

Atypical white matter microstructural integrity pattern in children with high functioning autism and low functioning autism identified with tract based spatial statistics

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Background: Autism spectrum disorders (ASD) are neurodevelopmental disorders typically diagnosed during childhood and characterized by impaired language and reciprocal social interaction, accompanied by repetitive and stereotyped behaviors. There have been several studies reporting alterations in white matter in ASD using diffusion tensor imaging (DTI). In this study, we have applied tract based spatial statistics (TBSS) to assess fractional anisotropy (FA) derived from DTI data in children with ASD with normal cognitive function (high functioning autism, HFA) or with impaired cognitive function (low functioning autism, LFA) compared to a group of typically developing children. FA is a quantitative DTI parameter measuring direction-dependent diffusivity of water molecules, which is an indicator of the diameter and density of fibers, myelination, and macrostructural features (such as fiber tract coherence) of white matter fibers (Beaulieu, et al., 2002).

Methods: FA maps of whole brain white matter, using DTI and TBSS (www.fmrib.ox.ac.uk/fsl/tbss), were measured in 14 children with HFA (mean age: 5.7 ± 2.0 years; 10 males), 14 children with LFA (mean age: 5.5 ± 3.4 years; 13 males), and 14 typically developing controls (TD, mean age: 7.1 ± 3.5 years; 9 males). Whole brain DTI acquisition was performed using a 3T Signa EXCITE scanner (GE Healthcare, Waukesha, WI) equipped with an eight channel phased-array head coil at a diffusion weighting of $b=1000$ s/mm² and 55 diffusion gradient directions, TR/TE = 1250/88.7 ms, voxel size = $1.88 \times 1.88 \times 3$ mm. An additional acquisition without diffusion weighting at $b=0$ s/mm² was also obtained. For TBSS analysis, all FA images were normalized using nonlinear registration into a pediatric MNI FA template. The normalized FA images of all participants were combined to create a group specific mean FA image. This mean FA image was then thinned to create a mean skeleton image of the white matter tracts. Following the search for the maximum FA value along the width of the white matter tract, perpendicular to the skeleton voxel, the maximum FA values were projected onto the skeleton voxel to be used as an input for further statistical test. Nonparametric permutation tests (5000 permutations/design) with a cluster size threshold of > 3 and a p value of <0.05 for significance were applied after correcting for multiple comparisons. Age was used as a covariate.

Results and Discussion: Children with HFA had a significantly lower FA than the control group in 11 clusters, while the children with LFA had a significantly lower FA than controls in 17 clusters (Fig. 1). These were largely bilateral and included white matter in the cerebellum, frontal, temporal, parietal lobes, and corpus callosum. The LFA group has more extensive involvement of cerebellum and superior longitudinal fasciculus (SLF) as compared to the HFA group. Bilateral clusters in the region of thalamus were found in LFA group whereas bilateral parahippocampal clusters were exclusively observed in HFA group.

Conclusions: Children with HFA and LFA have widespread significant differences from typically developing children in white matter microstructural integrity. Furthermore, there were differences in the pattern of involvement between HFA and LFA groups indicating potential areas of abnormality patterns and pathophysiology.

References: 1. Catani M, Jones DK, Daly E, Embiricos N, Deeley Q, Pugliese L, et al. Altered cerebellar feedback projections in Asperger's Syndrome. *Neuroimage* 2008;41:1184-91. 2. Frith U. 1989. Autism: explaining the enigma. Oxford: Blackwell. 3. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed* 2002;15:435-55

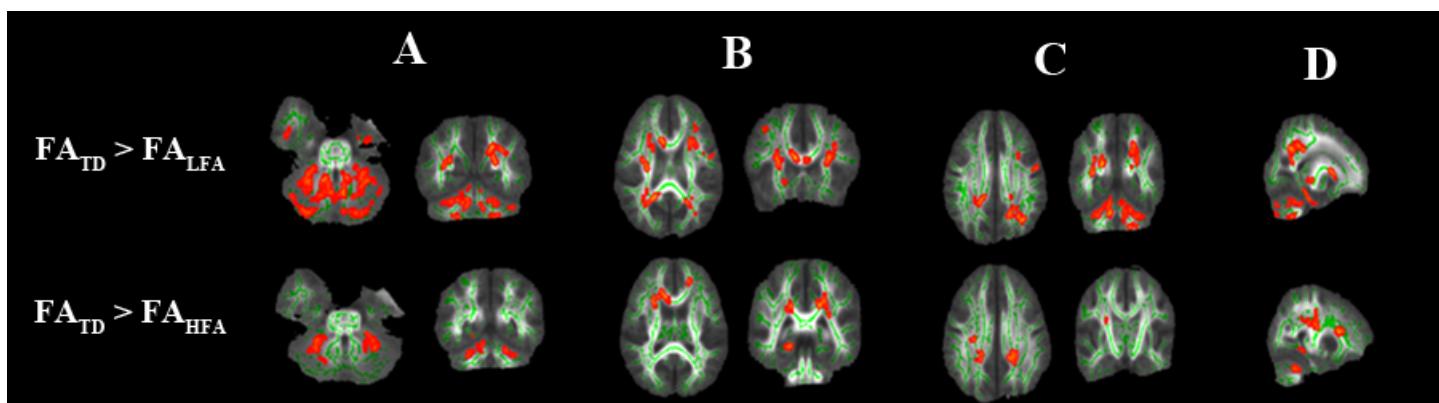


Fig. 1. Regions with significantly lower fractional anisotropy (FA) in subjects with LFA vs. controls (1st row) and HFA vs. controls (2nd row). (A) Clusters shown in the cerebellar region indicating large areas of decreased FA in children with LFA but are restricted to middle cerebellar peduncle and dentate nuclei in the HFA group. (B) Clusters shown in the frontal region showing large areas of decreased FA in LFA, whereas CC and superior corona radiata show decreased FA in the HFA group. (C) Clusters shown in the temporo-parietal region showing larger areas of decreased FA in LFA. (D) Sagittal section showing the major areas of decreased FA in both LFA and HFA groups. White arrows indicate the clusters in corresponding regions.