mcDESPOT-Derived MWF Improves EDSS Prediction in MS Patients Compared to Only Atrophy Measures

J. Su[1], H. H. Kitzler[2], M. Zeineh[1], C. Harper-Little[3], A. Leung[4], M. Kremenchutzky[5], S. C. Deoni[6], and B. K. Rutt[1]

[1]Department of Radiology, Stanford University, Stanford, CA, United States, [2]Department of Neuroradiology, Technische Universitaet Dresden, Dresden, Germany, [3]Robarts Research Institute, University of Western Ontario, London, Ontario, Canada, [4]Department of Diagnostic Radiology and Nuclear Medicine, University of Western Ontario, London, Ontario, Canada, [5]Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada, [6]Brown University, Providence, Rhode Island, United States

Introduction: Conventional magnetic resonance imaging (MR) is established as one of the most important surrogate markers of Multiple Sclerosis (MS) development and treatment outcome. Many clinical trials have used lesion volume as the principal MR-derived measure, but recent literature criticizes this metric as providing little information on top of conventional clinical scores [1]. New MR-derived measures that quantify the hidden burden of disease are urgently needed in the MS field. We present here results of applying the newest whole-brain, myelin-selective MR method, multi-component Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT)[2] in a pilot MS study. This study was designed to assess if the method can explain differences in disease course and degree of disability in subjects spanning a broad spectrum of MS disease severity. The normal-appearing white matter (NAWM) tissue compartment was of particular interest because it is only assessable with quantitative imaging. Exhaustive search multiple linear regression model selection was used to determine the best multi-variate predictors of disability.

Methods: Scans were collected for 26 patients. These included 16 with definite MS (5 relapsing-remitting [RRMS]; 6 secondary-progressive [SPMS]; and 5 primary-progressive [PPMS]) as well as 10 patients with clinical isolated syndrome (CIS). A healthy control group of 26 subjects was also scanned. In all patients, we measured the Extended Disability Status Scale (EDSS) score. Images were acquired using a 1.5T MR scanner (GE Signa HDx, GE Healthcare, Waukesha, WI) with an 8-channel head RF coil. The following parameters were used for the mcDESPOT collection: FOV = 22cm, matrix = 128x128, slice thickness = 2mm; SPGR parameters: TE/TR = 2.1/6.7ms, α = {3,4,5,6,7,8,11,13,18}°; bSSFP parameters: TE/TR = 1.8/3.6ms, α = {11,14,20,24,28,34,41,51,67}°. The total mcDESPOT imaging time was ~13min. For anatomical reference, an additional 2D T2-FLAIR sequence (TE/TR = 125/8800ms, TI = 2200ms, FOV = 22 cm, matrix = 256x256, slice thickness = 3mm) and 3D T1-MPRAGE (TE / TR = 3.8/9ms, TI = 600ms, FOV = 24cm, matrix = 256 x 256, slice thickness = 1.2 mm) were acquired. The total exam time was ~30min. Brain mask segmentation was performed via FSL's BET on the MPRAGE scan. GM and WM masks were generated from the same scan via SPM8. The WM masks were inspected and edited by a trained neuroradiologist. Brain parenchymal volume fraction (PVF) was computed as the GM+WM volume normalized by the brain mask volume. Myelin water fraction (MWF) maps were derived from the mcDESPOT data for each subject using the established mcDESPOT theory and processing method [2]. After non-linear registration to the MNI152 standard space brain, the maps were used to compute a z-score for every voxel in a subject. Voxels that fell in the range z-score < -4 were defined as "significantly demyelinated" because they were far outside the distribution of MWF in normal controls. The sum of all of such voxels was termed the Demyelinated Volume (DV) for that subject. Lesion tissue was segmented by first pre-selecting with an automated technique similar to the above standard space z-scoring but with the FLAIR images instead of the MWF maps. The results were then manually edited. Dirty-appearing white matter (DAWM) was also segmented in the same manner but did not require manual editing by a trained neurologist. The NAWM compartment was found by subtracting lesions and DAWM from the WM masks. Demyelinated Volume Fraction (DVF) was defined as the DV in a particular tissue compartment normalized by that compartment's volume. Using the R software environment, an exhaustive search was conducted to find the best multiple linear regression model for EDSS using the Mallows Cp criterion, among all possible combinations of the following imaging derived predictors: PVF, log-DVF in whole brain, log-DVF in WM, log-DVF in NAWM, log-DVF in lesions, log-DV in those four compartments, mean MWF in those four compartments, the volumes of those four compartments (lesion volume = T2 lesion load), and the volume fractions of those four compartments with respect to the whole brain mask volume. This constituted a total of 21 possible predictors.

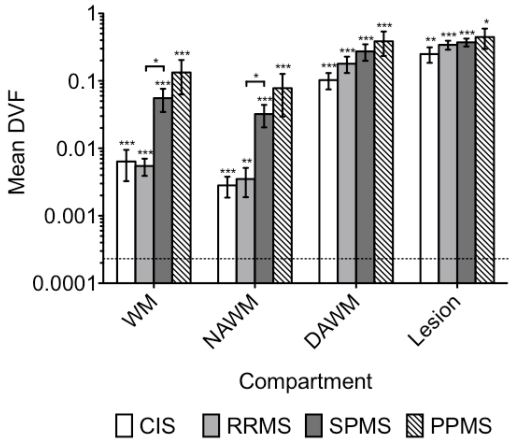

Fig. 1 The fraction of each tissue compartment that is demyelinated among the different MS courses. The dotted line shows mean DVF in WM for controls. Rank sum testing was done for each bar against this value. Testing was also done for RR vs. SP and CIS vs. RR. Significance: * $p < 0.05$, ** $p < 0.01$, ***, $p < 0.001$

Results: The patient group had a mean EDSS of 3.6 (max 7.5, min 0). The new measure of DVF in any given tissue compartment was able to distinguish every patient type from the DVF of WM in controls according to rank sum tests. RR and SP patients were also distinct when looking at DVF in WM or NAWM (see Figure 1). T2-lesion load was found to correlate poorly with EDSS. ($R^2 = 0.28$). The DVF in NAWM had a more substantial correlation ($R^2 = 0.37$) and PVF had the greatest ($R^2 = 0.56$) [3]. The best multiple linear regression model for EDSS contained PVF ($p < 0.001$), mean MWF in whole brain ($p < 0.001$), and WM volume fraction ($p < 0.01$). This model explained 76% of the variance in EDSS.

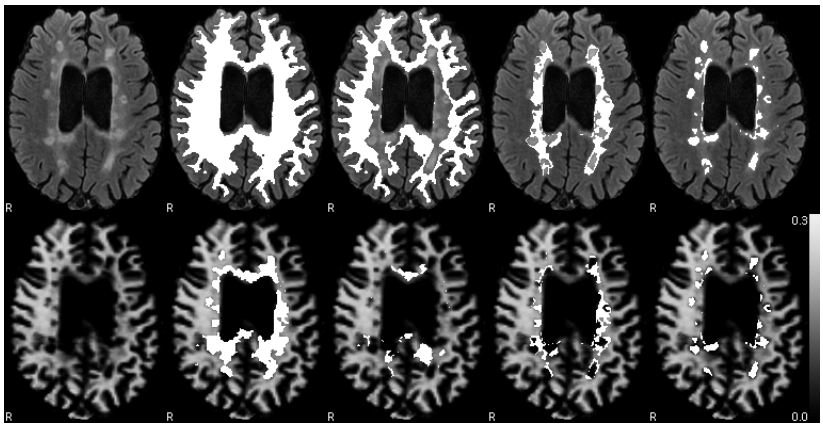

Fig. 2 Segmentation masks on top of an axial FLAIR slice (top row) and demyelinated voxels on top of MWF for the same slice (bottom row) in a SPMS patient. Top row from left to right: native FLAIR, WM, NAWM, DAWM, lesions. Bottom row from left to right: native MWF, DV in WM, DV in NAWM, DV in DAWM, DV in lesions.

Conclusion: DVF is a more intuitive measure for demyelination in a compartment than the raw volume of demyelinated voxels. It is also able to distinguish between controls and any patient group in any tissue compartment, which could not be done by the other measures we examined. This makes it promising as a marker for disease progression from CIS to MS or from RR to SP. The appreciable correlation between EDSS and DVF in NAWM as opposed to lesion load suggests that the invisible burden of disease may be more important than lesions in determining disability. PVF, a measure of brain atrophy, even better captures the broad state of disability of a patient. The results of the multiple linear regression model selection show that established atrophy measures in combination with new mcDESPOT-derived myelin water fraction parameters are far more capable at accurately estimating disability than either quantity alone.

References: [1] Daumer et al., Neurology. 2009 Feb 24;72(8):705-11. [2] Deoni et al., Magn Reson Med. 2008 Dec;60(6):1372-87. [3] Kalkers et al., Neurology. 2001 Oct 9;57(7):1253-8.