; Rocca et al., in press], the analysis of DT MRI metrics of the CC NAWM demonstrated the presence of widespread abnormalities in our patients. In addition, significant atrophy of the CC was also found. Diffuse CC atrophy is a well-known feature of MS [Evangelou et al., 2000] occurring since the early phase of the disease, in RRMS [Barkhof et al., 1998; Pelletier et al., 2001], and tending to progress over time, independently of the disease phenotype [Martola et al., 2007; Pelletier et al., 2001]. However, to the best of our knowledge, the occurrence and the rate of CC atrophy in patients with BMS has not been investigated yet. Several pathological processes might contribute to explain the observed diffusivity and volumetry findings in BMS patients, such as axonal and myelin loss, inflammation, astrogliosis, and expanded extracellular space [Rovaris et al., 2005]. The correlation of CC NAWM diffusivity and volumetry changes with brain and CC T2 LV, which is in agreement with the results of previous studies of patients with other disease phenotypes [Ciccarelli et al., 2003; Coombs et al., 2004; Ge et al., 2004; Lin et al., 2008], supports the role of Wallerian degeneration in the genesis of the observed CC injury.

The assessment of the topographical distribution of the CC abnormalities showed that, although ubiquitous in this WM fiber bundle, they tend to be more evident in the genu. On the contrary, atrophy was more prominent in the splenium. The splenium consists of fiber tracts connecting the temporal-parietal-occipital cortex, the superior parietal regions and the occipital lobe, whereas the fibers of the genu connect the frontal lobes [De Lacoste et al., 1985]. All of these regions are involved in cognitive processes in MS [Audoin et al., 2003; Lazeron et al., 2003; Mainiero et al., 2004; Morgen et al., 2006] and, moreover, have been shown to be severely damaged in CI BMS patients using MTR [Amato et al., 2008]. Among the reasons for such a different pattern of regional distribution of CC damage, a variable amount of thin fibers in the different portions of this structure should be considered, because thin fibers are more vulnerable to MS-related injury [Evangelou et al., 2001]. In addition, a recent VB study demonstrated a predominantly posterior location of MS lesion in patients with BMS [Ceccarelli et al., 2008], which can lead to Wallerian and transsynaptic degeneration of axons passing through

the posterior parts of the CC. An additional, but not mutually exclusive explanation, might be a different temporal involvement of CC portions. It is indeed conceivable that intrinsic damage may precede irreversible tissue loss (atrophy) and that when it is established the collapse of the residual axons may lead to a “pseudo normalization” of diffusivity.

One of the main objectives of our study was to investigate the relation between CC damage and cognitive impairment in patients with BMS. We found that NAWM MD and CC T2 LV were the only variables, among those analyzed, which differed between CI and CP patients. Using DT MRI tractography, a recent study showed significantly increased CC MD values and a reduction of CC area in RRMS patients with cognitive impairment when compared to those without [Lin et al., 2008]. In our study, contrary to MD metrics, CC FA and volumetry did not differ between patients with and without cognitive impairment, as shown by both the two methodological approaches used. Because FA represents a measure of structural integrity it seems plausible to speculate that CC fiber coherence is retained also in patients with cognitive impairment despite they might have experienced a more pronounced tissue loss, as suggested by the increase in MD values. The absence of significant between-group difference in atrophy could be related to a more pronounced astrocytic proliferation and reactive gliosis in patients without cognitive impairment, which in turn might be interpreted as a sign of an enhanced effectiveness of repair mechanisms in these patients.

The analysis of correlation between neuropsychological test performance and MRI derived metrics showed that, despite the highest frequency of abnormalities was observed in the performance of the WCST, the results of this test were only weakly correlated with CC diffusivity changes. This finding confirms the robustness of our data, because the WCST assesses conceptual reasoning and, as consequence, is typically associated with frontal lobe damage [Arnett et al., 1994; Rao et al., 1991; Swirsky-Sacchetti et al., 1992]. On the other hand, the performance of PASAT was moderately correlated with both brain and CC T2 LV. Previous studies in patients with MS have already demonstrated significant correlation between the performances at PASAT and brain T2 LV [Edwards et al., 2001; Lin et al., 2008], as well as frontal and parietal T2 LV [Sperling et al., 2001]. The PASAT scores were also significantly correlated with majority of the DT MRI-derived metrics of CC damage. This finding was confirmed and expanded by VB analysis, which showed that CC FA changes (and in particular those of the body and genu) were also strongly correlated with PASAT scores. As a consequence, our findings underpin the role of both the extent and location of MS lesion loads on cognitive performance in sustained attention and information processing speed.

These results suggest that the assessment of structural damage and clinical function on a regional basis may rep-

resent a rewarding strategy to identify patients with a “truly” benign disease course and prompt the inclusion of patients’ cognitive profile as additional criteria for the definition of this disease phenotypes. Such an approach might contribute to identify those patients with a “truly” benign course, in whom treatment may be unnecessary or, at least, postponed for many years.

Clearly, this study is not without limitations. First, limited portion of the brain was covered by DT MRI acquisition. Second, atrophy measurement can be affected by imaging artefacts because of field inhomogeneity and gradient field properties, which can cause distortions in the phase encoding direction of EPI images. However, considering that an *ad hoc* atlas has been produced using the same acquisition technique and that we performed a between-group analysis, we believe that, on average, differences due to these distortions should not have affected our findings at a great deal.

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