Short-term Stability of T_1 and T_2 Relaxation Measures in Multiple Sclerosis Normal Appearing White Matter

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Introduction

Substantial evidence exists for the presence of diffuse and widespread abnormalities within the 'normal appearing' white matter (NAWM) of multiple sclerosis (MS) brain[1]. T_1 histogram analysis reveals increased T_1 in segmented NAWM[2], while quantitative assessment of T_2 relaxation measures demonstrates decreased myelin water fraction (MWF, related to myelin content[3, 4])[5, 6] and increased geometric mean T_2 (GMT_2) of the intra/extracellular water pool[7]. Longitudinal studies have found NAWM T_1 changes over time[8, 9], however longitudinal changes in MWF and GMT_2 of segmented NAWM have not been examined. Elucidation of MWF and GMT_2 evolution in NAWM is warranted for the characterization of MS natural history, therefore we sought **to examine the short-term evolution of MWF, GMT_2 and mean T_1 in MS NAWM based on monthly scanning over 6 months.**

Methods

Subjects & MR Experiments: Eighteen subjects with relapsing-remitting MS (13F/5M; median EDSS = 2.5 (range 1.0-6.0); mean age = 40yrs (range 28-57yrs); mean disease duration = 9.1yrs (range 0.5-27yrs)) were scanned at months 0, 1, 2, 3, 4, 5 and 6 on a Philips Achieva 3.0T system. The MR examination was centered on a transverse slab superior to the ventricles, and included a **3D T_2 relaxation** sequence (utilizing a 90° excitation pulse followed by 32 slab-selective refocusing pulses, 7 slices, 32 echoes, 10ms echo spacing, TR=1200ms)[10] and a **T_1 inversion recovery** experiment (5 TIs (150 - 3500ms), 13 slices)[11]. Additional scans included a **3DT_1** turbo field echo (TFE) for segmentation (120 slices, TR = 10 ms, TE = 6 ms, matrix = 192 x 163, slice thickness = 1.1 mm) and an axial **FLAIR** for lesion detection (28 slices, TR = 10000 ms, TE = 125 ms, TI = 2800 ms, matrix = 256 x 203, slice thickness = 5 mm).

Analysis: All T_1 and T_2 data was registered to the baseline TI=1500ms T1 data using FSL[12] (ver 3.3). Lesion masks for each time point were created through segmentation of a combination of the FLAIR and 3DT_1 with FSL[12] followed by manual editing. A global lesion mask was then made by adding all lesions masks together. A white matter mask was created for each subject at baseline through segmentation of a combination of the TI=150ms, 400ms, 1500ms and 3DT_1 with FSL[12]. Finally, a NAWM mask was created by subtracting the global lesion mask from the white matter mask. T_2 distributions were calculated for every voxel in the T_2 relaxation data set using a regularized non-negative least squares (NNLS) algorithm[13]. MWF was the area under the T_2 distribution from 0-40ms divided by the total area. GMT_2 was calculated as the mean on a logarithmic scale from 40ms<T_2<200ms. T_1 was calculated using a mono-exponential fit for each voxel in the image. NAWM masks were applied to MWF, GMT_2 and T_1 maps. Histograms were created of all NAWM pixels and the following metrics were compared over time for each subject and as a group using a regression analysis: mean, median, 1st quartile, 3rd quartile, peak height and peak location. Bonferroni correction was applied to account for multiple comparisons (p-level set at <0.00014).

Results

Figure 1 shows the average histograms across all MS subjects for each study time point. On average, no change over time was observed for any MR histogram metric. Figure 1 insets demonstrate histograms from 2 subjects, highlighting that while MR measures remained stable over 6 months, clear inter-subject variability existed. Examining MR histogram metrics for individual subjects, no significant change over time was observed for any MR histogram metric. However, for individual subjects there were trends indicating change over time of several T_1 and MWF parameters including T_1 peak height and location and median MWF.

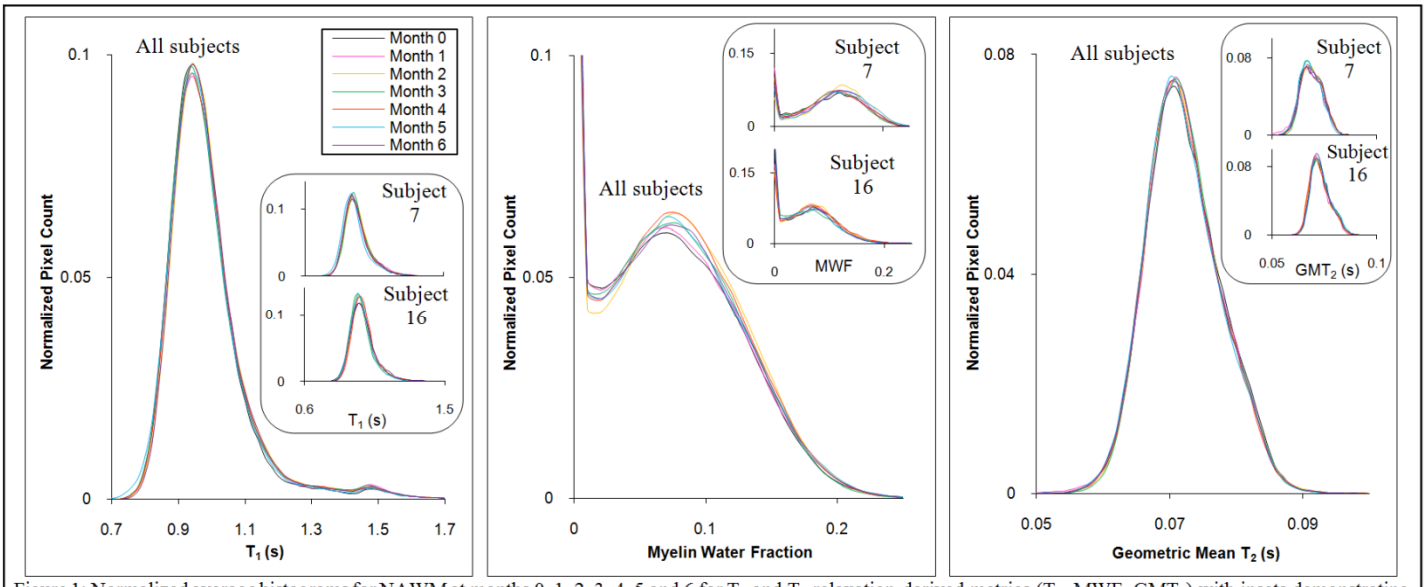

Figure 1: Normalized average histograms for NAWM at months 0, 1, 2, 3, 4, 5 and 6 for T_1 and T_2 relaxation-derived metrics (T_1, MWF, GMT_2) with insets demonstrating inter-subject variability in histogram characteristics

Discussion & Conclusion

Histogram metrics derived from quantitative assessment of T_1 and T_2 relaxation in MS NAWM demonstrated short-term (6 month) stability of mean T_1, myelin water fraction and geometric mean T_2. As previous studies have observed changes in NAWM T_1 over a longer period of time (14-22 months[8]; 3 and 5 years[9]) it is probable that a change in NAWM T_1 would also be expected with an extended follow-up period for our subjects. While the longitudinal evolution of mean T2 and myelin water fraction in NAWM is still unknown, because loss of myelin has been observed to varying degrees in MS NAWM[5, 6, 14] it is reasonable to hypothesize that diffuse progressive myelin loss will also occur given a longer follow-up period. Longitudinal follow-up on the order of years will be needed to assess the rate of global demyelination in NAWM.

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