WHITE MATTER DEVELOPMENT DIFFERENCES IN CHILDREN AND ADOLESCENTS WITH AUTISM

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INTRODUCTION: A recurrent finding in children with autism and autism spectrum disorder (ASD) is that of altered brain growth and functional "connectivity" across large-scale brain systems compared to typically developing children [1,2]. Imaging studies of white matter volume (morphometry) and micro-structure (predominantly assessed via diffusion tensor (DT)-MRI) throughout infancy, childhood and adolescence have shown consistent differences in regional white matter development. For example, volumetric studies have shown an early period of rapid overgrowth (between ages 1 and 4) followed by abnormally slow growth throughout the childhood and adolescence [3,4]. Investigations of white matter micro-structure and micro-organization, based on measures of water diffusion anisotropy (fractional anisotropy, FA) also suggest abnormal developmental differences in early childhood [5,6]. Recently, Wolf et al. showed the developmental rate in FA between 6 and 24 months is slower in infants that go on to a diagnosis of ASD, despite these infants having increased FA at 6 months [5]. Though the FA and volumetric literature is less consistent in older children (6 years and above) [7], there remains strong evidence that altered microstructure is associated with the disorder. Temporally coincident with the first reports of autistic symptoms and early micro-structural differences, is the process of myelination. Development of the myelinated white matter is essential for rapid and synchronized brain communication, and deviations in this process or myelin integrity may underlie the observed differences in functional connectivity, white matter volume and FA. However, to-date, no study of myelin development across childhood or adolescence has been performed. In this work, we sought to fill this knowledge gap, performing a cross-sectional study of myelin content in 42 male children diagnosed with ASD and 47 typically developing children, matched for gender and IQ, between the ages of 6 to 19 years.

METHODS: PARTICIPANTS: 42 male children with autism (7.3-18.2 years of age; mean±SD=12.3±3), diagnosed according the ICD 10 research criteria and confirmed using the Autism Diagnostic Interview-Revised (ADI-R), with all participants reaching ADI-R cut-offs in impaired social interaction, communication, and repetitive behaviors and stereotyped patterns. 47 age-matched typically developing male children (7.4-16.6 years of age; mean±SD=12.2±2.7; p=0.947) were also recruited. All children had IQ>70. **MRI** A surrogate measure of myelin content, termed the myelin water fraction (MWF) [8], was measured using the multi-component relaxometry technique, mcDESPOT [9]. mcDESPOT derives MWF estimates by fitting a three-pool model to a combination of T_1-*weighted* SPGR and T_2/T_1-*weighted* balanced SSFP imaging data, with additional correction for B_0 and B_1 inhomogeneities [10]. Whole-brain data were acquired of all 87 participants on a GE-750 3 Tesla scanner with an 8-channel head RF array. Specific imaging parameters were: 1.7 mm isotropic voxels (22 cm × 22 cm × 15.6 cm sagittal field of view), SPGR: TE/TR = 4.9ms/11ms; flip angles={2, 3, 4, 5, 7, 9, 13, 18} degrees; IR-SPGR: matched to SPGR with half the resolution in the slice direction; inversion time of 450ms; and SSFP: TE/TR = 3.8ms/7.6ms; flip angles={9, 14, 20, 27, 34, 41, 56, 70} degrees. Two sets of SSFP data are acquired with phase-cycling increments of 0 and 180° [10]. **ANALYSIS:** After voxel-wise calculation of MWF maps and non-linear co-registration to a common template place [11], mean myelin development trajectories (MWF as a function of age) were compared between the ASD and typical developing children in 12 white matter pathways previously identified in infant studies of ASD [5]; as well as voxel-wise restricted to white matter. In each case, a linear model was fit the MWF vs. Age data and a wild bootstrap [12] approach with 25000 resamples was used to estimate the trajectory slope distribution. An unpaired t-test was used to compare the two groups. Significance for the white matter pathway analysis was p<0.00417 (i.e. corrected for multiple comparisons using Bonferroni correction). Significance for the voxel-wise analysis was t > 10 (i.e., p<0.000001 uncorrected).

RESULTS: Figure 1 displays results of the voxel-wise analysis, with areas of t > 10 superimposed on the template image, as well as some example mean MWF vs. Age plots for three investigated white matter pathways. Also shown in Fig. 1 are the bootstrap-derived trajectory slope distributions for each example white matter pathway. Table 1 contains a summary of results form all white matter pathways investigated. In general, we found significance differences in MWF development in right frontal white matter, bilateral internal capsule and thalamic radiations, genu and splenium of the corpus callosum, bilateral posterior cingulum, right temporal lobe white matter, and bilateral cerebellar white matter. In all cases, children with ASD had lower MWF at 6 years of age and more rapid development (positive slope) across the age range. Averaged over white matter pathways, we found significant differences in all pathways except the body of the corpus callosum.

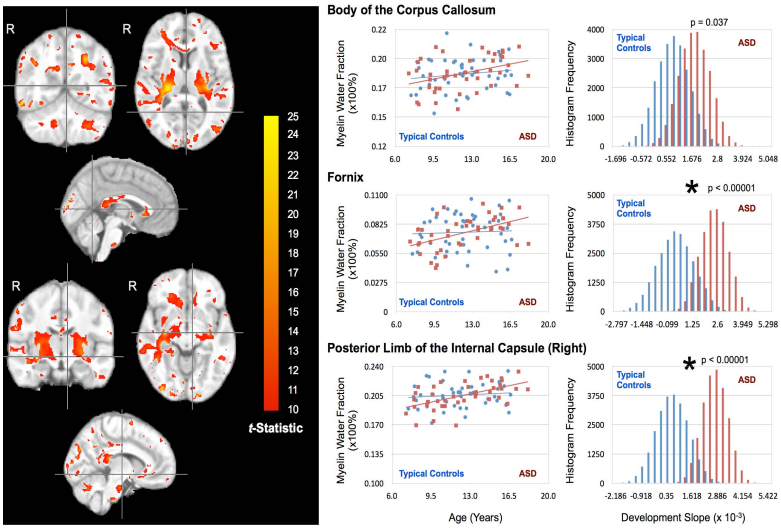

Figure 1: *(Left)* Areas showing significant (t > 10, p < 0.00001) differences in myelin development rate between 6 and 19 years of age in subjects with ASD relative to typically developing controls. *(Right)* Example plots of myelin water fraction change with age in ASD and typical controls and corresponding histograms of the bootstrap estimates of the development slope. In all identified regions, the ASD group showed significantly faster development than the typical controls.

Pathway	t Statistic	p Value
Corpus Callosum (Genu)	9.86	< 0.0001
Corpus Callosum (Body)	3.5	0.037
Corpus Callosum (Splenium)	9.87	< 0.0001
Fornix	12.11	< 0.0001
Anterior Thalamic Radiation (Left)	15.67	< 0.0001
Anterior Thalamic Radiation (Right)	10.33	< 0.0001
Posterior Limb of Internal Capsule (Left)	12.4	< 0.0001
Posterior Limb of Internal Capsule (Right)	14.7	< 0.0001
Inferior Longitudinal Fasciculus (Left)	7.01	< 0.0001
Inferior Longitudinal Fasciculus (Right)	5.9	< 0.0001
Uncinate (Left)	9.23	< 0.0001
Uncinate (Right)	10.1	< 0.0001

Table 1: Summary of white matter pathway analysis. All investigated pathways, except the body of the corpus callosum, showed significant differences between the children with ASD and typical controls.

DISCUSSION: In this first cross-sectional analysis of MWF development in older children and adolescents, we found that children with autism had a significantly greater myelin development rate compared with typically developing children in brain regions and pathways previously implicated in the disorder. Though the voxel-wise analysis was not corrected for multiple comparisons, the extremely conservative threshold used (t > 10 with > 70 degrees of freedom) strongly argues against a prevalence of type 1 errors. Our results overlap those of Wolf et al. [5], with the same white matter pathways exhibiting differential development trajectories. However, in this prior study of FA, infants with autism were shown to have slower developmental trajectories compared to healthy controls. This may suggest that after an early period of slow micro-structural organization or myelination, the autistic brain attempts to 'catch-up' throughout later childhood. However, as FA is a poor marker of myelin content, these results strongly argue for cross-sectional, as well as more powerful longitudinal, studies of MWF development in infants and toddlers who go on to a diagnosis of autism.

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