# Developmental changes in white matter microstructure in adolescence

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## Introduction

Both quantitative structural and functional magnetic resonance imaging studies and post-mortem histological analysis have demonstrated that myelination in brain white matter (WM) is not complete by childhood but continues throughout adolescence and adulthood. In recent years, diffusion tensor magnetic resonance imaging (DTI) has been used to investigate this issue [1, 2, 3]. However, there is not complete agreement over the presence and extension of DTI changes in childhood, and more limited DTI data are available for adolescents and young adults. The aim of this study is to define age-related structural WM changes in a group of adolescents and young adults using diffusion-weighted MRI.

## Methods

DTI and T1-weighted images were acquired in 42 healthy adolescents (22 males, 20 females; age range 13.5-21 years; 40 right-handed, 2 left-handed) and in 20 healthy young adults (11 males, 9 females; age range 23-42 years; all right handed). Voxelwise fractional anisotropy (FA) and diffusivity parallel ($\lambda_1$) and perpendicular (($\lambda_2 + \lambda_3$)/2) to the principal diffusion direction were calculated using the FMRIB Diffusion Toolbox (FDT), part of the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl). We used Tract-Based Spatial Statistics (TBSS), a method for statistical comparison of FA values between individuals [4], to test for local correlations between age and FA across the whole brain WM. To test for global changes in diffusion measures we found mean FA and diffusivity values across the whole WM skeleton for both subject groups. The Mann-Whitney U test was used to compare FA and diffusivity values across the skeleton between the adolescent group and the young adult group (using a significance threshold of $p<0.05$). A t-value was calculated for each skeleton voxel to represent the correlation between age and FA or parallel or perpendicular diffusivity. The resulting t map was thresholded at $t>3$ and we then used the randomize program within FSL to apply permutation testing in order to assign cluster-wise probability values to each resulting cluster. We considered only those clusters at which $p<0.05$ (corrected for multiple comparisons). Voxels identified in this way were used as seed masks for probabilistic tractography [5]. Pathways in each subject were then binarised and overlaid to produce population probability maps for each pathway, in which voxel values represent the number of subjects in whom a pathway is present. Tissue type classification was performed on T1-weighted images and then used to perform a voxel-based morphometry-style analysis of grey matter in the adolescent group.

## Results

*Relationship between white matter structure and age in adolescents*

When averaging white matter values across the whole skeleton, we found a positive correlation between age and mean FA within the adolescent group ($r=0.42$, $p<0.01$) and a negative correlation between age and ($\lambda_2 + \lambda_3$)/2 ($r=-0.35$, $p<0.02$). TBSS analysis of local correlations revealed a positive correlation between age and FA within two WM regions that probabilistic tractography identified as belonging to the right part of the body of corpus callosum (CC, Figure 1A,B,C) and to the right superior region of corona radiata (SCR, Figure 1D,E,F) ($r=0.55$ and $r=0.56$, respectively; $p<0.001$). TBSS analysis using voxel-wise values of $\lambda_1$ or ($\lambda_2 + \lambda_3$)/2 found no clusters showing correlation between age and $\lambda_1$, whereas some clusters showed a negative correlation with age for ($\lambda_2 + \lambda_3$)/2; these included a WM cluster on right part of the body of CC ($r=-0.53$, $p<0.001$) overlapping the cluster derived from cluster-corrected TBSS of FA. We also tested for significant age-related differences in FA by dividing our adolescent group into two subgroups – the 15 oldest subjects, and the 15 youngest subjects. This analysis revealed higher FA in the older subjects in the body of the corpus callosum.

*Relationship between GM volume and age in adolescents*

We did not find any significant correlations between grey matter (GM) volume and age in the adolescent group. When splitting the adolescent group into two groups, the 15 youngest and the 15 oldest subjects, the younger subgroup showed a trend toward an increased GM density in the right middle frontal gyrus and in right precentral gyrus after correction for multiple comparisons (Figure 2, $t>2.5$, $p<0.10$).

*Relationship between white matter structure and age in young adults.*

In contrast to the adolescent group, the young adult group did not show significant correlations between age and any DTI parameters when averaging values across the whole WM skeleton. TBSS analysis of local correlations with age revealed a single region that survived cluster-based correction for multiple comparisons within the right superior longitudinal fascicle (SLF) ($r=0.67$, $p=0.001$). No voxels showed significant correlation between age and $\lambda_1$ and ($\lambda_2 + \lambda_3$)/2.

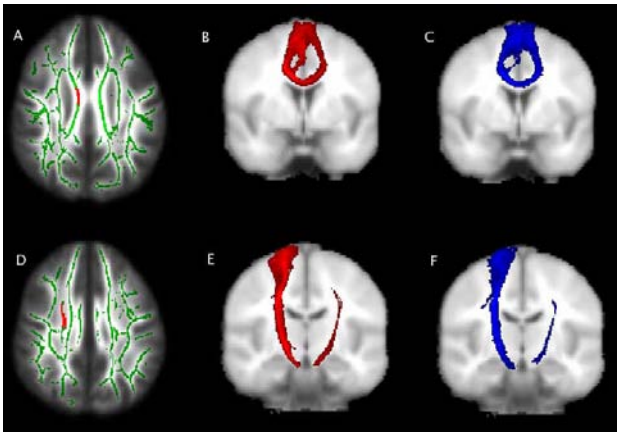
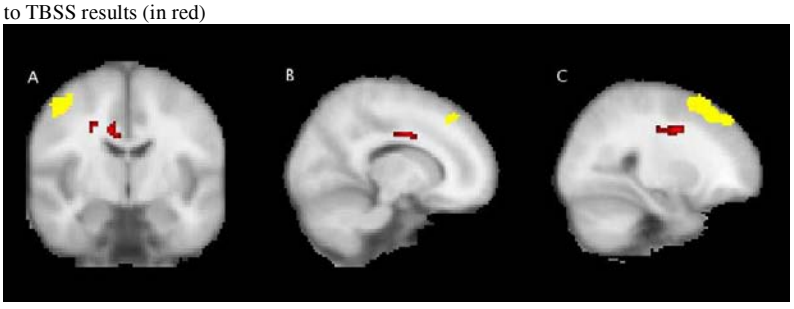



Figure 1 (*left*): in A and D, red shows clusters where FA correlates positively with age in adolescents, green shows the mean FA skeleton and the background image is the mean FA. In B, C, E and F the pathway probability distributions for the youngest (in red) and oldest (in blue) adolescents

Figure 2 (*bottom*): increased GM changes in the youngest adolescents (in yellow) in relation to TBSS results (in red)




## Conclusions

Our results suggest that widespread developmental changes in white matter microstructure continue throughout adolescence and are particularly prominent in specific fibre pathways including the body of corpus callosum. White matter changes plateau off in early adulthood with the exception of the cortical projection pathways travelling through the superior longitudinal fascicle. This study also demonstrates that, at least in adolescents, age-related increases in FA are driven by decreases in perpendicular diffusivity, suggestive of increases in myelin barriers to diffusion in this direction.

## References

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