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Tract-specific white matter correlates of fatigue and cognitive impairment in Benign Multiple Sclerosis

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Abstract

Background—Although benign multiple sclerosis (BMS) is traditionally defined by the presence of mild motor involvement decades after disease onset, symptoms of fatigue and cognitive impairment are very common.

Objective—To investigate the association between micro-structural damage in the anterior thalamic (AT) tracts and in the corpus callosum (CC), as measured by diffusion tensor imaging (DTI) tractography, and fatigue and cognitive deficits.

Methods—DTI data were acquired from 26 BMS patients and 24 sex- and age-matched healthy controls.

Results—General and mental fatigue scores were significantly impaired in patients compared with controls ($p \leq 0.05$ for both) and 38% of patients resulted cognitively impaired. Mean diffusivity (MD) of the AT and CC tracts was significantly higher and fractional anisotropy (FA) lower in patients compared with controls ($p < 0.001$ for all). Fatigue was associated with increased MD ($p = 0.01$) of the AT tracts whereas deficit of executive functions and verbal learning were associated with decreased FA in the body ($p = 0.004$) and genu ($p = 0.008$) of the CC. Deficits in processing speed and attention were associated with the T2 lesion volume of the AT tracts ($p < 0.01$ for all).

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Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Discussion—These findings suggest that fatigue and cognitive impairment are quite frequent in BMS patients and are, at least in part, related to micro-structural damage and T2LV of WM tracts connecting brain cortical and sub-cortical regions of the two hemispheres.

Keywords

benign multiple sclerosis; fatigue; cognitive impairment; diffusion tensor imaging; diffusion tensor tractography; anterior-thalamic tracts; Corpus callosum tracts

Introduction

The benign form of Multiple Sclerosis (BMS) is classically defined by minimal disease progression and motor disability decades after the clinical onset (1). The application of these traditional criteria results in a prevalence of 10–20% (2) after 10 years and of nearly 7–8% after 20 years of disease (3). Recent studies have reported that about 45% of patients fulfilling classical criteria for BMS (disease duration ≥15 years, expanded disability status scale (EDSS) score ≤3.0) (2) are affected by significant cognitive impairment and have proposed that cognitive preservation should be an additional criteria to define BMS (4). Although often underestimated in patients with BMS, fatigue is a very common symptom occurring at a frequency comparable to that reported in other forms of MS (2). Neither commonly used clinical scales such as the EDSS (5) nor conventional Magnetic Resonance Imaging (MRI) metrics such as T2-weighted lesion volume (T2LV) show a strong correlation with cognitive impairment and fatigue (6). This mismatch can in part be explained by the lack of histopathological specificity of conventional MRI metrics.

Advanced MRI techniques such as Diffusion Tensor Imaging (DTI) tractography have helped to overcome some of these limitations by providing specific tools to quantify and grade the extent of damage to selected white matter tracts reflecting neurodegeneration and demyelination in axonal pathways and to improve correlations with neurological deficits (7). Previous DT-tractography studies in patients with BMS (8–10) have identified lesional and diffuse damage of the corpus callosum (CC) as a major correlate of cognitive impairment. By connecting cortical and subcortical regions of the two hemispheres, the CC allows interhemispheric transfer of information that is crucial for maintaining normal cognitive performance (11). In contrast, the precise mechanisms underlying the development of fatigue in MS remain elusive (12). It has been suggested that lesions in frontal white matter networks, frontal gray matter atrophy and dysmetabolism of thalami and basal ganglia can contribute to development of central fatigue in MS (13–17). Since disruption of cortico-subcortical circuits linking the cortex with the deep gray matter has been proposed as a potential mechanism of symptoms of fatigue (12) we hypothesized that intrinsic damage of the anterior-thalamic tracts would be associated, at least in part, with symptoms of fatigue in BMS patients.

The aims of our study were: a) to investigate the association of symptoms of fatigue with damage of the anterior-thalamic tract (AT) measured with DTI tractography; b) to determine the contribution of regional (genu, body and splenium) intrinsic corpus callosum damage

estimated with DTI tractography to the impairment of specific cognitive domains in BMS patients.

Methods

Subjects

Twenty-six patients were recruited prospectively from the New York University MS Center. To be included all patients had to be relapse- and steroid treatment-free for at least one month prior to study entry; to be right-handed and do not have history of alcohol or drug abuse. All patients underwent a neurological examination with assessment of the expanded disability status scale (EDSS) score by a neurologist blinded to the MRI results.

Criteria for a diagnosis of BMS were an EDSS score equal or less then 3.0 and disease duration equal to or longer than 15 years (1, 18). Twenty-four age and gender matched healthy controls served as controls. Approval for this study was obtained from the Institutional Board of Research Associates of New York University Medical Center and informed consent was obtained from all subjects.

Neuropsychological and Behavioral Assessment

All MS patients underwent neuropsychological (NP) testing within 24 h of MRI using a battery examining the following cognitive domains: (1) verbal fluency (FAS test); (2) verbal learning and memory (California Verbal Learning Test-II [CVLT]); (3) processing speed (Symbol Digit Modalities Test [SDMT], 3-sec trial of the Paced Auditory Serial Addition Test [PASAT-3 secs]); (4) working memory (SDMT, and PASAT-3 secs); 5) executive functioning (Delis-Kaplan Executive Function System [D-KEFS] Color-Word Interference Test: Inhibition [D-KEFSI] and Inhibition Switching [D-KEFSIS]).

Raw NP scores were normalized using published norms and then converted to *Z*-scores based on the normal distribution. In cases in which no published norms were available (PASAT-3 sec), test scores were normalized against 38 normal controls comparable with the patients on variables such as age and years of schooling. In such cases, raw scores were converted directly to *Z*-scores based on the normal distribution using control means and standard deviations (SD). Subjects were classified as impaired if they failed two or more NP tests. The cutoff score for failing a NP test was a *Z*-score of −1.6 SD (5^{th} percentile) or below. Fatigue was assessed in both patients and controls using the multidimensional fatigue inventory (MFI) which consists of a 20-item self-report measure assessing 5 dimensions of fatigue: General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation, and Mental Fatigue. Each subscale is the sum of 5-items, which are rated on a 5-point scale ranging from 1 (no, not true) to 5 (yes, that is true). Half of the items in the questionnaire are reversed scored to prevent response pattern bias. Subscale scores range from 4 to 20, with lower scores indicating a higher level of fatigue. In addition to MFI, both patients and controls were also assessed with the Depression Subscale of the Brief Symptom Inventory (BSI) (19). This scale assesses clinical indications of depression such as dysphoric mood and affect as well as reduced motivation and a loss of interest. T scores of 63 or greater

indicate a clinically significant level of depression that is equal to or above the 91st percentile.

MR Imaging acquisition

Brain MRI was performed using a 3-T scanner (Tim Trio, Siemens Medical Systems, Erlangen, Germany) with an 8-channel phased array head coil. The following imaging protocol was collected in all subjects during a single session: 1) T2 Turbo Spin Echo (TSE) sequence (TR/TE = 5000/88 ms, FOV = 178*220 mm, matrix 284*448, 50 3-mm thick contiguous slices) 2) 3D T1 magnetization prepared rapid acquisition gradient echo (MPRAGE) (TR/TE= 2000/2.6 ms, TI 800 ms, FOV = 256*256 mm^2, matrix 256*256, 192 contiguous slices, isotropic voxel size 1*1*1 mm^3. 3) A single-shot twice refocused echo planar imaging (EPI) sequence, which has been shown to significantly reduce eddy current distortions, was used to acquire the DTI data (TR/TE = 8200/97 ms, FOV=230*230 mm^2, 128*128 matrix, 48 3-mm tick contiguous slices, in-plane voxel size 1.8*1.8 mm^2). Diffusion weighting (b=1000s/mm2) was applied along 6 noncolinear directions. One image without diffusion weighting (b=0) was acquired for each set of 6 diffusion encoding directions. DTI data acquisition was repeated four times and averaged to increase the image SNR 4) In patients, an additional 2D T1 Fast Low Angle Shot (FLASH) sequence was acquired after intravenous injection of gadopentate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ) with a standard dose of 0.1mmol/kg body weight (TR/TE = 354/2.73 ms, FOV = 191*230, matrix 768*640, 50 3-mm tick contiguous slices).

MRI Data Processing

All data processing was performed off-line on a PC workstation by an observer blinded to the subjects' identity.

DTI

DTI images were processed using an in-house developed program written in IDL (Exelis Visual Information Solutions, Boulder, Colorado). The diffusion weighted images were first corrected for motion using the linear registration implemented in the Automated Image Registration (AIR) software package (http://www.bishopw.loni.ucla.edu/AIR5/) (20). The diffusion tensor (DT) was estimated by linear regression (21) and FA and MD were calculated. A study specific FA atlas in MNI space was created from healthy subjects' data as described previously (22). This method

Using DT MRI tractography (in-house developed software) the CC and the AT tracts were computed for every healthy subject as described in (22–24). This method allows computing the tracts in a healthy cohort matched to the examined BMS patients to build a study specific tract template and avoid misleading results in tractography due to the presence of T2 visible lesions. For 3D tract reconstruction, a streamline algorithm employing a second-order Runge–Kutta integration method was used (Figure 1). Tracts were terminated if they reached regions with FA lower than 0.2 or if angles between two consecutive steps were larger than 41°.

Briefly, after whole brain tractography, the target tracts were extracted by applying predefined Regions of Interest (ROI). The anatomical limits of the tracts were defined by specified seedpoints in the tractography algorithm. Specifically, the CC was obtained by selecting all trajectories intersecting its midsagittal cross-section. The right and left AT (AT-R, AT-L) tracts were segmented using the approach outlined by Wakana et al. (25). Additionally the CC tracts were split in the callosal genu (CCG), body (CCB) and splenium (CCS) using an established scheme (26). Subsequently, probability maps of the calculated tracts derived from all patients (CC, CCG, CCB, CCS, AT) were warped on the FA atlas in the MNI space as described in detail elsewhere (22). In order to convert the probability maps back into the single subject space the affine transformation between the FA atlas and the single subject FA was calculated. Next, the calculated transformation matrix was applied to the CC, CCG, CCB, CCS and AT probability maps, which were superimposed on the individual FA and MD maps.

In order to avoid partial volume artifacts from adjacent areas containing gray matter or cerebral spinal fluid (CSF) tract specific FA and MD maps were additionally masked with an individual GM/CSF map. The WM/GM segmentation was obtained using the FAST utility in FSL with three channels, given by the major and minor tensor eigenvalues. To obtain values of NAWM in MS patients, the T2 lesion maps were subtracted from the masked FA and MD thus assigning the value of zero to the lesion area. Then, mean FA and MD values of NAWM tracts were calculated.

T2-weighted (T2W) lesion volumes

For all patients, T2-hyperintense lesion volume measurements were performed by a single experienced observer, blinded to the subject's identity, using a semiautomated segmentation technique based on user-supervised local thresholding (Jim version 3; Xinapse Systems, Northants, England, (http://www.xinapse.com). The value of total brain LV was calculated by multiplying lesion area by slice thickness. To obtain tract specific T2 lesion volumes (Figure 2), each patient's total lesion map was masked with each tract mask (CC, CCG, CCB, CCS and AT) and the resulting tract specific T2 LV was determined by multiplying lesion area by slice thickness

Brain volumes

For all subjects, normalized brain volume (NBV), normalized gray, and white matter volumes (GMV and WMV) were measured on MPRAGE images using SIENAX as described previously (27). SIENAX automatically segments brain from non brain matter, calculates the brain volume, and applies a normalization factor to correct for skull size (27). To correct for misclassification of T_1-W GM volume in presence of high T_1-W hypointense LV (28), each T_1-W hypointense lesion of each subject was filled with the mean intensity value of the normal appearing NAWM present in the same slice of the lesion.

Statistical Methods

Analysis of covariance (ANCOVA) based on ranks was used to compare patients and controls in terms of each imaging measure adjusted for age and gender and the group of patients with and without cognitive impairment adjusted for age and gender, disease

duration and treatment. A separate analysis was conducted for each measure. In each case, the ranks of the measure constituted the dependent variable and the model included the indicator of group membership as a classification factor and the other variables as covariates. Ranks were used in place of the observed data in order to better satisfy underlying assumptions. ANCOVA based on ranks was used to compare subject groups in terms of general, physical and mental fatigue, reduced activity and reduced motivation correcting for age, gender and BSI score. Spearman rank correlation coefficient was used to characterize associations among measures adjusting for covariates. All reported p values are two-sided and are Tukey-corrected for multiple comparisons. Results were declared statistically significant when $p<0.05$. SAS version 9.0 (SAS Institute, Inc., Cary, NC) was used for all computations.

Results

There was no statistically significant difference between BMS patients and controls in terms of age, gender, depression subscale score of the BSI, physical fatigue, reduced activity, and reduced motivation score. General ($p=0.05$) and mental ($p=0.04$) fatigue dimension scores were significantly lower in patients than controls. Demographic and clinical data are reported in Table 1. Sixteen BMS patients were under disease-modifying treatment: 11 with interferon β-1a and 5 with glatiramer acetate. Ten patients (38%) were classified as being cognitively impaired whereas none of the patients was classified as depressed according to the BSI depression subscale score. There was no statistically significant difference in age, gender, disease duration, and fatigue and EDSS scores between cognitively impaired (CI) and cognitively preserved (CP) patients.

DTI tractography analysis

Mean diffusivity (MD) and fractional anisotropy (FA) from the DT-tractography derived CC and AT tracts of BMS patients and controls are shown in Table 2. Compared with controls, BMS patients showed significantly higher MD and lower FA in all analyzed WM tracts.

Lesion and brain volumes analysis

All controls had normal MRI scans. In BMS patients, mean T2LV was 4.1± 6.2 ml; mean AT T2LV was 0.32±0.6 ml and mean CC T2L was 0.5±1.4 ml. NBV and GMV were significantly lower in patients (1467.5±132.4; 730.8±61.3 ml, respectively) than controls (1612.7±90.7; 871.8± 75.1 ml, $p<0.0001$) whereas there was no significant difference between patients (735.2± 81.2 ml) and controls (740.8± 52.2 ml) in terms of WMV ($p>0.1$)

Correlations of DT-derived metric and volume metrics with neuropsychological and fatigue scores

When DT-derived metrics of the CC tracts were correlated with NP tests, there was a moderate statistically significant direct correlation between FA CCG value and CVLTI score ($r=0.52$, $p=0.008$) and between FA CCB value and DKEFS-W score ($r=0.55$, $p=0.004$). Statistically significant inverse correlations were also found between T2LV of the AT tracts and PASAT score ($r=-0.60$, $p=0.002$) and between T2LV of right AT tract with PASAT score ($r=-0.65$, $p=0.0006$) and with SDTM score ($r=-0.70$, $p=0.0001$).

When DT-derived metrics of the AT tracts were correlated with the fatigue scores, there was a modest but statistically significant inverse correlation between MD of the AT-R and general fatigue score (r=−0.38, p=0.01) and a trend towards statistical significance between FA of the AT tracts and general fatigue score (r=0.38, p=0.06). In addition, the T2LV averaged over the AT tracts showed a trend towards statistical significance with general fatigue score (r=−0.36, p=0.07) and with mental fatigue score (r=−0.39, p=0.06). Although we found a correlation between whole T2LV and

Comparison between patients with and without cognitive impairment (CI)

DTI-derived metrics from the CC and AT tracts of BMS patients and controls are shown in Table 2. Compared with cognitively preserved (CP) patients, CI patients showed lower FA and higher MD in all analyzed WM tracts; however the difference reached the level of statistical significance only in the CCS and for the values averaged over the whole CC. When the two groups of patients where compared in terms of T2LV and brain volumes, only T2LV of AT-R (p=0.002), T2LV of the two AT tracts (p=0.01) and the WMV (p=0.02) showed a statistically significant difference. We did not find any correlation between DTI metrics and fatigue scores in the group with cognitive impairment (p>0.2).

Discussion

In this study, we investigated the relationship between microscopic structural damage of the anterior thalamic tracts measured with DT tractography and symptoms of fatigue in patients with BMS. In addition, we assessed the contribution of the intrinsic damage of the genu, body and splenium tracts of the corpus callosum to the impairment of specific cognitive domains in the same group of patients.

BMS patients showed lower scores than controls on each of the 5 dimensions of the MFI scale, the differences reached statistical significance in the general and mental fatigue domains supporting previous studies findings that fatigue is experienced by MS patients even in absence of severe disease course (2, 29, 30). Fatigue can be relevant in BMS despite relative sparing of motor functions and occurs in over 45% of patients and progresses over time with negative impact on daily social and work activities (2, 29–31). Since a dysfunction of networks connecting frontal cortex and deep gray matter structures has been suggested as a possible mechanism of fatigue, we used DT-tractography to detect microstructural damage of the antero-thalamic tracts of BMS patients. Both MD and FA of the AT tracts were significantly altered in patients compared to controls reflecting disorganization of structural barriers to water molecular motion that may result from diffuse astrocytic hyperplasia, patchy edema, perivascular infiltration, gliosis, abnormally thin myelin, and axonal loss(32). Interestingly, we found a significant association between MD of the right AT tract and general fatigue score (r=−0.38, p=0.01) and a trend towards statistical significance between FA of the AT tracts and general fatigue score (r=0.38, p=0.06). Our findings support the concept that symptoms of fatigues are likely the results of regional disruption of selected white matter networks connecting frontal cortical regions and sub-cortical structures rather than the effect of global T2 lesion volume and brain atrophy (33–35).

The analysis of the cognitive profile of our BMS patients demonstrated that 38% of patients had cognitive impairment, which is in good agreement with that reported in previous studies (2, 36, 37) and supports the concept that BMS patients, characterized by motor preservation (1), should be screened for their cognitive ability (4). In agreement with previous studies in MS patients including those with BMS (9, 10, 38), the tract-specific analysis of the CC demonstrated the presence of widespread abnormalities in our patients in the genu, body and splenium. However, when patients cognitively impaired where compared with those cognitively preserved in terms of tract-specific DTI metrics only the differences in the MD and FA of the CC splenium were statistically significant between the two groups. The involvement of the CC splenium is not surprising since it consists of fiber tracts connecting the temporal-parietal-occipital cortex, the superior parietal regions and the occipital lobe that are involved in cognitive processes (11, 39). In addition, our results are in agreement with those of a previous study showing a decrease of MTR, a marker of myelin content, in the CC splenium of BMS patients with cognitive impairment (40) and with those of a DTI study showing an increase of radial diffusivity, a marker of demyelination in patients with early relapsing-remitting MS (41). This might be explained by the fact that MS lesions seem to have a predominant posterior location in patients with BMS (10) leading to fiber transection and Wallerian degeneration of axons passing through the posterior parts of the CC.

T2LV of the AT tracts was higher in patients with cognitive impairment than in patients cognitively preserved. Since the thalamus is involved in awareness, attention, memory and language processes (42), the higher T2LV of the AT tracts in BMS may lead to disruption of fibers connecting the anterior and medial thalamic nuclei with frontal lobes and contribute to deficits of executive functions, sustained attention and information processing speed. Finally, we found a moderate correlation between damage of the genu and body of the CC tracts that connect prefrontal and supplementary motor areas of the two hemispheres and deficits of verbal learning and executive functions. Previous studies have suggested that the frontal cortex plays a role not only in executive functions but also in long-term memory (43). Specifically, it has been suggested that while both patients with lesions in the left medial temporal lobe and left frontal lobe exhibited impaired free recall performance; however, when given strategies at encoding and retrieval, the patients with frontal lobe lesions performed normally, whereas the patients with temporal lobe lesions continued to be impaired. Thus suggesting that frontal cortex plays a strategic role in memory whereas the medial temporal lobe plays an absolute role in memory formation and consolidation. Our study has some limitations. Although BMS patients showed lower normalized brain and gray matter volumes compared to healthy controls, only white matter volume was different between cognitively impaired and preserved patients. Since we did not perform a voxel-based analysis of gray matter volume and cortical thickness we cannot exclude that presence of frontal cortical and thalamic atrophy may have contributed to the presence of fatigue and cognitive impairment as suggested by previous studies in MS patients (44–46).The number of BMS patients with cognitive impairment was limited to 10, therefore the interpretation of our findings has to be cautious until studies with larger sample size become available. A further limitation of the study was the small number of encoding directions of our DTI sampling which has been shown to result in increased variability in the calculated values of both the diffusion metrics (FA and MD) and major tensor eigenvector direction. However,

diffusion-weighted data was acquired on a 3T scanner using 4 averages. Moreover, the reported FA and MD values were obtained by averaging across large ROIs which should further mitigate the effects of parameter variability due to noise and dependence on tensor orientation. Tract templates were obtained by averaging individual tractography results across the group of subjects thus lessening the impact of spurious tracts trajectories due to noise. Lastly, since we did not perform a whole brain analysis of the DT metrics, we cannot exclude that DTI abnormalities of WM tracts other than AT and CC may have contributed to the presence of fatigue and cognitive impairment.

In conclusion our findings suggest that fatigue and cognitive impairment are, at least in part, related to micro-structural damage and T2LV of WM tracts connecting brain cortical and sub-cortical regions of the two hemispheres and support the concept that mild motor disability over decades is not a sufficient criterion to classify benign MS.

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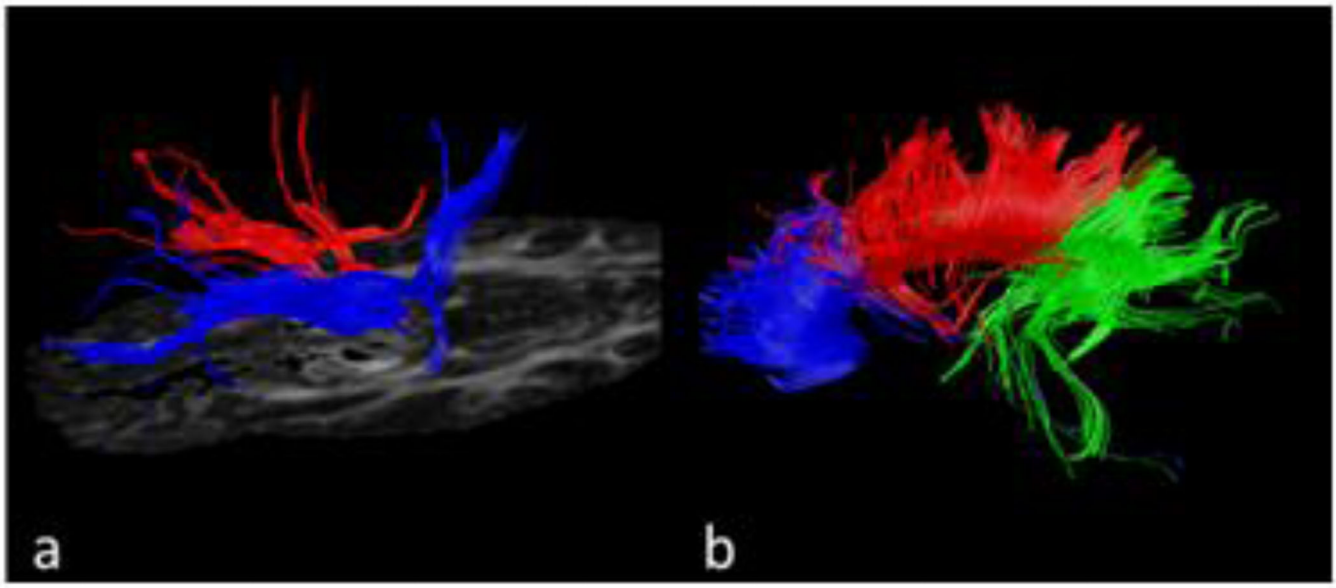

Figure 1.

Example of DT-tractography reconstruction of the anterior thalamic (AT) tracts (**a**) [right AT tract in blue and left AT tract in red] and the corpus callosum (**b**) [genu in blue, body in red and splenium in green] from a 30-year old healthy subject prior to spatial normalization.

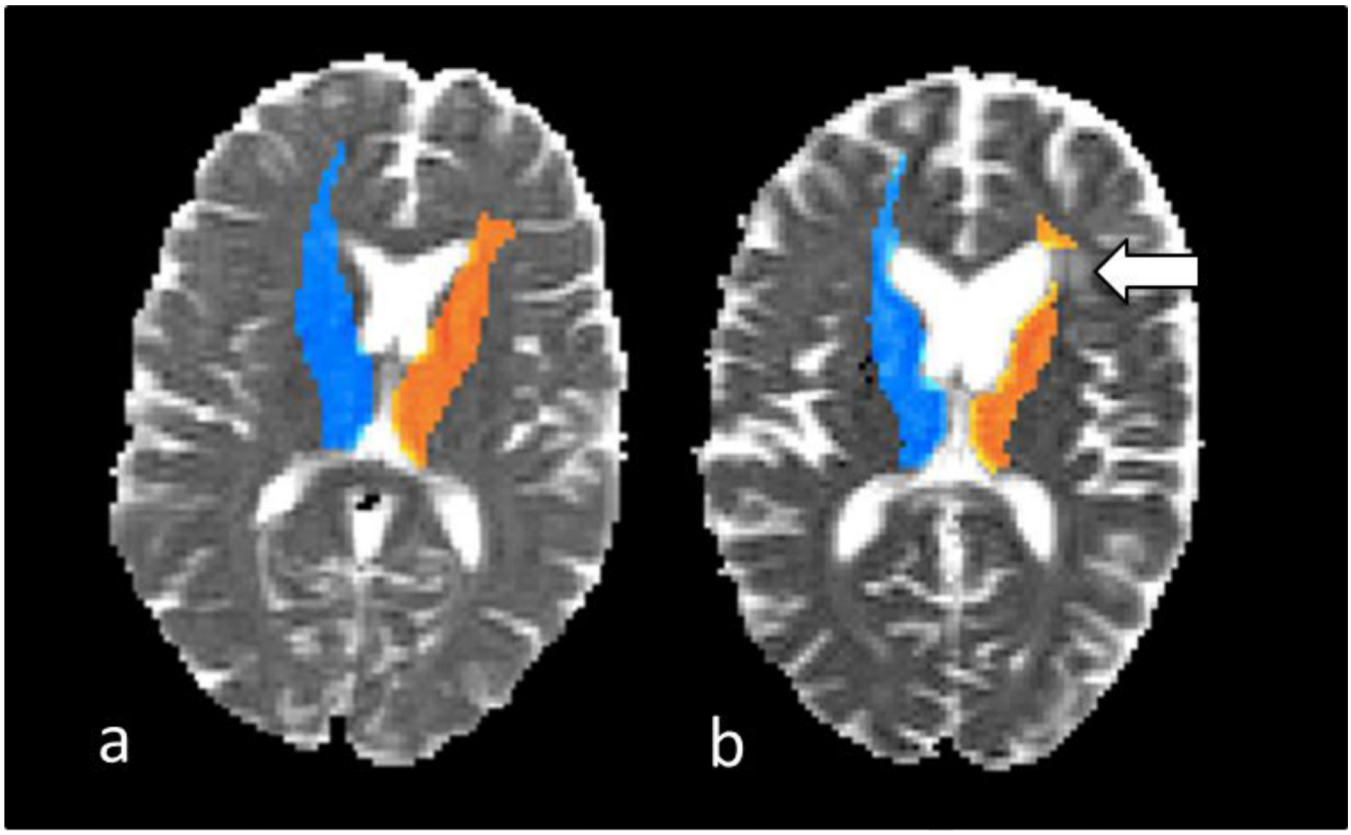

Figure 2.

Probability maps of the right and left AT tracts superimposed on axial MD maps in a healthy control (**a**) and in a patient with benign MS (**b**). The white arrow indicates a left paraventricular lesion which has been removed from the tract (see methods section for further details).

Table 1

Demographics and clinical data from BMS patients and healthy controls

	BMS	CTRLS
Gender (F/M)	16/10	14/10
Mean age in years (SD)	53.4 ± 7.1	51.6 ± 11.2
Mean disease duration in years (SD)	25.8 ± 9.6	-
Median EDSS (range)	1.5 (0–3)	-
General Fatigue	13.7 ± 2.6	15.2 ± 4.2
Mental Fatigue	15.0 ± 2.7	16.8 ± 2.9
Physical Fatigue	15.3 ± 2.5	16.5 ± 3.5
Reduced Activity	16.0 ± 2.7	17.1 ± 2.1
Reduced Motivation	16.6 ± 2.4	16.9 ± 3.3
BSI depression subscale score	50.5 ± 9.7	51.1 ± 10.4

SD: standard deviation; EDSS: Expanded Disability Status Scale; BSI: Brief Symptom Inventory; BMS: benign multiple sclerosis; CTRLS: controls.

Table 2

DTI-derived metrics from white matter tracts (mean ± SD) of BMS patients and controls.

	WM Tract	BMS	CTRLS	p value
FA	**CCG**	0.489 ± 0.044	0.538 ± 0.030	0.0001
	CCB	0.483 ± 0.034	0.531 ± 0.033	< 0.0001
	CCS	0.532 ± 0.047	0.598 ± 0.030	< 0.0001
	CC	0.501 ± 0.035	0.554 ± 0.027	< 0.0001
	AT-R	0.352 ± 0.031	0.392 ± 0.024	< 0.0001
	AT-L	0.347 ± 0.037	0.392 ± 0.037	0.0001
	AT-B	0.350 ± 0.028	0.392 ± 0.028	< 0.0001
MD	**CCG**	0.880 ± 0.067	0.837± 0.068	0.006
	CCB	0.900 ± 0.078	0.848± 0.051	0.04
	CCS	0.948 ± 0.099	0.852 ± 0.060	< 0.0001
	CC	0.903± 0.067	0.844 ± 0.047	0.001
	AT-R	0.832±0.065	0.778±0.050	0.002
	AT-L	0.859±0.061	0.795±0.055	0.0003
	AT-B	0.846 ± 0.058	0.786 ± 0.047	< 0.0001

FA: fractional anisotropy (dimensionless index); MD: mean diffusivity ($mm^2/s \times 10^{-3}$); WM: white matter, BMS: benign multiple sclerosis; CTRLS: controls; CCG: corpus callosum genu; CCB: corpus callosum body; CCS: corpus callosum splenium; CC: corpus callosum; AT-R: anterior thalamic tract-right; AT-L anterior thalamic tract-left; AT-B: anterior thalamic tract-bilateral.

Table 3

DTI-derived metrics from the white matter tracts of patients with and without cognitive impairment

	WM Tract	CP	CI	p value
FA	**CCG**	0.502 ± 0.037	0.470 ± 0.048	**0.1**
	CCB	0.495 ± 0.029	0.466 ± 0.036	*0.07*
	CCS	0.552 ± 0.027	0.503 ± 0.056	**0.02**
	CC	0.515 ± 0.023	0.480 ± 0.040	**0.03**
	AT-R	0.356 ± 0.030	0.347 ± 0.034	0.9
	AT-L	0.360 ± 0.030	0.328 ± 0.039	0.1
	AT-B	0.358 ± 0.030	0.337 ± 0.036	0.3
MD	**CCG**	0.863 ± 0.049	0.905± 0.085	0.1
	CCB	0.879± 0.063	0.931± 0.091	0.1
	CCS	0.904± 0.051	0.998 ± 0.098	**0.01**
	CC	0.879± 0.048	0.938± 0.079	**0.05**
	AT-R	0.818± 0.047	0.853± 0.083	0.3
	AT-L	0.840± 0.052	0.888± 0.064	0.2
	AT-B	0.829 ± 0.050	0.871 ± 0.074	0.2

FA: fractional anisotropy (dimensionless index); MD: mean diffusivity ($mm^2/s \times 10^{-3}$); WM: white matter, BMS: benign multiple sclerosis; CTRLS: controls; CCG: corpus callosum genu; CCB: corpus callosum body; CCS: corpus callosum splenium; CC: corpus callosum; AT-R: anterior thalamic tract-right; AT-L anterior thalamic tract-left; AT-B: anterior thalamic tract-bilateral, CP: cognitive preserved; CI: cognitive impaired.