White Matter Development During Late Adolescence in Healthy Males: A Cross-Sectional Diffusion Tensor Imaging Study

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Background: Adolescence is a time period when there are ongoing developmental changes in brain gray and white matter microstructure and organization. Previous cross-sectional studies have reported white matter anisotropy changes in some human brain regions involved in language development as age increases in healthy children and adolescents. The authors investigated white matter maturation as reflected by changes in anisotropy with age in a cohort of healthy adolescent males.

Methods: Twenty-four healthy male volunteers (mean age = 16.6 years, SD = 2.5; range 11 to 21 years) were divided into two groups based on a median age split for the entire sample and were studied with diffusion tensor imaging (DTI) using a voxelwise method. In addition to routine clinical scans diffusion tensor images (DTI) and a matching fast spin echo (FSE) double echo sequence were acquired. A 3D spoiled gradient recalled (SPGR) with inversion prep pulse (IR-Prep) (TR/TE, 10.1/4.2 msec, 256x192 matrix, 22 FOV, 124 partitions, 1.5mm coronal orientation, inversion time = 600 msec, and one NEX, total scan time = 7:59 minutes) was also obtained. The diffusion tensor sequence used in this study utilized a total of 25 non-collinear diffusion gradient directions and a diffusion sensitization b-factor of 1000 s mm^{-2} for acquisition of twenty-three slices through the whole brain. For each b value and gradient direction two images were acquired (NEX =2), increasing the signal-to-noise ratio (SNR) of the diffusion images. After complete description of the study to the subjects and their parents, written informed assent and consent were obtained.

Results: As illustrated in Figure 1 (first column), voxel wise analysis of the whole brain comparing two groups of normal controls only revealed one significant cluster of higher fractional anisotropy in older males in the left arcuate fasciculus. At lower thresholds, other clusters of higher fractional anisotropy along the arcuate fasciculus became evident (> 100 voxels, p = 0.01) and when we reduced the threshold further (> 200 voxels, p = 0.05) age-related increases in fractional anisotropy appeared to be bilateral but more spread along the left arcuate fasciculus. At lower levels of statistical significance other areas of increased FA in several anatomical locations such as frontal lobe, corpus callosum, basal ganglia, etc were observed. At the highest threshold (p<0.005), intermediate threshold (p=0.01) and low threshold (p=0.05), we also observed age-related increases in $\lambda_{\|}$ values in older healthy males (Figure 2) along the left arcuate fasciculus, similar to areas found with increased FA. There were no significant changes in $\lambda_{\perp}$ along the left arcuate fasciculus at high, intermediate, or low threshold levels. There was a positive significant correlation (r = .592, p = 0.002) between age and the cluster with increased FA (at p<0.005) located at the boundary of the posterior temporal and inferior parietal region (Figure 1, column 1). A similarly high correlation (r = .604, p = 0.002) existed between the increased $\lambda_{\|}$ values and age in the analogous location as the increased FA cluster.

Conclusions: These cross-sectional data demonstrate that there are striking white matter anisotropy changes in the left arcuate fasiculus in healthy adolescent males with increasing age. The increased FA and $\lambda_{\|}$ with no changes in $\lambda_{\perp}$ may reflect a tendency in reduced tortuousity and/or increased axonal fiber organization to a more parallel orientation during brain maturation in late adolescent. Increases in white matter fractional anisotropy and axial diffusivity in the left arcuate fasiculus over the age span also correlated in the expected direction with improved cognitive performance on tests measuring language functions. In conclusion, consistent with earlier post-mortem (Benes et al 1994) and in vivo conventional neuroimaging (Giedd et al 1999; Paus et al 1999) and DTI studies (Takahashi et al 2000; Schmithorst et al 2002, Barnea-Goraly et al 2005) we presented a striking pattern of maturation of white matter microstructure in healthy male adolescents during the second decade of life. Based on an animal study reported by Takahashi and colleagues (2000) and our results of parallel increase in axial diffusivity and fractional anisotropy, the late adolescent maturation changes may reflect tendency in reduced tortuousity and/or increased axonal fiber organization to a more parallel orientation.

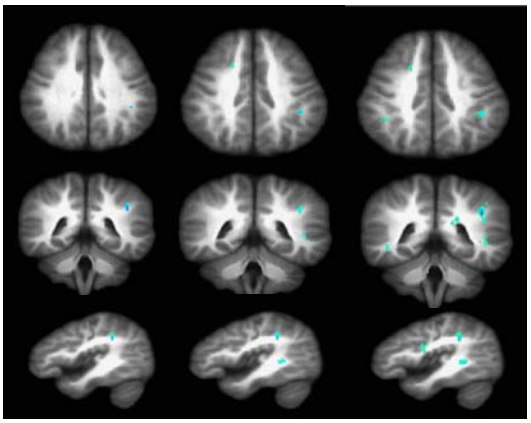

Figure 1. Increased Fractional Anisotropy in Left Arcuate Fa
At the highest statistical threshold (column A) only one cluste
in the inferior parietal lobule. At an intermediate threshold (cc
second cluster located at the middle temporal gyrus emerges
threshold (column C), a third cluster is depicted at the inferio

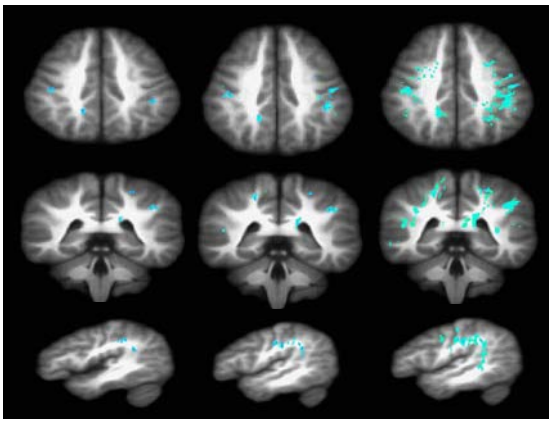

Figure 2. Increased $\lambda_{\|}$ values in the left arcuate fasciculus
versus younger healthy adolescents. Similar to FA, a more
statistical threshold in $\lambda_{\|}$ analysis (column B and C) result
extensive spread of increased $\lambda_{\|}$ clusters along the acrcua
fasciculus,