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) brain1. $T_1$ histogram analysis reveals increased $T_1$ in segmented NAWM, while quantitative assessment of $T_2$ relaxation measures demonstrates decreased myelin water fraction (MWF, related to myelin content) and increased geometric mean $T_2$ (GMT) of the intra/extracellular water pool. Longitudinal studies have found NAWM $T_1$ changes over time2,3, however longitudinal changes in MWF and GMT of segmented NAWM have not been examined. Elucidation of MWF and GMT evolution in NAWM is warranted for the characterization of MS natural history, therefore we sought to examine the short-term evolution of MWF, GMT, 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 $T_1$ 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 $T_2$ inversion recovery experiment (5 TIs (150 - 3500ms), 13 slices)11. Additional scans included a 3DT1 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 FSL12 (ver 3.3). Lesion masks for each time point were created through segmentation of a combination of the FLAIR and 3DT1 with FSL13 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 3DT1 with FSL12. Finally, a NAWM mask was created by subtracting the global lesion mask from the white matter mask. $T_1$ distributions were calculated for every voxel in the $T_1$ relaxation data set using a regularized non-negative least squares (NNLS) algorithm15. MWF was the area under the $T_2$ distribution from 0–40ms divided by the total area. GMT 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 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 inset 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.

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 months2, 3 and 5 years5) 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 $T_2$ and myelin water fraction in NAWM is still unknown, because loss of myelin has been observed to varying degrees in MS NAWM3,6,14 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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