Comparison of Three Putative MR Myelin Markers in Multiple Sclerosis Subjects and Healthy Controls

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Purpose: MRI is routinely used to assess changes in myelin in MS; advanced MRI sequences can be used to gain tissue specificity and allow quantitative measurements. The magnetization transfer ratio (MTR) is related to macromolecule content[1], while the myelin water fraction (MWF) uses relaxation characteristics to isolate the signal from water trapped between the myelin bilayers[2]. Relaxation can also be investigated using steady state imaging, from which we measure the fraction of myelin signal (f_M)[3]. Each metric has different biological influences, sensitivity, noise characteristics, and ease of acquisition. This study compared the results obtained from these 3 quantitative MRI measurements in white matter from subjects with MS and healthy controls.

Methods: 58 relapsing remitting MS patients participating in a randomized phase III clinical trial of ocreluzimab versus interferon beta-1a were scanned on a Philips 3T Achieva at baseline before treatment initiation (25 had MT imaging). 34 age/gender-matched healthy controls were included. Scanning sequences included a 32-echo GRASE sequence (TE/TR=10/1000ms, 1x1x5mm, 20 slices, EPI factor=3)[4], mcDESPOT imaging (1.7x1.7x1.7mm, whole brain)[5] and an MT sequence (TE/TR=3.7/85ms, 1x1x5mm, 20 slices, flip angle 18°). Average MTR, MWF and f_M values were calculated voxelwise across the whole cerebrum for all normal appearing white matter (NAWM), as well as for 5 white matter tracts: the corpus callosum (CC), cortical spinal tract (CST), minor forceps (MN), inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF).

Results: Across all NAWM, significant reductions were found in MTR (1.4%, p=0.001) and f_M (1.9%, p=0.02) for MS compared to healthy controls. MWF showed the largest decrease (4.2%, p=0.09). Across individual tracts, MWF always showed the greatest reductions with a much larger range of changes between structures, but all 3 metrics followed the same pattern showing the greatest decreases in the ILF, followed by the CC, SLF, MN and finally CST (Figure 1). All correlations between the different metrics were significant (Figure 2) for the mean across all NAWM. Individual tracts each showed similar regression slopes but different offsets.

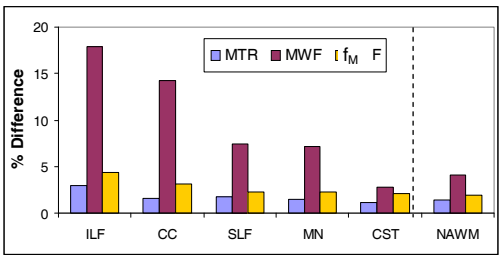

Figure 1: Plot of % difference between controls and MS subjects

Discussion: In all regions, the largest difference between MS and controls was found for MWF followed by f_M and then MTR; however, MWF also had the largest standard deviation resulting in MTR showing the most statistically significant decreases in MS. As previously found[6,7], measurements of MWF varied much more widely between white matter structures than MTR or f_M. Reasons contributing to this discrepancy could include the effect of exchange between water pools on MWF[9], the strong influence of water content on MTR[8], and the effects of magnetization transfer or 3-pool model limitations on f_M [5]. While correlations were found between each of these myelin-related metrics, the strongest correlation was between MWF and f_M (R=0.6); the slope of the regression was similar between structures while the offset varied, again stemming from the differences in influences on the metrics in various structures (for instance, MWF in the CST is over estimated due to broadened T_2 of intra/extracellular water, etc).

Conclusions: All 3 putative myelin MRI markers demonstrate reduction across structures in MS compared to controls however, MWF demonstrated the largest decreases and range of differences between structures. The strongest correlation between metrics was found between MWF and f_M. MS subjects and controls will be followed over 2 years to monitor myelin health and stability of these advanced imaging metrics, respectively.

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References: [1]Wolff SD (1989) MRM, 10:135-44. [2]MacKay A (1994) MRM, 31:673-7. [3]Deoni SC (2008) MRM, 60:1372-87. [4]Prasloski T (2012) NeuroImage, 63:533-9. [5]Deoni SC (2013) MRM, 70:147-54. [6]Whittall K (1997) MRM, 37:34-43. [7]Vavasour IM (2006) NeuroImage, 32:637-42. [8]Vavasour IM (2011) JMRI, 33:713-8. [9]Dula AN (2010) MRM, 63:902-9.

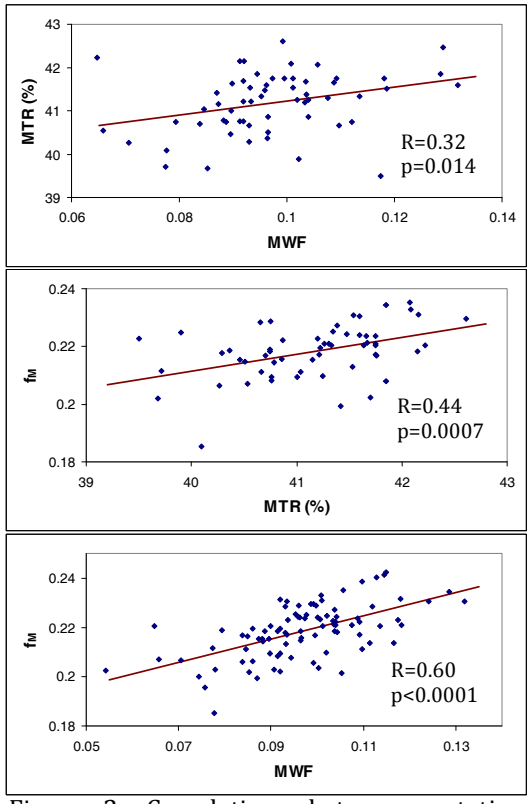

Figure 2: Correlations between putative myelin markers.