Is Myelin Water Fraction a Clinically Viable Biomarker of Disease in Primary Progressive Multiple Sclerosis?

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INTRODUCTION: Multiple sclerosis (MS) is the leading cause of neurological disability in young adults. MRI has potential for monitoring disease pathology in vivo and assessing effects of treatments, but it is important to distinguish between the different pathological processes, including inflammation, myelin damage and neuronal/axonal damage. As most current surrogate markers for MS disease progression focus only on areas of acute inflammation, they are insensitive to the more diffuse changes often associated with MS. This is a particular problem in primary progressive (PP) MS, as PPMS patients have fewer inflammatory lesions[1], but suffer more diffuse myelin and axonal damage[2,3] than patients with relapsing-remitting MS. Therefore, there is critical need for a sensitive and specific biomarker to monitor and predict disease progression in PPMS, and to aid in clinical trials of potential therapies. Quantitative evaluation of myelin content and integrity may provide this much-needed biomarker.

Alterations in myelin can be non-invasively interrogated using multi-component relaxometry (MCR)[4], which provides estimates of the myelin water fraction (MWF), a measure related to myelin content[5]. Unfortunately, conventional MCR acquisition techniques provide limited volumetric coverage, hindering the ability to study regional changes in myelin content throughout the brain. A recently introduced technique, multi-component Driven Equilibrium Single Pulse Observation of T_1 and T_2 (mcDESPOT)[6], permits high-resolution and whole-brain MCR in clinically feasible times, affording us the opportunity to study the diffuse myelin changes associated with MS throughout the brain.

Using mcDESPOT, the goal of this study was to establish the suitability of MWF as a biomarker of disease progression in a primary progressive cohort of MS patients; specifically, we investigated correlations between MWF and clinical measures of disability (Expanded Disability Status Scale (EDSS), and several Functional System (FS) scores, including bladder/bowel, brainstem, mental, pyramidal, visual and sensory scores), and examined whether these correlations occurred in appropriate brain regions anticipated to manifest the observed symptoms.

METHODS: mcDESPOT data were acquired of 16 PPMS patients (10 female; mean age: 51 years (range 34-66 years); median EDSS: 5.5 (range 2-6.5)) at 1.5T with the following parameters: SPGR: TE/TR = 2.5ms/6ms, α={3,4,5,6,7,9,12,18}°, BW=±22.4kHz; SSFP: TE/TR=1.9ms/3.8ms, α={10,14,21,28,34,41,51,68}°, BW=±60kHz, acquired with phase-cycling increments of 0º and 180º (for correction of off-resonance effects[7]). A 22cm x 22cm x 19cm sagittal FOV was used with a 128x96x90 (zero-padded to 128x128x90) matrix. Total mcDESPOT acquisition time was under 14 minutes. Diffusion Tensor Imaging (DTI) data was also acquired for the creation of a white matter skeleton (64 slices, TR = 8600ms, TE = 86ms, voxel size = 2.5x2.5x2.5mm, b = 1000s/mm^2, 12 directions, 2 averages).

Following acquisition, data for each volunteer were linearly co-registered[8], non-brain signal removed[9], and MWF maps calculated using mcDESPOT analysis[6]. The fractional anisotropy was calculated from the DTI data[10] and used to create a white matter tract skeleton using tract-based spatial statistics (TBSS)[11]. MWF data was projected onto the skeleton via non-linear registration to the DTI data. Voxelwise cross-subject statistics were carried out on the skeletonised MWF data. In contrast to voxel-based approaches, TBSS incorporates structural information of white matter tracts, increasing confidence in comparing like voxels. Randomise[12] was used to test for significant correlations between MWF and EDSS and the FS scores[13].

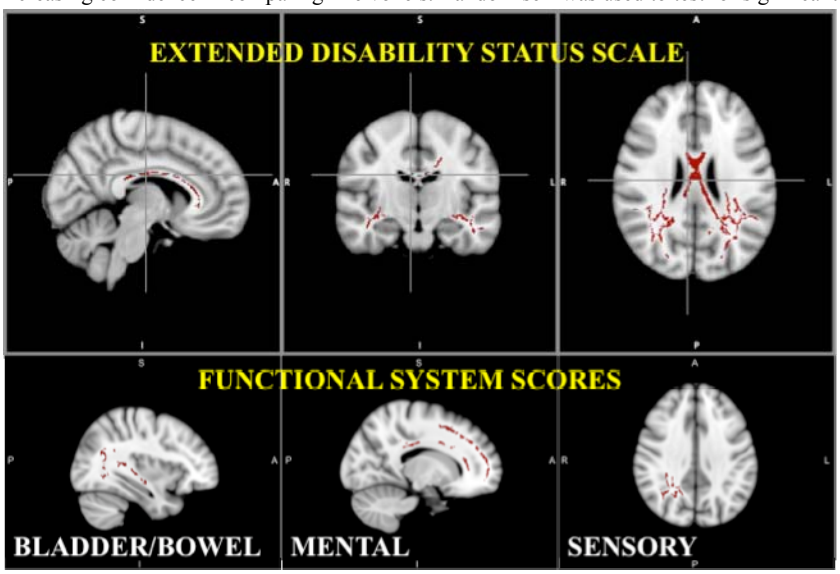

Figure 1: Significant correlations (p<0.05) between myelin water fraction and Expanded Disability Status Scale (EDSS) (top) and 3 of the Functional System (FS) scores (bottom)

RESULTS: White matter tracts showing significant correlations between the MWF and clinical measures are illustrated in Figure 1. Significant correlations between the MWF and the EDSS were found disseminated throughout the brain, including the corpus callosum, temporal lobes and parietal white matter. Correlations between the MWF and the FS scores were more regionally focused; the bladder/bowel FS score (generally associated with disease duration) correlated significantly with the MWF in the posterior limb of the internal capsule and the posterior thalamic radiation, correlations with the mental FS score were found in predominantly anterior regions such as the frontal lobes as well as the corpus callosum, while correlations with the sensory FS score were more posterior, in parietal white matter. Correlations with the brainstem, pyramidal, and visual FS scores did not reach significance, possibly owing to the small value range of these scores in this cohort, or the involvement of CNS tissue not studied here (such as the spinal cord or optic nerves) which may contribute to those FS.

DISCUSSION/CONCLUSIONS: The MWF shows great promise as a biomarker in MS. The strong correlation between the MWF and the EDSS indicates that the MWF reflects changes in pathology that are relevant to disease expression. Brain regions where the MWF was correlated with the more specific clinical FS scores strongly overlap with areas known to be involved in these functions, lending further support to the relevance of MWF changes to clinical manifestations. These results intimate the use of the MWF in predicting and understanding clinical symptoms. Further, the use of MWF values may provide a more objective and efficient means for identifying and evaluating potential therapies in early stage clinical trials.

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