White Matter Development and Asymmetry Mapped using DTI in 12-21 Year Old Twins

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Introduction: The development of the brain through adulthood is a topic of much interest in neuroscience; it allows for a deeper understanding of genetic influences on neuroanatomy and rates of neurophysiological evolution. Hemispheric asymmetry is also of great interest as it can shed light on the functional specialization and disease progression [1]. This study combines these two areas of research as we used diffusion tensor imaging (DTI) to examine white matter fiber architecture across three age groups. Linear mixed effects regression was performed on a voxel-wise level to determine age related trends in white matter integrity and its variations across hemispheres.

Methods: High magnetic field (4T) diffusion tensor MR images (30 gradients, 21 5-mm thick axial slices, 1.8x1.8 mm^2 in-plane resolution; 23 cm FOV, *b*-value=1132 s/mm^2) were acquired from 58 (30F) 12-year old, 67 (40F) 16-year old, and 59 (36F) 21-year old groups of mono-and dizygotic twins. Distortion corrected diffusion weighted images were used to calculate anisotropy measures for each subject. The fractional anisotropy (FA) maps were then linearly aligned standard FA map (JHU DTI Atlas). This atlas was then symmetrized by averaging the left and right hemispheres and thresholded at FA ≥ 0.25 to produce a template of high probability white matter regions. Each subsequent subject's FA image was also thresholded at FA ≥ 0.25 and elastically registered to the symmetrized high FA template. The deformation fields obtained from the registration were then applied to the unthresholded image and the template mask was applied to ensure adequate coverage of each subject. The differences between the hemispheres for each anisotropy measure were obtained by subtracting each subject's image from a copy reflected over the mid-sagittal plane. Using a random effects regression analysis to account for familial relations in the twin samples, the FA values along with their L-R difference values were regressed with age. Voxel-wise maps of the probability of FA-age and asymmetry-age correlation were obtained. Inter- and intra-age group statistical tests of mean and variance were performed on unrelated individuals.

Results: Age related changes in FA were highly significant across large portions of the brain after multiple comparison corrections using FDR in the white matter volume (**Figure 1a**; p^* (*FDR corrected critical p-value*)<0.017). Beta maps indicate a generally increasing trend in FA with age with as high as 0.01 increase in FA per year. The change in asymmetry in FA values with age was generally not found to be significant except for a few voxels of the thalamic region, confirming findings in [2] (**Figure 1b** $p^*<4x10^{-6}$). However, each age group independently had significant differences in inter-hemispheric FA (**Figure 2**; $p^*<0.013$(12yo), 0.013(16yo), 0.010(21yo)) with FA in the right frontal regions being greater than the left, and left splenium regions having higher FA than the right. Fixing the effects of gender in regression showed no changes in overall age-associated FA or FA asymmetry significance.

Conclusions: Frontal regions including areas of the corona radiata are amongst regions where age related differences in FA are most pronounced. As fiber-crossings and partial volume effects are well know shortcomings of scalar DTI measures like FA, further study using high angular diffusion imaging (HARDI) is needed to clarify whether or not these anisotropic variations in age are partially due to fiber organization in addition to integrity. While the overall FA appears to increase with age, the trend in lateralized anisotropy differences appears fairly constant with development. The asymmetry presented in the white matter tracts may instead be due to genetic associations and variations in the population. Further

investigation will also include quantitative genetic analysis of the white matter diffusivity in subjects of all ages as well as associations with asymmetrical associations with cognitive factors.

References:
[1] Toga AW, Thompson PM (2003). *Mapping Brain Asymmetry,* **Nature Reviews Neuroscience**, 4(1):37-48.
[2] Klingberg et al, (1999). Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study **NeuroReport**,10:2817-2821

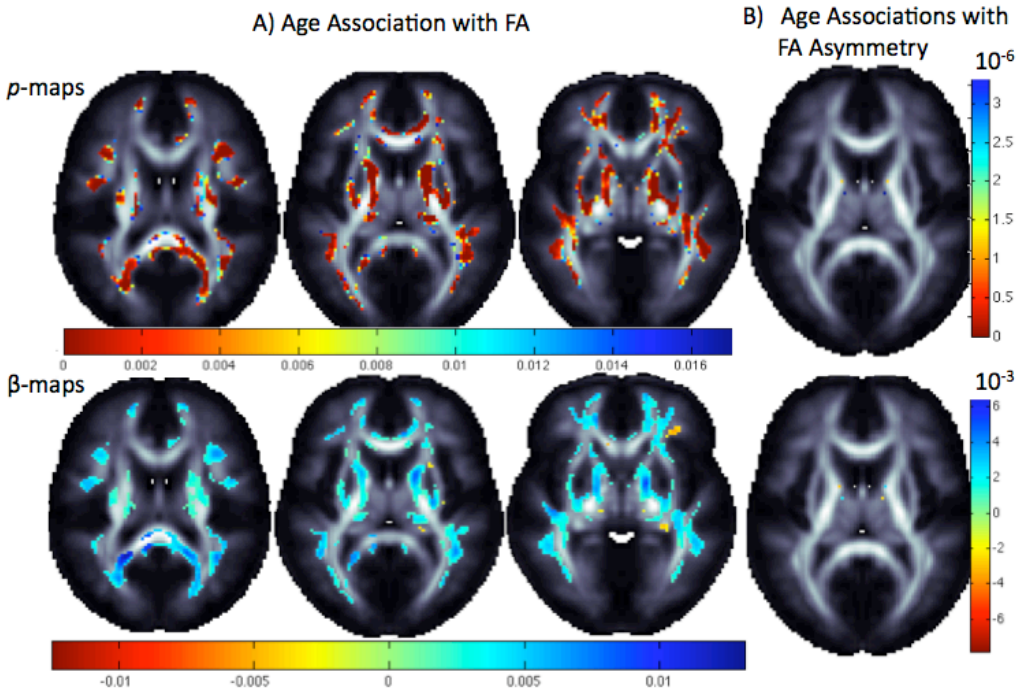

Figure 1: Top row- p-values, Bottom row: Beta values for : a) regions of age associated differences in FA, and b) regions of age associated asymmetry ($p < 4x10^{-6}$) with L > R FA in the thalamic region and R > L inside the white matter tract itself. The left handed side of the images correspond to the left hemisphere.

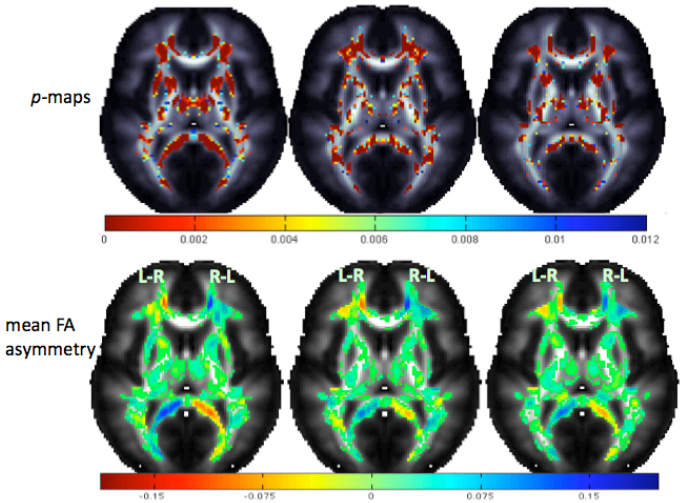

Figure 2: Group specific differences in FA asymmetry (L:12 yo, C:16 yo, R: 21yo). Top row shows significant p-values; bottom row illustrates the directionality