Sensitive Detection of Myelination Change in Multiple Sclerosis by mcDESPOT

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Introduction: There is a growing demand for metrics that can provide more detailed, sensitive, and spatially localized tracking of disease progression in Multiple Sclerosis than the common clinical scoring methods such as EDSS. These would be invaluable for assessing the efficacy of drug treatments, as well as for monitoring the natural history of the disease, and for potentially predicting disease onset within high-risk pre-MS cohorts. Quantitative MR techniques are promising in this regard because they provide whole-brain, high resolution volumes of quantitative parameters and offer the possibility of detecting changes in normal appearing white matter. Here, we present results of applying the whole-brain, myelin-selective MR method, multi-component Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT)[1] in a pilot MS study. We examined a cohort of patients and controls at baseline and 1 year in the first longitudinal application of this new MR methodology. This study was designed to assess if the method can sense different rates of progressive demyelination for different MS courses, as well as to compare the change in mcDESPOT-detected demyelination with the change in disability as measured by EDSS.

Methods: Baseline and 1-year follow-up scans were collected for 23 patients. These included 14 with definite MS (4 relapsing-remitting [RRMS]; 6 secondary-progressive [SPMS]; and 4 primary-progressive [PPMS]) as well as 9 patients with clinical isolated syndrome (CIS). A healthy control group of 26 subjects was also scanned at the baseline, 4 of which received a follow up exam. 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 scans. The volume of this mask was defined as the intracranial volume. Myelin water fraction (MWF) maps were derived from the mcDESPOT data for each subject using the established mcDESPOT theory and processing method [1].
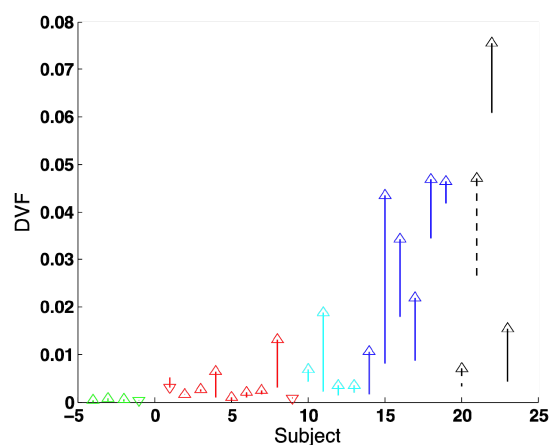

Fig. 1 A plot of the change in DVF for each subject. Colors denote the MS course: controls (green), CIS (red), RRMS (light blue), SPMS (dark blue), PPMS (black). Arrowheads indicates the direction of change and the DVF at 1-year. Dashed lines show subjects who also had a change in EDSS.
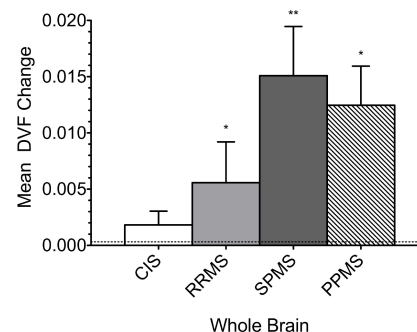
After non-linear registration to the MNI152 standard space brain, these maps were used to compute a z-score for every voxel in a subject. Voxels that fell in the range z-score < -4 were defined as "significantly demyelinated" because they were four standard deviations below the mean MWF value in normal controls. The sum of all of such voxels was termed the Demyelinated Volume (DV) for that subject. DV at 1-year was calculated by computing the z-score with respect to the baseline distribution Demyelinated Volume Fraction (DVF) of the whole brain was defined as the total DV normalized by the intracranial volume.

Results: The patient group had a mean EDSS of 3.6 (max 7.5, min 0) at the baseline. After 1 year, only 3 patients had a change in EDSS: a CIS (1.5 to 5.0), a PPMS (4.0 to 5.0), and another PPMS (6.5 to 7.0). In contrast to the relative insensitivity of EDSS, Figures 1 and 2 show the high sensitivity of mcDESPOT-derived DVF to changes in MS patient brain demyelination over the 1 year study period. Figure 1 shows that 21 out of 23 patients had an increase in DVF, with progressive MS patients showing consistently larger changes than non-progressive and CIS patients. Figure 2 shows that DVF in whole brain increased significantly among all classes of definite MS compared to controls according to rank sum tests (p < 0.05). Secondary progressive and primary progressive MS patients showed a substantially greater DVF change (group mean 0.014) compared to relapsing-remitting MS and CIS patients (group mean 0.003) with p < 0.01.

Conclusion: This longitudinal study shows that mcDESPOT-derived demyelination, specifically DVF, shows statistically significant sensitivity to changes in brain myelination in MS patients over a 1 year period, even within our small study cohort. We observed significant changes occurring in the diseased brain, especially among progressive patients, that were not reflected in their disability score. Those patients with a disability change measured by EDSS did not actually have the largest demyelination changes, showing that EDSS and DVF are measuring different

Fig. 2 Mean change in DVF over 1 year for the different MS courses. The dotted line shows mean change in DVF among controls. Rank sum testing was done for each bar against this value. Testing was also done for RR vs. SP and CIS vs. RR but not significant. Significance: * p < 0.05, ** p < 0.01

aspects of the disease. In summary, mcDESPOT-derived DVF is a highly promising new marker for disease development in CIS and MS patients.

References: [1] Deoni et al., Magn Reson Med. 2008 Dec;60(6):1372-87.