

Atypical Axonal Integrity in Young Adults with High-Functioning Autism

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Introduction

Autism Spectrum Disorders (ASD) are complex developmental disorders of unknown etiology and increasing prevalence. Recent work has suggested atypical brain connectivity as one of the underlying causes (1). Consistent with this hypothesis, microstructural white matter deficits in ASD have been reported by DTI studies generally showing reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in ASD. However, imaging reports have not generally been consistent across studies and the underlying physiological cause of the reported differences in FA and MD remains poorly understood (2). The goal of this study was to use advanced diffusion imaging techniques to more precisely characterize the white matter deficits in ASD by disentangling intra and extra-axonal diffusion and myelination and axonal deficits.

Methods

White matter microstructural differences between 16 young male adults (ages 18 to 25 year old) with a diagnostic of high functioning autistic disorder and 17 age, gender, handedness, and Full Scale IQ matched typically developing participants were examined using Diffusion Kurtosis Imaging (DKI) and a two-compartment diffusion model of white matter, which provides metrics that differentially describes intra- and extra-axonal white matter compartments (3). These metrics include the axonal water fraction (*AWF*), a measure of axonal density, the tortuosity of the extra-axonal space (*Ex-Tort*), an indirect measure of myelination, and compartment specific diffusivity measures such as intra-axonal and extra-axonal diffusivities (*InD* and *ExD*) and their axial (*AD*) and radial (*RD*) components. Three-dimensional parametric maps of the measures of interest were created for each subject (similar to 3, 4) and between group differences were examined using both Tract-Based Spatial Statistic (TBSS provided with the FSL software package) and Region of Interest (ROI) approaches focused on two tracts that have consistently been found to be affected in ASD, the corpus callosum and superior longitudinal fasciculus. Diffusion imaging data was acquired using EPI for two diffusion weighting, $b=1000$ (12 encoding direction) and $b=2000$ s/mm² (42 encoding directions) using two averages and for $b=0$ s/mm² using nine averages. Image pre-processing included correction for motion and image distortions from B₀-field inhomogeneities.

Results

Significant decreased *AWF* and *InAD* were observed in ASD compared to the control group in corpus callosum, superior longitudinal fasciculi, corticospinal tracts, left anterior thalamic radiations and parts of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and left cingulum (Figure 1). Additionally, differences were found in *Ex-AD* in regions of the prefrontal corpus callosum. There were no significant differences between groups in the *Ex-RD* and *Ex-Tort* indices describing the extra-axonal space. Moreover, there were no differences in the DTI based diffusivity measures or FA. Similar results were obtained for the ROI-based analyses of corpus callosum and superior longitudinal fasciculus.

Discussion

This is the first study, to our knowledge, to examine white matter diffusion properties in ASD using a two-compartment model of intra and extra-axonal white matter and DKI. The lack of between-group differences in typical diffusivity and FA measures is consistent with most studies published to date in early adulthood ASD populations (2, 5). Despite these findings, our data suggest that white matter microstructural differences do exist in this age group; importantly, metrics tailored to the affected compartment appear to be more sensitive to microstructural differences than the typical DTI metrics. In particular, we report decreased *AWF* (i.e., reduced intra-axonal volume) in several white matter regions, consistent with reduced axonal density and, perhaps more in line with current hypotheses in the field, with selective reduction in the number of the large caliber axons. Decreased *InAD*, observed in similar regions as the decreased *AWF* may reflect differences in axonal internodal distances and cytoskeletal composition and organization. For example, such differences are known to be significant between large and small caliber axons (6). Finally, the lack of difference in *Ex-Tort* and in particular in *Ex-RD* suggests that myelin volume is not significantly affected in young male adults with High-Functioning Autism. Future studies need to confirm these findings in larger populations and to evaluate white matter axonal and myelin integrity in both younger and older age groups, which may have different white matter profiles than the ones found in young adults.

Conclusions

We report for the first time decreased axonal density in young adults with High Functioning ASD and thus more precisely define the anatomical bases of the unreliable neural signal transmission in ASD (7). Moreover, our data suggest that white matter deficits, whereas perhaps more subtle, do persist during adulthood and can be detected using more specific metrics of white matter microstructure.

References 1: Belmonte et al., *J Neurosci* 24, p. 9228, 2004; **2.** Travers et al., *Autism Res* 5, p. 289, 2012; **3.** Fieremans et al., *Neuroimage* 58, p. 177, 2011; **4.** Jensen and Helper, *NMR Biomed* 23, p 659, 2010; **5.** Kleinhans et al, *Brain Res* 1479, p. 1, 2012; **6.** Waxman et al, *The Axon: Structure, Function and Pathophysiology*, 1995; **7.** Dinstein et al. , *Neuron* 75, p.981, 2012.

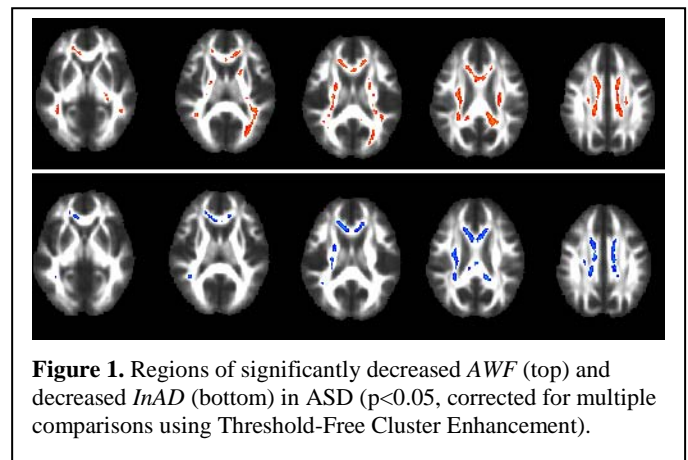


Figure 1. Regions of significantly decreased *AWF* (top) and decreased *InAD* (bottom) in ASD ($p < 0.05$, corrected for multiple comparisons using Threshold-Free Cluster Enhancement).