NAWM Changes as assessed by Q-space analysis correlate inversely with T1- and T2-lesion volumes in MS Patients

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Introduction: Slight tissue changes have been demonstrated histopathologically in the so called normal appearing white matter (NAWM) of Multiple Sclerosis (MS) patients. The detection of NAWM changes with MR methods is challenging and there is a great need for MRI techniques with higher sensitivity. We investigated q-space imaging of slow diffusion component in this regard. It has been suggested, that the slow diffusion might predominantly represent intra-axonal/intra-cellular water diffusion and recent studies at 1.5 T have shown that the slow diffusion component is sensitive to white matter pathology in MS. This new technique might help to overcome the limitations of conventional MRI to differentiate the pathology beyond visible lesions in the NAWM. We optimised the imaging approach using the increased SNR of a 3 T system to study the NAWM. We therefore developed and implemented sequences and analysis strategies along the lines suggested by Assaf, Cohen et al.

Methods: We examined 71 MS patients (sex (f:m) = 48 : 23; mean age = 49 (23-68); mean disease duration = 15.6 years; mean EDSS = 3.2 (0-6.5)) with various disease courses (CIS, RRMS, SPMS, PPMS) and 10 normal controls (NC) (5 women and 5 men; mean age 32.7 years (26-46)) on a 3 T Siemens ALLEGRA system. The standardized brain MRI protocol included transverse 5mm T2w-TSE, FLAIR and DWI including high *b*-value measurements for q-space analysis. DWI: 6 directions, 16 *b*-values in each direction, *b*-value range: *b*= 0 to 9021 s/mm^2 by linearly increasing the diffusion gradient amplitude, d/D = 43/48 ms; TE/TR = 125/1450 ms, 128x128 matrix, voxel size = 1.875x1.875x5 mm^3. This sequence provided 8 axial slices centered at the level of the corpus callosum. Acquisition time for the whole DWI data set was 14 minutes. The NAWM was analysed on probability of zero displacement (PZD) maps (the peak intensity of the displacement distribution probability function). The maps display the information using a color scaling scheme. Lesions were marked on FLAIR images and after coregistration with the DWI data, lesion areas were excluded from quantitative analysis. Grey and white matter were segmented and the NAWM was analysed on histogramm analysis. Spearmans rank was used to analyse for correlation of mean PZD, T2-volumes and clinical parameters.

Results: *Normal controls:* PZD maps provided strong contrast between grey and white matter emphasizing the relatively low diffusion in normal white matter (warm colours = high probability for zero displacement; cold colours = higher water proton mobility, e. g. CSF). The mean white matter PZD values were 1617±43 for NC (see Fig.2). *MS patients:* All visible lesions and areas of questionable hyperintensity on T2-weighted MRI were strongly contrasted and displayed on PZD maps (see Fig.1). Furthermore large parts of NAWM have lost slow diffusion components which was visually apparent (by increase of cold colours). The mean white matter PZD value in MS patients was 1545 ± 63 which was significantly lower than in NC (two-tailed t-test ($p<0.005$)). Furthermore a cluster analysis (see Fig.3) demonstrated differences of 49/71 patients to NC, which also matched the visual analysis, that identified the same individuals as showing pathology. There was no correlation of EDSS with mean NAWM PZD. PZD correlated inversely with T1 or T2 lesion volumes (SR= -0.61;-0,63, p-level: <0,001; <0,001).

Discussion/Conclusion: In this 3T study we used an adapted protocol for clinical use of color coded PZD maps that were highly sensitive to detect reductions of the slow diffusion component in the NAWM of MS patients. This was both visually and quantitatively evident and underlines the usefulness of this imaging and analysis approach to detect otherwise covert pathology. The technique shows a strong relationship of the amount of conventionally measured T1 and T2 lesion volumes with the reduction of slow diffusion in the NAWM. In contrast clinical characteristics were not predictive of the NAWM changes, and particularly in patients with slight functional compromise (EDSS 0-2) additional MRI information on NAWM may be useful.

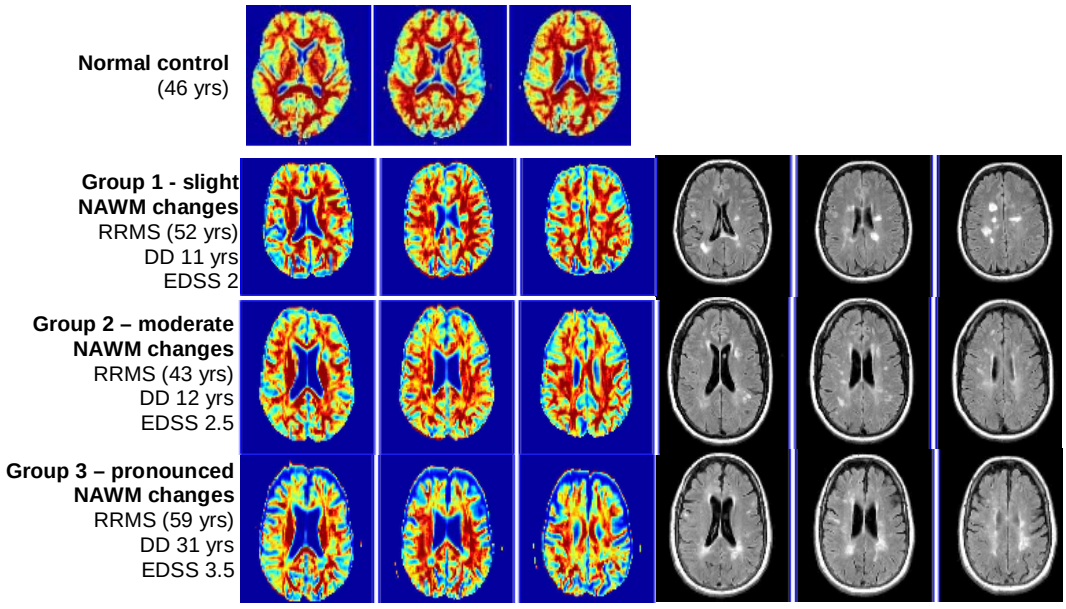

Fig. 1: Demonstration of 3 exemplary MS patients representing the different cluster with different degrees (mild, moderately severe, severe) of slow diffusion component reduction in direct comparison to a representative normal control. Note the diffuse reduction of the warm colors (red, brown-red) besides the focal lesions, which can be seen as well.

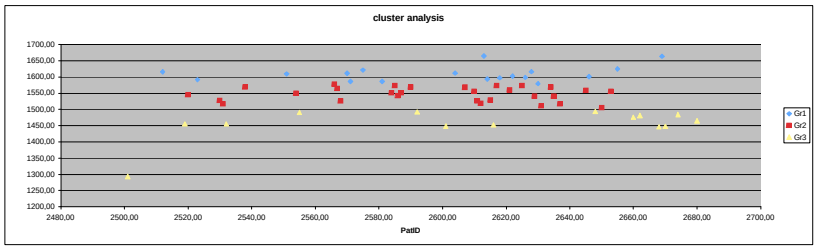

Fig. 3: Demonstration of the cluster analysis allowing for 3 clusters: 1456±50, 1547±21, 1610±24.

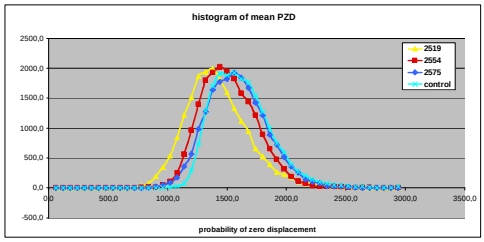

Fig. 2: Demonstration of three representative histograms of each cluster compared to normal control.