How does white matter microstructure change in human early development based on WMTI and NODDI?

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Target audience: Biophysicists involved in white matter (WM) modeling and neuroscientists interested in human brain development.

Purpose: During the first two years of life, large non-linear increases in fractional anisotropy (FA) and in mean kurtosis (MK), and decreases in diffusivities have been reported in the human brain using DTI[1] and DKI[2]. Reported changes are consistent with on-going myelination and with the expected asynchrony of WM bundle maturation. However, both DTI and DKI lack structural specificity. **The two goals of this study are:**

• *to gain specificity to structural changes in development* by analyzing microstructural changes in major WM tracts during early development (0 up to 3 years) using two biophysical models applicable to clinical data: White Matter Tract Integrity (WMTI) metrics[3], and Neurite Orientation Dispersion and Density Index (NODDI)[4], and

• *to compare parameters for each model* (Table 1) *and relate differences to the models' different simplifying assumptions.* In particular, WMTI approximates the intra-axonal space (IAS) as a Gaussian compartment (valid for a fiber dispersion <30°), assumes $D_a \leq D_{e,\parallel}$ and neglects the CSF contribution, while NODDI assumes a Watson distribution of axons, and enforces $D_a = D'_{e,\parallel} = 2$ μm^2/ms and $D'_{e,\perp} = D'_{e,\parallel}(1-f_{ic})$ (the "prime" symbol identifies local diffusivities of the extra-axonal space (EAS) within a coherent sub-bundle of a given voxel).

Parameter	Biophysical meaning
f_{intra}	Intra-axonal water fraction
f_{iso}	CSF fraction
$\langle\cos^2\psi\rangle$	Orientational fiber dispersion
D_a	Axonal diffusivity
$D_{e,\parallel}$	Axial diffusivity of the EAS
$D_{e,\perp}$	Radial diffusivity of the EAS
α	Tortuosity

Table 1. Biophysical parameters inferred from both NODDI and WMTI. $\langle\cos^2\psi\rangle$ varies from 1/3 (isotropic) to 1 (parallel).

Methods: An IRB approved retrospective study was performed on 55 pediatric subjects who underwent a routine brain MRI exam, including DKI[2], under sedation on a 1.5T Avanto Siemens MR scanner (Erlangen, Germany). Subjects ranged from 1 day to 2 years and 9 months in age and all had an exam interpreted as normal by board-certified neuroradiologists. Diffusion data consisted of one b=0 image and two shells (b = 1 and 2 ms/μm^2) with 30 directions each. An in-house developed pipeline was used for noise level estimation, motion and eddy current correction. Selective smoothing was applied using a CSF-excluding mask, to reduce Gibbs ringing artifacts with no additional CSF contamination. Diffusion and kurtosis tensors were estimated in each voxel using a constrained weighted linear least-squares algorithm[5], and further used to extract the WMTI parameters[3]. Three regions of interest (ROIs) consisting of highly aligned WM bundles – the genu and splenium of the corpus callosum and the posterior limb of the internal capsule (PLIC) – were drawn on the FA map for each subject. For every voxel of each ROI, NODDI parameters were also extracted using the non-linear fitting pipeline[4]. Next, the mean of the model parameter P of interest (Table 1, left column) estimated from both WMTI and NODDI was calculated over each ROI and each subject, and correlated with subject age X; the best relationship between a non-linear (of the form $P=ae^{-bX}+c$), a linear, and a constant was selected based on the corrected Akaike information criterion[6]. The two WM models were compared in terms of parameter trend with age and correlations of absolute estimated values.

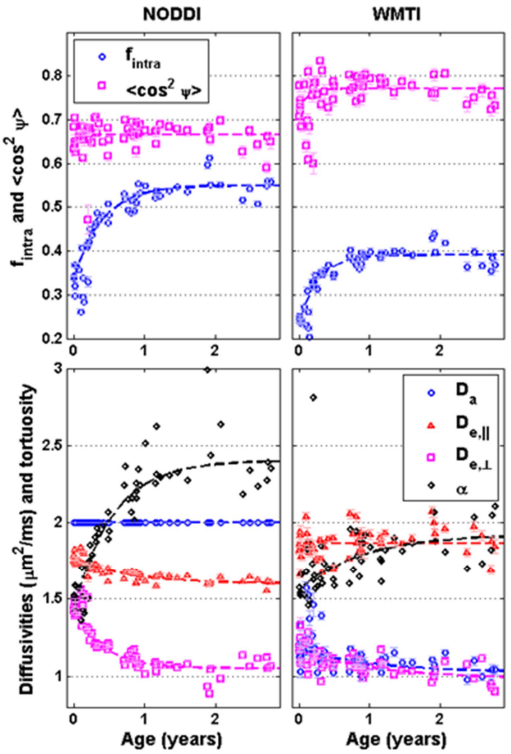

Figure 1. Parameter evolution with age in the PLIC. The dashed lines are the best fit found for the parameter trend with age.

Results and discussion: For all three ROIs, both models revealed a non-linear increase in f_{intra}, decrease in $D_{e,\perp}$ and increase in tortuosity, consistent with on-going myelination. Figure 1 shows results in the PLIC, as an example. The aforementioned changes occurred most rapidly in PLIC, followed by splenium and lastly genu, consistent with a rostro-caudal pattern. By age three, the splenium was the most aligned and tortuous bundle, followed by genu and PLIC. D_a and $D_{e,\parallel}$ did not change significantly with age. However, quantitatively, the two models did not solidly agree and the poorest agreement was found in PLIC. The NODDI estimates of f_{intra} were higher than WMTI's. The axial diffusivities fixed by NODDI differed significantly from WMTI estimates. NODDI did not display any trend in fiber dispersion with age, while WMTI showed an increase in alignment in all three ROIs, potentially a result of on-going pruning. These differences are likely due to the different assumptions made by each model.

Conclusion: WM modeling gives access to a more specific description of microstructural changes occurring during early development compared to empirical DTI and DKI metrics. The parameter trends with age are qualitatively similar in both models, and are consistent with known developmental patterns. However, the examined models enforce additional assumptions in the interest of robustness, but at the expense of accuracy. The validity of these assumptions is yet to be established. Better conceived models could perhaps be both accurate and parsimonious in assumptions.

References: [1] Dubois et al., Neuroimage 30, 1121-1132, 2006. [2] Paydar et al., AJNR 35, 808-814, 2014. [3] Fieremans et al., Neuroimage 58, 177-188, 2011. [4] Zhang et al., Neuroimage 61, 1000-1016, 2012. [5] Veraart et al., Neuroimage 81, 335-346, 2013. [6] Hurvich and Tsai, Biometrika 76, 297-307, 1989. Work supported by NIH R01 NS088040.