Myelin water fraction reduction in multiple sclerosis normal appearing white matter: Where are all the zeroes?

C. Laule[1,2], S. H. Kolind[3], I. M. Vavasour[1], B. Mädler[2], J. Oger[4], A. L. Traboulsee[4], W. Moore[5], D. K. Li[1], and A. L. MacKay[1]
[1]Radiology, University of British Columbia, Vancouver, BC, Canada, [2]Physics & Astronomy, University of British Columbia, Vancouver, BC, Canada, [3]FMRIB Centre, University of Oxford, Oxford, United Kingdom, [4]Medicine, University of British Columbia, Vancouver, BC, Canada, [5]Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

BACKGROUND

Quantitative assessment of T_2 relaxation in central nervous system tissue using a multi-echo T_2 relaxation technique can provide information about specific water environments which may become altered in multiple sclerosis (MS). Previous work, based on data from a single slice acquisition at 1.5T and using a region of interest (ROI) based approach, showed a reduction in the myelin-associated water pool in MS normal appearing white matter (NAWM) of 16% in brain[1] and 25% in spinal cord [2]. Recent technological improvements have led to the development of a 3D multi-echo T_2 relaxation sequence at 3T, which provides a 5-fold increase in coverage and improved signal to noise ratio[3], thereby allowing for potentially improved and more comprehensive characterization of brain tissue. **We sought to further characterize changes in MWF in MS NAWM with the advantage of greater volumetric coverage. In particular, we investigated the anatomical distribution of reduced MWF to determine whether MWF decreases in NAWM are globally homogeneous or regionally heterogeneous**.
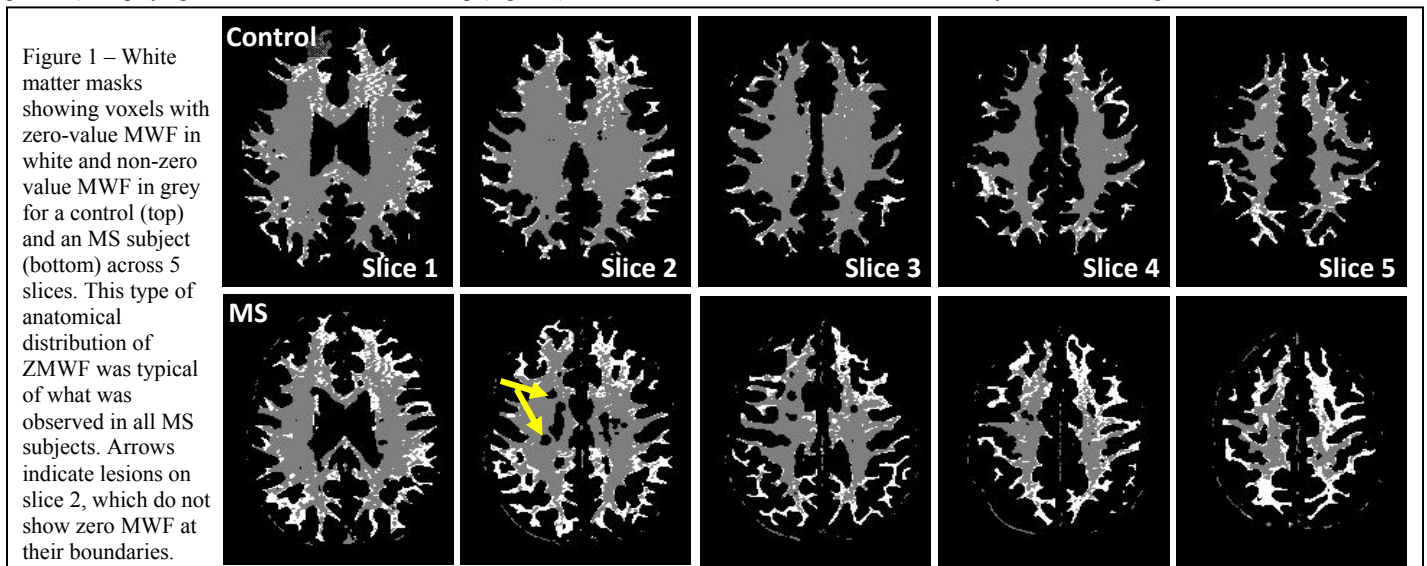
METHODS

MRI Experiments: 13 subjects with relapsing-remitting MS (10 female, 3 male; median EDSS = 2.5 (range 1.0-6.0); mean age = 40yrs (range 28-57yrs); mean disease duration = 8.5yrs (range 0.5-27yrs)) and 13 healthy age and gender matched controls were scanned on a Philips Achieva 3.0T system. Following a true-midline sagittal and a T_2-weighted axial scan, the 3D T_2 relaxation sequence[3], centered on a transverse slab superior to the ventricles, was acquired (7 slices, 32 echoes, TR = 1200ms, voxel size = 0.94x1.88x5mm, 10ms echo spacing).Additional scans included a 3DT_1-weighted turbo field echo (TFE) (120 slices, TR/TE = 10/6 ms, matrix = 192x163, slice thickness = 1.1 mm) and an axial FLAIR (28 slices, TR/TE = 10000/125 ms, TI = 2800 ms, matrix = 256x203, slice thickness = 5 mm).
Data Analysis: The FLAIR, T_2-weighted, and 3D T_1 TFE images were registered to the T_2 data. ROIs were drawn around MS lesions on the FLAIR images and were masked on the 3D T_1 TFE images and NAWM/NWM (normal white matter for controls) was segmented using FSL. The NAWM and NWM masks were eroded by 2 voxels in order to minimize potential error from partial volume effects. The 32 echo decay curve for each voxel in the T_2 relaxation data set was decomposed into an unspecified number of exponentials using a regularized non-negative least squares (NNLS) algorithm with 120 input relaxation times spaced logarithmically from 15 ms to 2s [4]. MWF was defined as the area 15ms<T_2<40ms over total area. NWM and NAWM masks were applied to MWF maps. The average MWF for NAWM and NWM was determined, as was the percentage of voxels in the NAWM/NWM mask with MWF values of zero. Group comparisons were made using a two-tailed Student's t-test (p<0.05); Spearman rank correlation coefficients (R) were used to assess correlations between NAWM MWF and EDSS or disease duration.

RESULTS

Mean MWF: Mean MWF for NAWM was 21.8% less than NWM (7.0 (SD=0.6) versus 9.0 (0.3%). MS NAWM MWF was negatively correlated with EDSS (R=-0.57, p=0.02). Mean NAWM MWF was not significantly different between male and female MS subjects, however, there was a trend for female control subjects to have a higher mean NWM MWF than males (10 (1) % versus 7.4 (0.6) %, p=0.054).
Zero-value MWF (ZMWF) : MS NAWM had significantly more voxels with MWF values equal to zero than NWM (10 (1) % versus 4.2 (0.8) %, p<0.001). The percentage of ZMWF in NAWM correlated with EDSS (R=0.58, p=0.038). Male MS subjects had a significantly higher percentage of ZMWFs than female MS subjects (15 (3) % compared to 9 (1) %, p=0.04) and male control subjects also had a higher percentage of ZMWFs than female controls (8 (2) % compared to 3 (1) %, p=0.007). Displaying the locations of ZMWF as a map (Figure 1) showed that the ZMWF voxels were not uniformly distributed throughout the NAWM.

Figure 1 – White matter masks showing voxels with zero-value MWF in white and non-zero value MWF in grey for a control (top) and an MS subject (bottom) across 5 slices. This type of anatomical distribution of ZMWF was typical of what was observed in all MS subjects. Arrows indicate lesions on slice 2, which do not show zero MWF at their boundaries.

DISCUSSION & CONCLUSIONS

The average MWF reduction in MS NAWM was similar to that previously reported using an ROI based approach on a single slice at 1.5T[1] and slightly higher than found in another study of segmented NAWM at 3T[5]. Voxels with zero-value MWF values were not uniformly distributed throughout the NAWM, but tended to be more prevalent near grey/white matter interfaces in the periphery of the brain. It is unlikely this observed distribution of ZMWFs is purely due to partial voluming of cerebrospinal fluid or grey matter as NAWM masks were eroded by 2 voxels. Also, this effect was not observed at other tissue boundary interfaces such as white matter/ventricle or white matter/lesion. Confirmation and further study of the basis for the distribution of zero MWF values in pathological tissues may provide more insight into MS. pathophysiology.

1. Laule C. J of Neuro, 2004;251(3):284-293 2. Wu Y. JCAT 2006;30(2):304-306. 3. Mädler B ISMRM 2006 p. 2112 4. Whittall KP JMR 1989;84:134-152
5. Oh J. J of Neuroimaging 2007;17(2) 156-163