Gender differences in the rate of white matter microstructural development during late childhood and adolescence

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Introduction

There is evidence for various changes in white matter microstructure during development. Particular pathways in which effects of increasing age have been observed using diffusion MRI (dMRI) include the arcuate fasciculi (AFs), corticospinal tracts (CSTs) and uncinate fasciculi (UFs) [1,2]. However, whilst absolute gender differences in dMRI parameters such as mean diffusivity (MD) and fractional anisotropy (FA) have been previously investigated—although few effects have generally been observed—to our knowledge no previous study has studied gender differences in the *rates* of change of these parameters. Here we demonstrate significant differences in the rates of change of MD between the sexes.

Methods

Data were acquired from 59 subjects in late childhood or adolescence (25 male, mean age 11.5 ± 2.1 yr, age range 8–17 yr). All subjects were healthy, without any neurological, psychiatric or developmental problems, and none had any MR-visible structural abnormalities. Each subject underwent a dMRI protocol on a Siemens Avanto 1.5 T clinical scanner. Echo-planar diffusion weighted images were acquired along 20 noncollinear directions at a b-value of 1000 s mm^{-2}, along with a b=0 image. This protocol was repeated three times, and the data combined without averaging. Reconstructed image resolution was 2.5 x 2.5 x 2.5 mm.

Correction for eddy current induced distortions, brain extraction, and calculation of diffusion tensor MD and FA

Fig. 1: *Effects of age on MD in the three tracts of interest. Top row: group maps of the right sided tracts of interest, shown in maximum intensity projection in MNI standard space. Bottom row: plots of age against MD for each bilateral pair of tracts, along with linear regression lines for each gender/tract combination. The shaded areas represent the standard error associated with each fit.*

values was carried out using FSL tools (http://www.fmrib.ox.ac.uk/fsl). The tractography algorithm used was the multicompartment version of FSL ProbTrack [3], which allows for the presence of two white matter fibre populations in each voxel. The probabilistic neighbourhood tractography (PNT) technique [4], as implemented in the TractoR package (http://code.google.com/p/tractor), was used to select seed points for segmentation of the AFs, CSTs and UFs in each subject. This fully automated approach is based on a probabilistic model of tract shape variability, and a reference tract which represents prior anatomical knowledge for each tract trajectory. The model was also used to exclude false positive pathways by rejecting "unlikely" streamlines [5], thereby obviating the need to threshold visitation maps. Mean FA and MD, weighted by voxel visitation count, were finally obtained from within each segmented region. The PNT framework also provides a natural measure of segmentation goodness-of-fit, representing the extent to which the shape of a given segmented tract matches that of the reference pathway. Tracts with abnormally low goodness-of-fit scores (more than 1.5 times the interquartile range below the first quartile) were excluded from further analysis.
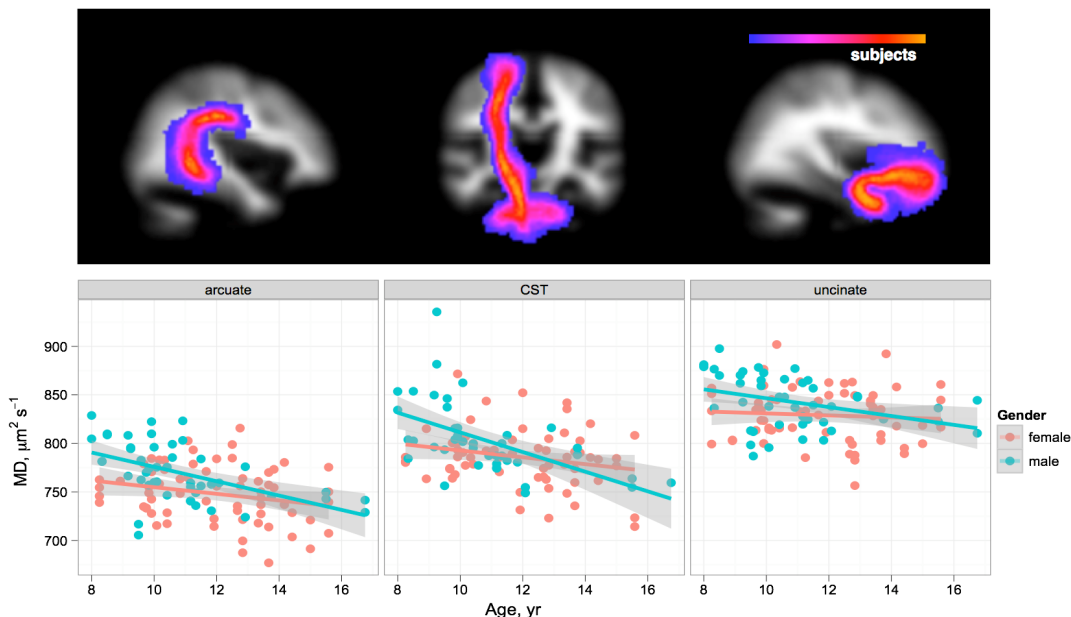
Results

The top row of Fig. 1 shows group maps of the segmented tracts of interest. After applying PNT, including the rejection of false positive pathways, segmentation specificity is high, even without thresholding individual visitation maps.

FA and MD values were each regressed against a linear model containing main effect terms for gender, tract and age, as well as interaction terms between gender and age (allowing for differences in slope between genders), and tract and age (allowing for differences in slope between tracts). Bilateral tracts were treated as repeated measurements. In the case of FA, ANOVA showed that all three main effects were statistically significant, but neither interaction was. All main effects were likewise significant for MD, but there was also a significant interaction between gender and age ($F_{1,322}$=8.49, $P<0.01$). There was no significant interaction between tract and age. Looking at each tract individually, we observed a significant difference in slope between the genders only in the CSTs ($|t_{103}|$=2.18, $P<0.05$), but the bottom row of Fig. 1 shows that the pattern of shallower slopes in females is common across all the tracts of interest. Direct correlation tests between diffusion parameters and age in each tract revealed that FA correlated significantly with age only in the AFs, while MD was significantly correlated with age in all tracts.

Discussion

We have shown, in what we believe to be the first study of this effect, substantial evidence that the microstructural development of white matter takes place at different rates in the two sexes, over the age range of 8–17 years. This difference was broadly specific to mean diffusivity, reflecting changes in the mobility of water in tissue, perhaps due to myelination. That MD is more stable in girls over this age range may reflect later development of white matter in boys, with the equivalent changes in girls taking place at a younger age.

References: [1] Eluvathingal, T.J. et al., *Cereb Cortex* **17**:2760 (2007); **[2]** Giorgio, A. et al., *NeuroImage* **49**:94 (2010); **[3]** Clayden, J.D. et al., *NeuroImage* **45**:377 (2009); **[4]** Behrens, T.E.J. et al., *NeuroImage* **34**:144 (2007); **[5]** Clayden, J.D. et al., *Lect Notes Comp Sci* **5762**:150 (2009).