Normative Modeling of Early Brain Maturation from Longitudinal DTI Reveals Twin-Singleton Differences

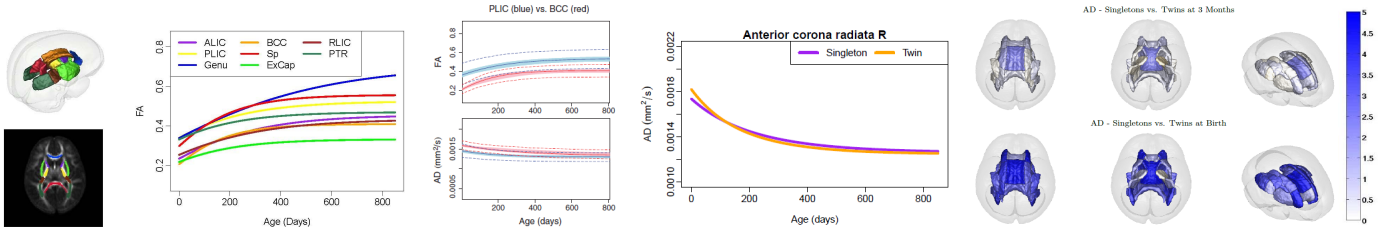
Neda Sadeghi[1], John H Gilmore[2], Weili Lin[3], and Guido Gerig[1]

[1]*Scientific Computing and Imaging Institute, Salt Lake City, UT, United States,* [2]*Department of Psychiatry, University of North Carolina, Chapel Hill, NC, United States,* [3]*Department of Radiology, University of North Carolina, Chapel Hill, NC, United States*

Introduction: Early brain development of white matter is characterized by rapid organization and structuring. Magnetic Resonance diffusion tensor imaging (MR-DTI) provides the possibility of capturing these changes non-invasively by following individuals longitudinally in order to better understand departures from normal brain development in subjects at risk for mental illness [1]. Longitudinal imaging of individuals suggests the use of 4D (3D, time) image analysis and longitudinal statistical modeling [3].

Methods: Mothers were recruited during their second trimester of pregnancy from clinics at the University of North Carolina for a longitudinal singleton/twin neuroimaging study, initiated in 2002. Infants were scanned at about 2 weeks, 1 year and 2 years without sedation during natural sleep (UNC IRB approved). In total, 26 singletons and 76 twins (mono- and dizygotic) with 2 or 3 DTI scans were used for this study, resulting in 238 DTI scans in total. Scanning was done on a 3T Allegra head-only MR system using a single shot EP SE sequence with 6 gradient directions, repeated 5 times, b-value of 1000s/mm^2. Image registration and processing followed longitudinal registration and tensor estimation as outlined in [2,3], resulting in co-registration of all subjects and all longitudinal scans into one unbiased atlas coordinate system. 21 regions of interest (ROI) were obtained by mapping the Susumo Mori white matter template to this atlas space, and DTI indices such as fractional anisotropy (FA), mean diffusivity (MD), and axial and radial diffusivities (AD, RD) were averaged within these regions for each subject and time point. Modeling of temporal trajectories was obtained via a 3 parameter Gompertz growth function (delay, speed, asymptote) and nonlinear-mixed-effect-modeling (NLME) [3], resulting in average growth trajectories (fixed effects) and subject-specific individual trajectories (random effects). The freely available software "R" was applied to model hypothesis testing across regions and populations for the growth curve parameters. Confidence intervals were obtained with Monte Carlo simulations based on distributions of the maximum likelihood estimates of fixed effects. Please note that we used gestational age for modeling to account for twins born 25days earlier (this study) than singletons.

Results: Longitudinal trajectories of FA, MD, RD and AD of all 21 ROIs were computed and compared among singletons, MZ and DZ twins. MZ and DZ were combined into one "twin" group after testing revealed no MZ-DZ differences. Maturation trajectories illustrate the expected continuous increase of FA and decrease of MD, RD and AD (see Fig. b for FA and AD in PLIC and BCC regions). Statistical testing showed significant singleton-twin differences in axial diffusivity for left and right ALIC and ACR regions (Fig. c), with differences becoming insignificant after 2-3 months. Although not different, all other ROIs depicted the same trend of AD (Fig. d) and also RD changes, with twins higher at birth but rapidly decreasing over the first 2-3 months. 3D visualizations of %-differences of AD at 39 weeks and 3 months later illustrate this common decrease but also shows the variability across different ROIs.



(a) (b) (c) (d)

Figure: From left to right: a) Unbiased DTI atlas with overlay and 3D display of Mori wm template, with FA maturation curves for 8 major regions. b) Gompertz NLME fits with confidence bounds for FA (top) and AD (bottom) and PLIC and BCC regions. c) Singleton-twin differences in AD for the ACR region. d) 3D visualizations of singleton-twin %-differences in AD at 3months (top) and at 39 weeks (bottom).

Conclusions: This research shows our ability to build normative 4D trajectories of white matter diffusivity of the early developing brain, similarly to normative data for length and height, e.g.. Data includes average temporal trajectory and confidence intervals, to be used to compare individuals with neurological disease to the norm. The pattern of white matter diffusivity differences between twins and singletons at birth but disappearing over the first few months, shown in the delay parameter of the growth function, still has to be interpreted in terms of specific knowledge on neurodevelopment. However, this study demonstrates the sensitivity of our DTI-based modeling to detect subtle group differences in maturation trajectories based on personalized, subject-specific measurements.

References:

[1] Dubois, J. et al., Assessment of the early organization and maturation of infants' cerebral white matter fiber bundles: a feasibility study using quantitative diffusion tensor imaging and tractography. NeuroImage 30, 1121-1132.

[2] Geng, X., Gouttard, S., Sharma A., Gu, H., Styner, M., Lin, W., Gerig, G., Gilmore, J.H., Quantitative tract-based white matter development from birth to age 2years, NeuroImage, Volume 61, Issue 3, 2 July 2012, Pages 542-557

[3] Sadeghi, N., Prastawa, M., Fletcher, P. T., Wolff, J., Gilmore, J. H., Gerig, G., 2013. Regional characterization of longitudinal DT-MRI to study white matter maturation of the early developing brain. Neuroimage 2013 Mar;68:236-47