# Sex Differences in White Matter Diffusion Anisotropy in the Normal Pediatric Population

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## Introduction

Diffusion tensor imaging (DTI) provides a non-invasive methodology for *in vivo* measurement of microstructural properties of brain white matter. Sex differences in fractional anisotropy (FA) have previously been reported for adult subjects. Women showed higher FA in the left frontal lobe compared to men [1] and exhibited leftward asymmetry of FA, while men displayed higher FA in the corpus callosum [2]. We report results from an investigation of sex differences in FA in a cohort of normal children ages 5-18.

## Materials and Methods

Data was acquired from 106 children (52M, 54F, mean age = 12.3 ± 3.5 yrs.) on a Bruker 3T system. The Wechsler Full-Scale IQ was in the normal range (mean IQ = 110.9 ± 13.7). 99 of the subjects were right-handed; 6 were left-handed (4M, 2F) and one (M) was ambidextrous. EPI-DTI scan parameters were: TR = 6070 ms, TE = 87 ms, FOV = 19.2 X 25.6 cm, slice thickness = 5 mm, matrix = 64 X 128, $\Delta$ = 40 ms, $\delta$ = 18 ms, diffusion gradient strength = 30 mT/m, b-value = 710 s/mm$^2$. Three scans were acquired without diffusion weighting, and 25 diffusion-weighted scans were acquired, with diffusion directions determined using the electrostatic repulsive model [3]. Geometric distortion due to gradient eddy currents was minimized using an automated gradient preemphasis adjustment routine [4]. To minimize artifacts from subject motion, the Robust EStimation of Tensors by Outlier REjection (RESTORE) method was utilized [5] to compute the tensor components. Empirical visual analysis showed the method to be robust in rejecting datapoints corrupted by gross motion or by motion during the diffusion-sensitizing gradient. FA maps were computed and transformed into normalized space using procedures in SPM (Wellcome Dept. of Cognitive Neurology, London, UK) applied to T1-weighted anatomical images from each subject. For each subject, analysis was restricted to voxels with a posterior probability of > 0.9 of being in white matter from the SPM segmentation results, as well as FA > 0.30; globally, analysis was restricted to voxels (averaged over all subjects) with average FA > 0.35 and average white matter probability > 0.5. The strict thresholds used for restricting the subset of voxels analyzed minimize the risk of spurious results due to partial volume effects and imperfect spatial normalization. A voxelwise General Linear Model (GLM) was then used to analyze the data, with gender the regressor of interest and age (in months) as a covariate of no interest. The T-score maps from the GLM were converted into Z-score maps, and filtered with a Gaussian filter of width 4 mm. A threshold of Z = 5 with spatial extent threshold of 50 voxels was used, resulting in a corrected $p < 0.01$ using Monte Carlo simulation [6], estimating the intrinsic spatial autocorrelation from the residuals.

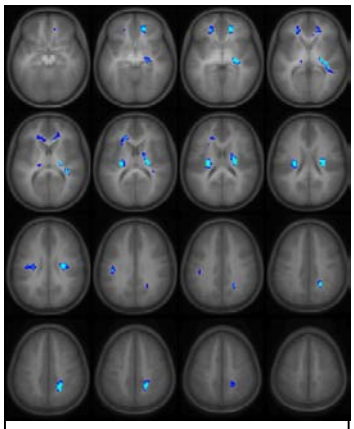

**Figure 1.** Regions with FA in boys > girls, All regions significant with corrected $p < 0.01$. All images in radiologic orientation; slice range Z = -12 mm to Z = +60 mm.

## Results and Discussion

Boys showed higher FA in inferior fronto-temporal white matter, the genu of the corpus callosum, and the corticospinal tract including the corona radiata bilaterally (Figure 1), as well as left parietal white matter. No regions were found with higher FA in girls. ROIs were drawn around each region, and a two-way ANCOVA was performed with age and sex being the independent variables. All regions, as expected, displayed a significant ($p < 0.01$) main effect for sex; all regions also displayed a significant ($p < 0.01$) main effect for age, with the exception of the frontal regions, agreeing with previous results [7]. No age-by-sex interactions were detected, even at a nominal significance level of $p < 0.05$ uncorrected for multiple comparisons, indicating that the sex-related differences detected may persist throughout the entire developmental period. Since handedness was a potential confounder, the analysis was re-run using only right-handed subjects; every region still met the significance criterion.

The differences found in the frontal lobes, with boys showing greater FA than girls, are opposite to the previous results showing greater FA asymmetry in adult women [1]. The frontal regions found in our study however are inferior to those regions found in [1]; additionally our population spans the entire developmental age range. It is possible that greater FA in women in more superior frontal regions only develops later in childhood or in early adulthood, as the cortical circuitry in these frontal regions may be the latest to develop [8]. A previous study using DTI [2] found significantly greater anisotropy in all subregions of the corpus callosum in adult men compared to adult women. Our study however only displayed significant differences in the genu; further research using ROI-based analysis techniques will investigate whether this result is a merely an artifact of the decreased sensitivity of the voxel-based analysis technique or whether there is in fact an age dependence in sexual dimorphism of diffusion anisotropy in the corpus callosum. The FA differences in the corticospinal tract may be related to superior performance in fine-motor tasks shown in girls throughout the developmental period [9]. FA in the corticospinal tract has been previously shown to inversely correlate with musical training in normal adults [10], hypothesized to be the result of motor-related practice effects. Further research will be necessary to elucidate the significance of the greater FA displayed by boys in the left inferior parietal lobe, which may be associated with gender differences in activation patterns for visuospatial tasks [11].

## Conclusion

A DTI study was conducted on a cohort of normal children ages 5-18. Significant sex differences were found in FA, with boys having greater FA in inferior fronto-temporal white matter, the genu of the corpus callosum, the corticospinal tract, and left inferior parietal white matter. The results indicate different developmental trajectories in white matter maturation between boys and girls and possibly indicate a developmental basis for differences in the neuroanatomical correlates of cortical function found later in adulthood [12].

## References

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