Whole-Brain Voxel-Wise Analysis of Myelin Water Volume Fraction in Multiple Sclerosis

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INTRODUCTION: The development of sensitive and specific biomarkers for diagnosis, prognosis and treatment monitoring in multiple sclerosis (MS)remains a significant challenge. Currently, measures of disease activity in MS include lesion volume on T_2-weighted images, and the number of enhancing lesions on T_1-weighted contrast-enhanced images. However, only weak correlations between these measures and clinical disability have been demonstrated[1,2]. This is likely owing to the observation that lesion location and extent, and not just burden load, play the more significant roles in defining clinical disability. Whole-brain histogram analysis of MR parameters (including T_1, T_2, magnetization transfer ration, etc.) provides an alternative avenue for investigating global and diffuse tissue changes[3], however, this approach provides no spatial information, making correlations with specific functional defects difficult. Here we outline an alternative approach to distinguishing and localizing areas of myelin change through voxel-wise comparisons of myelin water fraction estimates of individual MS patients, derived using the multi-component Driven Equilibrium Single Pulse Observation of T_1 and T_2 (mcDESPOT)[4] multi-component relaxometry method, with a reference population-matched atlas. This patient-specific approach highlights not only well-defined lesions visible on conventional T_1 or T_2 weighted images, but also accentuates areas of reduced myelin content within the "normal appearing" white matter tissue.

METHODS: ***Atlas Development:*** mcDESPOT data were acquired of 14 healthy individuals (6 male/ 8 female, 23-43 years of age) at 1.5T with the following parameters: SPGR: TE/TR = 2.4ms/6.7ms, α={3,4,5,6,7,8,11,13,18}°, BW=±19.23kHz; SSFP: TE/TR=1.7ms/3.5ms, α={11,14,19,24,28,34,41,51,67}°, BW=±50kHz. A 22cm x 22cm x 15cm sagittal FOV was used with a 128x96x90 (zero-padded to 128x1128x90) matrix. Total acquisition time was 14 minutes per volunteer. Following acquisition, data for each volunteer were linearly co-registered[5], non-brain signal removed[6], and myelin water volume fraction (f_{MW}) maps calculated using mcDESPOT analysis[4]. Finally, data from each volunteer were non-linearly co-registered to MNI standard space[7], smoothed with a Gaussian kernel (full-width-at-half-maximum = 2mm) and the average and standard deviation across all volunteers calculated voxelwise. ***Comparison to Individual Data:*** Using the acquisition and analysis approach described above, f_{MW} maps of 3 relapsing-remitting MS patients (EDSS Scores of 1, 5, and 7.5, respectively) and 3 additional healthy controls were acquired and co-registered to standard space. Ages of patients and controls ranged from 26 to 41. T_2-weighted fluid attenuated inversion recovery (FLAIR) images were also acquired of each MS patient to identify lesions. Using the atlas, voxel-wise z-score calculations were performed for each of the patients and controls to identify voxels in which the myelin volume fraction differed significantly from the population distribution.

RESULTS: Example axial slices through the reference mean and standard deviation atlas volumes are shown in Fig. 1. Figure 2 contains example slices through the f_{MW} and z-score maps of each of the healthy controls. Figure 3 contains images through the T_2-weighted FLAIR images, f_{MW} and z-score maps of each MS patient. Figure 3 also contains z-score images masked at $z > +4$ and $z < -4$. From the healthy control results, no areas were found to be substantially different from the reference values ($-4 < z < +4$), as should be expected. From the patient data, the EDSS = 1 individual reveals only a focal white matter lesion (also visible on the FLAIR image), with the remaining white matter showing no substantial deviations from the reference atlas values. For the EDSS=5 and 7.5 individuals, however, significant white matter alternation (defined by voxels with $z < -4$ or $z > +4$) is evident, extending well beyond the boundaries of the enhanced lesions defined by the FLAIR images and indistinguishable on conventional T_1 or T_2 weighted images.

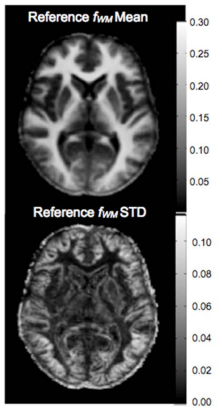

Figure 1: Representative slices through the reference f_{MW} mean and standard deviation volumes.

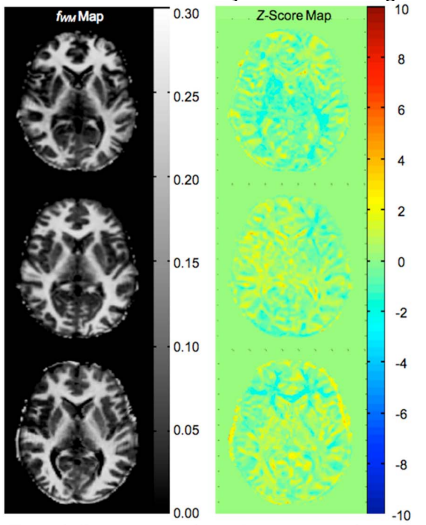

Figure 2: Representative f_{MW} and z-score maps for three healthy volunteers. As should be expected, no areas of significant difference ($z < -4$, $z > +4$) were found.

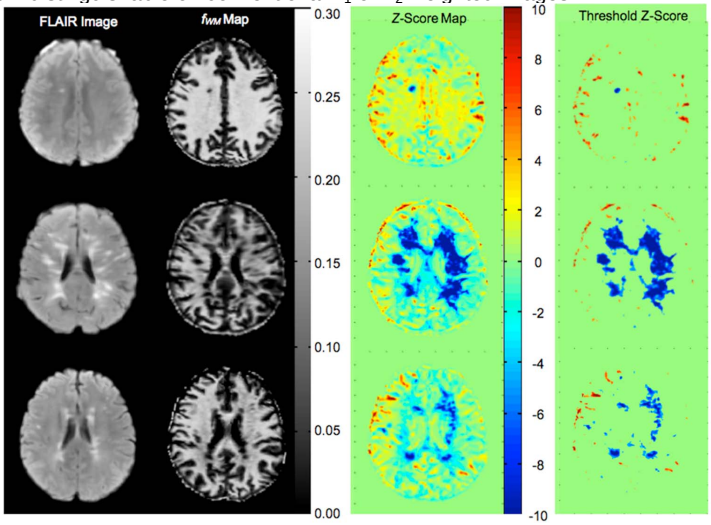

Figure 3: Representative FLAIR, f_{MW} and z-score maps for the MS patients with EDSS scores of *top*:1, *middle:* 7.5, *bottom:* 5. Also shown are maps showing only voxels with z-scores less than -4 and greater than +4. Within the more severely disabled patients, the z-score maps indicate significant white matter alteration (reduced myelin volume) well beyond the visible lesion boundaries on the FLAIR images.

DISCUSSION / CONCLUSIONS: The ability to visualize at-risk or subtly affected, but normal appearing, white matter has potential clinical application in the diagnosis and prognosis of MS, as well as evaluating the efficacy of treatment therapies. To date, whole-brain histogram analysis has been the predominant means of investigating the normal appearing white matter, however, this approach provides no spatial information and can blur or mask subtle and localized changes. Here we have demonstrated a voxel-based approach allowing easy identification of abnormal tissue indistinguishable on conventional T_1 or T_2-weighted scans. The spatial information provided may allow improved understanding of disease progression and observed clinical symptoms by pin-pointing implicated white matter pathways and neural systems. While more work is required to determine the sensitivity of the approach, we are confident the method will provide a new avenue for investigating MS and other white matter disorders on a patient-specific basis.

REFERENCES: [1] Koopmans RA et al. Ann. Neurol. 1989; 34: 74-81. [2] Jacobs L et al. Neurology. 1986; 42 27-34. [3] Iannucci G et al. J. Neurol. Sci. 1999; 76: 121-129. [4] Deoni SCL. et al. Magn. Reson. Med. 2003; 46:515-526, [5] Jenkinson M, Smith SM. MIA. 2001; 5: 143-156. [6], Zhang Y, et al. IEEE Trans Med. Imag. 2001; 20: 45-57. [7] Collins DL. et al. J Comput. Assist. Tomogr. 1994; 18: 192-205.