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Left-Hemispheric Microstructural Abnormalities in Children With High Functioning Autism Spectrum Disorder

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Abstract

Current theories of the neurobiological basis of Autism Spectrum Disorder (ASD) posit an altered pattern of connectivity in large-scale brain networks. Here we used Diffusion Tensor Imaging to investigate the microstructural properties of the white matter that mediates inter-regional connectivity in 36 high-functioning children with ASD (HF-ASD), as compared to 37 controls. By employing an atlas-based analysis using LDDMM registration, a widespread, but left-lateralized pattern of abnormalities was revealed. The Mean Diffusivity (MD) of water in the white matter of HF-ASD children was significantly elevated throughout the left hemisphere, particularly in the outer-zone cortical white matter. Across diagnostic groups there was a significant effect of age on left hemisphere MD, with a similar reduction in MD during childhood in both TD and HF-ASD children. The increased MD in children with HF-ASD suggests hypomyelination, and may reflect increased short-range cortico-cortical connections subsequent to early white matter overgrowth. These findings also highlight left hemispheric connectivity as relevant to the pathophysiology of ASD, and indicate that the spatial distribution of microstructural abnormalities in HF-ASD is widespread, and left-lateralized. This altered left-hemispheric connectivity may contribute to deficits in communication and praxis observed in ASD.

INTRODUCTION

Brain development of children involves genetically programmed synaptogenesis and synaptic pruning in the formation of neural circuitry, which includes intra-cortical, cortico-cortical and subcortico-cortical pathways necessary for inter-regional coordination (Tau and Peterson, 2009; Levitt, 2003; Casey, Giedd and Thomas, 2000). Such pathways, present as early as two years of age, comprise a full-brain network with economic small world

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topology (nodal regions that efficiently maximize information processing), and nonrandom modular organization (Fan, 2011). These networks are integral in the development of motor, cognitive, communicative, and social functioning (Blakemoore 2006) as the brain proceeds on its neurodevelopmental trajectory.

Autism spectrum disorder (ASD) is a highly heritable neurodevelopmental disorder characterized by deficits in social communication and restricted and repetitive behaviors (Diagnostic and Statistical Manual, Fifth Edition, DSM-5, American Psychiatric Association, 2013) with accompanying deficits in motor skills (Jansiewicz 2006; Dziuk 2007), sensory processing (Ben-Sasson 2009) and a range of cognitive functions (Hill 2004). In the atypically developing brains of children with ASD, synaptogenesis and synaptic pruning may be affected by the presence of genetic variants or mutations in the neurexin and neuroligin gene families (Wang et al, 2009; Yates 2012), impacting the regional microstructure and the development of brain networks (Geschwind 2007; Ecker, Spooren and Murphy, 2012). Based upon these findings, an extant hypothesis of the underlying neurobiological basis of ASD attributes it to developmental disconnection (Belmonte, 2004) or disordered connectivity (Wass 2011, Schipul 2011, Vissers 2012, Rippon 2007) of the neural circuits; this may lead to functional underconnectivity of certain circuits, for example: frontal-posterior circuits (Schipul 2011, Just 2012). Additionally, dysmaturation of WM in ASD may contribute to altered connectivity in the neural networks that subserve developing social, communication and motor skills (Washington et al, 2013; Uddin, 2013).

Neuroimaging techniques, such as structural MRI (sMRI), functional MRI (fMRI) and Diffusion Tensor Imaging (DTI) (reviewed by Anagnostou and Taylor, 2011), have been instrumental in revealing these abnormal WM patterns in vivo. Of these, DTI has been found to be useful in studying the WM that mediates inter-regional connectivity (Basser 1996). DTI measures the magnitude and directional dependence of water diffusion within each voxel (volumetric pixel) of the brain image. Assessment of WM by DTI is based upon the principle that microstructural features of WM restrict water diffusion perpendicular to the axons to a greater degree than they restrict diffusion parallel to them, and so directional water diffusivity is an in-vivo, noninvasive probe of WM tissue. Two commonly used DTI metrics include Fractional Anisotropy (FA) and Mean Diffusivity (MD). FA is a measure of WM integrity; it measures the strength of the directional preference of the water diffusion, being higher in thick core WM tracts and lower in areas with localized microstructural disorganization, damaged myelin sheaths, and crossing WM fibers (Wedeer 2008). MD is a measure of the overall speed of diffusion regardless of direction; it is higher in the presence of reduced myelination and lowered by barriers to water diffusion - such as axonal membranes and myelin sheaths (Basser 2002). In typically developing (TD) children, FA tends to increase with age while MD decreases. Therefore, DTI indices can reflect the maturity and development of WM regions. DTI has been used to study the neural basis of normal developmental WM changes (Huang et al, 2012; Tamnes et al, 2010; Westlye et al, 2010; Yoshida et al, 2013) as well as in developmental (Ashtari et al, 2005; Peterson et al, 2011) and acquired (Shenton et al, 2012) disorders in children.

In children with ASD, DTI findings across previous studies have been inconsistent (see review by Travers et al, 2012) due to variability in the inclusion criteria, broad age ranges

(rather than a developmentally homogeneous range) (Pugliese 2009, Alexander 2007) and small sample sizes (Noriuchi 2010, Brito 2009). Inconsistency has also been seen in the DTI metrics - with group differences in FA in different WM structures including corpus callosum (Lo 2011), internal capsule (Brito 2009), cerebellar peduncles (Sivaswamy 2010), the superior longitudinal fasciculus (Wan 2012), the uncinate fasciculus (Sahyoun 2010) and other tracts. Consistent with findings of increased cerebral volume, very young children with ASD (<3–4 years old) tend to show increased FA compared with TD children, while older children and adolescents tend to show decreased FA as cerebral volume plateaus and declines (Cheung, 2009; Weinstein et al, 2011; Wolff, 2012). Reduced FA in older children with ASD has been reported in the WM of the frontal and temporal lobes (Travers 2012), as well as in corpus callosum. To a lesser extent, increased MD has also been reported in these regions.

The variability across DTI findings observed in ASD may also be due to the analytic techniques used. Voxel-Based Analyses (VBAs) and Region-Of-Interest (ROI) analyses are commonly used DTI methods. VBAs employ whole brain examination and are most sensitive to small focal abnormalities (Jones 2005). However, with VBM the problem of multiple comparisons is severe, and widespread but subtle abnormalities may not survive correction. If the WM abnormalities in ASD are spatially distributed, an atlas-based ROI analysis may be more revealing than VBA. In this approach, the brain image is parcellated according to a warping to a standard template with previously delineated ROIs. If the brain-wide survey is done at the ROI level, fewer comparisons can be made, and statistical sensitivity to subtle effects is increased (at the expense of localizing power). Atlas based ROI analyses rely on accurate registration methods, as Inaccurate registration can generate both false positives and negatives (Crum 2003). To mitigate this, alternative registration techniques such as Large Deformation Diffeomorphic Morphic Mapping (LDDMM) (Beg 2005) may provide highly valid and accurate mappings between brain images (Faria, 2010) by modeling the warping of a target image to a template as a geodesic flow of diffeomorphisms - simultaneously maximizing the similarity of the warped target to the template, and minimizing the severity of warping required. LDDMM has been applied to study a wide range of conditions including autism (Qiu et al 2010a) as well as cerebral palsy (Hoon and Faria, 2011), schizophrenia (Reading et al, 2011), velocardiofacial syndrome (Radoeva et al, 2012), ADHD (Qiu, et al, 2009), Alzheimer's disease (Qiu et al, 2012) and neonatal stroke (van der Aa, 2013). When applied to DTI, LDDMM may be an important tool in investigating the WM abnormalities in ASD.

In this study, we had the following objectives: a) Exploration of the utility of LDDMM in DTI mapping of whole brain WM in a homogenous cohort of children with high functioning ASD (HF-ASD), b) Comparison of these DTI findings in HF-ASD children with a TD cohort, in an analysis sensitized to subtle and spatially widespread abnormalities. We hypothesized that children with HF-ASD would demonstrate reduced WM integrity, reflected in reduced FA and increased MD. Given established findings for impairments in language and praxis, we further hypothesized that the findings would be more prominent in the left hemisphere, and given previous anatomical findings (Herbert 2004), more so in the outer cortical WM than in the deep, major WM tracts.

METHODS

Subjects

Seventy three children, ages 8 through 12 years, participated in the study: 36 HF-ASD children (age 10.1 ± 1.4 ; 31 male, 5 Female; 28 right handed, 4 left handed; 4 mixed dominance), and 37 TD children (age 10.5 ± 1.4 ; 31 male and 6 female; 33 right handed, 1 left handed, 4 mixed dominance) (See Table 1 for summary). Sources of recruitment included advertisements posted in the community, local pediatricians' and psychologists' offices, schools, and social service organizations and chapters of the Autism Society of America, the Interactive Autism Network (IAN) database, outpatient clinics at Kennedy Krieger Institute and word of mouth. The study was approved by the Johns Hopkins Medical Institutional Review Board. Consent and assent were obtained from parents and children, respectively.

None of the subjects in either group had a history of seizures, other neurological disorders, or diagnosed genetic disorders. For the TD group, additional exclusions included children with history of a neurologic disorder, any ongoing psychiatric disorder (except social phobia), and a speech/language or other developmental disorder. We also excluded participants with any first degree relatives with ASD so as to preclude the presence of subclinical broader autism phenotypic traits (Gerdtz 2012).

ASD Diagnosis

All subjects met DSM-IV TR (Diagnostic and Statistical Manual, DSM-IV, Text Revision, American Psychiatric Association, 2000) criteria for ASD – either autistic disorder (AD) or Asperger syndrome (AS). These diagnoses were confirmed using the Autism Diagnostic Interview-Revised (ADI-R: Lord, Rutter and LeCouteur, 1994) and Autism Diagnostic Observation Schedule-Generic (ADOS-G: Lord et al., 2000) administered by research-reliable masters-level or higher psychologists, as well as the clinical impression of the senior investigator (S.H.M.). AD and AS were merged into a single HF-ASD group, in line with the new DSM-5 criteria for ASD as these do not represent distinct clinical entities (Kamp-Becker 2010, Verté 2006, Macintosh and Dissanayeke, 2004, Frazier, 2012).

IQ

Intellectual ability was assessed by the Wechsler Intellectual Scale for Children 4th edition, WISC-IV (Wechsler 2003). 70 of the 73 subjects had FSIQ of 80 or above. Three AD subjects with FSIQ below 79 were included on the basis of discrepant sub-scores, having a Perceptual Reasoning Index (PRI) of 85 or greater. PRI, a measure of nonverbal abilities, may be a better measure of cognitive abilities than the FSIQ (Motttron, 2004). As in previous studies from our group (Dowell 2009, MacNeil 2012, Qiu 2010b, Fuentes 2009), PRI was therefore used as the measure of intellectual reasoning ability.

Psychiatric Comorbidity

Comorbid psychiatric diagnoses were assessed with the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV: Reich, Welner, and Herjanic, 1997), a computerized parent reported measure. DICA-IV is an established semi-structured measure

of current and lifetime diagnosis of DSM-IV psychiatric disorders in children and adolescents ages 6–17 years, with good psychometric properties (Diagnostic interview for children and adolescents, Reich 2000).

In the HF-ASD group, 26 children met criteria for one or more of the following psychiatric comorbid disorders: ADHD (n=16), generalized anxiety disorder, GAD (n=3), simple/social phobia (n=11), oppositional defiant disorder, ODD (n=10), past major depressive episode (n=3), obsessive compulsive disorder, OCD (n=2), and dysthymic disorder (n=1). None had somatization, mania, hypomania or current diagnosis of major depressive disorder (MDD) or psychotic symptoms. Seven children met criteria for two comorbid disorders, three met criteria for three disorders, one met the criteria for four, and one for five disorders. In the TD group, four children met criteria for simple/social phobia (n=3), and a past major depressive episode (n=1). None met the criteria for ADHD, ODD, GAD, OCD or dysthymic disorder; none had somatization, mania or hypomania or current diagnosis of MDD or psychotic symptoms.

To preclude effects on cognitive and behavioral assessments, stimulant medications were discontinued the day prior to and on the day of testing. However, participants were allowed to continue treatment with other psychotropic medications that would normally require a longer washout period, for both ethical and practical reasons; these included anticonvulsants (valproic acid and divalproate), antidepressants (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, venlafaxine and bupropion), antipsychotics (haloperidol, risperidone and clonidine), alpha agonists (clonidine), and others (atomoxetine).

Neuroimaging acquisition and preprocessing

All subjects participated in a mock scan training session wherein an inactive, life-size scanner was used to simulate the actual scanning environment. A behavioral training protocol was employed that focused on first, getting the children to willingly enter the MRI environment and second, keeping their heads sufficiently still to acquire good data. Cooperation and inhibition of head movement were verbally reinforced throughout the training session. No sedation was used during this process.

DTI images were acquired with single-shot EPI (SENSE factor 2.5) on a 3T Phillips scanner, with an 8-channel head coil. Two runs were collected in each subject, with 32 gradient directions ($b=800 \text{ s/mm}^3$) and one b_0 in each run. 60 2.2mm axial slices were acquired for each volume, with 0.9mm in-plane reconstructed resolution. Preprocessing was performed using CATNAP (Landman 2007), with the RADAR motion correction procedure. The gradient table was adjusted according to the motion correction transformation, and the tensors were estimated using RESTORE (Chang, 2005) in order to reduce the impact of motion artifacts. In order to quantify the magnitude of motion, average frame-wise displacement values were computed from the motion-correction linear transformation using the 'rmsdiff' utility in FSL (Jenkinson, 2012).

EPI distortions were corrected by LDDMM transformation of each subject's mean b_0 image to a non-EPI axially acquired T2 weighted image that was taken as part of the same imaging

protocol. Tensor images were then resampled into 1mm isotropic resolution to match the resolution of the template image.

Image analysis

Inter-subject registration was accomplished by LDDMM multi-channel transformation of FA and b0 images to the FA and b0 templates in the JHU-DTI atlas, subsequent to an initial linear transformation. The inverse transformations were then applied to the atlas labels, in order to project the ROIs back into each subject's distortion-corrected native space. As the cortical ROIs contain both GM and WM, an FA threshold of 0.25 was applied to the cortical labels in order to interrogate just the cortical WM. 114 labels comprising the cortical WM and deep WM structures were chosen for analysis, excluding the cerebellum, midbrain, pons, and other non-WM structures.

Statistical analysis

A series of non-parametric hypothesis tests were conducted to test for spatially-distributed and focal white matter abnormalities associated with HF-ASD. Each test was performed separately on FA and MD. The tests were implemented using MATLAB and R routines.

First, several tests were conducted to test for widespread abnormalities. A Wilcoxon rank-sum test (Wilcoxon 1945) over the entire brain was performed to test for global abnormalities. Next, a rank-sum test was conducted within each hemisphere to test for hemisphere-wide abnormalities. To investigate abnormalities in the outer-zone (cortical) and inner-zone (deep) WM, separate rank-sum tests were conducted within the cortical ROIs and within the deep white matter tracts of each hemisphere. Finally, rank-sum tests for group differences in Laterality Index (LI), defined as (Left-Right)/(Left+Right), were performed within the cortical WM, within the deep WM, and across all WM. If FA or MD within these regions is found to correlate with age, these tests may be repeated as ANCOVAs, with age entered as a covariate.

Second, to assess the pattern of abnormalities, a rank-sum test of differences in diffusivity metrics within each ROI was performed. To control for multiple comparisons across the 114 ROIs, we computed the q-value of each region and chose a threshold of $q < 0.05$ (Storey 2003). This is equivalent to identifying all regions with p-values below a certain threshold as significant. However, since some regions truly associated with diagnosis may not be identified as significant after this correction procedure, we estimated the number of true positives among the ROIs significant before correction. We employed a method proposed by Storey and Tibshirani (Storey 2003) to estimate the false discovery rate (FDR): If S regions have significant p-values before correction and $F = S * \text{FDR}$ of these are false positives, $T = S - F = S(1 - \text{FDR})$ is the number of true positives. The proportion of N regions that are truly null is estimated as $\pi(\lambda) = \#\{p_i > \lambda\} / N(1 - \lambda)$, where we conservatively set $\lambda = 0.2$. The FDR is then estimated as $\text{FDR}(\alpha) = \pi N \alpha / \#\{p_i < \alpha\}$. While this approach does not specify *which* discoveries from among the statistically significant findings are true positives, it has more power to identify the *number* of true positive regions than most methods of correcting for multiple comparisons. This method originated in genomics but has also been applied in neuroimaging (Magnotta 2008, Vasic 2009).

RESULTS

As indicated by Table 1, the HF-ASD and TD groups were balanced on gender, age, PRI and handedness. There was no difference in average framewise displacement between the two groups ($p=0.41$). The groups differed in FSIQ, with the TD group having higher scores, although in both the groups, the mean FSIQ was in the average range.

The tests of global, hemispheric and focal WM abnormalities did not show statistically significant group differences in FA.

The test of global WM abnormalities in MD showed a trend-level increase in MD in HF-ASD relative to TD controls ($p=0.06$). The tests of hemisphere-wide WM abnormalities in MD showed a significant increase in children with HF-ASD in the left hemisphere ($p=0.014$) (Figure 2A), but not in the right hemisphere. The tests of cortical WM abnormalities showed a significant increase in MD in children with HF-ASD across both hemispheres ($p=0.01$) and in the left hemisphere ($p=0.002$), but not in the right hemisphere ($p=0.11$). In the deep WM, MD was also elevated in the left hemisphere ($p=0.018$), but not in the right hemisphere ($p=0.69$). The tests for group differences in Laterality Index (LI) were not significant for the cortical WM ($p=0.37$), deep WM ($p=0.24$), or all WM ($p=0.37$).

Subsequent to these initial tests of global WM abnormalities, it was observed that MD was negatively correlated with age in these large WM regions, even over the narrow age range in our sample. In a follow-up analysis, the tests for global WM abnormalities were repeated as ANCOVAs, with age entered as a covariate. Controlling for age, a significant effect of diagnosis was seen on total WM MD ($p=0.012$), left cortical WM MD ($p<0.001$), and right cortical WM MD ($p=0.041$), and left hemisphere deep WM MD ($p=0.0095$). Diagnosis was not predictive of right hemisphere deep WM ($p=0.33$). Age was significantly and inversely predictive of MD in each one of these models (decreasing MD with increasing age), while the Age x Diagnosis interaction term was non-significant in each case.

The test for focal abnormalities in the 114 ROIs identified three regions in which MD was found to be higher in children with HF-ASD after correcting for multiple comparisons at $q=0.05$: The left parahippocampal gyrus ($q=0.0039$), the left sagittal stratum ($q=0.027$), and the left superior temporal gyrus ($q=0.042$) which are all located in the left temporal lobe. Twenty-four ROIs showed an increase in MD in children with HF-ASD before multiple comparisons correction. All but four of these 24 regions lie in the left hemisphere. These regions are shown in Figure 1 and listed in Table 2. At $\lambda = 0.2$, the FDR among these 24 ROIs was conservatively estimated at 0.175, or 4.2 estimated false discoveries out of 24 nominally significant ROIs.

DISCUSSION

In this study, we used DTI imaging to compare WM microstructure in the brains of a cohort of children with HF-ASD to a cohort of TD children in a homogenous age range of 8 through 12 years using LDDMM registration, a technique that has not been previously applied to DTI studies in this population. We studied both the cortical WM and the deep subcortical WM tracts. Our study showed no significant differences in regional FA. The sub-

threshold differences observed were predominately in the direction of decreased FA in HF-ASD, which is broadly consistent with the previous literature. In contrast, robust differences were observed for MD, particularly in cortical (outer zone) WM, noted diffusely within the left hemisphere, and focally in the left temporal lobe. Our finding of decreasing MD with increasing age is in agreement with the developmental neuroimaging literature (Simmonds 2014), and a similar pattern of reduction was observed in both children with ASD and TD children.

Established neuroimaging and neuropathological findings in ASD have indicated that the increase in brain size observed in HF-ASD is primarily due to an increase in the outer radiate WM of the cerebral cortices, rather than the WM in the deeper WM tracts or subcortical regions (Herbert, et al, 2003). Further, there is an increase in arcuate fibers - shorter fibers in the outer radiate WM connecting more locally as opposed to the decrease in commissural fibers - that connect with distant regions (Herbert, 2004). Increased gyrification, especially in the frontal lobes (Hardan 2004) and a smaller gyral window (gyral space that limits the passage of afferents and efferents from the cortex) also favor shorter range fibers and connections over the long range ones (Casanova, 2009b, Casanova and Pickett, 2013).

This increased WM volume is especially notable in the developmentally later myelinating WM regions such as within prefrontal regions (Herbert, et al, 2004; Carper et al, 2002; Carper and Courchesne, 2005). These cortical areas have been consistently found to have increased numbers of minicolumns per unit volume of the cerebral cortices (Casanova, 2004; Courchesne and Pierce, 2005). Post mortem studies of the autistic brains have indicated narrower minicolumns, and crowding of minicolumns, especially in the frontal and temporal cortices (Casanova, 2004).

In the current study, the finding of increased left hemisphere MD may reflect the above described microstructural abnormalities, as short-range connections are less strongly myelinated than long-range connections, and would restrict diffusion to a lesser degree. A study of post-mortem histology of the frontal lobe of individuals with ASD linked short-range overgrowth of WM to the presence of undermyelinated, thinner neurons (Zinkopoulos and Barbas, 2010). A preliminary report of myelin water fraction imaging (Zinkstok 2010) in ASD revealed a decrease in myelin content in the WM of the frontal, temporal, and occipital lobes, as well as in the corpus callosum, predominately on the left hemisphere.

Alternatively, increased MD in ASD may be the consequence of narrow minicolumns, as observed in postmortem studies (Casanova, 2006). A recent study, using both DTI and histology (McKavanaugh, 2013) linked increased diffusivity to decreased cortical minicolumn width. Thus, increased MD could putatively be an indirect biomarker of the abnormal minicolumn size and spacing.

Consistent with our hypothesis, our findings indicate a pattern of widespread left lateralized WM abnormalities. Past literature is replete with the “left hemispheric dysfunction theory” in ASD (Fein 1984, Hier 1979, Dawson, 1983). This has, in part, been based upon the observation that children with ASD may not have the normal lateralization that involves

dominance of the left hemisphere in language and motor functions as compared to the right hemisphere's dominance in spatial processing (Chiron, 1995; Annett, 1999). Reduction in inter-hemispheric connectivity due to reduced size of the corpus callosum relative to the increased peripheral WM may contribute to this abnormal lateralization (Herbert, 2005). Studies that have reported impairments in left hemispheric faculties such as language (Escalante-Mead, 2003) and praxis (Mostofsky, 2006; Dzuik, 2007; Kleinhans et al, 2008) in children with ASD provide support for this model. Others have also implicated dysfunction of left hemispheric frontal (Courchesne 2005) and temporal regions (Eyler 2012) more specifically in ASD. Significantly, a recent study of sleeping 2–3 year olds who were later diagnosed with ASD, found an abnormally symmetrical response in the temporal cortex to language related activation, indicating an early delay in hemispheric specialization (Eyler 2012). It is conceivable, therefore, that in children with ASD, deficits in left-lateralized functions, including language and praxis, may be the consequence of abnormalities in WM connectivity.

Strengths of the study

Our cohort is well-balanced for age, gender and overall cognitive functioning. It is a developmentally homogeneous sample of school-aged children as it spans a narrow age range, but is large enough to detect clinically relevant effects (Friston 2012); the number of participants in our study is also relatively high as compared to previously published DTI studies of ASD. Additionally, the validity of the findings is enhanced by the confirmation of the clinical diagnosis of ASD by gold standard ASD diagnostic instruments.

The methodology used is another area of strength in this study. The impact of subtle imaging artifacts on our analysis was reduced by using the RESTORE procedure, and by using robust statistical procedures. Partial volume error was reduced by LDDMM inter-subject registration, as well as by a stringent FA cutoff of 0.25. Increased motion artifact in our patient group cannot explain the abnormalities reported here, as the diagnostic groups were balanced on a measure of in-scanner motion.

Limitations of the study

This study had some limitations - related to subject population and neuroimaging methods. Participants were selected to match across the diagnostic groups, with narrow inclusion criteria; as such, our participants are not entirely representative of the entire population of children with ASD. While this approach was chosen to enhance the interpretability of our results and minimize confounds, it may limit the generalizability of our findings. The study was restricted to a higher functioning (HF-ASD) cohort, and the findings may not be directly applicable to those with ASD and intellectual disability (ID). Alternatively, the focus on HF-ASD may provide specificity, allowing for interpretation of the impact of ID, as individuals with ID can have WM changes independent of their ASD status (Tranel & de Haan 2007, Yu 2008). Additionally, several participants in the HF-ASD group had more than one psychiatric comorbidity and were on psychotropic medications (other than stimulant medications); it is unclear if these may have affected the study findings.

As has been noted by others (Wedeen 2008), DTI is unable to resolve crossing fibers, or sub-populations of fiber tracts with differing trajectories within a single voxel. This makes FA a confounding measure of fiber integrity, especially in regions with multiple intersecting WM tracts, such as in the cortical WM regions. Using an FA threshold to define WM regions also introduces a positive bias in the mean FA values, reducing potentially meaningful variability. Additionally, while misregistration error is greatly reduced by the use of LDDMM, it is not completely eliminated, as no current registration method is perfect; it is possible that the group differences here may be partially due to differences in the size and shape of the structures between groups, rather than their microstructural properties.

Future directions

The widespread pattern of microstructural abnormalities within the left hemisphere identified here is likely to be a marker of disrupted or altered connectivity within multiple cortical regions. Investigating these disruptions more directly using fiber-tracking methods may further enhance the understanding of the network-wide pathophysiology. Given the spatially distributed nature of these alterations, it is less likely that individual white matter tracts will be found to be specifically impacted in ASD. Use of recently developed network-centric approaches, such as those based upon graph theory that are sensitive to alterations in the whole-brain topology of neuroanatomical networks (Bullmore 2009), may additionally allow direct assessment of globally altered connectivity and characterization of how these microstructural abnormalities may impact connectivity in the autistic brain. Future investigations in ASD should also focus on large interregional connections rather than focusing on specific brain regions. Lastly, further studies should focus on developmentally homogeneous groups, both in younger children and adolescents, so that an accurate longitudinal pattern of the neurodevelopmental trajectories in ASD can be discerned at specific ages in childhood and adolescence. Interpreting the findings within the context of these trajectories is essential.

Conclusions

Children with HF-ASD have atypical brain development that manifests as alterations in the microstructure of the WM. Understanding of these altered microstructures and the consequent functional underconnectivity has been enhanced by in vivo neuroimaging techniques, including DTI. Children with HF-ASD have subtle and widespread WM abnormalities on DTI when compared to TD peers; specifically increases in mean diffusivity (MD) in cortical WM. In this study, these abnormalities were more pronounced in the left hemisphere, possibly indicating atypical lateralization in children with HF-ASD. As demonstrated by this study, LDDMM, a registration technique, when applied to DTI, may be useful in helping to delineate these abnormalities.

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Figure 1.
Regions where Mean Diffusivity is elevated in HF-ASD. The colored regions correspond to the atlas regions that survive the initial $p < 0.05$ threshold test.

Figure 2.

Scatterplots of group difference in Mean Diffusivity (MD). Left hemisphere cortical MD is elevated in HF-ASD ($p=0.002$), as is left hemisphere core WM ($p=0.0185$).

Table 1

Participant characteristics: FSIQ and PRI assessed by the WISC-IV TD: Typically developing, HF-ASD: High-functioning autism spectrum disorder, FSIQ: Full-scale intelligence quotient, PRI: Perceptual reasoning index, ADOS: Autism diagnostic observation schedule, ADI: Autism diagnostic inventory.

	TD n=37		HF-ASD (n=36)		
Sex	31M / 6F		31M / 5F		
Handedness	33R / 1L, 4 Mixed		28R / 4L, 4 Mixed		
Aspergers			18 met criteria		
	mean ± stdev	range	mean ± stdev	range	TD vs HF-ASD p-value
Age	10.5 ± 1.4	8.02 – 12.98	10.1 ± 1.4	8.09 – 12.82	p=0.236
FSIQ	108.7 ± 8.5	84 – 124	102.3 ± 15.5	84 – 131	p=0.001
PRI	107.6 ± 12.2	79 – 137	107.6 ± 13.2	84 – 135	p=0.460
Edinburgh integer	0.73 ± 0.4	-0.89 – 1.0	0.60 ± 0.6	-0.83 – 1	p=0.114
ADOS Total Score			15.0 ± 3.9	23 – 8	
ADI Social			19.4 ± 5.7	10 – 30	
ADI Communication			14.5 ± 4.6	3 – 23	
ADI Restricted Interests			5.8 ± 1.7	3 – 10	

Table 2

List of left and right hemispheric regions where Mean Diffusivity was found to be elevated in HF-ASD. The p-value is from the two-tailed rank-sum test of group differences, and Cohen's d is the effect size, calculated as the difference between the mean of each group, divided by the standard deviation across both groups.

Region Left Hemisphere	Rank-sum p-value	Effect size (Cohen's d)	HF-ASD MD (mean $\pm$ stdev)	TD MD (mean $\pm$ stdev)
L inferior frontal gyrus	0.0051	0.75	10.16 $\pm$ 0.28	9.95 $\pm$ 0.28
L middle frontal gyrus	0.0179	0.58	10.15 $\pm$ 0.32	9.98 $\pm$ 0.27
L superior frontal gyrus	0.0214	0.54	10.28 $\pm$ 0.33	10.12 $\pm$ 0.26
L gyrus rectus	0.0458	0.55	10.27 $\pm$ 0.50	10.05 $\pm$ 0.30
L parahippocampal gyrus	0.0001*	0.93	10.18 $\pm$ 0.67	9.58 $\pm$ 0.62
L superior temporal gyrus	0.0017*	0.46	10.41 $\pm$ 0.41	10.60 $\pm$ 0.41
L sagittal stratum	0.0007*	0.69	8.91 $\pm$ 0.48	8.58 $\pm$ 0.47
L cingulum (hippocampus)	0.0052	0.63	8.84 $\pm$ 0.57	8.51 $\pm$ 0.48
L middle temporal gyrus	0.0289	0.52	10.45 $\pm$ 0.35	10.27 $\pm$ 0.34
L inferior temporal gyrus	0.0157	0.52	10.69 $\pm$ 0.40	10.48 $\pm$ 0.41
L entorhinal area	0.0464	0.45	11.34 $\pm$ 1.59	10.68 $\pm$ 1.34
L postcentral gyrus	0.0082	0.68	9.42 $\pm$ 0.43	9.17 $\pm$ 0.31
L precentral gyrus	0.0076	0.65	9.92 $\pm$ 0.45	9.67 $\pm$ 0.32
L supramarginal gyrus	0.0440	0.51	9.87 $\pm$ 0.43	9.66 $\pm$ 0.39
L anterior corona radiata	0.0174	0.64	8.57 $\pm$ 0.24	8.40 $\pm$ 0.29
L superior longitudinal fasciculus	0.0247	0.54	7.89 $\pm$ 0.55	7.63 $\pm$ 0.41
L splenium of corpus callosum	0.0196	0.49	9.80 $\pm$ 0.76	9.41 $\pm$ 0.82
L cingulate gyrus	0.0323	0.48	9.87 $\pm$ 0.42	9.68 $\pm$ 0.37
L superior corona radiata	0.0169	0.41	7.86 $\pm$ 0.32	7.73 $\pm$ 0.32
Right Hemisphere				
R superior temporal gyrus	0.0314	0.61	10.61 $\pm$ 0.70	10.28 $\pm$ 0.39
R cingulum (hippocampus)	0.0423	0.49	8.64 $\pm$ 0.40	8.46 $\pm$ 0.33
R fusiform gyrus	0.0077	0.47	9.99 $\pm$ 0.40	9.81 $\pm$ 0.36
R lingual gyrus	0.0147	0.92	10.23 $\pm$ 0.61	9.74 $\pm$ 0.46

* Significant at FDR $q=0.05$ MD: Mean Diffusivity given in units of 10^{-4} mm²/sec