TOWARDS SPINAL CORD MICROSTRUCTURE MAPPING WITH THE NEURITE ORIENTATION DISPERSION AND DENSITY IMAGING

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TARGET AUDIENCE This work is targeted at imaging scientists and clinicians who deal with Diffusion–Weighted (DW) MRI of the spinal cord.

PURPOSE The study aims to assess the feasibility of the Neurite Orientation Dispersion and Density Imaging (NODDI) [1] in the spinal cord.

INTRODUCTION It is well known that Diffusion Tensor Imaging (DTI) provides a number of indices sensitive to tissue microstructure, such as Fractional Anisotropy (FA) and Mean Diffusivity (MD). These parameters, although meaningful, only provide summary information as they cannot disentangle the contribution of specific features such as orientation dispersion and density of axon bundles [1]. Such features may be important biomarkers for diseases like Multiple Sclerosis (MS), whose tissue damage is likely to alter normal fibre density and coherence [2]. The NODDI technique provides estimates of these physical quantities and here we demonstrate its feasibility in the spinal cord, comparing the technique to DTI in healthy controls (HCs) and then in MS patients.

METHODS *Data* We performed MRI scans in the cervical spine of 10 HCs (4 males and 6 females, mean age 34, SD 9.10) and 10 MS patients (3 males and 7 females, mean age 47, SD 10.86) with a large range of disability (median EDSS 3, range 1–7, 5 RRMS and 5 SPMS). DW images were acquired axially on a clinical 3T TX Philips Achieva scanner, from C2 to C4 intervertebral discs. The imaging parameters were: TE = 52 ms, TR = 12 RRs (cardiac gated), reduced FOV of 64x48 mm^2, SENSE factor = 1.5, acquisition matrix 64x48 for a voxel resolution of 1x1x5 mm^3. The DW imaging protocol consisted of 30 b = 1000 s mm^{-2} DWI volumes with gradient directions evenly distributed over the sphere and 3 non–DWI (b = 0) volumes. The protocol for this feasibility study departs from the original NODDI one [1], which was designed according to [3] and includes two different b shells. The original protocol may not be optimal for spinal cord imaging as it was intended for whole brain scans, so we used a simple DW protocol to evaluate the feasibility of NODDI, leaving the design of an appropriate spinal cord acquisition procedure to further work. Here, we account for our single b value–data in the model fitting procedure (see below).

Tissue models and fitting The open–source toolkit Camino [4] was used to fit the standard Diffusion Tensor (DT) and derive indices of FA, MD, Radial Diffusivity (RD) and Axial Diffusivity (AD) in each spinal cord voxel. The NODDI model was fitted using the freely available NODDI Matlab toolbox. The NODDI methods fit a three compartment model accounting for intracellular (IC) and extracellular (EC) spaces and for Cerebrospinal Fluid (CSF). The IC space is represented by a set of geometrically restricted zero–radius cylinders (sticks) exhibiting orientation dispersion according to a Watson distribution. The EC compartment is considered hindered and is modeled by an axially symmetric DT. However, in this work, the volume fraction of the CSF was constrained to 0 to account for the reduced number of b shells [1]. The parameters of the NODDI model analyzed in detail were the Orientation Dispersion Index (ODI) and the Fractional IC Volume (FICV).

Analysis Whole cord segmentation was carried out by an experienced reader using a semi–automatic segmentation method [5]. We successfully reconstructed DTI and NODDI indices for all the subjects and calculated the histograms over all the cord voxels of the HCs. We applied the Otsu's method [6] on the ODI histogram to estimate a reasonable threshold to distinguish between high and low ODI values. The threshold was calculated after removing the few occurrences of ODI = 1, which are likely due to noise and residual CSF voxels. Pearson's correlation coefficients were also computed among the different parameters on HCs. Lastly, we studied significant differences between HCs' and MS patients' average DTI and NODDI measures over the whole cord using a two–sided Wilcoxon rank sum test.

RESULTS AND DISCUSSION *Indices and histograms* DTI and NODDI indices for one of the HCs are shown in figure 1. DTI measures such as FA and AD (figure 1.a and 1.c) showed a core of lower anisotropy and lower diffusivity respectively, resembling grey matter. Such a core was also noticeable on the ODI but with enhanced contrast (figure 1.f). FA, MD, AD, RD and FICV histograms showed a single peak distribution with symmetric or asymmetric tails, whereas the ODI histogram, shown in figure 2.a, exhibited a second peak, suggesting the existence of two kinds of tissue within the cord: highly and less dispersed. They were separated with the Otsu's method (threshold 0.088) and we show them as green and blue in figure 2.a. We used the voxel separation obtained from the ODI distribution to plot normalized FA histograms for each group, i.e. for highly and less dispersed tissue (respectively green and blue in figure 2.b). The plots reveal that the two groups are characterized by similar FA distributions, with a certain amount of overlap though they are shifted compared to each other. The Otsu's thresholding on ODI (cf. figures 2.c and 2.d, 2.e and 2.f) showed that the two clusters correspond well with the known anatomical location of grey and white matter, even if some inaccuracy occurred along the cord border where unitary ODI and low FICV were fitted.

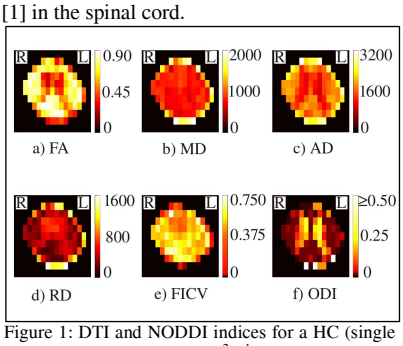

Figure 1: DTI and NODDI indices for a HC (single slice). Diffusivities are in μm^2 s^{-1}.

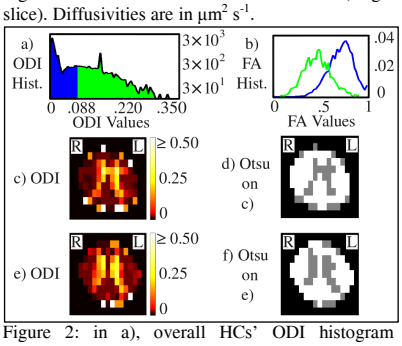

Figure 2: in a), overall HCs' ODI histogram showing values for highly (green) and less (blue) dispersed tissue. In b), overall HCs' normalized FA histograms evaluated for highly (green) and less (blue) dispersed tissue. From c) to f), thresholding on two HC's ODI slices (Otsu's threshold 0.088).

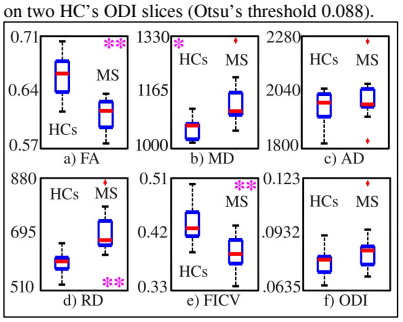

Figure 3: box plots of the average indices for HCs and MS patients. Diffusivities are in μm^2 s^{-1}.

Correlations among indices All correlation tests provided p values < 0.001. FICV exhibited a good correlation with all the DTI measures (stronger correlation with RD, r = – 0.874; weaker correlation with AD, r = – 0.650), whereas a weaker correlation is seen for ODI (higher correlation with RD, r = 0.453) and between FICV and ODI (r = – 0.377). This seems to suggest that the observed variation of DTI metrics related microscopically to the variation of FICV rather than that of ODI.

MS effects Figure 3 shows box plots of average DTI and NODDI measures over the whole cord for HCs and MS patients. Single (p < 0.05) or double (p < 0.01) asterisks stand for significant differences. MS caused both FA and FICV to decrease significantly. Moreover, it was likely to cause the overall isotropy within the spinal cord to grow, as MS patients exhibited higher RD than HCs. This led also to an increase of MD even if AD did not change significantly. We did not detect any significant differences between HCs' and MS patients' mean ODI values. These finding suggests that ODI is not much affected by MS. If confirmed in more subjects, ODI may be useful to segment white and grey matter in the cord, should the highly and less dispersed fractions prove to be related to grey and white matter.

CONCLUSION In this work we demonstrate the feasibility of NODDI in the spinal cord. The NODDI analysis identified FICV as the primary source of microstructural variation that contributes to the observed pattern of DTI indices. In contrast, ODI was robust towards the effects of MS and enhanced the differences between two clusters within the cord resembling grey and white matter. Therefore, NODDI did not just replicate standard DTI measures but provided additional information, even with just one b shell. Future work is required to evaluate the acquisition of the full two shells protocol, to optimize a new NODDI protocol for spinal cord anatomy and to analyze the differences exhibited by grey and white matter in the NODDI indices.

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