mcDESPOT-Derived Demyelination Volume in Multiple Sclerosis Patients Correlates with Clinical Disability and Senses Early Myelin Loss

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

[1]Dept. of Neuroradiology, Technische Universitaet Dresden, Dresden, SN, Germany, [2]Department of Radiology, Stanford University, Palo Alto, CA, United States, [3]Department of Engineering, Brown University, Providence, RI, United States, [4]Imaging Laboratories, Robarts Research Institute, London, ON, Canada, [5]Department of Diagnostic Radiology and Nuclear Medicine, University of Western Ontario, London, ON, [6]Department of Clinical Neurological Sciences, University of Western Ontario, London, ON

Introduction: Conventional magnetic resonance imaging (MR) is established as one of the most important surrogate markers of Multiple Sclerosis (MS) development and treatment outcome. Based on the assumption that the clinical course of MS is adequately reflected by focal white matter changes, many clinical trials have used lesion volume as the principal MR-derived measure; however, such measures have been recently criticized as adding little or no independent information over and above non-imaging disability outcome measurements when evaluated retrospectively [1]. Therefore, new MR-derived measures that characterize and quantify the hidden burden of disease are urgently needed in the MS field. One of the most promising such measures is myelin-selective MR [2]; however, these methods did not allow whole-brain high resolution imaging in clinically practical scan times until very recently. We present here the results of applying the newest myelin-selective MR method, multi-component Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT)[3], in a pilot MS study. This preliminary 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.

Methods: 15 patients with definite MS (relapsing-remitting [RRMS] n=5; secondary-progressive [SPMS] n=5; and primary-progressive [PPMS] n=5) as well as 10 patients with clinical isolated syndrome CIS, a precursor of definite MS (low risk CIS, n=5, and, high risk CIS, n=5) were recruited, along with a healthy control group (n=21). In all patients, we measured the Extended Disability Status Scale (EDSS) score, an average number derived from measures of various functions of the central nervous system, using a scale from 0 to 10, with 10 representing greatest disability. Image acquisition used a 1.5T MR scanner (GE Signa HDx, GE Healthcare, Waukesha, WI) with an 8-channel head RF coil. We acquired isotropic whole-brain mcDESPOT data; this method derives multi-component T1 and T2 information from sets of spoiled and fully-balanced steady state free precession (SPGR and bSSFP, respectively) images acquired over a range of flip angles at constant TR [3]. Relevant imaging parameters were as follows. Common parameters: FOV = 22cm, matrix = 128x128, slice thickness = 1.7mm; 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 2DFLAIR sequence (TE/TR = 125/8800ms, TI = 2200ms, FOV = 24 cm, matrix = 192x192, slice thickness = 3mm) was acquired. Myelin water fraction (MWF) maps were derived from the mcDESPOT data for each subject using the established mcDESPOT theory and processing method [3]. Voxel-based analysis was then applied to these maps, whereby all MWF maps were registered to "standard space" (defined by the non-linear MNI152 1mm isotropic resolution brain) and a mean and standard deviation volume was computed from the normal controls. On a patient-by-patient basis, each MWF voxel was compared to the normal mean/standard deviation, to produce a z-score value for that voxel. Voxels that fell in the range z-score < -4 were defined as "significantly demyelinated" -- the sum of all of such voxels for a specific patient was termed the Demyelinated Volume (DV) for that patient. Brains were also segmented into gray matter, white matter and CSF, and Normalized Brain Volume (NBV) was computed as GM+WM volume normalized by GM+WM+CSF volume. We computed DV and NBV for each patient, and studied the correlation between these features and with the EDSS score.

Results: The average EDSS score for the patient group was 3.6 (max 8.5; min 0). Fig. 1 shows representative images, with the significantly demyelinated voxels extracted from the MWF fraction map (right), computed by the above procedure, shown as a colour overlay (middle) on the anatomical reference (FLAIR, left). Fig. 2 shows that within the study cohort, highly significant correlations were found between DV and EDSS (r^2 = 0.44, p<0.001), between NBV and EDSS (r^2 = 0.51, p<0.001), and between DV and NBV (r^2 = 0.51, p<0.001). Moreover, DV was significantly different for the CIS subgroup than for the age-matched normal control group (p<0.001), which was not the case for the NBV measure. These results demonstrate the potentially high sensitivity of mcDESPOT in detecting early and conventionally invisible changes in brain tissue, even as early as the pre-MS CIS stage.

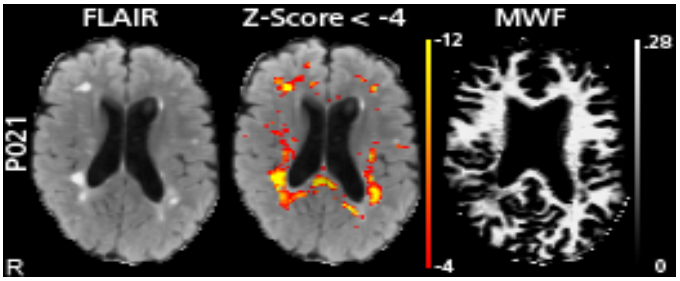
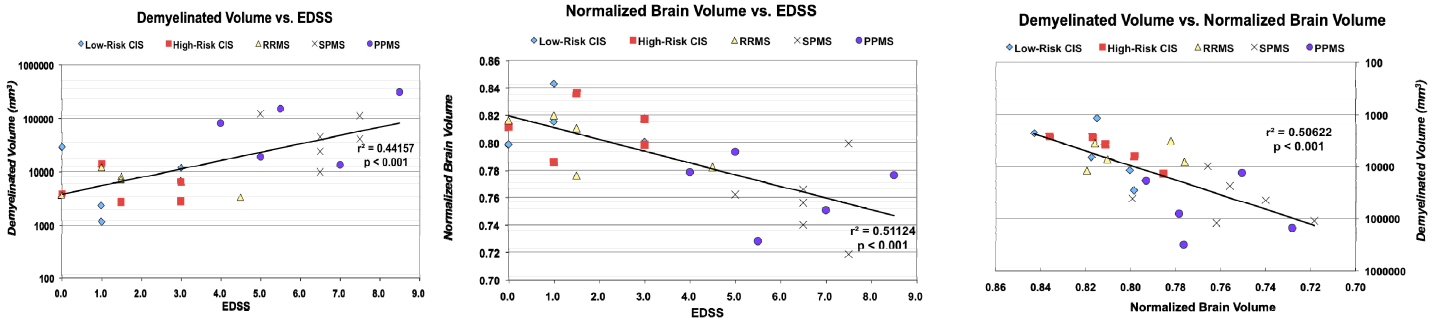


Fig.1 Hyperintense FLAIR lesions (left) are correlated with decreased focal MWF map (right). Significantly demyelinated voxels (coloured, middle) overly lesions but also extend well into normal appearing white matter.

Fig .2 (below) Linear regression: Demyelinated Volume (DV) vs EDSS (left), Normalized Brain Volume (NBV) vs EDSS (middle), DV vs NBV (right).



Conclusion: We have demonstrated that myelin-selective mcDESPOT allows the assessment of whole-brain tissue volumes in clinically relevant scan times. The high correlations to clinical and atrophy measures means that this new imaging method has strong potential to act as a surrogate measure of disease severity. Moreover, our results show that mcDESPOT is sensitive to brain tissue changes even at the pre-MS stage, and well before established volumetric measures register significant changes. The mcDESPOT method may discern the relationship between multiple sclerosis and subtle micro-structural demyelinating changes that likely occur in brain tissue well before lesions can be detected with conventional MRI.

References: [1] Daumer et al., Neurology. 2009 Feb 24;72(8):705-11 **[2]** Laule & MacKay, A et al. J Neurol Sci. 2007 Aug 15;259(1-2):7-15 **[3]** Deoni et al., Magn Reson Med. 2008 Dec;60(6):1372-87