White matter structural development from mid-fetal stage to normal time of birth

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Target Audience: MR physicist, pediatric neurologist, pediatric radiologist and neonatologist

Purpose: Structural characterization of white matter (WM) maturational processes from mid-fetal stage (around 20 weeks of gestation (wg)) to normal time of birth (40wg) is critical for understanding not only the normal development of WM tracts but also the clinical implications associated with abnormal WM development such as periventricular leukomalacia (PVL) [e.g.1]. Valuable insights into microstructural and macrostructural processes of the WM maturation in this period have been offered by DTI of fetal brain specimens [2] and DTI of *in vivo* preterm and term brains [e.g. 3-5]. We hypothesized that spatiotemporally heterogeneous microstructural and macrostructural development takes place across different time periods of 20-35wg and 35-40wg and across different WM tracts. With high resolution DTI of early developing brains at 20wg, 35wg and 40wg, establishment of population-averaged age-specific template, WM skeleton extraction and DTI-based tractography of individual tracts, we aimed to understand the dynamics of structural changes of individual tracts, including myelination, axonal packing and volume growth, in 2nd half of fetal development.

Methods: *Ex vivo fetal brain specimens at 20wg and in vivo neonates at 35wg and 40 wg:* 46 normal subjects were involved in this study and divided into three groups according to the weeks of gestation, including 10 *ex vivo* fetal brain specimens in the middle of 2nd trimester (age: 19.5±0.52 wg), 19 preterm brains scanned in the middle of 3rd trimester (age: 35.1±0.55 wg) and 17 term brains scanned around normal time of birth (age: 40.7±0.55 wg). *DTI data acquisition:* The *ex vivo* fetal brains at 20wg were scanned with a 4.7T Bruker scanner. The details of high resolution DTI with resolution of 0.3x0.3x0.3mm^3 can be found in the literature [2]. DTI of *in vivo* 35wg and 40wg brains was acquired with a 3T Philips Achieva MR system. The diffusion MRI imaging parameters were: TE=78ms, TR=6850ms, in-plane field of view = 168x168mm^2, in-plane imaging resolution=1.5x1.5mm^2, slice thickness=1.6mm, slice number=60, 30 independent diffusion encoding directions, b-value = 1000 sec/mm^2, repetition=2. DTI tensor fitting and DTI metric calculation were conducted offline using DTIStudio. Fractional anisotropy (FA) was obtained for all subjects. *Identification of core WM with population-averaged FA maps at 20wg, 35wg and 40wg:* Both affine and large deformation diffeomorphic metric mapping (LDDMM) [6] were used for establishing population-averaged FA maps at 20wg, 35wg and 40wg following the protocol in the literature [7]. All transformations were conducted with *DiffeoMap* software (mristudio.org). Whole brain skeleton was extracted with "tbss_skeleton" function in TBSS of FSL (www.fmrib.ox.ac.uk/fsl). Note that with high cortical FA, the cortical skeleton was also extracted. WM skeleton was manually segmented as the green lines shown in Fig. 1. *Measurement of tract level FA at core WM and tract volumes:* Following tractography protocol described in the literature [8], streamline method was used for tracing the following major tracts, forceps major (fmajor), forceps minor (fminor), left and right cingulate part of cingulum bundle (cgc-L/R), left and right hippocampal part of cingulum bundle (cgh-L/R), left and right corticospinal tract (cst-L/R), left and right inferior fronto-occipital (ifo-L/R), inferior longitudinal (ilf-L/R), superior longitudinal fasciculus (slf-L/R) and uncinate fasciculus (unc-L/R) for 35wg and 40wg brains. Only cst-L/R, cgc-L/R, ifo-L/R, unc-L/R, fminor were reliably traced for 20wg brains. Binary masks of the individually traced tracts and the WM skeleton were used to compute the tract-level FA. The binary masks of traced tracts were used for measuring the tract volumes. The homologous tracts in both hemispheres were integrated for measurements. *Statistical analysis:* The following equation was used for fitting a linear model between y (FA, fiber volume) and age t, $y=\beta_0+\beta_1 t+\varepsilon$, where ε was an error term. The linear model was used to test 1) if the change rates of FA or fiber volume over time were significantly different from 0 and 2) if the change rates during 20-35wg was significantly different those during 35-40wg. The null hypothesis for 1) was that change rate of FA or fiber volume is 0. The null hypothesis for 2) was that the change rates over the two time periods were the same.

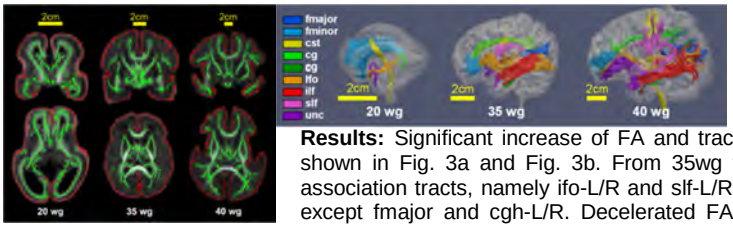
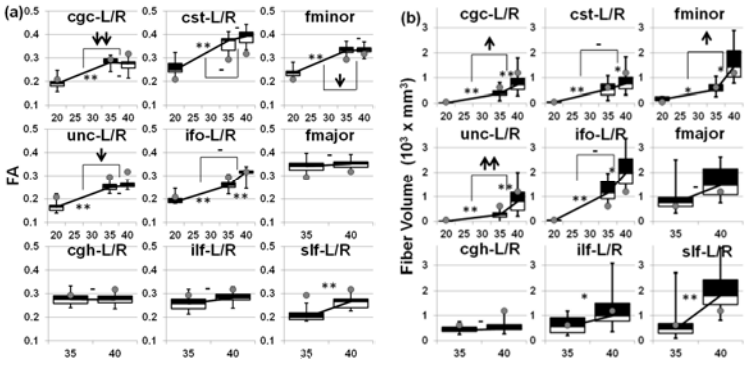


Fig. 1 (left): WM skeleton shown as green lines was extracted from underlying gray-scale population-averaged FA map at 20wg, 35wg and 40wg. The red lines are the cortical skeleton.

Fig. 2 (right): 3D reconstructed major WM tracts in a typical 20wg, 35wg and 40wg brain. Different tracts are encoded by different colors. See the text in Methods section for abbreviation of the WM tracts.

Results: Significant increase of FA and tract volume can be found for all investigated tracts from 20wg to 35wg, as shown in Fig. 3a and Fig. 3b. From 35wg to 40wg, the significant increases of FA can be only found for several association tracts, namely ifo-L/R and slf-L/R; the significant increase of tract volume can be found in almost all tracts except fmajor and cgh-L/R. Decelerated FA increases were found in cgc-L/R, fminor, unc-L/R, while no significant changes of FA increase rates were found for cst-L/R and ifo-L/R (Fig. 3a); on the contrary, the accelerated increases of tract volumes were found in these same tracts of cgc-L/R, fminor, unc-L/R (Fig. 3b) where decelerated FA increases were found (Fig. 3a).



Discussion and Conclusion: The significant microstructural enhancement takes place for all investigated tracts from 20wg to 35wg, while the microstructural enhancement occurs only in association tracts from 35wg to 40wg (Fig. 3a). The FA change rates are decelerated during 35wg to 40wg compared to 20wg to 35wg, suggesting temporal heterogeneity of microstructural development of WM. The periods of 20wg to 35wg and 35wg to 40wg are featured with distinguished WM maturational processes. From Fig. 3a and Fig. 3b, rapid microstructural WM maturation in terms of FA happens during 20wg to 35wg, while rapid macrostructural WM maturation in terms of tract volume takes place in later 3rd trimester from 35wg to 40wg.

References: [1] Huppi et al. (2001) Pediatrics 107: 455. [2] Huang et al. (2009) J Neurosci 29: 4263. [3] Mukherjee et al (2002) AJNR 23: 1445. [4] Huppi et al. (1998) Pediatr Res 44: 584. [5] Neil et al. (2002) NMR Biomed 15: 543. [6] Miller MI, et al. (2002) Annu Rev Biomed Eng 4: 375. [7] Oishi et al. (2011) Neuroimage 56: 8. [8] Wakana et al. (2007) Neuroimage 36: 630.

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Fig. 3: Boxplots of FA values (a) and fiber volumes (b) for individual WM tracts. The lines in all panels connect the median values. Small gray dots showing averaged measurements across all tracts are displayed as references in all plots. Significance of the rate change across two periods: - no significance, ↑/↓ 0.001<p<0.05, ↑↑/↓↓ p<0.001; significance of the rate change compared to 0 in each period: - no significance, * 0.001<P<0.05, ** P<0.001.