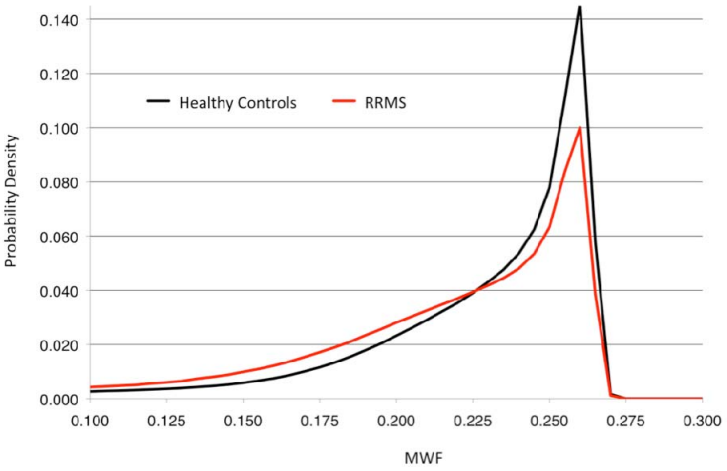
Multi-Component Relaxation In Untreated Relapsing-Remitting Multiple Sclerosis

Hagen H Kitzler[1], Jason Su[2], Frank Noack[1], Christine Schmidt[1], Tjalf Ziemssen[3], Sean C Deoni[4], and Brian K Rutt[2]

[1]*Department of Neuroradiology, Technische Universitaet Dresden, Dresden, SN, Germany,* [2]*Department of Radiology, Stanford University, Palo Alto, CA, United States,* [3]*Department of Neurology, Technische Universitaet Dresden, Dresden, SN, Germany,* [4]*Department of Engineering, Brown University, Providence, RI, United States*

Introduction: Multiple Sclerosis (MS) is an immunologically mediated demyelinating and axonal disease. Beyond multifocal signal abnormalities throughout white matter (WM) in both T2- and T1-weighted conventional magnetic resonance imaging (MRI) studies widespread WM changes are found in Normal Appearing White Matter (NAWM) with quantitative MRI methods. The newest whole-brain relaxation MRI method [1], *multi-component Driven Equilibrium Single Pulse Observation of T1 and T2* (mcDESPOT), a method that allows evaluating WM myelination by means of measuring myelin water fraction (MWF) [2] showed great promise to quantify the hidden demyelination burden of disease [3]. We present preliminary results of applying mcDESPOT to a cohort of untreated relapsing-remitting multiple sclerosis (RRMS) patients. The study was designed to assess if parameters of the MWF histogram measured within NAWM and the whole brain *Deficient MWF Volume* (DV) could differentiate the RRMS cohort from healthy controls.



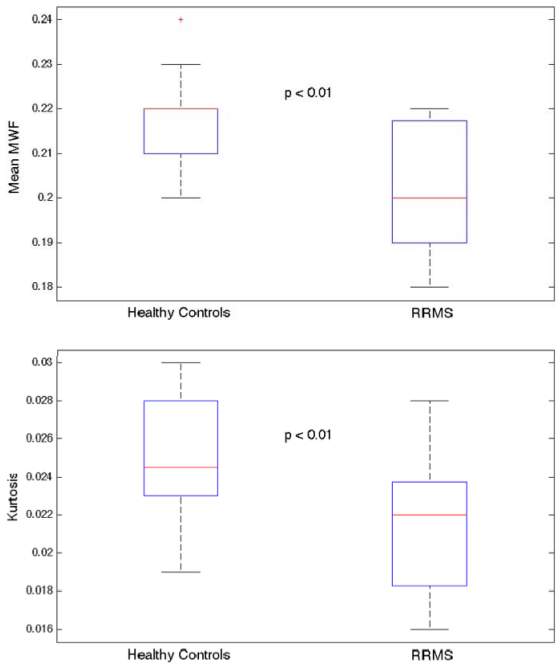
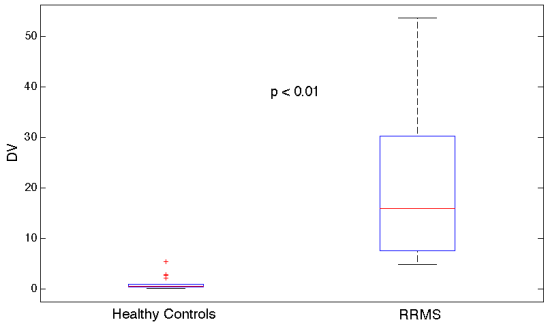


Fig. 1 *(above) Averaged MWF histogram over NAWM in RRMS and healthy controls.*

Fig. 2 *(right) Mean MWF (top) and MWF distribution kurtosis in RRMS cohort and healthy controls. Both measures significantly distinguish between both cohorts.*

Methods: A 1.5T MR scanner (Siemens Sonata, Siemens AG, Erlangen Germany) and an 8-channel head RF coil was used to derive multi-component T1 and T2 information from sets of *Fast Low Angle SHot* (FLASH) and true *fast imaging with steady state precession* (TrueFISP) data acquired over a range of flip angles at constant TR [2]. FOV=22cm, matrix=128x128, slice thickness=1.7mm; FLASH: TE/TR=2.0/5.7ms, α={5,6,7,8,9,11,13,18}°; TrueFISP: TE/TR=1.71/3.42ms, α={9,14,19,24,28,34,41,51,60}°. The total mcDESPOT imaging time was ~13min. MWF maps were derived from the mcDESPOT data using the established mcDESPOT theory and processing method [2]. 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 for histogram analysis. MWF maps were masked to the NAWM masks. Median, peak location, skewness, and, kurtosis of MWF distribution in NAWM were achieved. MWF maps were non-linearly registered to the MNI152 1mm^3 isotropic resolution standard brain. Patient MWF values at each voxel were compared to the healthy controls' normal distribution mean and standard deviation to produce a z-score value for that location. The resulting whole brain z-score maps allowed to calculate voxels with z-score < -4, i.e. that had a MWF at least 4 standard deviations below the mean control value. Those voxels were defined as deficient and summed as whole brain *Deficient MWF Volume* (DV).



A clinically homogeneous cohort of untreated n=15 relapsing-remitting (RRMS) patients (32.2 ± 9.2 yrs; F/M 12/3) was recruited. The mean Extended Disability Status Scale (EDSS) was 2.6 ± 0.8, annualized relapse rate (ARR) 0.9 ± 0.5, and, disease duration 146 ± 44.8 months. An age-matched healthy control group (n=26; 34.8 ± 11.3 yrs; F/M 17/9) free of neurological diseases was additionally acquired.

Fig. 3 (left) *Whole brain DV revealed greatest distinguishability between both cohorts.*

Results:
Myelination distribution was abnormal in RRMS NAWM (Fig.1). Mean MWF and histogram kurtosis were significantly different in the two groups (Fig.2). Also skewness ($p<0.01$), MWF peak location ($p<0.05$) and peak height ($p<0.05$) revealed significant differences (not shown here).

Conclusion: Whole brain high-resolution data acquisition of mcDESPOT allowed myelination assessment and to analyze its distribution in NAWM in both RRMS patients and healthy controls in clinically relevant scan times. It allowed clear distinction of RRMS from healthy subjects. The evaluation of sensitive MRI tools to monitor disease development and treatment response is fundamental since remyelination therapy is on the rise. Distribution characteristics of MWF data again suggest an independent underlying demyelination in NAWM in RRMS that needs to be monitored. We will continue with longitudinal evaluation of mcDESPOT in this clinical trial.

References:

[1] Laule & MacKay et al. J Neurol Sci. 2007; 259: 7-15

[2] Deoni et al., Magn Reson Med. 2008; 6:1372-87

[3] Kitzler et al. NeuroImage. 2011, EPub ahead of print