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Increased left hemisphere impairment in high-functioning autism: A tract based spatial statistics study

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ABSTRACT

There is evidence emerging from Diffusion Tensor Imaging (DTI) research that autism spectrum disorders (ASD) are associated with greater impairment in the left hemisphere. Although this has been quantified with volumetric region of interest analyses, it has yet to be tested with white matter integrity analysis. In the present study, tract based spatial statistics was used to contrast white matter integrity of 12 participants with high-functioning autism or Aspergers syndrome (HFA/AS) with 12 typically developing individuals. Fractional Anisotropy (FA) was examined, in addition to axial, radial and mean diffusivity (AD, RD and MD). In the left hemisphere, participants with HFA/AS demonstrated significantly reduced FA in predominantly thalamic and fronto-parietal pathways and increased RD. Symmetry analyses confirmed that in the HFA/AS group, WM disturbance was significantly greater in the left compared to right hemisphere. These findings contribute to a growing body of literature suggestive of reduced FA in ASD, and provide preliminary evidence for RD impairments in the left hemisphere.

1. Introduction

Autism spectrum disorders (ASD) are pervasive, developmental, neurological conditions, which adversely impact behavior in two key domains: social communication, and repetitive and/or stereotyped patterns of behavior (DSM V, 2013). ASD is estimated to have a global prevalence of approximately 2.0% of the population (Blumberg et al., 2013). The symptoms of ASD are believed to be associated with atypical neurological development, where environmental factors alter the function of complex, multi-focal, neural networks across the lifespan (Amaral et al., 2008). Support for this view comes from fMRI evaluations of functional connectivity (FC), which examines inter-regional, co-activation across the brain. Among participants with ASD, research has demonstrated both increased and decreased FC compared to typically developing (TD) individuals (cf. reviews by Just et al. (2012) and Muller et al. (2011)).

An inherent limitation of FC is that it is unable to probe the underlying structure and organization of white matter (WM) that underlies cortical connectivity (Travers et al., 2012). Overcoming this limitation, Diffusion Tensor Imaging (DTI) is a non-invasive technique that can identify differences in microstructural and macroscopic organization of WM (Lange et al., 2010). In WM bundles, the membranes of axons and myelin cause the diffusivity of water perpendicular to WM tracts (Radial Diffusivity) to decrease relative to directions parallel to WM (axial) (Lee et al., 2007). This directional restriction is known as diffusion anisotropy, and is represented by three eigenvalues (λ_1, λ_2, and λ_3), which reflect the length of each eigenvector (Travers et al., 2012).

In DTI, several measures can be extracted. Fractional Anisotropy (FA) is a normalized value ranging from 0 to 1, which represents the fraction of the tensor that can be assigned to anisotropic diffusion, and is sensitive to structural differences in myelination, axonal density, axonal caliber and fiber coherence (Cheng et al., 2010). Mean diffusivity (MD) represents the average radius of the three eigenvalues, and is sensitive to the density of tissue barriers in all directions.

Separating the eigenvalues is argued to provide a more complete picture of WM structure (Song et al., 2005). Axial diffusivity (AD) looks at water diffusivity parallel to WM tracts (λ_1), whilst Radial Diffusivity (RD) expresses water diffusivity perpendicular to tracts ($[\lambda_2,+\lambda_3]/2$). RD is believed to be sensitive to dysmyelination and demyelination (Harsan et al., 2006), whilst AD is sensitive to axonal injury (Travers et al., 2012).

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There are several approaches to analyzing DTI data. Region of interest (ROI) based analyses involve placing a seed, which follows pathways of maximal diffusion to reconstruct a specific WM tract. However, this method is limited in that only preselected WM tracts can be investigated (Gibbard et al., 2013). Voxel-based analyses such as statistical parametric mapping (SPM) have also been utilized, but are limited by issues related to registration error and smoothing techniques (Jones et al., 2005). Tract based spatial statistics (TBSS) addresses several of these shortcomings by implementing non-linear registration, producing an FA WM skeleton with alignment invariant tract representation, and by avoiding smoothing statistics which do not require normally distributed data (Tamm et al., 2012).

Compared to TD participants, the most common finding to arise from TBSS based analyses of ASD participants has been reductions in FA, and increases in MD distributed widely across the brain (Cheon et al., 2011; Kumar et al., 2010; Shukla et al., 2011). Using TBSS, WM tracts commonly associated with reduced FA in participants with ASD include the superior longitudinal fasciculus (SLF), cingulum bundle, uncinate fasciculus (UF) and the corpus callosum (Barnea-Goraly et al., 2010; Jou et al., 2011; Kumar et al., 2010; Pardini et al., 2009; Shukla et al., 2010; Thakkar et al., 2008). There are also reports of increased FA in ASD samples (Billeci et al., 2012; Cheng et al., 2010; Weinstein et al., 2011), which is usually attributable to younger cohorts of participants. Additionally, there are reports of increased RD . (Amies et al., 2011; Shukla et al., 2010), and decreased AD (Barnea-Goraly et al., 2010). Thus, the distribution of WM anomalies in participants with ASD remains heterogeneous, and there is a need to identify more specific WM disturbances linked to the disorder.

A past theory (Hier et al., 1979) that has received renewed interest since the advent of DTI is that participants with ASD demonstrate greater left hemisphere impairment. Among TD participants, there is a trend toward increased FA in the arcuate and uncinate fasciculi of the left hemisphere (Catani et al., 2007). In participants with an ASD, ROI based research has identified reduced lateralization in the left hemisphere (Fletcher et al., 2010; Lo et al., 2011; Nagae et al., 2012), whilst another study investigating tensor shape reports this asymmetry as being reversed in ASD, with reduced FA in the left compared to right hemisphere (Lange et al., 2010). Moreover, a recent meta-analysis of six previous DTI studies reported that participants with ASD demonstrated significantly reduced FA in the left, but not right SLF and UF (Aoki et al., 2013). There is also evidence from volumetric (Rojas et al., 2002) and functional neuroimaging (Eyler et al., 2012) research for greater left hemisphere impairment in participants with ASD.

No research to date has implemented voxel-based methods to explore hemispheric WM differences in ASD participants. Thus, the present study used TBSS to examine WM integrity of adolescent and adult participants with high functioning autism or Aspergers' syndrome (HFA/AS). In this study FA, MD, RD and AD were investigated as outcome measures. Based upon previous literature, two hypotheses were generated. Firstly, that the HFA/AS group would demonstrate reduced FA by comparison to TD participants. Secondly, based upon the limited literature to have investigated hemispheric differences, the HFA/AS group would demonstrate greater WM impairment in the left compared to right hemisphere.

2. Methods

2.1. Participants

This study investigated 24 adolescent and adult males, comprised of 12 TD participants, and 12 individuals who had been diagnosed with either high-functioning autism or Asperger's syndrome (HFA/AS). A clinical psychologist experienced in the assessment of ASD confirmed diagnosis using DSM-IV-TR criteria (American Psychiatric Association, 2000). Participant characteristics are summarized in Table 1. In both groups, 10 of 12 (83%) participants were right handed. In the HFA/AS group, four of 12 possessed a comorbidity, which included anxiety, depression and tactile defensiveness, with two participants taking antidepressants, and one taking beta-blockers. Further, three of 12 in this group had a family member with autism (in all three cases a brother, and in one case also a father). TD participants were recruited by word of mouth. Participants with HFA/AS were recruited from various autism support organizations (i.e., *Autism Victoria*) and specialist schools (*Western Autism*), advertisements, mail outs and from pediatric clinics. All participants gave written consent to participate in this study. For those participants under the age of 18, a parent or guardian gave written consent.

2.2. Procedure

Participants lay flat on the bed of the scanner with their head placed within the head coil. Cushions around the head coil restricted head movement. All MRI images were conducted in a 3T Siemens Tim Trio scanner (Erlangen, Germany) with a birdcage quadrature head-coil. The DTI sequence was performed with the following parameters: TR=8000 ms, TE=90 ms, diffusion encoding directions=25, number of excitations=2, slice thickness=2.5 mm, percent phase field view=100, acquisition matrix=96 0 0 96, and b value=1000 s/mm^2, with one acquisition for each run with b=0 s/mm^2.

DTI data sets were analyzed with FSL 5.0 (Functional Magnetic Resonance Imaging of the Brain Software Library; Smith et al., 2006). Raw DICOM images for each participant were converted into a single, multivolume Neuroimaging Informatics Technology Initiative (NIFTI) files using MRICron (Chris Rorden, Columbia, SC, USA, www.mricro.com), enabling TBSS to be performed. Analyses were undertaken using the protocol of Smith et al. (2006). Using the FDT diffusion module, all participants' data was corrected for gradient coil eddy current distortions. This was done by registering the diffusion-weighted images to a non-diffusion weighted image by affine transformation. Whole-brain mask files were created and manually edited for each participant brain using the draw and erase tools in FSL view (http://www.fmrib.ox.ac.uk/fsl/fslview/).

2.3. Pre-processing and analysis

Whole brain voxel-wise statistical analysis of the FA, MD, RD and AD data was carried out using TBSS. The TBSS method constructs a WM "skeleton", which is restricted to the center of major WM tracts. Using both linear and non-linear alignment, participants' FA images were registered into standard space using the FMRIB58 FA template. Each participant's individual FA values were mapped onto this skeleton to permit group comparisons. TBSS has the advantage of minimizing potential misalignment problems of other voxel-based methods when analyzing diffusion data.

Each participant's aligned FA image was projected onto the FA skeleton to correct for residual misalignments. An FA value of 0.2 was used as a threshold for the FA skeleton, to exclude tracts with high inter-individual variability, those containing a high level of partial volume, and those consisting of gray matter or CSF. This threshold has been commonly used in past research (Cheng et al., 2010; Spitz et al., 2013). This was achieved by calculating the difference between the skeletonized tracts and the WM tract centers in each individual image. The averaging procedure constrains the skeleton to exclude tracts at the outermost edges of the cortex, which effectively excludes parts of the brain where good tract correspondence cannot be achieved.

Voxelwise statistics were then undertaken using the general linear model to compare differences in FA, RD, AD and MD between the two groups. As there were group differences in age, this variable was used as a covariate to ensure that age differences did not influence the present results. The "randomize" tool was used to conduct significance testing, applying a threshold-free cluster enhancement (Smith and Nichols, 2009) with 5000 permutations. For FA, thresholds of $p<0.05$, $p<0.01$ and $p<0.005$ were examined, corrected for multiple comparisons across space. For

Table 1
Participant characteristics for high-functioning autism and Asperger's syndrome (HFA/AS) group and typically developing (TD) participants.

Characteristics	HFA/AS (N=12)	TD (N=12)
Gender (male/female)	12/0	12/0
Age (mean)	19.75 ± 4.93	18.50 ± 2.50
Age (range)	16–30	16–26
Handedness (right/left)	10/12	10/12
Medication (yes/no)	4/12	0/12
Comorbidity (yes/no)	4/12	0/12
Family diagnosis (yes/no)	3/12	0/12