Gray Matter Involvement in Different Multiple Sclerosis Phenotypes: A Diffusion Tensor and Magnetization Transfer Imaging Study

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Introduction
The pathological mechanisms underlying the different courses of multiple sclerosis (MS) are still not well defined, even thought the presence and the severity of macro- and micro-scopic axonal damage are thought to be important for the development of clinical disability. Previous magnetization transfer imaging (MTI) studies showed that low MT ratios (MTR) values correlate with histopathological findings of myelin and axonal loss (1). Diffusion tensor magnetic resonance (MR) imaging (DT-MRI) (2) is sensitive to pathological processes which result in loss of tissue anisotropy. Measures derived from DT-MRI, such as mean diffusivity (MD), is increased in MS lesions and normal-appearing white matter (NAWM) compared to normal white matter (3). Cercignani et al. (4) recently described a novel segmentation technique, based on fractional anisotropy (FA) thresholds, to evaluate separately NAWM and normal appearing gray matter (NAGM) in patients with MS. These authors showed that NAGM is not spared by the MS pathological process (4). In this study we used such method to evaluate the extent of NAGM damage in the three main phenotypes of MS.

Methods
We studied 30 patients with primary progressive (PP) MS, 30 with secondary progressive (SP) MS and 30 with relapsing-remitting (RR) MS. The following scans were obtained from each subject, during a single session: a) dual-echo turbo spin echo (TSE) (TR/TE/NEX = 3300/16-98/1; number of slices: 24, contiguous, 5 mm thick); b) T1-weighted conventional spin-echo (CSE) (TR/TE/NEX=768/15/2; ETL=5; number of slices: 24, contiguous, 5 mm thick); c) 2D gradient-echo (GE) (TR/TE/NEX=640/12/2; number of slices: 24, contigous, 5 mm thick) with and without an off-resonance radio-frequency (RF) saturation pulse (offset frequency=1.5 kHz, Gaussian envelope duration = 7.68 ms, flip angle=500º); d) pulsed-gradient spin-echo echo-planar (EP) pulse sequence (inter-echo spacing = 0.8, TE = 123; number of slices. 10, contiguous, 5 mm thick), with diffusion-weighting applied in 8 non-collinear directions. (maximum *b* factor = 1044 s mm^{-2}. For the EP scans, the 10 slices were acquired with the same orientation of the dual-echo and GE scans positioning the second-last caudal slice in order to match exactly the central slices of the dual-echo and GE sets. This brain portion was chosen since these central slices are less-affected by B_0 distortions. MS lesions were marked on hardcopies by an experienced observer, unaware to whom the scans belonged, and outlined on a computer display by a trained technician. After co-registration of the two GE images, MTR maps were derived pixel-by-pixel. Finally, extra-cerebral tissue was removed from MTR maps using a local thresholding technique. For the subsequent analysis, only the 10 slices corresponding to the EP images were considered. After correction for eddy current-induced distortion, the diffusion tensor was estimated linearly for every voxel, assuming a mono-exponential relationship between the signal attenuation and the elements of the tensor matrix. Next, MD and FA were derived for each voxel. After interpolation to same matrix size as the dual-echo, the b=0 step of the EP images were co-registered with the T2-weighted scans of the dual echo. The same transformation parameters were then used to register MD and FA maps. FA and MD maps of the normal appearing brain tissue (NABT) were created by superimposing the lesion outlines and nulling out the corresponding regions on the co-registered images. NAWM and normal appearing gray matter (NAGM) were segmented using an automated technique based on FA thresholding (4). NABT, NAWM and NAGM MD and MTR histograms were created as previously described (5).

Results
Average NABT-MD was higher and NABT-MTR and MD histogram peak heights were lower in SPMS than in PPMS patients (Table 1). RRMS had a higher average NABT-MD and a lower average NABT-MTR and histogram peak height when compared to PPMS patients (Table 2). When considering NAGM, average MD, MD peak height and peak location were all different in SPMS and PPMS patients (Table 1), whereas average MD from PPMS was higher than that from RRMS. Consistently, MD peak height was lower in PPMS than in RRMS patients (Table 2). NAWM histogram peak height was significantly lower in SPMS when compared with both, PPMS (Table 1) and RRMS, while no significant differences were found between PPMS and RRMS patients.

Discussion
Tissue damage beyond the resolution of conventional MR scanning has been shown to occur in the NAWM of patients with MS and different disease courses (5). More recently, subtle tissue changes have also been described in the NAGM of MS patients (4). This study reports a systematic assessment of NAGM in the three major phenotypes. It shows that NAWM and NAGM tissue damage is more pronounced in SPMS than in RRMS and PPMS patients. It also shows that NAGM damage is more pronounced in PPMS than in RRMS. These results fit with the notion that patients with progressive MS have clinical pictures characterized by severe physical disability and cognitive impairment.

References
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Table 1. Statistically different histogram metrics between PPMS and SPMS patients.

	PPMS	SPMS	p
Average NABT-MD	1.00 (0.05)	1.04 (0.07)	<0.001
NABT-MD peak height	82.7 (15.9)	73.3 (15.0)	0.001
NABT-MTR peak height	103.4 (11.8)	98.8 (13.9)	0.05
Average NAGM-MD	1.12 (0.05)	1.17 (0.08)	<0.001
NAGM-MD peak height	54.3 (9.2)	48.9 (9.0)	0.002
NAGM-MD peak location	0.90 (0.06)	0.93 (0.08)	0.03
NAWM-MD peak height	145.7 (46.2)	131.9 (24.0)	0.05

Table 2. Statistically different histogram metrics between PPMS and RRMS patients.

	PPMS	RRMS	p
Average NABT-MD	1.00 (0.05)	0.95 (0.05)	<0.001
NABT-MD peak height	82.7 (15.9)	93.3 (15.2)	0.001
Average NABT-MTR	39.5 (1.2)	41.9 (2.1)	<0.001
Average NAGM-MD	1.12 (0.05)	1.05 (0.06)	<0.001
NAGM-MD peak height	54.3 (9.2)	67.0 (11.2)	<0.001