Longitudinal Diffusion Tensor Imaging of Healthy Brain Development in Children

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INTRODUCTION: Longitudinal brain development studies using conventional MRI have shown regional variation in development trajectories of white and gray matter volume, as well as gender differences[1]. Cross-sectional studies using diffusion tensor imaging (DTI), a more sensitive measure of tissue microstructure than conventional imaging, have demonstrated increases of fractional anisotropy (FA), a measure of white matter integrity related to myelination and axonal density, during infancy[2], childhood[3] and adolescence[4-6]. Longitudinal studies reduce variability, and thus provide more power to detect maturational trends and sex differences. DTI studies have examined longitudinal development in a small number of infants[7], but, to our knowledge, longitudinal DTI has not yet been used to study healthy development during childhood and adolescence. The goal of this study was to examine longitudinal development of brain white matter using DTI in a group of 45 healthy children scanned at 2-4 different time points.

METHODS: This study included 45 subjects initially aged 5-12 years (26m/19f) with no history of neurological disease or injury. Each subject had 2-4 MRI scans at 1-6 year intervals. All scans were performed on the same 1.5T Siemens Sonata scanner using the same protocol. DTI was collected using dual spin echo EPI, 40 3mm slices (no gap), image matrix 96x128 zero-filled to 256x256, TE/TR = 88 ms/6400 ms, b=1000 s/mm^2, 8 averages and 6 directions, 6:06 minutes long. Images were normalized to a homemade template using non-affine registration. Tractography was performed in ExploreDTI using a semi-automated method in which seeding, inclusion, and exclusion regions were drawn on the template FA map and automatically mapped to native space for each individual. FA was calculated in each subject for each of eleven major white matter tracts: the cingulum, corticospinal tract (CST), superior and inferior longitudinal fasciculi (SLF, ILF), superior and inferior fronto-occipital fasciculi (SFO, IFO), fornix (columns/body only), uncinate fasciculus (UF), and genu, splenium, and body of the corpus callosum (gCC, sCC, bCC). Where appropriate, left and right sides were measured separately and if differences were not significant, combined for further analysis. Linear mixed models accounting for the repeated measures were used to fit the following equation to the FA data for each tract: $FA = C + A_1 age + A_2 age^2 + A_3 gender$.

RESULTS/DISCUSSION: Longitudinal DTI revealed significant age-related changes in all eleven tracts (two are shown in Fig. 1). In general, there was good agreement between hemispheres, with only the IFO showing significant left-right differences. In the gCC, sCC, and right IFO, the age^2 term was significant, indicating faster development at younger ages that levels off toward the upper end of the age range. All other tracts showed linear changes with age; a wider age range is needed to determine when the trajectories for these tracts would level off. Males had significantly higher FA than females in four tracts: gCC, cingulum, SFO and CST. The observed longitudinal increases of FA are consistent with previous cross-sectional studies[4-6, 8]. Furthermore, with the increased sensitivity of longitudinal measures, development of the fornix during childhood and adolescence was observed. Development seems to occur earlier in the gCC, sCC, and right IFO than other tracts, with FA in these pathways leveling off at the upper age range, confirming cross-sectional findings of early callosal development[5, 6]. In addition, sex-related differences of FA were evident in the gCC, cingulum, SFO and CST, supporting previous cross-sectional studies showing sex differences in frontal white matter, cingulum, and internal capsule[9,10]. This study, one of the first longitudinal DTI studies of healthy brain development, provides insight into white matter maturation during childhood and adolescence, including timing and sex differences.

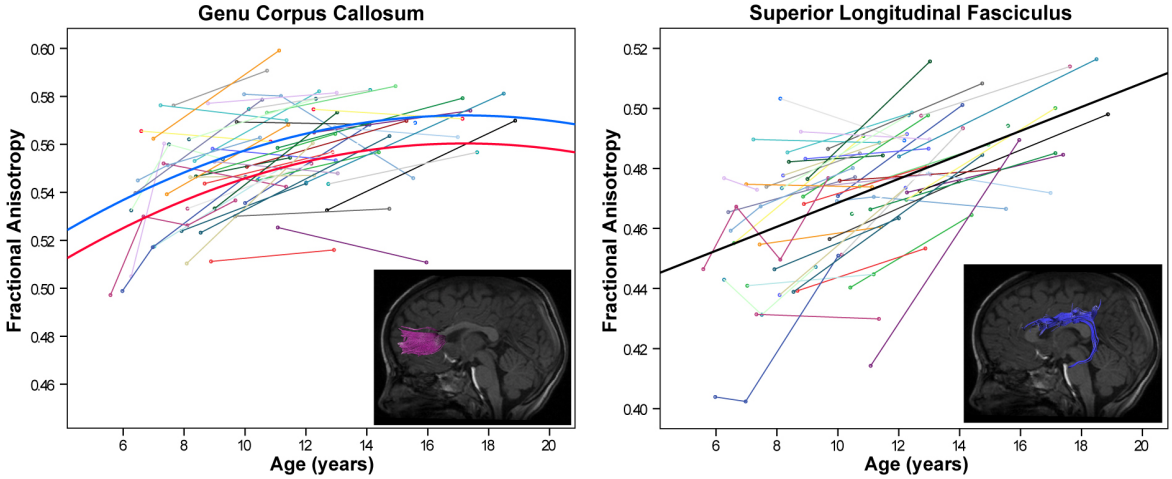

Figure 1: Development plots showing each subject's fractional anisotropy (FA) values (connected with a line) vs. age, and the overall best fit development curves for the genu of the corpus callosum and the superior longitudinal fasciculus (SLF). Development occurred earlier in some tracts (such as the genu), as indicated by the leveling off toward the upper end of the age range, compared to others, which continue to increase (such as the SLF). The genu showed sex differences with the male curve (blue) higher than the female curve (red), whereas the SLF did not show any gender dependence.

REFERENCES: 1.Lenroot *et a.*, *Neuroimage* **36**, 1065 (2007). 2.Dubois *et al*, *Neuroimage* **30**, 1121 (2006). 3.Hermoye *et al*, *Neuroimage* **29**, 493 (2006). 4.Barnea-Goraly *et al*, *Cereb Cortex* **15**, 1848 (2005). 5.Ben Bashat *et al*, *JMRI* **21**, 503 (2005). 6.Lebel *et al*, *Neuroimage* **40**, 1044 (2008). 7.Partridge *et al*, *JMRI* **22**, 467 (2005) 8.Eluvathingal *et al*, *Cereb Cortex* **17**, 2760 (2007) 9.Schmithorst *et al*, *Hum Brain Mapp* **29**, 696 (2008) 10.Schneiderman *et al*, *Neuropsychobiology* **55**, 96 (2007).