Sexual dimorphism in white matter development in pre-adolescence: a tract based spatial statistics study

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Introduction The structure of the brain develops throughout childhood, into adolescence and early adulthood [1]. Although the most significant brain changes occur in children up to the age of 5 years, structures continue to develop well into early adulthood. In addition to this, there is some evidence that the development of male and female brains differs [1, 2]. Diffusion MRI (dMRI) offers unique insights into brain development by allowing us to probe tissue microstructure. Several studies [2, 3, 4, 5] have investigated the effect of age and/or gender on brain development using dMRI, but they typically use a large age range (childhood to early adulthood). This work investigates brain development in the late childhood age range (8.0-12.8 years) using Tract-Based Spatial Statistics (TBSS) [6]. The results suggest there are widespread white-matter changes in boys in this age range but not in girls.

Methods The dataset consists of 41 healthy children aged from 8.0 to 12.8 years old (mean age 10.4±1.3 years), of which 21 are female. Imaging data was acquired using a Siemens Avanto 1.5T clinical scanner. Echo-planar diffusion-weighted images were acquired along 20 non-collinear gradient directions at b=1000 s mm^{-2}, with a single b=0 image for normalisation. A voxel matrix of 96 × 96 was used to obtain 45 contiguous axial slices with a 240 × 240 mm field of view. The voxel dimensions were 2.5 × 2.5 × 2.5 mm. Other acquisition settings: TR=6300 ms, TE=89 ms, gradient strength=40 mT m^{-1}. We repeated the acquisition three times to improve the signal-to-noise ratio. T1-weighted images were also acquired in the same session. The study was approved by the local ethics committee and informed consent was obtained from both children and their parents.

Preprocessing of the data involved removal of eddy-current distortions, skull-stripping of the brain volume and fitting the diffusion tensor (DT) using FSL (http://www.fmrib.ox.ac.uk/fsl). The standard TBSS algorithm was used to analyse the data. To improve alignment, a study specific template was generated, to which all the subjects were registered. In addition to FA, changes in the mean diffusivity (MD), axial diffusivity (λ_{axial}) and radial diffusivity (λ_{radial}) of the DT were also investigated. The mean of each diffusion parameter over the white-matter skeleton was also calculated for each subject and plotted against age to show overall trends.

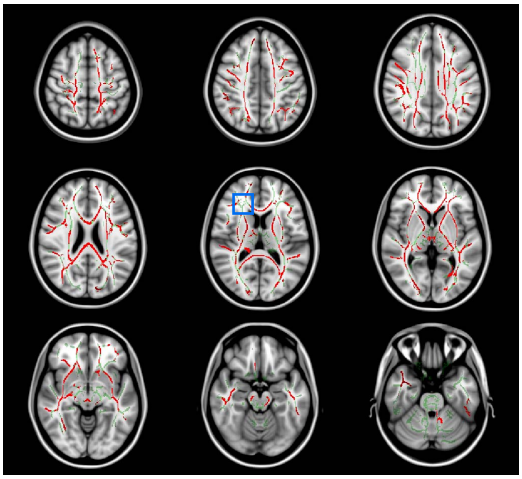
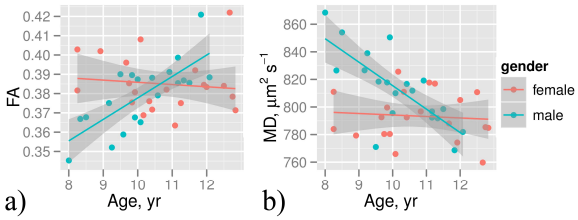


Figure 1 – TBSS skeleton showing significant ($p<0.05$) positive correlation between FA and age for the male subjects in red.



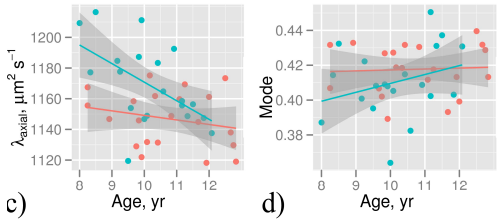


Figure 2 – Plots of mean a) FA, b) MD, c) λ_{radial} and d) λ_{axial} over skeleton against age for both males (blue) and females (red).

Results The TBSS analysis of the female subgroup showed no significant correlation of the diffusion measures with age after correction for multiple comparisons. In contrast, the male subgroup showed widespread differences across the white-matter skeleton. Figure 1 shows TBSS results (correlation between FA and age) for the male subjects overlaid onto the FSL MNI152 T1 template. The areas highlighted in red indicate regions where there is a significant ($p<0.05$) positive correlation between FA and age in the male subjects. FA increases occur throughout the brain, which is in agreement with findings on child-adolescent development [7, 8]. We also see decreases in MD, λ_{radial} and, to a lesser extent, λ_{axial} (not shown). There are, however, some differences between the TBSS results for FA compared to MD and λ_{radial}. For example, there is no significant correlation of FA with age in the crossing fibre region of the periventricular white-matter (highlighted by the blue box in figure 1), but there is a significant negative correlation between MD/λ_{radial} with age.

Figure 2 shows plots of the DTI measures, averaged over the white-matter skeleton, against age for each subject. The figure shows a significant increase in FA (a) and significant decreases in MD (b) and λ_{radial} (c) for the male subjects, but no correlation with age for the female subjects. Correlation between λ_{axial} and age (figure 2d) did not reach significance for male or female subjects.

Discussion and Conclusions As far as the authors know, this is the first TBSS study to look at sexual dimorphism in children in the age range 8-13 years. The TBSS study shows widespread changes in white-matter across the brain in males but not in females in this age range. Specifically, there is a positive correlation between FA and age in male subjects and a corresponding significant negative correlation between MD/λ_{radial} and age. In addition to this, MD and λ_{radial} significantly correlate with age in several regions that FA does not.

The further analysis in figure 2 suggests that the FA for male subjects is initially lower than that of the female subjects, but the difference between genders gradually decreases and is negligible by the age of around 10-12 years. The MD and λ_{radial} plots show similar trends, where the diffusivity is higher for the male subjects but gradually converges to the range of the female subjects. These findings suggest that development seen in males may have already occurred in the female subjects. Taken together, these findings suggest a different course of white-matter development in males and females in this age range. These differences may be related to pubertal stage [8] and testosterone/oestrogen levels and are the subject of ongoing research.

References **[1]** R.K. Lenroot and J.N. Giedd, Neurosci Behav Rev, 30: 718-729, 2006 **[2]** V.J. Schmithorst *et al*, HBM, 32:696-710, 2008 **[3]** C. Lebel *et al*, NeuroImage, 40:1044-1055, 2008 **[4]** A. Giorgio *et al*, NeuroImage, 39: 52-61, 2008 **[5]** L. Snook *et al*, NeuroImage, 26:1164-1173, 2005 **[6]** S.M. Smith *et al*, NeuroImage, 31:1487-1505, 2006 **[7]** A. Giorgio *et al*, NeuroImage, 49:94-103, 2010 **[8]** M. R. Asato *et al*, Cereb Cortex, 20:2122-2131, 2010

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