Application of multi-shell NODDI in Multiple Sclerosis

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TARGET AUDIENCE: Researchers with an interest in diffusion imaging in Multiple Sclerosis

PURPOSE: Diffusion tensor imaging (DTI) is routinely applied to study microstructure in the human brain. In Multiple Sclerosis (MS), DTI metrics such as fractional anisotropy (FA) and mean diffusivity (MD), axial and radial diffusivities (AD, RD) are used as markers for loss of WM integrity both in normal appearing white matter (NAWM) and MS lesions[1]. However, DTI is known to not adequately reflect the microstructure within a voxel. Neurite orientation and dispersion and density imaging (NODDI)[2] is a new technique that aims to distinguish two contributions to changes in DTI parameters - neurite density and orientation dispersion. The NODDI model has 3 compartments: *neurites* (sticks with zero radius with an orientation distribution modeled by a Watson distribution); *extra-neurite* (simple Gaussian anisotropic diffusion) and *isotropic Gaussian diffusion* such as CSF. The method produces maps of neurite density index (NDI), orientation dispersion index (ODI) and isotropic volume fraction (isoVF). In this pilot study we apply NODDI for the first time to MS patients and compare with standard DTI metrics. We show that NODDI detects and provides more distinction of the microstructural disruption in MS in both lesional tissue and NAWM compared to healthy controls (HC).

METHODS: <u>*Subjects:*</u> Five MS patients (mean age 39 +/- 9 years, median EDSS score 4, 3 female) and 5 age and sex-matched HC. <u>*MR acquisition:*</u> Scanning was performed on a 3T Philips Achieva system with a 32-channel head coil, using the following sequences (i) multi-echo PD/T2 sequence for tissue segmentation and lesion marking: voxel size 1x1x3mm[3], FOV=240x240mm^2, 50 slices, TE=19/88ms, TR=3500, SENSE=1.7 (ii) NODDI DWI protocol: voxel size 2.5mm^3, axial FOV=220x220mm^2, 60 slices, SENSE=2, TE=73ms, b-values 300/711/2000s mm^{-2} with 6/15/30 isotropically distributed directions and 10 interleaved non-diffusion weighted (b=0) images. <u>*DWI analysis:*</u> NODDI data was corrected for motion and eddy current distortions using the eddy tool of FSL5[3] and denoised using the joint anisotropic non local means algorithm[4]. NODDI fitting was performed with the NODDI Matlab Toolbox[5]. Maps of NDI, ODI and isoVF were generated. For comparison standard DTI parameter maps of FA, MD, AD and RD were derived from the same dataset, using only the b=0 and b=711s mm^{-2} acquisitions. <u>*Post-processing:*</u> In each dataset, WM was segmented on the high-resolution T2w scan using the EM algorithm of NiftySeg[6]. In MS patients, lesions were manually marked by an experienced neurologist on the T2w scans. The T2w scan was then non-linearly registered with NiftyReg[7] to the mean b=0 of each subject and the resulting transformation was applied to the WM mask and lesion mask to align them with the NODDI and DTI maps. In HC the whole WM mask was used for ROI analysis. In MS patients a mask of NAWM was generated by subtracting the lesion mask from the whole WM mask. The differences between ROI-averages in HC WM, NAWM and lesions were assessed with a two-sided t-test.

RESULTS: Figure 1 summarises the average DTI and NODDI parameters over the three tissue ROIs. MS lesions show significantly increased AD and RD, and consequently MD compared to HC WM. Lower FA in MS lesion is also observed, albeit not significant. None of the DTI metrics show differences between NAWM and HC WM. In NODDI, NDI and ODI are reduced and isoVF is increased in lesions compared to HC WM. Furthermore NODDI detects significant differences between NAWM and HC WM tissue, with NDI decreased and ODI increased in the NAWM. Moreover, Figure 2 shows that NDI can be a more specific marker of axonal loss in regions with fanning or kissing fibre tracts or where CSF contribution contaminates the DTI parameters.
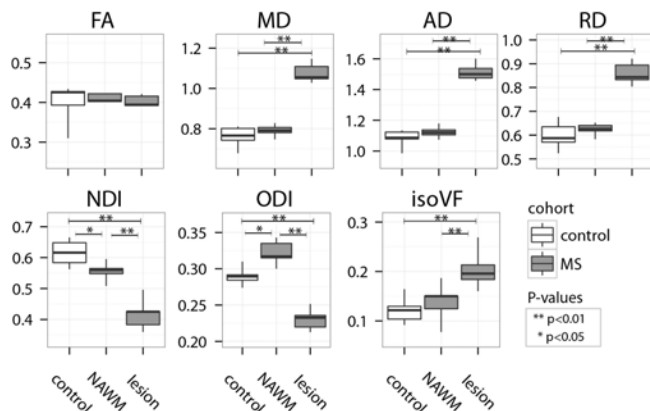

Fig. 1: Boxplot of average DTI and NODDI parameters over ROIs of HC WM and MS NAWM and lesion tissue. Symbols highlight statistical significant differences (**p<0.01,*p<0.05).
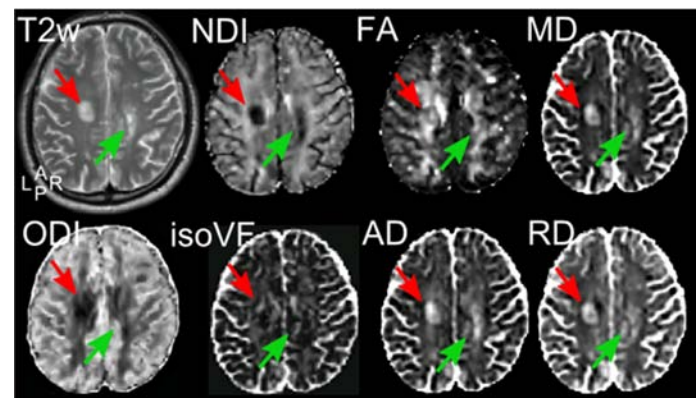

Fig. 2: Maps of NODDI and DTI parameters in a single MS subject. The MS lesion in the major white matter tracts is clearly marked in AD, MD and RD and NDI map (red arrow). NDI gives superior constrast over DTI metrics in periventricular lesion (green arrow) with CSF contribution.

DISCUSSION AND CONCLUSION: We demonstrate for the first time the application of multi-shell NODDI in MS. Our findings suggest loss of axonal tissue and fibre integrity in both NAWM and lesion in MS compared to HC, which is consistent with findings from previous studies using DTI[1,8] and other complementary MRI techniques[8] as well as histological assessment of MS specimen[9]. NODDI analysis further suggests a loss of fibre coherences (i.e. an increase of dispersion) in NAWM, which cannot be directly detected with DTI metrics. The low ODI values found in lesional tissue compared to HC WM and NAWM can be attributed to the severe loss of axonal tissue, which impairs the accurate estimation of dispersion. Furthermore NODDI provided additional value by disentangling neurite density and dispersion in MS pathology, particularly in regions where intra-voxel fibre orientation coherence is naturally low. Given the small sample size, these results are preliminary but encouraging and warrant future work including additional subjects and different MS subgroups.

REFERENCES: 1. Werring, Neurology (1999) 2. Zhang, NeuroImage (NI) (2012) 3. Jenkinson, NI (2012) 4. Tristan-Vega, IEEE Eng Med Biol Soc (2013) 5.http://goo.gl/VG9XU6 6. Cardoso, MICCAI (2011) 7. Modat, Comput Methods Programs Biomed (2009) 8. Cercignani, Neurology (2000) 9. Schmierer, NI (2007)