Assessing microstructural substrates of white matter abnormalities using NODDI - application to a metabolic disease

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PURPOSE Diffusion-weighted imaging (DWI) can be used to assess properties and potential abnormalities of tissue microstructure. Widely used is the single compartment diffusion tensor model, with fractional anisotropy (FA) as its main parameter. FA has shown to be a very sensitive measure, but is inherently non-specific[1]. The recently developed *neurite orientation dispersion and density imaging* (NODDI) enables more specific characterisation of tissue microstructure by estimating neurite density and orientation dispersion, two key contributors to FA[2]. However, the value of analysing these parameters has yet to be demonstrated in the context of population-based clinical studies. Using multi-shell DWI data from a metabolic disease study, the present work assesses the added values of NODDI parameters for investigating specific microstructural substrates of white matter abnormalities over FA. The secondary aim is to determine whether standard single-shell DWI data can be used for NODDI-based tissue quantification.

METHODS Acquisition: Diffusion-weighted images with multiple shells were acquired in a group of 8 healthy controls and 8 patients with classic galactosemia (an inherited metabolic disease with white matter pathology[3]). A double-refocused single-shot spin-echo EPI sequence was used to obtain 64 slices with a voxel size of 2.2 mm (TR=8500 ms; TE=97 ms), with 64 diffusion-encoding gradient directions spanning the entire sphere for both shells (b=1000 s/mm^2 and b=2000 s/mm^2). In addition, 5 b=0 images were collected (2 using a reversed phase encoding direction). Analysis: After pre-processing, including estimation and correction of susceptibility induced distortions and motion (using *fsl5.0:* topup and eddy tools), the diffusion tensor was estimated with the standard log-linear fit (using b1000 DWI; single compartment model), and tensor-based registration to a group template was performed using DTI-TK[4]. NODDI fitting was performed in parallel, both on multi-shell as well on single-shell (b1000) data. NODDI distinguishes intra-neurite space (modelled as a collection of sticks forming a Watson distribution); extra-neurite space (anisotropic Gaussian diffusion); and a CSF compartment (isotropic). The main resulting parameters of NODDI are: the neurite density index (NDI), which is the intra-neurite volume fraction, and the orientation dispersion index (ODI). NDI and ODI maps were normalised to the group template using the transformation estimated above with tensor-based registration. Statistics: All data were projected onto the mean FA skeleton on which voxel-wise permutation-based statistics were carried out (using *fsl5.0*'s tract-based spatial statistics [TBSS]). P-values were corrected by Threshold-Free Cluster Enhancement (TFCE).

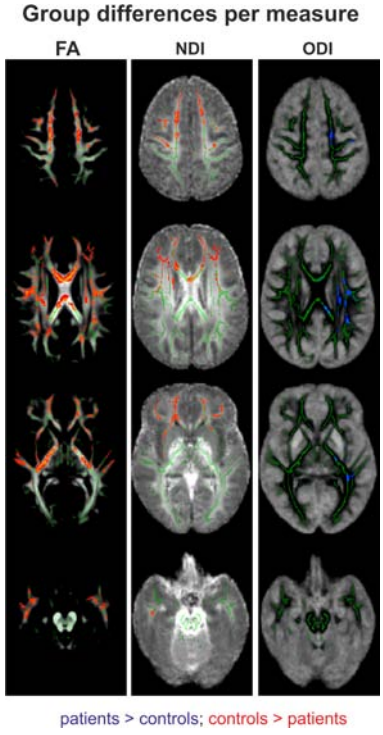

Figure 1: Statistical group differences overlaid on the mean FA skeleton (green) and the corresponding averaged maps.

RESULTS Multi-shell fitting: The NODDI analysis showed several group differences in NDI and ODI that give more specific insights into white matter changes as compared to the general pattern of FA findings (Figure 1): NDI changes were found mainly in bilateral anterior regions, while ODI changes were left lateralized and more posterior. The group differences in NDI and ODI are complementary, supported by a minimal overlap in results (dice coefficient = 0.07). Further, the combination of NDI and ODI can explain much of the FA results, supported by a significant overlap between the NODDI parameters and FA (dice coefficient = 0.55). In addition, the NODDI parameters identified unique group differences: 33.6% and 10.3% of significant voxels in NDI and ODI, respectively, were not captured by the FA analysis (Figure 2). Single-shell fitting: The NODDI analysis using single-shell data could estimate ODI sufficiently well to be used for group inference, supported by a large overlap in its findings with multi-shell ODI results (dice coefficient = 0.74). NDI could not be reliably estimated using single-shell data (the results showed little overlap with the multi-shell NDI results; dice = 0.09).

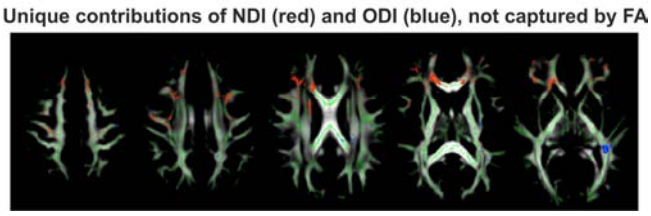

Figure 2: Statistical group differences identified by the NODDI parameters, that were not captured by the FA analysis. Displayed are mean FA maps, mean FA skeleton (green) and the unique-to-FA ODI (blue) and NDI (red) changes.

DISCUSSION Using a metabolic disease as an example, we demonstrated that the NODDI analysis can be of added value to standard diffusion tensor imaging (DTI), by revealing specific microstructural substrates to white matter changes detected with FA. NODDI parameters complement each other, have substantial overlap with FA, and give unique contributions not captured by FA. The reduction in NDI is consistent with myelin loss associated with the disorder[5], as myelin loss increases in the extra-neurite space, which (indirectly) leads to a reduction in the (relative) volume fraction of the intra-neurite space. The anterior pattern of NDI results and the left-lateralized ODI changes are in line with the known cognitive profile of the disease[3]. The secondary finding that ODI can be estimated reliably using single-shell data may allow the retrospective analysis of standard DTI with NODDI.

REFERENCES [1]Pierpaoli et al., 1996, Radiology; [2]Zhang et al., 2012, NeuroImage; [3]Timmers et al., 2012, J Inher Metab Dis; [4]Zhang et al., 2007, IEEE TMI; [5] Nelson et al., 1992, Radiology