Myelin water is an independent measure of pathology in multiple sclerosis

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Introduction: Although conventional magnetic resonance imaging (MRI) has become an indispensable tool for visualising lesions and diagnosing multiple sclerosis (MS), it lacks pathological specificity. Consequently, many new techniques have been developed which aim to distinguish between the different pathologies including inflammation, demyelination and axonal loss. The short T_2 component of T_2 relaxation measurements in white matter is quantitatively related to myelin on histopathological studies and has the potential to measure myelin in-vivo [1,2]. Magnetization transfer has also been shown to be related to myelin content [3]. The goal of this study was to determine correlations between water content (WC), myelin water content (MWC), T_1 relaxation time (T_1), T_2 relaxation time (T_2) and magnetization transfer ratio (MTR) to determine to what extent these MR measurements are independent measures of brain pathology in MS.

Methods:

MRI procedures: Seven clinically definite MS patients (4 female, 3 male, 5 relapsing-remitting/1 primary progressive/1 secondary progressive, median EDSS 3.0 (range 2.0-6.5), mean age 42 years (range 30-50 years), disease duration 2-11 years) were scanned on a GE Signa 1.5 T MR scanner 5 times over one year (month 0, 2, 4, 6, 12). Seven age and gender matched controls were scanned once. MR studies performed included localizers, 22 slice axial proton density (PD) and T_2 images (TR 2500ms, TE 30ms), a single-slice 32-echo T_2 relaxation sequence [4] (TE 10ms, TR 3000ms, 4 averages, matrix 256x128) for the T_2 measurement, a single-slice fast gradient echo (GE) with inversion recovery preparation (TE 8ms, 1 NEX, 15 TIs from 0.05-3s) for the T_1 measurement, a 3D-GE with and without a 2000 Hz off-resonance sinc saturation pulse for the MT measurement (TR 106ms, TE 5ms, flip 12^O) and a post- Gadolinium-DTPA enhanced T_1-weighted spin echo scan (TR 550ms, TE 8ms). All exams used a 22 cm field of view and slice thickness of 5mm. Water standards were placed within the slice.

Data Analysis: All images were registered to the PD/T_2 scan at month 0. Regions of interest (ROIs) were outlined on the PD images for 15 isointense T_1 lesions, 15 chronic hypointense T_1 lesions (>6 months old) and 19 new lesions at time of first appearance. 17 ROIs at times before the new lesions appeared and 15 ROIs at times after the new lesion appeared were also drawn. Regions of contralateral normal appearing white matter (NAWM) and location matched normal white matter (NWM) were also drawn. All ROIs were mapped onto the registered T_2, T_1 and MT images. The T_1 relaxation data was fit to a single exponential (T_1). T_2 relaxation distributions were extracted from the 32-echo sequence using a regularised least-squares algorithm [5]. The total water content (WC) and myelin water content (MWC) were defined as the total area and area from 0-40ms under the T_2 distribution, respectively, normalised to the water standards and corrected for T_1 relaxation. Geometric mean T_2 (T_2) was calculated on a log scale between 40-200ms [6]. MTR was calculated by MTR = $(M_o - M_t)/M_o \times 100\%$ where M_o and M_t are images without and with the MT pulse, respectively.

Statistics: The Pearson correlation coefficient was calculated between pairs of MR measurements. P-values < 0.05 were considered significant. Discriminant function analysis (DFA) was applied to two groups of tissues. The first consisted of isointense T_1 lesions, hypointense T_1 lesions, new lesions (i.e. lesions at the time of first appearance) and NAWM. The second included NAWM and NWM. 1/WC, $1/T_1$, $1/T_2$, MWC and MTR were entered into the analysis and DFA determined which of the MR measurements was most important, independent and necessary in discriminating between the tissue categories.

Results: Correlation coefficients between the various measurements are shown in Table 1 for all tissues, for lesions only and for NAWM alone. The most significant correlation was between 1/WC and $1/T_1$, although 1/WC was also related to $1/T_2$, and T_2 correlated to MTR. Two example correlations are shown in Figure 1. Using DFA, the measurements that were most important at separating isointense T_1 lesions, hypointense T_1 lesions, new lesions and NAWM were MTR and 1/WC. In separating NAWM from NWM, $1/T_2$, 1/WC and MWC were the most important independently and in descending order.

Discussion: Although both MWC and MTR have been reported to be related to myelin content, the present study confirms their correlation is very weak [7] or non-existent [8,9]. MTR was however found to be highly correlated with T_1 and WC indicating that edema, inflammation and changes in extracellular water can play a strong role in determining lesion MTR. Although correlations in NAWM were generally non-significant due to the narrow range of values, the data points fell within the linear correlation for all tissues.

Conclusions: WC, T_1, T_2 and MTR were all found to be correlated whereas MWC appears to be an independent measure of pathology.

Table 1: Correlation coefficients (R^2) between different MR measurements

Correlations	All tissues	Lesions only	NAWM
1/WC vs $1/T_1$	0.67	0.70	0.29
1/WC vs $1/T_2$	0.53	0.55	ns
T_2 vs MTR	0.47	0.39	ns
$1/T_1$ vs $1/T_2$	0.46	0.57	0.07
WC vs MTR	0.41	0.30	ns
MTR vs$1/T_1$	0.33	0.35	ns
MWC vs $1/T_1$	0.09	ns	ns
WC vs MWC	0.08	ns	ns
MWC vs MTR	0.03	ns	ns
MWC vs $1/T_2$	ns	ns	0.14

ns=non-significant

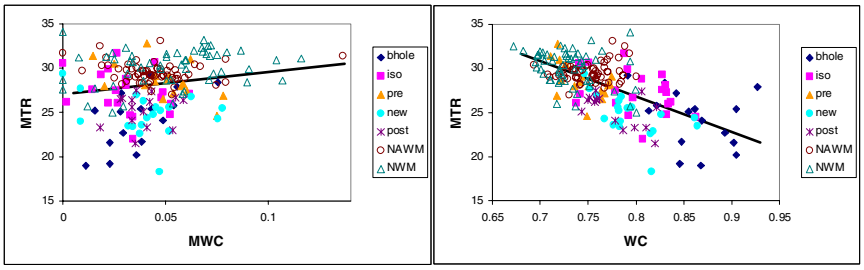

Figure 1: Example correlations between MWC and MTR (left, R^2=0.03) and WC and MTR (right, R^2 = 0.41) for different tissue categories: bhole=chronic back holes, iso=isointense T1 lesions, pre=time points before the lesion appeared, new=time of lesion first appearance, post=time points after lesion appeared, NAWM=contralateral NAWM and NWM=age and gender matched normal white matter. The regression line is for all tissues.

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