Psychiatry Research: Neuroimaging 233 (2015) 64–72

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

# Diffusion tensor imaging reveals no white matter impairments among adults with autism spectrum disorder

Melissa Kirkovski [a,b,*], Peter G. Enticott [b,a], Jerome J. Maller [a], Susan L. Rossell [c,a], Paul B. Fitzgerald [a]

[a] Monash Alfred Psychiatry Research Centre, The Alfred and Central Clinical School, Monash University, Melbourne, Victoria, Australia
[b] Cognitive Neuroscience Unit, School of Psychology, Deakin University, Burwood, Victoria, Australia
[c] Brain and Psychological Science Research Centre, Faculty Health, Arts and Design, Swinburne University, Hawthorn, Victoria, Australia

ARTICLE INFO

*Article history:*
Received 30 May 2014
Received in revised form
22 December 2014
Accepted 6 May 2015
Available online 14 May 2015

*Keywords:*
Autism spectrum disorder
Diffusion tensor imaging
Tract-based spatial statistics
Gender
Magnetic resonance imaging

ABSTRACT

Abnormalities within white matter (WM) have been identified in autism spectrum disorder (ASD). Although there is some support for greater neurobiological deficits among females with ASD, there is little research investigating sex differences in WM in ASD. We used diffusion tensor imaging (DTI) to investigate WM aberration in 25 adults with high-functioning ASD and 24 age-, sex- and IQ-matched controls. Tract-based spatial statistics (TBSS) was used to explore differences in WM in major tract bundles. The effects of biological sex were also investigated. TBSS revealed no differences in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), or axial diffusivity (AD) between groups. There were no effects of biological sex. We consider whether methodological differences between past studies have contributed to the highly heterogeneous findings in the literature. Finally, we suggest that, among a high-functioning sample of adults with ASD, differences in WM microstructure may not be related to clinical impairment.



## 1. Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental condition characterized by impairments in social communication and interaction, and the presence of restricted and repetitive patterns of behavior or interests (RRBI) (American Psychiatric Association, 2013). The condition affects more males than females, with an approximate male-to-female ratio of 4:1 across the spectrum (Fombonne, 2003, 2009; CDC, 2012). Females with ASD may present with a different clinical manifestation of ASD compared to affected males, and there is a growing body of evidence to suggest that affected females may experience greater neurobiological deficit, or at least differ neurobiologically compared to affected males (see Kirkovski et al. (2013), for a review).

Brain based abnormalities are often identified in ASD. Volumetric studies demonstrate that individuals with ASD experience a pattern of atypical brain growth, including structural size enlargement and reduction (Redcay and Courchesne, 2005; Courchesne et al., 2011), a phenomenon mediated by age (Aylward et al., 2002) and biological sex (Bloss and Courchesne, 2007; Schumann et al., 2009, 2010; Lai et al., 2013). Diffusion weighted magnetic resonance imaging (DW-MRI; a magnetic resonance imaging [MRI] modality) is the most direct, non-invasive way of mapping white matter (WM) tracts in vivo (Le Bihan et al., 2001). Diffusion tensor imaging (DTI) allows for the investigation of WM architecture by providing a measure of diffusion (most often of water molecules) within imaging voxels (Le Bihan et al., 2001; Assaf and Pasternak, 2008). There are four main measures used to explore the diffusivity of tissue microstructure.

Most commonly investigated are: fractional anisotropy (FA), which provides a quantitative measure of diffusion anisotropy, ranging from completely isotropic (the same in all directions) to completely anisotropic (directionally driven), and fiber coherence (Le Bihan et al., 2001; Beaulieu, 2002) and mean diffusivity (MD), a measure of mean-squared displacement of water, or average size of an ellipsoid (Le Bihan et al., 2001). Axial (AD) and radial (RD) diffusivity are used to describe diffusivity parallel and perpendicular to axonal fibers, respectively. These measures have also been suggested to represent axonal structure and form as well as myelin aberration, however further investigation is required to verify these claims (Song et al., 2002).

Previous research has largely suggested that WM microstructural abnormality may be reflected by reduced FA, and increased

* Corresponding author. Tel.: +61 3 9251 7795; fax: +61 3 9244 6858.
*E-mail address:* melissa.kirkovski@deakin.edu.au (M. Kirkovski).

http://dx.doi.org/10.1016/j.pscychresns.2015.05.003
0925-4927/

MD in ASD in various tracts and structures throughout the brain (Keller et al., 2007; Catani et al., 2008; Thakkar et al., 2008; Bloemen et al., 2010; Groen et al., 2011; Jou et al., 2011b; Shukla et al., 2011b; Langen et al., 2012), see Travers et al. (2012) for a comprehensive review. There are however, some exceptions, as will be discussed below. Spatial proximity has been identified as a mediating factor when investigating neural connectivity (NC; including structural and functional) in ASD. Broadly, abnormal NC in ASD can be characterized by short distance hyper-, and long distance hypo-connectivity (see, Courchesne and Pierce (2005) and Kana et al. (2014)). Shukla et al. (2011b) highlight that a great deal of the DTI literature in ASD is predominantly focused on long-distance connections, and hence sought to explore WM in various tract lengths. Overall, the authors report a similar pattern as described above (of reduced FA and increased MD) in individuals ASD, however they demonstrate subtle differences in the degree of WM differences comparing short- and long distance connection.

A great deal of past DTI literature has relied on analysis techniques whereby regions of interest (ROIs) or tracts have been manually specified, and hence have not allowed for the whole brain to be investigated. Whole brain analysis modalities such as voxel based morphometry (VBM) can overcome this, however are limited by misalignment of data across subjects and also variability in smoothing parameters (Jones et al., 2005; Smith et al., 2006). Tract-based spatial statistics (TBSS) is a voxel-wise DTI analysis technique that allows for investigation of WM throughout the brain, using a skeleton based on the center of each major WM tract (Smith et al., 2006), where FA is expected to be highest. The technique attempts to optimize whole brain DTI analysis by addressing some of the limitations associated with older analysis techniques (for a detailed explanation, see Smith et al. (2006)). Direct comparison of TBSS with older analysis techniques remains limited; hence, the primary focus of this paper form hereinafter will be on TBSS based research, unless otherwise stated.

More recent studies using this method have revealed somewhat variable findings. It seems however, that WM abnormality in ASD is widespread throughout the brain. Roine et al. (2013), for example, found that individuals with ASD, on a global level, had increased FA compared with neurotypical controls (Roine et al., 2013) using both TBSS and tractography. In terms of single structures and pathways however, WM abnormality has most consistently been identified in the corpus callosum (CC). Studies have identified both reduced (Barnea-Goraly et al., 2010; Kumar et al., 2010; Cheon et al., 2011; Shukla et al., 2011a; Kleinhans et al., 2012; Walker et al., 2012; Gibbard et al., 2013; Perkins et al., 2014) and increased (Weinstein et al., 2011; Billeci et al., 2012) FA, and increased MD (Cheon et al., 2011; Shukla et al., 2011a; Kleinhans et al., 2012) and RD (Shukla et al., 2011a; Kleinhans et al., 2012) in individuals with ASD compared with neurotypical (NT) controls in various regions within the CC. Other areas often implicated as having atypical FA values among individuals with ASD include the cingulum (Kumar et al., 2010; Jou et al., 2011a; Shukla et al., 2011a; Weinstein et al., 2011; Billeci et al., 2012; Kleinhans et al., 2012; Perkins et al., 2014), superior longitudinal fasciculus (SLF) (Barnea-Goraly et al., 2010; Sahyoun et al., 2010; Jou et al., 2011a; Shukla et al., 2011a; Weinstein et al., 2011; Kleinhans et al., 2012; Gibbard et al., 2013; Perkins et al., 2014), the internal and external capsules (Barnea-Goraly et al., 2010; Shukla et al., 2011a; Billeci et al., 2012; Kleinhans et al., 2012; Walker et al., 2012; Gibbard et al., 2013), uncinate fasciculus (Kumar et al., 2010; Sahyoun et al., 2010; Cheon et al., 2011; Jou et al., 2011a; Kleinhans et al., 2012; Perkins et al., 2014), arcuate fasciculus (Barnea-Goraly et al., 2010; Billeci et al., 2012; Walker et al., 2012) and the temporo-parietal regions (Barnea-Goraly et al., 2010; Walker et al., 2012); again the direction of these differences in FA is inconsistent across studies. These regions identified as being most often implicated as having a WM microstructure atypical to that of NT controls are consistent with an earlier review by Travers et al. (2012). Supplementary Tables S1 and S2 provide more detailed information about previous research in ASD using TBSS methodology.

Findings with regard to other DTI measures of WM abnormality are again heterogeneous. Walker et al. (2012) noted increased MD, RD and AD in the ASD sample in posterior WM tracts, while Ameis et al. (2011) noted increased MD and RD values in the frontal regions of the brain. Others note that MD, RD (Shukla et al., 2011a; Kleinhans et al., 2012) and AD (Barnea-Goraly et al., 2010) differences between ASD and NT are more widespread throughout the brain, and expand across association, commissural and projection fibers, as well as the brainstem (Kleinhans et al., 2012).

While it has been suggested that differences in WM microstructure between individuals with ASD and NT controls may persist from childhood through to adulthood (Keller et al., 2007), more recent literature does provide some support for an effect of age, and potentially some degree of normalization in WM microstructure. For example, among a sample aged 13.58–40.92, Kleinhans et al. (2012) note that with age, FA increased in those with ASD and decreased in the control group. The inverse pattern was noted for MD and RD, while there was no apparent age related effect on AD. Further, in a sample of children and adolescents, Ameis et al. (2011) noted that analysis of a combined child/adolescent sample and analysis of the adolescent only sub-sample, revealed no significant differences in WM between ASD and NT individuals. In this study, when data of children only were analyzed, many areas were identified as having abnormalities in WM formation, as outlined above. It is important to note however, that the adolescent-only cohort in this study comprised only 14 participants (ASD=8, NT=6). Bakhtiari et al. (2012) reported a similar finding in an older sample: analysis of adolescent-only data identified differences in at least a dozen affected WM tracts, but no significant differences were noted using adult-only group comparisons. This notion is further supported by Bode et al. (2011), who reported increased FA value in the ASD group for various structures, including clusters of optic radiation and the right inferior fronto-occipital fasciculus. This effect however, was diminished when controlling for age, sex and handedness. It is important to note that such effects are not consistent throughout the literature. In studies controlling for age, IQ (Cheng et al., 2010; Gibbard et al., 2013), and gender (Gibbard et al., 2013), widespread differences in WM microstructure have been identified among adolescent and adult samples. The degree of influence held by each covariate, however, is unclear.

Importantly, whilst often described as a confounding factor in the literature, biological sex is rarely investigated as a primary focus. While gender was controlled for in some of the aforementioned studies (Bode et al., 2011; Bakhtiari et al., 2012; Gibbard et al., 2013), none had the statistical power to systematically explore the effects of female gender on WM in ASD. Beacher et al. (2012), using a ROI based technique, explored the effects of biological sex on WM in adults with Asperger's Syndrome (AS). Within the CC, bilateral cingulum, and the corona radiata, the authors note significant interactions whereby NT males had increased FA compared with NT females, a result that was not noted between affected males and females in any site.

Potential confounds to these data however, are not limited to within subject factors. Different analysis methods, for example, can affect results, as described above. Furthermore, methodological factors such as magnetic field strength (Rutt and Lee, 1996; Schick, 2005) and gradient direction parameters (Jones et al., 1999; Papadakis et al., 1999) can influence image resolution, signal-noise-ratio (SNR) and hence results. A recent comment by Jones et al. (2013) provides a comprehensive guide to acquisition and appropriate interpretation of diffusion weighted data.