NODDI intra-axonal volume fraction shows stronger correlation with developmental age than fractional anisotropy in preterm human newborns

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PURPOSE This work investigates new markers of white matter maturation provided by the biophysical diffusion model NODDI in the preterm human newborn brain during the first months of life. This period is known to be critical for brain development; as aberrant maturation at this stage has been linked with many neurological disorders and cognitive disabilities later in life.

Diffusion magnetic resonance imaging (dMRI) has demonstrated to be an excellent tool to investigate brain development [1]. Recently, biophysical diffusion compartment models, such as CHARMED, NODDI or AxCaliber [2], have been proposed to provide more specific marker of the cellular microstructure with measure of the intra-axonal volume fraction, axonal orientation dispersion within a voxel and axonal diameter. Whereas axonal diameter estimation techniques remains too challenging for clinical application, NODDI model has demonstrated reliable performance in newborn study [3] and provided more specific information on the microstructural changes during development. In this work, we investigate changes of the intra-axonal volume fraction (ficvf) and orientation dispersion index (ODI) of the NODDI model in a cohort of premature neonates between the 30th weeks of gestation until term equivalent age over multiple time points.

METHODS Subjects: In accordance to local ethical committee, 18 preterm newborns born at 28±1 weeks of gestation were scanned over three time points: **T1**) at 30 weeks of gestational age (min-max: 28-32 weeks, n=9); **T2**) at 34 weeks (31-36 weeks, n=8); and **T3**) at 40 weeks (39-43 weeks, n=14) corresponding to term equivalent age. Imaging: All imaging were conducted on a 3T Siemens Trio system. The data were acquired using a double refocusing spin echo echo-planar imaging pulse sequence. Acquisition parameters are: TE/TR = 95/3500ms, spatial resolution 2×2×2mm^3, matrix = 80×80, and 22 axial slices centered on the corpus callosum. Diffusion imaging scheme: 66 DW images with 3 reference b_0 images. The remaining 63 non-collinear directions are split into 5 shells with b-values ranging from 50 to 2000 s/mm^2. The acquisition time is 4 mins. Image Processing: **1.** Diffusion tensor (DT) images for each subjects are reconstructed with Camino [4] using only the 4 first shells (i.e. bmax = 1400 s/mm^2, 56 directions); **2.** DT images are then spatially normalized to the study-specific DT template using DTI-TK [5]; **3.** 20 white matter regions of interest (ROI) are drawn on the study-specific template; **4.** ROIs are transformed back to the subject space to compute ROI-averaged estimates from DTI and NODDI maps. 5. Linear correlation are estimated between the subject age at scan time and the diffusion parameters in all ROIs **1.A.** The NODDI model is estimated using NODDI Matlab toolbox [6], with intra-axonal diffusivity (D_{ic}) fixed to $2x10^{-3}$ mm^2/s and isotropic diffusivity to $3x10^{-3}$ mm^2/s. A tortuosity model is used for the perpendicular extra-cellular diffusivity ($D_{ec,\perp}=(1-\nu_{ic})\cdot D_{ic}$). The estimated NODDI parameters are intra-cellular volume fraction (ν_{ic}) and isotropic volume fraction (ν_{iso}) and orientation dispersion index (ODI). Signal is modeled as: $S/S_0=(1-\nu_{iso})\cdot[\nu_{ic}\cdot S_{ic}+(1-\nu_{ic})\cdot S_{ec}]+\nu_{iso}\cdot S_{iso}$ **2.A** We additionally warp the NODDI parameter maps to the template space to generate corresponding study averages.

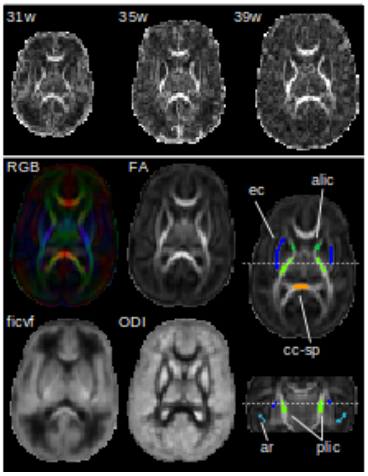

Figure 1: *Top row show FA maps of a single subject scanned longitudinally at three time points (31, 35 and 39 weeks of gestational age). Bottom of the figure show the study-specific DT template maps from DTI and NODDI model. On the right are displayed the ROI on an axial and coronal view.*

RESULTS & DISCUSSION Despite the large changes in volumes and morphology DTI-TK was successful in generating a unique study-specific DT template over all newborn age (Fig 1, top row). It ensured a good localization of the ROIs at all ages and minimizes operator induced variability. A total of 20 white-matter regions were possible to delineate on the study-specific DT template scalar maps, but this abstract will details the results for only 6 of them (Fig 1, bottom-right).

As expected from previous work with DTI, FA values show positive correlation in almost all the regions (R-square: cc-sp=0.087, alic=0.29, ar=0.35, plic=0.45, ec=0.51 and slf-cent=0.7, Fig 2). Intra-cellular volume fraction measured by the NODDI model show stronger correlation with age compared to FA, and all regions without exceptions show increase during the first months of development (R-square: cc-sp=0.41, plic=0.57, alic=0.7, ar=0.72, ec=0.82 and slf-cent = 0.82). The correlation of ODI as a function of age was less clear; half of regions show negative trend while the other half positive, but not significantly except for the plic (R-square: cc-sp=0.059, plic=0.82, ar=0.097, slf-cent=0.23, alic=0.27 and ec=0.37).

The intra-cellular volume fraction exhibits the strongest correlation with age at scan in all white matter regions, which indicates an increase of the restricted water intra-axonal compartment in the developing brain during the first months of life. This increase of restriction in the measured diffusion signal could be attributed to the preparation (increase of axonal diameter) or beginning of myelination. ODI show a larger dispersion with age and did not show significant correlation except in the plic.

CONCLUSIONS We demonstrate for the first time that new diffusion parameters from the biophysical NODDI model show stronger correlation with age than conventional FA measured by DTI. ODI, on the other hand, did not show any significant changes with development. These results suggest an increase of the axonal space, probably in preparation for myelination (increase of ficvf), with a preservation of the global organization (constant ODI).

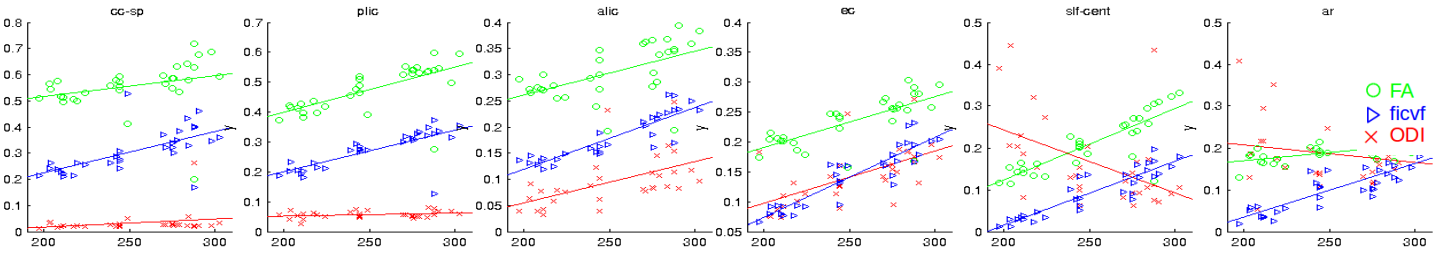

Figure 2: *Correlation plot of diffusion parameters: FA (green, round), ficvf (blue, triangle) and ODI (red, cross) in 6 chosen brain regions (from left to right): splenium of corpus callosum (cc-sp), posterior and anterior limb of the internal capsule (plic and alic, respectively), external capsule (ec), central part of the superior longitudinal fasiculus (slf-cent), and acoustic radiation (ar). The x-axis represent the newborn gestational age at scan time in days. FA, ficvf and ODI are normalized metrics ([0 1]).*

REFERENCES [1] Hüppi, PedR-98, [2] Assaf, NI-13 [3] Kunz, NI-14 [4] Cook, ISMRM-06 [5] Zhang MedIA-06 [6] http://www.nitrc.org/projects/noddi_toolbox/. **Acknowledgements** Supported by the CIBM of the UNIL, UNIGE, HUG, CHUV, EPFL, Leenards and Jeantet foundation, the SNSF (32-102127) and CONNECT EU FP7.