Normal-appearing White Matter Quantitative Magnetization Transfer Imaging correlates with Disability in Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, whose neuroradiological hallmark are multifocal white matter (WM) lesions. Several pathological and MRI studies based on quantitative techniques have clearly demonstrated that diffuse abnormalities are present in the normal appearing WM (NAWM) and in lesions, and that they partially explain symptom severity. Nevertheless, the correlation between lesion loads, indexes of NAWM damage, and measures of disability still remain largely unsatisfactory. Magnetisation transfer imaging (MTI) is based on the exchange of magnetisation existing between protons in tissue water and those bound to the macromolecules. This technique has already been used to investigate MS and it was found to correlate with myelination and axonal count in a post-mortem study [1]. Quantitative MTI (qMTI) [2] is an extension of MTI which allows the binary spin bath model parameters to be estimated. The application of qMTI to the study of MS is promising although it has been limited so far, due to the relatively long scan times required. Aims of this study are to use a clinically feasible whole-brain qMTI protocol to investigate the different pathological substrates of NAWM and lesions in MS, and to assess whether qMTI parameters may explain the clinical disability of relapsing remitting (RR) MS patients.

Methods

We recruited 13 patients with RRMS [F/M ratio=8/5; mean (SD) age=39.38 (9.6) years; median (SD) expanded disability status scale [EDSS] score 2 (range 1.0-4.0)] who underwent a neurological examination and an MRI acquisition at 3.0T. Fourteen age-matched healthy subjects were recruited as controls [F/M ratio=6/8; mean (SD) age=35.14 (8.37) years]. The MRI session included for every subject: 1) a dual-echo turbo spin echo (TSE); 2) a fluid attenuated inversion recovery (FLAIR) scan; 3) a Magnetization Prepared Rapid Gradient Echo (MPrage) for tissue segmentation; 4) a series of 12 MT-weighted 3D FLASH sequences, with various combinations of amplitude and offset frequency of the MT pulse, optimised according to [3]; 5) three 3D FLASH sequences with variable flip angle for T_1 mapping [4], and 6) three 3D FLASH sequences with near-180° flip angles for B_1 mapping [5]. White matter lesions were outlined on proton density weighted scans using a semi-automated contouring technique (http://www.xinapse.com/), using the FLAIR and the T_2-weighted scans as reference. T_1 and B_1 maps were obtained as described in [4] and [5], respectively. We fitted Ramani's model [6] of MT to the data to yield R_A, F, T_{2B}, and RM_{0B} (where R is the exchange rate, F= M_{0B}/M_{0A}, with M_{0A} and M_{0B} being the fully relaxed values of longitudinal magnetisation for the two pools, and R_B=1s). The MPrage scans were segmented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/) to produce a map of WM. An image of the NAWM was obtained by subtracting from this WM image the voxels corresponding to lesions. After image coregistration, NAWM masks were applied to the RM_{0B}, T_{2B}, F, and R_A maps to compute the mean NAWM parameters. T tests were performed to compare mean NAWM parameters of patients with, respectively, the mean WM parameters of controls, and with patients lesions. Correlation between lesion load values and qMT parameters were calculated. Two models were investigated using ordered logistic regressions, with the EDSS as the dependent variable. In the first one, mean NAWM MT parameters (RM_{0B}, T_{2B}, F, R_A) and lesion load were entered as explanatory variables; in the second one, mean MT variables within lesions and lesion load were entered as explanatory variables. In both models age was added as a covariate of no interest.

Results

The mean T_2 lesion load in patients was 5.95 (SD=4.96)mL (Table 1). Mean comparisons showed significantly lower values of F and RM_{0B}, and approaching significance for R_A in patients NAWM compared to controls WM (Table 1). Significantly higher values including RM_{0B}, T_{2B}, F, and R_A were also observed when comparing patients NAWM and lesions (Table 2). Significant inverse correlation was found between T_2 lesion load (p=0.01) and both F (r=-.64) and R_A (r=-65) in patients NAWM.

Within the NAWM, the best variable predicting EDSS score was T_{2B} (adjusted for age), which was inversely correlated with EDSS. The model was less significant when adding remaining MT parameters and lesion load values as additional explanatory variables. Conversely, in patients lesion model, disability scores were the best predicted by T_{2B}, together with RM_{0B}, F, R_A, and lesion load (again, adjusted for age).

Parameter	Control WM Mean (SD)	NAWM Mean (SD)	P value
Fpu	21.5(1.79)	19.9(1.46)	0.008
RM_{0B} [s^{-1}]	2.03(0.15) s-1	1.87(0.18)	0.008
T_{2B} [µs]	11.15(0.26)	11.08(0.35)	n.s
R_A [s-1]	1.15 (0.89)	1.10 (0.10)	0.07

Table 1. *qMT parameters in controls WM and patients NAWM (two-tailed significant).*

Parameter	NAWM Mean (SD)	Lesions Mean (SD)	P value
Fpu	19.9(0.014)	11.2(0.018)	0.0000
RM_{0B} [s^{-1}]	1.87(0.18)	1.00(0.28)	0.0000
T_{2B} [µs]	11.08(0.35)	10.59(0.40)	0.0000
R_A [s^{-1}]	1.10 (0.10)	0.66 (0.12)	0.0000

Table 2. *. qMT parameters and RA in patients NAWM and lesions (two-tailed significant).*

Discussion

F and RM_{0B} values were significantly lower in patients NAWM than in controls WM. In the NAWM, F (which is thought to correlate with myelin content) and R_A were the only parameters associated with lesion load, suggesting the presence of Wallerian degeneration, at least to some extent. RM_{0B}, T_{2B}, F, and R_A were significantly lower in lesions than in NAWM, confirming that qMT parameters reflect structural properties of tissue. Unexpectedly, despite its minimal variation across individuals, T_{2B} was the most significantly associated with EDSS in NAWM. This parameter is likely to represent a weighted average of the relaxation times of spins with different molecular environments, and therefore its reduction in MS lesions could be interpreted as a change in the balance between subpopulations of macromolecular spins. Conversely, in lesions, RM_{0B}, T_{2B}, F, and R_A and lesion load significantly predicted disability only when combined together. This might reflect the complex interaction between demyelination, remyelination, gliosis, inflammation and axonal loss taking place within lesions.

References

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