Normal Appearing White Matter Myelin Water Fraction Distribution Analysis in Multiple Sclerosis

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Introduction: Multiple Sclerosis (MS) is an immunologically mediated demyelinating and axonal disease. Conventional magnetic resonance imaging (MRI) studies reveal focal signal abnormalities throughout white matter (WM), and less frequently in grey matter (GM), of brain and spinal cord in both T2- and T1-weighted scans. Widespread WM changes are found in Normal Appearing White Matter (NAWM) also with quantitative MRI methods, e.g. by measuring the magnetization transfer ratio (MTR) [1], or, the apparent diffusion coefficient (ADC) [2]. A promising measure to quantify the hidden demyelination burden is myelin-selective MR [3]; however, these methods have not allowed whole-brain imaging in clinically practical scan times until very recently. We present results of applying the newest whole-brain, myelin-selective MR method, *multi-component Driven Equilibrium Single Pulse Observation of T1 and T2* (mcDESPOT)[4] to MS. This method allows evaluating WM myelination by means of measuring myelin water fraction (MWF). The study was designed to assess if parameters of the MWF histogram measured within NAWM could explain differences in disease courses or correlate with disability across a spectrum of disease duration and severity.

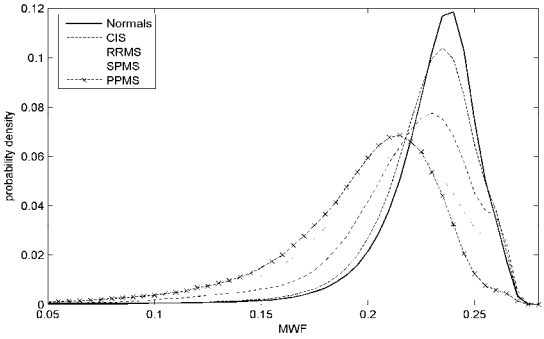
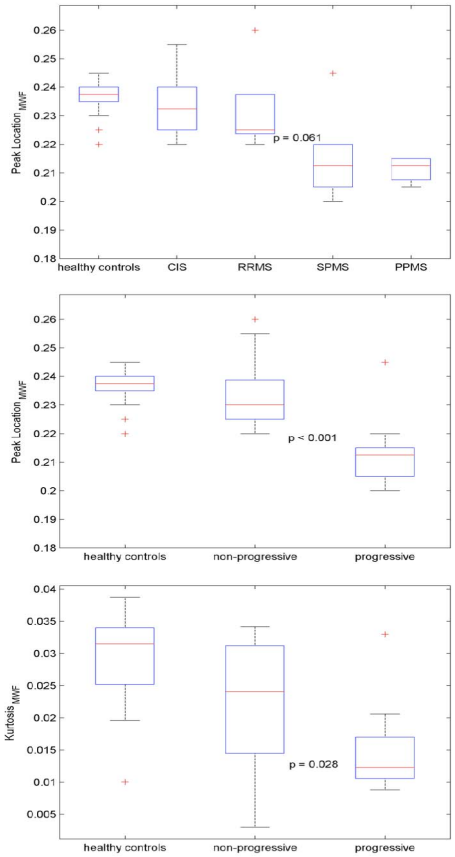


Fig. 1 *(above) Averaged MWF histogram over NAWM in different MS subgroups*
Fig. 2 *(left) MWF peak location within MS subgroups (top) reveals a cohort trend justifying the allocation into non-progressive and progressive courses, subsequently tested peak location and Kurtosis (bottom)*



Methods: 15 MS patients (relapsing-remitting [RRMS] n=5; secondary-progressive [SPMS] n=6; and primary-progressive [PPMS] n=4) and 9 with clinical isolated syndrome CIS, were recruited, along with healthy controls (n=20). The Extended Disability Status Scale (EDSS) score and recorded disease duration. A 1.5T MR scanner (GE Signa HDx, GE Healthcare, Waukesha, WI) and an 8-channel head RF coil was used to derive multi-component T1 and T2 information from sets of spoiled and fully-balanced steady state free precession (SPGR and bSSFP, respectively) data acquired over a range of flip angles at constant TR [4]. FOV=22cm, matrix=128x128, slice thickness=1.7mm; SPGR: TE/TR=2.1/6.7ms, α={3,4,5,6,7,8,11,13,18}°; bSSFP: TE/TR=1.8/3.6ms, α={11,14,20,24,28,34,41,51,67}°. The total mcDESPOT imaging time was ~13min. MWF maps were derived from the mcDESPOT data using the established mcDESPOT theory and processing method [4]. NAWM masks were conservatively segmented according to T1 values of between 500ms and 750ms within the single-component T1 maps generated by the mcDESPOT fitting process to exclude MS lesion tissue. Subsequently MWF maps were masked to the NAWM masks. Median, peak location, skewness, and, kurtosis of MWF distribution in NAWM were achieved. Hypotheses were tested by Wilcoxon rank sum tests. Spearman's Rho was used for the analysis of correlation significance of probability density measures and clinical data.

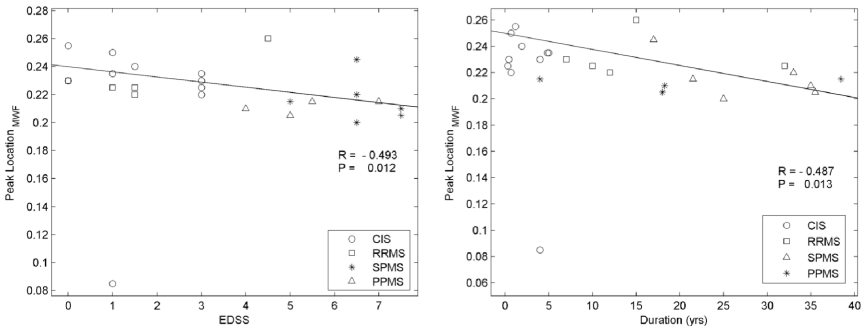


Fig. 3 *MWF peak location correlation with disability (EDSS) and disease duration of all MS patients*

Results: Myelination distribution was abnormal in MS NAWM. We found unique averaged probability distribution of MWF of different MS subgroups with decreasing maximum MWF values and increasing partition of lower MWF; from healthy controls, to non-progressive and progressive MS courses (*Fig.1*). This was reflected in differences in peak location of MWF (*Fig.2*). Significant correlation was found between the MWF peak location vs. average EDSS score or duration of disease (*Fig.3*), additionally also median MWF correlated significantly with duration of disease (R -0.412; p 0.041, plot not shown). We further analyzed EDSS subscores and found correlation of MWF peak location with 'pyramidal' (motor function) and 'mental' (neurocognition) categories (R -0.466, p 0.019; R – 0.406, p 0.044, respectively).

Conclusion: Whole brain high-resolution data acquisition of mcDESPOT allowed myelination assessment of the entire NAWM compartment. Distribution characteristics of MWF data suggest an independent underlying demyelination in NAWM in MS patients. The development from non-progressive to progressive MS disease course is fundamental since it implies treatment change and escalation and no clinical predictive value exists to forecast. The results also imply an important impact of NAWM changes in myelination properties revealed by MWF measurements. The analysis presented is a robust and efficient method to be used in a clinical setting. Once studied in broader cohorts myelination distribution characteristics may become clinical tools to predict the evolution of demyelinating diseases.

References:
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