Normally Appearing White Matter of Subjects with Multiple Sclerosis Probed by Magnetization Transfer and Rotating Frame relaxation Methods

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Introduction

The brain of individuals with multiple sclerosis (MS) is characterized by hyperintense lesions on T_2-weighted images and/or hypointense lesions on T_1-weighted images. Magnetization transfer (MT) experiments have successfully detected abnormalities even in brain areas that appear normal on conventional MRI, the so-called normal appearing white matter (NAWM) [1]. Differences between MS patients and healthy controls in the MT ratio (MTR) of the NAWM were subtle however, in the range of 6%. In another study of quantitative MT [2], MTR failed to detect differences between patients and controls in the NAWM, and only the fraction of bound water was found to be different. Recently, we have developed a quantitative protocol for estimating relaxation parameters of MT, which is based on the application of on-resonance inversion prior to the off-resonance irradiation of the MT experiment [3]. This approach was shown to produce robust and reliable parametric maps in healthy subjects. In addition, in our prior works on Parkinson's disease (PD) patients [4] and animal models for PD [5], acute ischemia [6] and rat glioma gene therapy [7] we have demonstrated that novel adiabatic $T_{1\rho}$ and $T_{2\rho}$ methods are sensitive to pathological tissue alteration. In the present work, we aimed at determining whether the inversion-prepared MT protocol and the adiabatic $T_{1\rho}$ and $T_{2\rho}$ methods are more sensitive than the MTR to characterize the NAWM of the brain of MS patients as compared to healthy controls.

Methods

We quantified MT parameters, namely MTR and T_1 in the presence of off-resonance saturation (T_{1sat}), along with adiabatic $T_{1\rho}$ and $T_{2\rho}$ in the brain of nine relapsing-remitting MS patients and seven controls of similar age. Images were acquired with a 4-T/90-cm magnet using fast spin echo readout, TR=5s, TE=0.073s, in plane resolution=1x1mm^2, slice-thickness=4mm. The MT, $T_{1\rho}$ and $T_{2\rho}$ measurements were obtained as described previously [3,8] in a single axial slice just above the lateral ventricles. MTR were calculated as $(1\text{-}SI_{MT=600ms}/SI_0)$. Regions of interest including T_2 lesions (T2L) and NAWM were identified from T_2-weighted images of the MS subjects. T_{1sat}, $T_{1\rho}$ and $T_{2\rho}$ values were finally compared with unpaired two-side t-test between MS patients and controls in similar regions of NAWM, and with paired two-side t-test between regions including T2L and NAWM in the MS patients.

Results and dicussion

Representative relaxation maps for one MS patient and one healthy control are shown in Figure 1. All measured MR parameters had coefficient of variations below 7% in the NAWM of healthy controls, except MTR whose c.v. was 13% (see table). Statistically significant differences of NMR parameters in the NAWM between patients and controls were observed for T_{1sat} (p=0.0218), but not for MTR (p=0.436) and adiabatic $T_{1\rho}$ and $T_{2\rho}$ (p=0.340 and p=0.276, respectively). More in details, T_{1sat} values of NAWM regions were in average 12% longer in patients as compared to controls, while MTRs were 4% lower (see table). As expected, T2L were clearly identified in the all relaxation maps of MS patients, showing significant differences relative to NAWM regions (p=0.0043, p=0.007, p=0.0046 and p=0.0107 for T_{1sat}, MTR, $T_{1\rho}$ and $T_{2\rho}$, respectively).

As observed in other studies [1,2], differences in MTR values of the NAWM between patients and controls were subtle and not significant in our subject population; on the other hand, significant changes were observed in T_{1sat} values of the NAWM of patients *vs* controls as measured by the inversion-prepared MT protocol [3]. Interestingly, $T_{1\rho}$ and $T_{2\rho}$ measurements did not result in significant differences in the NAWM of patients *vs* controls, suggesting that these methods are likely not sufficiently sensitive to pathological processes which are specific to the white matter of MS. We conclude that the inversion-prepared MT protocol is a robust and sensitive approach to detect abnormalities in the NAWM of MS patients.

	Regions	T_{1sat} (s)	MTR (%)	$T_{1\rho}$ (s)	$T_{2\rho}$ (s)
Controls (N=7)	NAWM	0.63 ± 0.04	27.7 ± 3.5	0.17 ± 0.01	0.080 ± 0.005
MS patients (N=9)	NAWM	0.71 ± 0.07	26.6 ± 2.1	0.17 ± 0.02	0.08 ± 0.01
	T2L	1.26 ± 0.42	16.4 ± 8.4	0.34 ± 0.13	0.15 ± 0.05

Data are presented as mean ± SD.

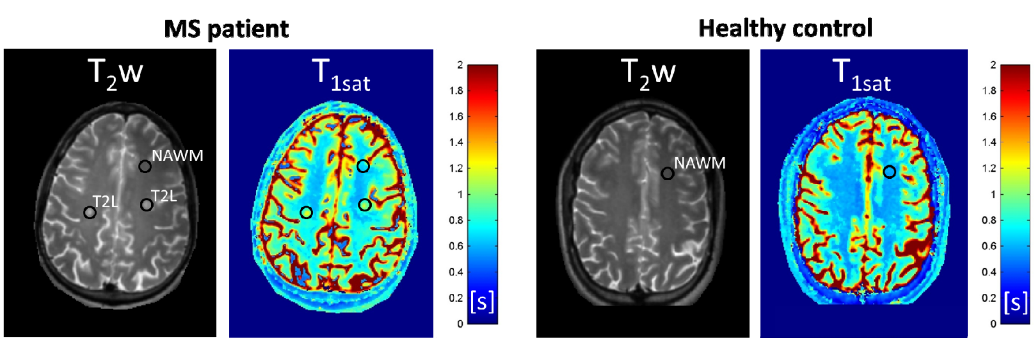

Figure 1. T_2-weighted (T_2w) images and T_{1sat} relaxation maps for one representative MS patient and one representative healthy control. The regions of interest that were used for statistical analysis, including T2L and NAWM, are also shown.

References. [1] Ge J Comput Assist Tomogr 2002;26:62-8. [2] Tozer et al. MRM 2003;50:83. [3] Mangia et al. MRI 2011;29:1346-50. [4] Michaeli et al. Mov Disord 2007; 22:334. [5] Michaeli et al. J Neurosci Methods 2009;177:160. [6] Jokivarsi et al. JCBFM 2009;29:206. [7] Sierra et al. MRM 2008;59:1311. [8] Mangia et al. MRI 2009;27:1074. **Acknowledgments**: NIH P41RR08079 and P41EB015894, S10 RR023730 and S10 RR027290, NIH KL2 RR033182, R01NS061866 and R21NS059813, AHC seed grant U o M, W. M. Keck Foundation and MIND Institute.