Sharp curvature in frontal lobe white matter pathways of children with autism spectrum disorder

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Introduction: Autism spectrum disorders (ASD) are neurodevelopmental disorders behaviorally characterized by impaired language and reciprocal social interaction, accompanied by repetitive and stereotypical behaviors. Over past decades, many structural imaging studies have reported abnormal white matter (WM) development in children with ASD. In our previous study using diffusion tensor imaging (DTI) [1], we found microstructural and macrostructural abnormalities in several frontal lobe WM pathways in children with ASD, along with altered shape and trajectory of some of these pathways. The purpose of this study was to examine the curvature of frontal lobe WM tracts in ASD children using an objective tract based morphometry (TBM) analysis [2] and investigate the curvature-specific changes in diffusion parameters of these tracts. **Materials and Methods**: DTI with 6 directional gradients and one b0 image was performed in 32 children with ASD (mean age: 58.8±22.64 months, 29 males) and 14 typically developing children (TD, mean age: 67.36±23.81 months, 11 males). Conventional streamline tractography and SPM DARTEL were used to isolate whole brain fiber tracts spatially normalized to MNI space. Subsequently, an atlas-based ROI approach was used to isolate bilateral uncinate fasciculus (UF), arcuate fasciculus (AF), and genu of corpus callosum (gCC). For each fiber tract, tract-based morphometry (TBM) analysis was applied to localize the regions showing significant change in the curvature and radial diffusivity (RD). The longest fiber penetrating the highest fiber density region of a given tract in the TD group was selected as a 'prototype' for that particular tract and was used to define the common arc-length coordinates for that tract. Common coordinates were placed every 2 mm arc-length of the prototype fiber (i.e, common arc-length coordinates). This prototype was used to find the corresponding coordinates of individual fibers of the respective tract in each subject by using the Hungarian matching algorithm [2]. Subsequently, DTI parameters (RD, and curvature using Frenet's equation [3]) of each fiber tract at each coordinate was evaluated in each subject, and group differences were examined by two sample t-test under each of two hypotheses (H_0: TD > ASD, H_1: TD < ASD). We assessed False Discovery Rate p-value (P_{FDR}) to account for multiple comparisons. Finally, the correlation of curvature to RD was evaluated using Pearson's correlation coefficient. **Results and Discussion**: Significantly higher curvatures were found in children with ASD (Figures 1 and 2, arrows), especially at the parieto-temporal junction for AF (left: $P_{FDR} < 0.001$; right: $P_{FDR} < 0.01$), at the fronto-temporal junction for UF (left: $P_{FDR} < 0.005$; right: $P_{FDR} < 0.03$), and at the midline of the gCC ($P_{FDR} < 0.0001$). In addition, the children with ASD showed higher RD at the bending regions of AF (left: $P_{FDR} < 0.03$, right: $P_{FDR} < 0.02$), UF (left: $P_{FDR} < 0.04$), and gCC ($P_{FDR} < 0.01$), respectively (Fig. 2). There were strong correlations between the values of curvature and RD that were sampled from sharply bending regions of bilateral AF, UF, and gCC of both groups (Figure 3). There was significant *positive* correlation between curvature and RD (increased curvature and increased RD; $R^2 = 0.61$ and 0.94 for gCC,
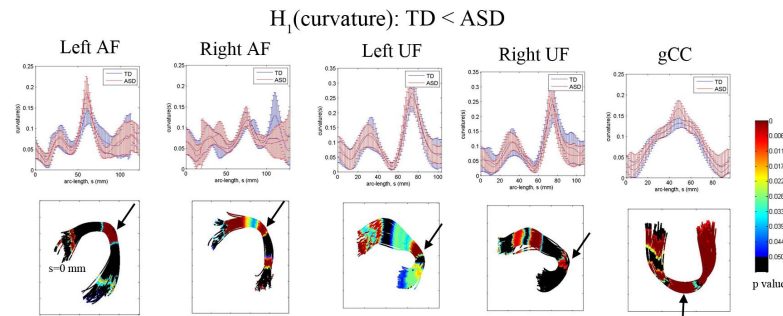
0.59 and 0.74 for AF and UF, respectively in TD and ASD groups). Compared with the TD group, the ASD group showed higher correlation between curvature and RD in AF, UF, and gCC. Higher curvature and higher RD in ASD is consistent with increased number of fibers demonstrated in our prior study [4]. In conclusion, we found that children with ASD have higher curvature and sharper bending along with curvature dependent diffusivity changes in bilateral AF and UF, and gCC, perhaps resulting from higher numbers of smaller axons.

Reference: [1] Kumar A. et al., Cereb. Cortex, Epub 2009. [2] O'Donnell et al., 2009, NeuroImage, 45:832-44. [3] P. Batcherlor et al., 2006, MRM, 55:894-903. [4] Sundaram S.K et al., 2008, Cereb Cortex, 18:2659-65.

Fig. 1: Results of TBM analyses for various fiber tracts under the hypothesis, H_1(curvature): TD<ASD. Upper panel: the group mean and standard deviation of fiber curvature at each common arc-length coordinate is plotted at the respective common coordinates. Lower panel: the multiple comparison P_{FDR}-value for the group difference in fiber curvature at each common arc-length coordinate is overlaid on a respective TD group fiber bundle. The regions with the highest p-values are marked with an arrow.
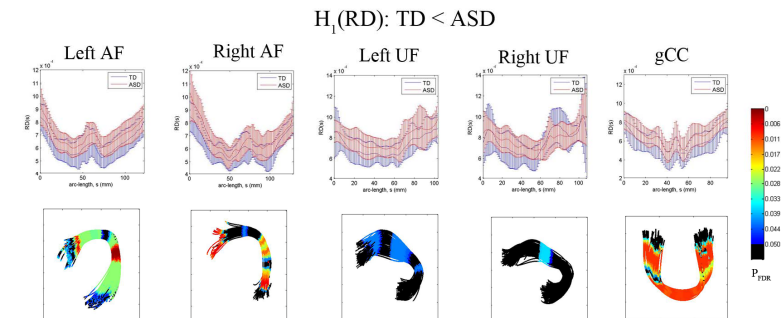

Fig. 2: Results of TBM analyses for various fiber tracts under the hypothesis, H_0(RD): TD<ASD. Upper panel: the group mean and standard deviation of RD at each common arc-length coordinate is plotted at the respective common coordinates. Lower panel: the multiple comparison P_{FDR}-value for the group difference in RD at each common arc-length coordinate is overlaid on a respective TD group fiber bundle.
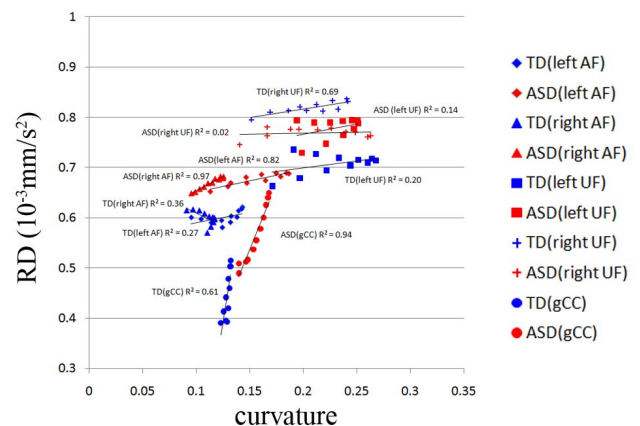

Fig. 3: Correlation between curvature and RD at the bending regions of bilateral AF and UF, and gCC.