Multicomponent Relaxation in Clinically Isolated Syndrome

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Introduction: The Clinically Isolated Syndrome (CIS) is the precursor of Multiple Sclerosis (MS), an immunologically mediated demyelinating and axonal disease. Clinically silent white matter (WM) lesional pathology suggestive of demyelination is only found in up to 70% of patients at initial presentation [1] and there is only a moderate correlation of the initial volume of the WM lesions with the risk of clinically definite MS development [2]. Hence widespread non-lesional myelin changes are assumed in Normal Appearing White Matter (NAWM) in both CIS and MS. Multi-component Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT) is a whole-brain relaxation method that allows evaluation of the WM myelination by means of measuring myelin water fraction (MWF) [3] and shows great promise to quantify the hidden burden of disease [4]. We present preliminary results of applying mcDESPOT to a cohort of CIS patients at initial presentation to investigate the potential sensitivity of mcDESPOT-derived measures in detecting early and conventionally invisible disease-related myelin loss. Further longitudinal investigation will explore if those measures determine the time period and the overall risk factor for conversion into clinically definite MS.

Methods: A 1.5T MR scanner (Siemens Sonata, Siemens AG, Erlangen Germany) and 8-channel head RF coil were 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 [3]. 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 using the established mcDESPOT processing method [3]. MWF maps were non-linearly registered to the MNI152 1mm isotropic standard brain. Patient MWF values at each voxel were compared to the healthy controls’ MWF mean and standard deviation. The resulting whole brain z-score maps allowed the identification of “demyelinated voxels, defined as voxels with z-score < -4, i.e. that had a MWF at least 4 standard deviations below the mean control value. We labeled these voxels as DV and the fraction of demyelinated voxels within a given anatomical compartment as DVF [4]. WM masks were created by segmentation from conventional T1 images. WM lesion maps, diffusely abnormal (DAWM), and NAWM masks were created by segmentation from FLAIR images [4]. The reproducibility of measurements was assessed by calculating the scan-rescan coefficient of variance (COV) of MWF in WM. Additional atrophy measures were obtained by using the parenchymal volume fraction (PVF). A cohort of n=15 patients (32.0 IQR 9.5 yrs; F/M 10/5) diagnosed with Clinically Isolated Syndrome (CIS) was recruited. An age-matched healthy control group (n=18 ; 36.0 IQR 22 yrs; F/M 10/4) free of neurological diseases was additionally recruited. For the patient group, the median time since onset of symptoms was 71 days (range 34 to 201 days). Clinical scores (Extended Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and a specialized neurocognitive score) were obtained.

Results: In all patients WM lesions were identified in conventional FLAIR data. The median lesion volume per patient was 25 (range 4–97) cm³. The mean MWF in WM in scan-rescan data revealed a mean COV of 6.55 ± 9.66%. However, the mean and standard deviation of MWF in WM was 21.06 ± 0.49%, whereas it was 20.57 ± 0.04% in MNI registered WM. The average MWF in WM was 22.32 ± 0.67 %, whereas patients had 22.01 ± 0.96%. The MWF in NAWM (21.97 ± 0.97%) and DAWM (21.34 ± 1.72%), was lower, and in lesions (12.37 ± 3.05%; p<0.01) significantly lower in patients than in healthy controls. (** significance level p < 0.01)

Conclusion: Whole brain high-resolution data acquisition of mcDESPOT allowed myelination assessment in both CIS and healthy controls in clinically relevant scan times. Scan-rescan experiments revealed only minor deviation of MWF mean from healthy control average value. The inter-subject variance was higher than the scanning intra-subject variance (COV 17.1 vs. 6.55 %) proofing the consistency of repeated measurements. This establishes a reliable experimental foundation for the subsequent data analysis. The initial lack of correlation between myelination measures and the specialized clinical scores may be due to the fact that this baseline data is obtained immediately following clinical onset. The average time since symptom onset was much lower (median 71 days, IQR 51) than in another CIS cohort recently published (median 395.5 days, IQR 1026) [4]. Longitudinal data is being analyzed to address the question if these correlations are established over time, reflecting disease development. We assume that progressive global changes in myelination are the reason for the difference found between these studies so far. The correlation between time since symptom onset and decreasing of MWF in fact suggests very early global tissue changes reflected by brain volume measures.

References:  