Investigating the neural correlates of autistic traits using a dimensional approach

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Declaration

I, Varun Arunachalam Chandran, confirm that the work presented in this thesis is my own and the use of all materials from other sources has been properly and fully acknowledged.

Abstract

Autism Spectrum Disorders are a set of neurodevelopmental conditions characterised by difficulties in social interaction and communication as well as stereotyped and restricted patterns of interest. With recent advances in neuroimaging techniques and analytical approaches, a considerable effort has been directed towards identifying the neuroanatomical underpinnings of Autism Spectrum Disorders (ASD). Most of the previous studies have treated ASD as a category, using a case-control design to identify the neuroanatomical correlates of ASD. However, it is well-recognised that autistic traits exist in a continuum across the general population, whilst the extreme end of this distribution is diagnosed as clinical ASD. Therefore, we sought to investigate the neural correlates of autistic traits in the clinical and non-clinical population using a dimensional approach. To this end, the proposed research measured the structural brain volumes (using voxel-based morphometry and surface-based morphometry; chapter 1), white matter microstructure properties (using Diffusion Tensor Imaging; chapter 2) and intrinsic functional connectivity (using resting state functional MRI; chapter 3).

Previous studies have primarily used case-control design on ASD and applied voxel-based morphometry (VBM) and surface-based morphometry (SBM) analysis. Some of these studies showed widespread grey matter abnormalities including the social brain regions (orbitofrontal cortex, amygdala, superior temporal sulcus and fusiform gyrus) of individuals with ASD as compared to controls. Several studies also used Diffusion Tensor Imaging (DTI) in adults with HFA, which showed white matter microstructure abnormalities with reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in the superior longitudinal, uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corpus callosum and cortico-spinal tracts. Resting state functional MRI (rs-fMRI) studies showed atypical functional connectivity in different brain regions/resting state networks including the default mode, executive control, fronto-parietal and visual networks in individuals with ASD. However, this pattern of results is far from unequivocal. In addition, these variations can be accounted by the different analytical approaches used. There is considerable variance inherent in the case-control design due to the sampling of the controls. A dimensional approach avoids this source of variance by sampling across the whole population.

High resolution whole brain MPRAGE, DTI and rs-fMRI data were collected from a sample of research volunteers across the population (including those with a clinical diagnosis of ASD) using

a 3T MRI Scanner, based at the Centre for Integrative Neuroscience and Neurodynamics (CINN), University of Reading. All volunteers also filled in a questionnaire measuring autism-related traits, such as the Autism Spectrum Quotient.

VBM analysis was conducted at a whole-brain level using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) incorporated within the SPM analysis package. The regional grey matter volumes were calculated by summing up all voxels in the corresponding tissue maps. In addition, SBM analysis was performed using FREESURFER, a brain imaging analysis suite. The cortical thickness, surface area, volume and gyrification were measured by inflating the whole-brain structural images. Then, a robust regression method was used to test the relationship of the neuroanatomical measures and autism-related traits. Diffusion Tensor Imaging (DTI) data were pre-processed and analysed to measure the Fractional Anisotropy (FA) and Mean Diffusivity (MD) values using tract-based spatial statistics (TBSS), and skeleton-based tracts of interest approach using the FSL analysis package. Correlations and regression analyses were conducted, similar to the VBM. The rs-fMRI data were pre-processed using independent component analysis (ICA) approach and dual regression analysis (based on Beckmann's eight resting state networks) incorporated in FMRIB FSL software package.

Our findings demonstrated widespread grey matter abnormalities including the social brain regions (chapter 1), a partial evidence for white matter microstructure abnormalities (chapter 2) and intrinsic functional connectivity (chapter 3) related to higher autistic traits. Thus, the proposed set of studies addressed the key gap in the literature on grey matter abnormalities, atypical white matter microstructure properties and aberrant intrinsic functional connectivity related to autistic traits. By taking a dimensional approach, this project has the potential to offer new insights into the aetiology of the autistic phenotype.

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Chapter 1: General introduction

1.1 Definition and history of Autism Spectrum Disorders

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental conditions characterised by persistent deficits in social interaction and communication, as well as repetitive and restricted patterns of behaviour and interests (American Psychiatric Association, 2013). In addition, ASD may be associated with common comorbid conditions including attention deficit hyperactivity disorder (ADHD), epilepsy, intellectual disability and anxiety disorder (Buck et al., 2014). In 1943, Leo Kanner, an Austrian-American psychiatrist, identified and discovered the primary symptoms of autism (Kanner, 1943). Kanner first observed deficits in social interaction and communication, restricted and circumscribed interests (earlier referred to as sameness), failing to recognise and display emotions, and also certain abnormal behavioural manifestations. However, the latest DSM-V criteria has classified ASD into two broader symptoms: persistent deficits in social interaction/communication and restricted, repetitive patterns of behaviours and interests (RRBI). Deficits in social interaction/communication show behavioural manifestations including difficulties in initiating back-and-forth conversation, maintaining eye contact, paying attention, making emotional judgements and recognising facial expression (Pepper et al., 2018). RRBI show behavioural manifestations including repetitive use of speech or objects, hand flapping, and narrow interests in specific activities (Harrop et al., 2014). In recent years, sensory atypicalities were also included as a part of ASD diagnosis: these are characterised by a fascination in bright and coloured lights and different patterns of moving objects or water, as well as an unusual responsiveness to noisy settings (Horder et al., 2014).

1.2 Assessment and diagnostic criteria of ASD

Individuals with ASD can be assessed based on their symptom domains, age and severity using different tools. To facilitate this, some structured tools and interviews have been designed and developed to measure the symptoms of ASD. The Autism Diagnostic Observation Schedule (ADOS) is an assessment and validating method used for evaluating difficulties in social interaction and communication and restricted and repetitive behaviours for individuals with symptoms of autism. ADOS module III is used for children/adolescents, whereas the ADOS module IV is used for adolescents/adults (Lefort-Besnard et al., 2020; Lord et al., 2000). ADOS was primarily developed for identifying autistic children and is not optimised for identifying autistic adults, especially those who do not have high service needs. The Autism Diagnostic

Interview Revised (ADI-R) (Lord et al., 2000) is an interview between the clinician and parent/caregiver, which could provide a description of developmental history and current functioning in individuals with autism. These two methods offer detailed and structured information about the behavioural manifestations in individuals with autism.

According to an earlier *diagnostic and statistical manual (DSM)* III, Autism was introduced as a separate developmental disorder and termed as 'Infantile autism' (Volkmar et al., 1986). Previous *diagnostic and statistical manual (DSM)* IV criteria classified ASD into pervasive developmental disorder (PDD-NOS), classic autism and Asperger's syndrome, childhood disintegrative disorder and Rett's syndrome (American Psychiatric Association et al., 1994). Pervasive Developmental Disorder (PDD)-not otherwise specified are characterized by the primary deficits in social interaction and communication (Fred R. Volkmar et al., 2004). Asperger's syndrome and High Functioning Autism (HFA), both manifest with primary symptoms of social interaction and communication deficits, and stereotyped behaviours. However, the main difference between these two conditions are that children with HFA exhibit developmental delay in acquiring language skills, despite having average/higher Intelligent Quotient (IQ), whereas the AS diagnosis do not exhibit any delay in acquiring language skills (Szatmari et al., 1995). However, the latest DSM V diagnostic criteria (commonly applied in the United States) primarily defines ASD based on the two broader symptom domains including the social interaction and communication, and restricted and repetitive patterns of behaviours and interests. On the other side, an *International Statistical Classification of Diseases* (ICD-10) diagnostic criteria for autism spectrum disorders recognised by the *World Health Organisation* (WHO) is applied in the United Kingdom and many other countries worldwide. The ICD-10 and DSM-IV criteria used for diagnosing ASD are comparable. But the significant difference between these ICD-10 and DSM-IV diagnostic criteria is the former emphasizes the classification, whereas the latter emphasizes the diagnoses on ASD (Doernberg & Hollander, 2016). Despite the diagnostic criteria applied, the quality of ASD diagnosis may also significantly vary depending on the factors such as age, severity and IQ during the onset of the condition.

1.3 Prevalence of ASD

It was estimated that 1 in 59 individuals were diagnosed with ASD in the United States in 2014, according to the Centres for Disease Control and Prevention (CDC) (Baio et al., 2018). On the other hand, 1 in 100 individuals were diagnosed with ASD in the United Kingdom in 2014, according to the National Autistic Society (NAS) (Onaolapo & Onaolapo, 2017). The global ASD

prevalence is 1 in 132 individuals as reported in 2010 (Baxter et al., 2015). These ASD prevalence estimates may vary globally and regionally based on the criteria and quality of the diagnosis. The gender ratio of individuals diagnosed with ASD is estimated at 4:1 (male/female) (Baron-Cohen et al., 2020; Halladay et al., 2015; Lai & Szatmari, 2020). The lower prevalence of ASD in females may be due to the presence of higher levels of oxytocin which may provide a protective mechanism for ASD. Moreover, the lower levels of vasopressin in males could lead to increased risk factors contributing to the development of ASD. However, the rate of production of vasopressin and oxytocin may also vary in the opposite direction in male and female individuals with ASD. These neuropeptides are believed to contribute to the gender-biased high prevalence of ASD in males compared to females (Carter, 2007).

1.4 Behavioural manifestation of autistic symptoms and psychological theories

Social cognition refers to behavioural responses to socially relevant stimuli such as perceiving, interpreting and understanding the intentions of others and responding appropriately. However, the deficits in such social skills may reflect the differences in understanding and interpreting the intentions of other individuals (associated with theory of mind deficits), a skill which appears to be impaired in individuals with ASD (Leekam, 2016; Morrison et al., 2019). Theory of mind deficits in the field of ASD research has been a highly discussed topic over the last two decades. In our routine life, it is very important to analyse one's own thoughts and understand others' intentions in order to facilitate social interaction and communication. However, individuals with ASD show a wide range of behavioural abnormalities based on their inability to analyse their own thoughts and judge others' intentions. As a consequence, individuals with ASD may not be able to predict the actions following the behaviour of other people, which will hinder their ability to interact and communicate socially (Baron-Cohen, 2000; Happé, 1995).

Previous studies suggest that individuals with ASD also show atypical empathy (A. Smith, 2009). While the TOM deficit hypothesis explains the social and communication difficulties more specifically, the Empathising-Systemising (E-S) theory explains not only the empathy as a main component, but also the systemising ability related to the symptoms of autism (Baron-Cohen, 2009). The empathising and systemising abilities are two components which may differ significantly in males and females with ASD. The empathising ability is defined as one's affective response to others' emotional feelings, whereas the systemising ability is defined as judging and manipulating the input and output responses based on the constructs. Systemising ability can also be defined as characteristics of individuals with high technical abilities (handling computers,

machines and instruments). In general, males have relatively higher systemising ability (S>E) than females, whereas females have greater empathising ability (E>S) than males. However, according to the extreme male brain theory in autism, males have far greater systemising ability (S>>E) than females. The systemising and empathising abilities are measured using the systemising quotient (SQ) and empathising quotient (EQ) respectively (Baron-Cohen, 2002).

Individuals with ASD tend to focus on local information and fail to integrate other relevant details. This attention bias of superior local information processing limits them from seeing the big picture in a given scenario. This atypical behaviour is related to attention bias rather than attention deficits, known as 'weak central coherence theory' in individuals with ASD (Happé & Frith, 2006). Some previous studies have suggested that weak central coherence may be related to/co-occur with theory of mind deficits in individuals with ASD (F. G. E. Happé, 1997). This can also be seen in individuals with autistic traits in the general population (Jarrold et al., 2000). Despite the fact that many theories for understanding ASD already exist (mindblindness, weak central coherence, extreme male brain theory), new evidence increasingly suggests that early abnormal brain development may play a significant role in the neural underpinnings of autism.

Communication skill deficits are defining features of autism spectrum disorders. Communication skills are classified into verbal (speech and language) and nonverbal communication (eye-to-eye contact, facial gestures, pointing to objects) and these both elements are crucial for the current diagnostic criteria for ASD (American Psychiatric Association, 2013). These communication skills are poorly developed in individuals diagnosed with ASD. One of the key elements of acquiring communication skills in infants is joint attention According to many researchers, acquiring joint attention skills are very important and an indicator for typical development in young children. On the contrary, deficits in joint attention skills in infants and young children may be an early sign of developing autism (Charman, 2003; Mundy & Sigman, 1989). Previous studies showed that infants and young children with ASD showed significant differences in acquiring joint attention skills compared to typically developing children (Chiang et al., 2008; Horovitz & Matson, 2010). In addition, several studies reported that language deficits are common in individuals with ASD (Rapin & Dunn, 2003; Tager-Flusberg, 2000). It was demonstrated that infants with ASD (12 months) showed difficulties in language development compared to age matched unaffected siblings of infants with ASD and typically developing controls (Mitchell et al., 2006). A follow-up language assessment (18 months) also showed significant language delay in children with ASD compared to unaffected siblings of ASD and typically developing controls.

This finding suggested that difficulties in acquiring language abilities may be an early sign of communication deficits in young children with ASD. A number of studies compared between typically developing controls and individuals with ASD showed significant differences in verbal and nonverbal communication domain in individuals with ASD (Lam & Yeung, 2012; Mundy et al., 1986; Pecukonis et al., 2019). Therefore, deficits in verbal and non-verbal communication may be a suggestive indication for an early diagnosis of ASD.

Restricted and Repetitive patterns of Behaviour and Interests (RRBI) are characterised by motor stereotypes and circumscribed preoccupation in individuals with ASD. RRBI includes stereotyped movements, adherence to routines, resistance to change and unusual intense preoccupation (American Psychiatric Association, 2013). Stereotyped behaviours are common and considered as a part of typical development in infants until the age 12 months. The subsequent events of typical development gear up the progress towards the adaptive and goal-oriented behaviour at later stages. However, these patterns of stereotyped behaviour are substantially altered in individuals diagnosed with ASD (12-24 months) (Wolff et al., 2014). Previous studies reported differences in repetitive and stereotyped movements between the typically developing young children and children with ASD (Joseph et al., 2013; Morgan et al., 2008). In light of this evidence, it was suggested that assessing the repetitive and stereotyped behaviour in the second year of life is crucial to identify the symptoms of autism in the early developmental stages (Watt et al., 2008) which may continue to persist in adulthood.

Several studies have reported widespread brain structural abnormalities including the social brain regions supporting the cognitive and psychological theories of autism. However, to date, identifying definite neuroimaging biomarkers for ASD has been a major challenge. On the other hand, based on the dimensional nature of autistic symptoms, it has been hypothesised that autistic traits lie as a continuum in the general population (Bölte et al., 2011; Skuse et al., 2005). In light of this dimensional nature of autistic symptoms, some previous studies have consistently reported neuroanatomical abnormalities related to higher autistic traits. Considering this, the evidence for atypical brain structural findings associated with symptoms of autism/autistic traits are reviewed in the empirical chapters. I have provided a brief overview of various psychological theories of autism in this section – this is not our main focus, but necessary for the sake of completeness.

1.5 Broader autism phenotype and autistic traits

It has been reported that unaffected parents and siblings (first-degree relatives) of children with ASD may exhibit higher autistic traits than the general population. Therefore, these first-degree relatives are considered to be a part of the 'broader autism phenotype (BAP)'. In this case, individuals who fall under the umbrella of the BAP are believed to have very similar genetic characteristics between each other, which are also observed in individuals with ASD. Previous studies have shown that both parents of children with ASD exhibited autistic traits, while some of the trait subscale measures (as measured by the Social Responsiveness Scale) were similar as observed in the children with ASD. This suggests that the heritability of the autistic traits may be higher in the broader autism phenotype (Bora et al., 2017; Rubenstein et al., 2019). In a twin population study using a monozygotic and dizygotic sample, Constantino and colleagues found that the presence of autistic traits varied from moderate to high enough to be heritable, suggesting that autistic traits may be continuously distributed across the general population (Constantino & Todd, 2003).

Autistic traits can be measured using the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001) and Social Responsiveness Scale (SRS) (Constantino et al., 2003). Both offer different measures of autistic traits in terms of domain-specific behavioural symptoms. AQ measures social skills, communication, attention to detail, attention switching and imagination, whereas the SRS measures the social and non-social behavioural domains of autistic traits. The presence of autistic traits is highly associated with genetic factors as reported in the twin study (Taylor et al., 2020). This suggests the possibility of autistic traits along the continuum. On the other hand, males show a higher prevalence of autistic traits than females. This supports the growing evidence indicating the influence of genetic factors on ASD (Hoekstra et al., 2007).

1.6 Aetiology

ASD is primarily driven by genetic and environmental factors (Hallmayer et al., 2011). Many twin-, family- and population-based studies support the evidence that there is a link between genetic factors and ASD. In light of this, approximately 50% genetic factor contributions have been reported in twin studies of autism (Colvert et al., 2015). ASD can be classified as idiopathic or syndromic based on its aetiology. Idiopathic autism refers to variations of the disorder that are passed down through generations and where the aetiology is unknown, while syndromic autism represents a known single gene disorder which may have resulted from mutation or chromosomal

aberrations. Syndromic autism includes conditions such as Fragile X Syndrome, tuberous sclerosis (TSC), Rett's syndrome MECP2 (Sztainberg & Zoghbi, 2016). Although there are a number of autism risk genes reported in idiopathic ASD, only 20% of genetic factors account for de novo mutations in individuals with ASD. It is now well understood that ASD is highly genetic. For instance, it has been suggested that the Fragile X Syndrome (associated with Fragile X Mental Retardation Protein gene) and autism phenotype share a common aetiology associated with social-communication skill deficits, which are believed to underlie the widely distributed atypical neural networks in individuals with ASD (Belmonte & Bourgeron, 2006). On the other hand, the common gene variants including the deletion/duplication of copy number variants (15q11-13) rather than one specific genetic factor may underlie the neuropathology of ASD (Vorstman et al., 2017).

While many studies have reported significant evidence showing the influence of genetic factors on ASD, some environmental factors during conception and gestation may also underlie the aetiology of ASD (Hertz-Picciotto et al., 2018). Although various autism risk candidate genes may account for the majority of clinical ASD and subclinical autistic traits, the environmental factors (such as parental age, stress factors, prenatal infection during pregnancy, malnutrition) may also play an important role in the aetiology of ASD. Selective Serotonin Reuptake Inhibitors (SSRI) is used as an antidepressant during pregnancy (environmental factors). SSRI may cause hyperserotonemia. This serotonin could influence the fetal brain development such as neuronal migration, synaptogenesis in autism. Previous studies (Hadjikhani, 2010; Yang et al., 2014) using a rodent model reported an increased serotonin level may also trigger the reduced oxytocin levels during pregnancy, which could influence the abnormal fetal brain development in autism. This increased serotonin level may underpin the brain structural differences in amygdala and hypothalamus related to social skills in autism. In addition, immune system deficiency and abnormal zinc homeostasis may also lead to aberrant synaptogenesis in ASD (Grabrucker, 2012). Further, certain environmental factors such as exposure to antidepressants/stress hormones and anticonvulsants during the prenatal stages and to maternal/first-degree relatives associated with autoimmune disorder may underlie the risk factors for abnormal brain development in children with ASD (Edmiston et al., 2017; Park et al., 2016).

1.7 Post-mortem brain studies of ASD

Previous meta-analysis and systematic review showed differences in head circumference and brain structure in the post-mortem brains of individuals with autism (Pickett & London, 2005; Redcay & Courchesne, 2005). The significant brain enlargement was particularly noticed in young

children with ASD (2-5 years old) than the adults. This meta-analysis report suggested unusual brain overgrowth may occur as a result of cortical neuropathology beginning in the early postnatal period before the atypical behavioural manifestations are apparent in children later diagnosed with autism. Several post-mortem brain studies have suggested that abnormal brain structures (including medial prefrontal cortex, amygdala and superior temporal sulcus) may underlie cortical neuropathology in autism (Amaral et al., 2008; Schumann & Amaral, 2006; Schumann & Nordahl, 2011). These latter social brain regions are believed to underpin the primary social behavioural deficits in ASD. Based on this, we will review the structural brain imaging studies of autism in the subsequent chapters. Some human brain post-mortem studies have suggested that minicolumnopathy (associated with an increase in number of neurons and density) may underlie the cortical disorganisation in individuals with ASD (Casanova, 2006). Based on the cortical neuropathology, some previous reports have suggested higher microglial density in the fronto-insular cortex and visual cortex in post-mortem brains of ASD individuals compared to controls. In light of this previous evidence, it is possible that these differences in the density of microglial cells may spread across different brain regions in the cerebral cortex which may be associated with atypical brain structure and connectivity in ASD (Tetreault et al., 2012). It was further shown that the number of neurons was higher in the dorsal and medial prefrontal cortices which may be suggestive of early neurobiological signs in ASD (Courchesne, et al., 2011). Considering this, a post-mortem brain study specifically demonstrated that the dendrite spine density in cortical layers including III and V in the prefrontal cortex are higher throughout the course of early development in children and adults in the human prefrontal cortex (Petanjek et al., 2011). However, the dendrite spine density was found to vary abnormally in the post-mortem brains of individuals with ASD. This appears to be associated with atypical behavioural manifestations in individuals with ASD (Lee et al., 2017). The long-established evidence of post-mortem brain abnormalities in ASD may underlie the cortical neuropathology in ASD. However, it is very important to understand whether these post-mortem brain abnormalities are in line with the neuroanatomical alterations of living human brains in individuals with ASD.

1.8 Social brain hypothesis in autism

Over several decades, numerous studies have reported widespread structural brain abnormalities in individuals with ASD (Aylward et al., 2002; Courchesne et al., 1987; Gaffney et al., 1987). However, specific neuroanatomical landmarks in the frontal and temporal lobes may be significantly associated with deficits in social interactions and communication and stereotyped behaviours in individuals with ASD (Gaffney et al., 1989; Hashimoto et al., 1989; Hetzler &

Griffin, 1981). It is only since the introduction of Brothers et al. theoretical framework that the study of social brain hypothesis has gained momentum. A social brain model was developed consisting of different regions including orbitofrontal cortex, amygdala, superior temporal sulcus and fusiform face area which are believed to underlie the atypical social behaviours in autism (Brothers, 1990). Previous studies explained the social brain hypothesis in typically developing infants and high-risk infant siblings diagnosed later with autism (Elsabbagh & Johnson, 2016; Silver & Rapin, 2012). The social and communication skills are primary characteristics in typically developing infants indicating normal development. Typically developing human brains are developed in such a way to prioritise social orienting to salient features, such as paying attention to facial expression, following the motion cues of eyes and mouth. These social behavioural manifestations related to the synchronised key brain regions (orbitofrontal cortex, inferior frontal gyrus, amygdala, posterior superior temporal sulcus and fusiform gyrus) are considered crucial for achieving appropriate developmental milestones in typically developing individuals (Misra, 2014). However, high-risk infant siblings with autism fail to develop such social skills which may be driven by the neuroanatomical differences in the key brain regions, so called the 'social brain'. This social brain model yielded more attention and spurred more research on social cognition in ASD. Volkmar highlighted the importance of these social brain regions associated with face processing, joint attention and social information processing and suggested that application of such theoretical models are crucial for the advancement of social neuroscience research in autism (Volkmar, 2011).

The orbitofrontal cortex/ventromedial prefrontal cortex is an important brain region believed to be involved in theory of mind abilities (interpreting self and others in terms of thoughts, feelings and mental representations) in the normal healthy population. However, many researchers suggested that disruptions in the orbitofrontal cortex may underpin the primary deficits of social interaction and communication in individuals with ASD (Weston, 2019). While OFC plays an important role in TOM, the amygdala, an almond-shaped subcortical brain region plays a key role in processing emotions. According to the amygdala theory of autism, it was suggested that the malformation in the latter brain region may underlie the difficulties in recognising the different socio-emotional patterns of behaviour (fear, disgust, sad, happy) in individuals with ASD (Howard et al., 2000; Zalla & Sperduti, 2013). Thus, the amygdala is considered to be a crucial part of the social brain in individuals with autism.

The superior temporal sulcus, mainly the posterior part of the brain is significantly involved in analysing and predicting the biological motion cues and body movements, which is widely reported in autism (Yang et al., 2015). A substantial body of brain imaging research revealed that abnormalities in the posterior superior temporal sulcus may be associated with difficulties in social perception processing in autism. Such brain abnormalities in the superior temporal sulcus may underlie the impairments in social information processing in individuals with ASD as well as individuals with significant autistic traits (Saitovitch et al., 2012).

Individuals with ASD show difficulty in recognising the faces of others. For instance, discriminating between different faces and some objects resembling faces may be a difficult task for individuals with ASD compared to neurotypicals (Pavlova et al., 2017). In light of this, the fusiform gyrus is an important brain region associated with face recognition, which is consistently reported in individuals with ASD (Schultz, 2005a). The experience of attending facial stimuli underpinning the fusiform gyrus may not be anatomically and functionally integrated with the other social brain regions (eg., amygdala) in individuals with ASD (Trontel et al., 2013). According to a theoretical account, the input of facial stimuli may not be rewarding for individuals with ASD which may underlie the lack of social motivation. Thus, these social brain regions may be integrated into a common framework which is essential for the development of social cognition. The failure of communication/social information processing between any of these regions may have an impact on social cognition in individuals with ASD.

Current practices of diagnosing ASD are purely based on atypical behavioural manifestations. This is because of unavailability of standard and definite biomarkers for the clinical diagnosis of ASD. However, growing evidence suggests that neural basis may underlie the deficits in social communication and stereotyped behaviours in individuals with ASD. Many studies have used post-mortem brain and genetic studies to understand the neurobiological factors associated with ASD despite some limitations of applying in-vitro examinations. To overcome these challenges, we may require a wide range of neuroimaging biomarkers in ASD. There is growing evidence across different modalities suggesting that aberrant functional and structural connectivity in the different brain regions is associated with ASD. In light of this, the aberrant alpha-coherence during the resting state Electroencephalography (EEG) may reflect the atypical default mode network (DMN) associated with atypical social behaviours in individuals with ASD relative to controls. In addition, the abnormal gamma-coherence in the frontoparietal regions during facial processing

tasks may be associated with the atypical facial processing in children who are at high risk of developing ASD compared to low-risk controls (Schwartz et al., 2017).

A number of studies using functional Near Infrared Spectroscopy (fNIRS) have shown differences in functional connectivity across different brain regions/networks in children with ASD (Cheng et al., 2019; Keehn, Wagner, et al., 2013; Li et al., 2016). One previous study using fNIRS investigated the visual and auditory social stimuli response in infants with high-risk (unaffected siblings/parents of children with autism) and low-risk controls. This study identified an increase in oxyhaemoglobin associated with greater visual and auditory response in the posterior STS in the low-risk control infants compared to the high-risk infants. These findings suggested that infants with a risk of developing autistic traits may show a lack of response to social stimuli observed in the broader autism phenotype (Lloyd-Fox et al., 2013). Some previous studies used Magnetoencephalography (MEG) and reported differences in functional connectivity across large-scale resting state networks (including DMN) in individuals with ASD (Cornew et al., 2012; Lajiness-O'Neill et al., 2018). A previous study using MEG demonstrated greater differences in highly integrated network properties in the alpha and gamma frequency bands in individuals with ASD compared to controls (Kitzbichler et al., 2015). The eminently integrated spatiotemporal patterns in the high frequency bands suggest that the atypical functional connectivity is widely distributed across networks and subnetworks in individuals with ASD.

Several studies have reported differences in Cerebral Glucose Metabolic Rate (CGMR) in individuals with ASD (Mitelman et al., 2018; Rumsey et al., 1985). A previous study has demonstrated hypoperfusion in the superior temporal gyrus using a Positron Emission Tomography (PET) with both individual and group differences in an exploratory and validation sample in children with autism compared to children with non-autistic mental retardation. This study finding suggested that the reduced cerebral blood flow may be characteristic of localised temporal lobe dysfunction in individuals with ASD (Zilbovicius et al., 2000). Previous studies have reported differences in the various neurotransmitters; however, glutamate/ Gamma AminoButyric Acid (GABA) ratio has been increasingly examined for its crucial role in excitatory/inhibitory imbalances in individuals with ASD. Considering this, Rojas and colleagues used 1H Magnetic Resonance Spectroscopy (MRS) to demonstrate reduced inhibitory neurotransmitter GABA in the auditory cortex in individuals with ASD and their unaffected siblings compared to healthy controls. These abnormalities of neurotransmitter findings in individuals with ASD and their unaffected siblings suggest that the excitatory/inhibitory imbalance

ratio of GABA/creatine in the auditory cortex and other brain regions in the neocortex may be associated with behavioural deficits in the autism endophenotype (Rojas et al., 2014). In another study, Ford and colleagues demonstrated the increased glutamate to GABA ratio in the superior temporal gyrus in association with autistic and schizotypal traits in the non-clinical population (Ford et al., 2017). This suggested that the E/I neurotransmitter imbalance may reflect the abnormal cortical excitation, which may be associated with the aberrant neural migration and plasticity related to autism and schizotypal traits.

In summary, the psychological theories and their neural correlates have been informative in parts. However, an overarching theory of the neurobiology of autism is missing. This gap may be filled by focussing on theories that examine brain structure rather than behaviour. In the subsequent sections, I will explore one such theory that suggests atypical neural connectivity in autism.

1.9 The importance of understanding the autistic behaviour and traits

Growing evidence from previous studies (Carper & Courchesne, 2005; Catani et al., 2016; Courchesne et al., 2001; Ecker, et al., 2013; Geschwind & Levitt, 2007a; McAlonan et al., 2005; Sato et al., 2014a) suggests that structural abnormalities and poor functional integration of different brain regions may underlie deficits in social interaction and communication and stereotyped behaviours in individuals with ASD. Therefore, it is very important to understand structural and functional connectivity associated with symptoms of autism/autistic traits because the brain abnormalities underlying ASD mainly affect social cognition, communication and stereotyped behaviours. The developmental milestones (joint attention, imitation, responding to social vocal sounds, recognising the face identity and adapting to daily routines) required at each and every stage of human life is very crucial to attain the social cognitive function and develop motor skills to lead a normal and healthy life. However, these social skills and complex motor functions are poorly developed in individuals with ASD and those with a higher level of autistic traits, from early childhood and throughout adulthood. Although clinical ASD has increasingly gained more attention because of its high prevalence, autistic traits in the general population have been less seriously taken into account. Nevertheless, the emerging evidence suggests that autistic traits lie across the continuum in the clinical and non-clinical population. While this concept has been put forward, the neural underpinnings of higher autistic traits is still yet to be systematically investigated. Some studies have suggested that the grey matter and white matter microstructure properties may underlie the symptoms of ASD which can also be observed in individuals with higher autistic traits. Some previous studies have attempted to examine the relationship between

the neural basis of ASD and autistic traits but several factors, including heterogeneity, data quality, and different sample characteristics, obscured the development in research. Therefore, considering these challenges, we sought to investigate the relationship between the brain structure and intrinsic resting state networks and autistic traits across the clinical and non-clinical population using a dimensional approach. In summary, our main objective is to explore the relationship between the grey matter, white matter microstructural properties and also the intrinsic resting state networks related to autistic traits. To achieve this, we used multimodal brain imaging techniques including structural MRI (Chapter 2), diffusion tensor imaging (Chapter 3) and resting state functional MRI (chapter 4).

Chapter 2: Investigating the relationship between grey matter properties, cortical morphometry and autistic traits across the diagnostic divide: a voxel-based morphometry and surface-based morphometry study

This chapter consists of an introduction to grey matter properties including the minicolumn architecture, grey matter composition and cortical morphometry. The main aim of this study was to investigate the relationship between the regional grey matter volume, cortical thickness, surface area and gyrification and autistic traits. To this end, voxel-based morphometry and surface-based morphometry were applied on the structural MRI dataset to address our primary research question. Our results showed strong evidence for regional differences (including the social brain regions) in the grey matter volume, cortical thickness, surface area and gyrification associated with higher autistic traits.

2.1 Introduction

2.1.1 Basic principles of Magnetic Resonance Imaging

Traditionally histopathological techniques were used to examine the brain structure in humans and animal models. However, it was a great challenge to study and understand the structure and function of a living human brain. One of the most important events in the history of medical imaging was the invention of Magnetic Resonance Imaging (MRI) scanner based on the principle Nuclear Magnetic Resonance (NMR) (Mansfield & Maudsley, 1977). MRI is a non-invasive medical imaging modality used to examine the structures of soft tissues/internal organs in primates and non-primates. MRI primarily uses strong magnetic field and Radio Frequency (RF) signal to produce a magnetic resonance signal and obtain the images of vital internal organs such as the brain. Human body comprises a large number of protons (positively charged). When these protons are placed in a strong magnetic field, these protons (which act like a bar magnet) themselves align parallel/antiparallel to the high magnetic field strength (B0) (Currie et al., 2013). Consequently, these protons experience a spin which are parallel or antiparallel depending upon the strong applied magnetic field. This phenomenon of spinning of protons in the strong magnetic field is known as precision. The number of times these protons wobbles per second around the magnetic field is known as 'precision frequency'. Since this was discovered by Joseph Larmour, it is named as the 'Larmour frequency'. This can be mathematically expressed as $\omega = \gamma B0$. ω=Larmor frequency; γ=gyromagnetic ratio (constant); B0= applied magnetic field. This equation indicates that the precision frequency is directly proportional to the magnetic field strength (Tubridy & McKinstry, 2000).

Longitudinal and transverse magnetization are the two net magnetization vectors which play an important role in T1 and T2 relaxation time respectively. The longitudinal magnetization is defined as the number of protons aligned with the direction parallel to the main magnetic field, whereas the transverse magnetization is defined as the number of protons aligned with the direction anti-parallel (perpendicular) to the main magnetic field. The T1 and T2 relaxation times play an important role in determining the tissue contrast in MRI images. These T1 and T2 relaxation times are incorporated in the application of T1 and T2 weighted MRI images respectively. In T1-weighted images (longitudinal magnetization), the fat appears hyperintense and water components appear hypointense, whereas in T2-weighted images (transverse magnetization) water components appear hyperintense and fat appears hypointense. These later MRI sequences use gradient echo pulse with initial 90 degree RF pulse and the spin echo pulse is produced due to a first 90 degree

RF pulse followed by a 180 degree flip of refocusing pulse. The application of gradient echo/spin echo in the T1 weighted and T2 weighted MRI are based on the specific requirements to improve the tissue contrast, signal to noise ratio, magnetic field inhomogeneity and duration of the scan time (Pui & Fok, 1995).

This principle of MRI is a great scientific innovation and a boon for the field of medical imaging. The advancement of this concept has been widely used in the application of different MRI techniques such as structural MRI, diffusion tensor imaging and BOLD imaging to examine the grey matter and white matter properties and neural activity underlying normal and abnormal development in the brain (Kennedy et al., 2002). In the current chapter, we will use T1-weighted structural MRI to assess the differences in the brain structure.

2.1.2 A brief introduction to human brain architecture

The human brain is made up of a complex network consisting of a large number of neurons (more than 80 billion) connected to each other. The alterations in the numbers, size and shape of neurons may reflect the differences in brain volume (Braitenberg, 2001; Knickmeyer et al., 2008; Piven et al., 2018)). Considering this, many efforts are consistently being applied to examine and understand the relationship between brain structure and behaviour. However, the differences in brain volume throughout the course of development make it difficult to elucidate this relationship (Braitenberg, 2001; Knickmeyer et al., 2008; Piven et al., 2018). The regional brain volume is measured by averaging the voxel intensities of localised Grey Matter (GM)/White Matter (WM) tissues. The GM is made up of a large number of neuronal cell bodies, whereas the WM is made up of axons and myelin sheath (Timmler & Simons, 2019). These different tissue classes are segmented based on the voxel intensities in the brain images. As such, the voxel intensity of the grey matter is lower than the white matter images. More specifically, the inconsistency in segmenting between these tissue boundaries may also lead to partial volume effects (Tohka, 2014). For instance, if the voxels in the grey matter are hyperintense, similar to the white matter, then it may be a challenge to differentiate the tissue classes of grey and white matter. Therefore, the tissue contrast properties are crucial to differentiating the grey and white matter boundaries, which could in turn facilitate measuring the cortical morphometry.

The cerebral cortex is composed of a large number of minicolumns in the human brain (Purves et al., 2001). The minicolumns are also referred to as an elementary unit of cortex in the brain. These minicolumns are cylindrical in structure and closely packed with each other to form

macrocolumns. In general, this minicolumn forms a basis for the cortical grey matter components in the brain structural organisation (Buxhoeveden et al., 2006; Jones, 2000). Over the past three decades, several attempts have been made to develop a standard brain imaging technique to measure cortical morphometry. Voxel-based Morphometry (VBM) and Surface-based Morphometry (SBM) were the two different analytical approaches developed to measure regional brain volume and cortical thickness, as well as surface area and gyrification, respectively.

VBM is a volumetric analysis that uses a whole brain voxel-by-voxel comparison to compute the local concentration of the regional grey and white matter volume in the brain (Ashburner & Friston, 2000). Presently, VBM mainly estimates the differences in local deformation fields of high-resolution structural brain images. The local deformation field represents the regional differences in the Jacobian matrix of all voxels after undergoing stretching and shearing to match all voxels in the template space. Conventional structural MRI images are commonly used to identify the atrophy/any sort of structural brain alterations caused by disease progression in individuals with neuropsychiatric or neurological conditions, but not across groups. However, VBM will help us to measure the differences in GM/WM volume between groups as well as its relationship with behavioural patterns.

Surface-based morphometry is used to measure the properties of cortical folding including the thickness, surface area, volume and gyrification (Fischl, 2012). SBM primarily performs cortical surface reconstruction. This is because it is a challenge to measure the deep hidden cortical and subcortical brain structures from raw structural MRI brain images. The cortical surface reconstruction enables the user to inflate, unfold and flatten the cortical structures including gyri and sulci (comprises two-third of the deeply hidden cortical structures). Another advantage of SBM is that it generates cortical surface tessellations using a connected component algorithm which adds more reliability for the surface reconstruction technique.

The main similarity between VBM and SBM is that both the analytical approaches can be used to measure the regional grey matter volume. However, the difference between the VBM and SBM is that the former uses volume-based analysis and while the latter uses surface-based analysis. A major relative advantage of VBM is that it helps us to compute the regional grey matter volume for both cortical and subcortical structures, whereas the SBM helps us to compute the cortical thickness, surface area, volume and gyrification only in the cortical structures, but not the subcortical structures. As a result, the development of VBM and SBM was promising and facilitated many researchers to assess mainly the grey matter properties associated with different

brain abnormalities. Overall, VBM and SBM serve as an efficient analytical approach to assess the cortical neuropathology (Mechelli et al., 2005) in various neurodevelopmental conditions like Autism Spectrum Disorder (ASD).

2.1.3 Overview of cortical organisation and morphometry in ASD

According to synaptic reorganisation theory, synaptic pruning occurs in the human prefrontal cortex in early childhood and continues to develop until early adolescence. It was further hypothesised that, although the overdevelopment of dendrite spine density occurs naturally in early childhood (two times higher than adults), the selective elimination of the dendrite spines are based on the evolutionary aspects of the neuronal activity in the cerebral cortices in primate brains (Petanjek et al., 2011). The maladaptive functioning of pyramidal neurons and interneurons may underlie aberrant minicolumnar organisation, which may in turn influence the cortical connectivity in individuals with ASD (Courchesne & Pierce, 2005). Consequently, the narrowed minicolumns and increased cell dispersion may underlie the reduced alignment of pyramidal cell columns in autism (Casanova & Trippe, 2009).

Several studies reported abnormal early brain overgrowth in younger children (2-5 years old) with ASD (Courchesne et al., 2001; Hardan et al., 2001). In light of this preliminary evidence, it was suggested that the enlarged brain structural abnormalities were accompanied by an increase in head circumference and total grey and white matter volume including the cerebrum and cerebellum in children with ASD (Courchesne et al., 2003). Further, it was suggested that early brain volume overgrowth may be responsible for cortical morphometry abnormalities (thickness, surface area and sulcal depth) in individuals with ASD (Im et al., 2008). Supporting this, there is a consensus that abnormalities in the cortical micro-circuitry and macro-circuitry may underlie the atypical brain development in individuals with ASD (Ecker, 2017). Considering this, previous studies have highlighted the importance of understanding the atypical brain development and connectivity in individuals with ASD (Müller, 2007; Rippon et al., 2007).

Based on the developments in structural neuroimaging studies, the following have been emphasised as hallmark features of children with ASD: atypical brain connectivity in the frontal lobe circuit including dorsal medial prefrontal cortex and anterior cingulate cortex, and ventro medial prefrontal cortex related to joint attention and theory of mind skills, respectively (Mundy, 2003). These brain structural abnormalities, accompanied by atypical behavioural manifestations, continue to persist from childhood to adulthood in individuals with ASD. To date, many efforts

have been made to understand the cortical surface morphometry in individuals with ASD. However, it has been suggested that intrinsic grey matter structures embedded within the cortical surface may underlie the neuropathology which may coincide with the phase of brain overgrowth occurring in individuals with ASD. Considering this, the aberrant cortical morphometry related to grey matter pathology is more complex in individuals with ASD than in neurotypicals.

Collectively, the early atypical brain development and connectivity may underlie the abnormal minicolumnar organisation in ASD. More importantly, the atypical intrinsic properties of the cortical grey matter architecture are believed to underpin the abnormal behavioural manifestations in ASD. Therefore, it is crucial to understand the cortical organisation and morphometry in individuals with ASD. Despite some inconsistencies in varying brain volumes, great efforts have been made to understand the atypical brain structure and connectivity in individuals with ASD, with the help of state-of-the-art structural neuroimaging techniques.

2.1.4 VBM and SBM studies of ASD - evidence review

Deficits in social interaction and communication, as well as circumscribed interests are accompanied by differences in brain structure and connectivity in individuals with ASD (Belmonte et al., 2004; Ecker et al., 2010a; McAlonan, 2004; Riva et al., 2011). One longitudinal study demonstrated increased Head Circumference (HC) and brain volume in children (18-35 months of age) with ASD relative to controls. The increase in brain volume measures included both grey matter and white matter in the ASD group. The evidence of increased global brain measures suggested that the brain structural abnormalities may be associated with atypical behavioural manifestations in young children with ASD in the first year of their life (Hazlett et al., 2005). In line with this, further investigations by Courchesne and his colleagues showed increased HC and brain volume consistently across a number of studies in children (2-5 years old) with ASD (Courchesne, 2002; Courchesne et al., 2001; Courchesne, et al., 2011a; Courchesne & Pierce, 2005). Several neuroanatomical studies have demonstrated widespread grey and white matter volume differences including the social brain regions in individuals with ASD (Ke et al., 2008; Mengotti et al., 2011; Yamasaki et al., 2010).

Previous cross-sectional studies showed reduced regional grey matter volume (GMV) in cortical brain regions including the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC) (Hardan et al., 2006; Mueller et al., 2013a), amygdala, fusiform gyrus (FG) (Sato, et al., 2017), and superior temporal sulcus (STS) (Boddaert et al., 2004a) in individuals with ASD compared to controls.

These social brain regions are believed to play a significant role in theory of mind abilities, emotional judgement, face recognition and interpreting biological motion cues respectively (Brothers, 1990; Pelphrey et al., 2011; Schultz, 2005b). However, individuals with ASD show brain volume abnormalities in the social brain regions which may underpin the behavioural deficits in higher order functions. On the other hand, individuals with ASD also showed increased regional GMV in the lingual gyrus (LG), cuneus, caudate nucleus and putamen (Ecker et al., 2012a; Sato et al., 2014b). The increased regional GMV in the occipital and striatal brain regions may underlie the difficulties in visual information processing and stereotyped behaviours, respectively, in individuals with ASD.

In the social brain model, the orbitofrontal cortex is functionally connected to the amygdala, superior temporal sulcus (STS) and fusiform face area (FFA). Prior theoretical work suggested that impairments in the orbitofrontal cortex and amygdala circuit may be associated with abnormal socio-emotional functioning in individuals with ASD (Bachevalier & Loveland, 2006). The superior temporal sulcus is mainly involved in processing the biological motion cues of the eyes, hands and body to interpret the intentions and predict the actions of others (Allison et al., 2000). The weaker neuroanatomical integrity of brain regions including the OFC, amygdala, STS and fusiform gyrus are believed to underpin the atypical socio-emotional skills in individuals with ASD (Ashwin et al., 2006; Pelphrey et al., 2011). Using voxel-based morphometry, Toal and colleagues showed differences in grey and white matter volume in frontal and temporal lobes, extending to cerebellum when compared between three groups i.e., Asperger's syndrome, high-functioning autism and healthy controls. This difference in regional brain volume suggested that brain anatomy may vary between the subclinical phenotypes of ASD (Toal et al., 2010). Another VBM study showed grey matter volume differences in the temporoparietal junction in individuals with ASD compared to controls. In addition, the interaction of eye test (visual processing ability) scores between the two groups revealed weaker association in processing socially relevant stimuli, indicating difficulties in reading the mind in eyes in individuals with ASD (Sato, et al., 2017). In line with this, a VBM study showed common sites of grey matter differences in the brain regions including the right temporoparietal junction and left frontal lobe associated with atypical higher-order multisensory functions in ASD compared to controls (Mueller et al., 2013a).

Apart from the regional grey matter volume differences in ASD, an alternate source-based morphometry approach was used in an attempt to examine the network level grey matter volume differences in ASD. One study using source-based morphometry showed grey matter volume

differences in the superior, middle and inferior frontal and temporal gyri, fusiform gyri, parahippocampal gyrus and precuneus in individuals with ASD compared to controls, thereby suggesting that these brain regions may constitute an autism-specific structural network related to the clinical phenotype (Grecucci et al., 2016). As such, the brain imaging findings using different MRI techniques provide support for the long-standing hypothesis that ASD is associated with impairments in higher-order multisensory functions. In recent years, structural brain volumetric studies have shown grey matter volume differences in the frontal, temporal and posterior brain regions in ASD relative to typical controls, thus corroborating previous research findings related to social skills (Boddaert et al., 2004b; Eilam-Stock et al., 2016; Toal et al., 2010).

Restricted and repetitive behaviours and interests (RRBI) in ASD are conceptualised into lower-order and higher-order behaviours (Turner, 1999). Previous studies suggested that RRBI may be associated with the regional brain volume differences in the basal ganglia (Calderoni et al., 2014; Eisenberg et al., 2015; Schuetze et al., 2016). Individuals with ASD show common sites of brain structural abnormalities in the striatum, related to restricted and repetitive behaviours and interests. In a VBM study, an increased regional GMV was found in the caudate nucleus and putamen in individuals with ASD compared to controls. In the same study, the age interaction effects between the ASD and controls showed increased GMV in the latter brain regions, and a positive association between the regional GMV of the caudate nucleus and RRBI in individuals with ASD. These findings suggested that the brain structural abnormalities in the striatum may be associated with repetitive and restricted behaviours across different developmental stages in ASD (Langen et al., 2009). In line with this, another study using VBM showed significant positive association between regional GMV in the right caudate nucleus, putamen and RRB domain scores in individuals with ASD (Hollander et al., 2005). Rojas and colleagues used VBM in their study and reported increased GMV in several brain regions including the medial frontal gyrus, middle temporal gyrus, fusiform gyrus and caudate nucleus, and reduced GMV in the cerebellum in individuals with ASD compared to typically developing controls. In addition, regional grey matter volume in the medial frontal gyrus, inferior frontal gyrus, superior temporal gyrus, precentral gyrus, caudate nuclei and cerebellum were associated with social and communication difficulties as well as repetitive behavioural scores in individuals with ASD (Rojas et al., 2006).

On the other hand, a previous study using VBM reported inconsistent findings, with no significant increased or decreased regional GMV in individuals with high-functioning autism relative to controls (Riedel et al., 2014). In an attempt to examine the relationship between brain

morphometry and autistic traits, another study found that there was no significant association between regional GMV, cortical thickness and surface area (Koolschijn et al., 2015). In contrast to previous brain morphometry findings using VBM analysis, some studies have reported increased regional GMV in the medial prefrontal cortex, dorsolateral prefrontal cortex and medial temporal lobe in individuals with ASD (Bonilha et al., 2008a; Waiter et al., 2004).

Growing evidence suggests that cortical folding abnormalities may also underlie the neuropathology which disrupts brain morphometry in individuals with ASD (Pappaianni et al., 2018; Patriquin et al., 2016) . Previous studies have used VBM to examine the regional GMV in individuals with ASD. However, the cerebral cortex is made up of a 2-D like cortical sheet with intrinsic properties of highly folded curvature. Therefore, a traditional VBM approach is not helpful in measuring the complexity of grey matter such as cortical thickness, surface area and gyrification. Considering this, several studies used surface-based morphometry to investigate the differences in latter surface-based metrics in individuals with ASD (Hyde et al., 2010; Jiao et al., 2010a). These cortical folding abnormalities can be assessed with surface-based metrics including cortical thickness, surface area, cortical volume and gyrification which may reflect the atypical behavioural manifestations in ASD (Libero et al., 2014; Nordahl et al., 2007).

In a longitudinal study, Hardan and colleagues found no significant differences in whole brain volume, but reduced total GMV over time, with greater decreases in the frontal lobe brain regions in individuals with ASD compared to controls. In addition, the cortical thickness was reduced in the frontal lobe with increased socioemotional reciprocity as measured by ADI-R scores in ASD. Despite some inconsistency between the whole and regional brain volumes, this finding suggested that age-related structural brain differences may be associated with symptom severity in ASD (Hardan et al., 2009). Mak-Fan and colleagues found differences in cortical thickness, surface area, and regional and total brain volume across age groups between individuals with ASD and controls. In this study, the cortical morphometry findings showed increased total brain volume and cortical thickness in the left inferior frontal gyrus and precuneus in children with ASD compared to adolescents. This suggested that the cortical morphometry may vary across different age cohorts in ASD relative to controls (Mak-Fan et al., 2012). In a longitudinal study, Hazlett and colleagues investigated the differences in the trajectories of cortical thickness, surface area and total brain volume which are believed to be involved in the brain overgrowth in infants and children (6-24 months) with high and low familial autism risk. In this study, the high familial autism risk group showed a significant increase in total brain volume compared to the low familial autism risk group

in the second year, whereas no significant differences were found in cortical thickness between the latter groups. However, the surface area was increased in the bilateral middle occipital gyrus, cuneus and lingual gyrus in the high familial risk autism compared to the low familial risk autism group. In a subsequent analysis, these findings were also supported by a deep-learning algorithm in classifying the low and high familial autism risk groups based on the knowledge incorporated by surface area and total brain volume measures. These differences in the cortical morphometry across these subgroups suggested that atypical brain development may underlie the neural basis for behavioural deficits in the ASD phenotype (Hazlett et al., 2017). This atypical cortico-cortical connectivity in the social brain regions (including the frontal and temporal lobe) has been consistently reported in individuals with ASD (Ecker, et al., 2013). Some conflicting findings of grey matter volume and surface-based metrics in the literature on ASD might reflect the differences between their study population such as age, level of impairment, presence of medical and behavioural comorbidities in the selected groups, and challenges in data quality and various analytical approaches. Therefore, it is crucial to understand these surface-based metrics affecting the laminar structure and properties of different cortical layers underlying the neuropathology of ASD.

To summarise, many studies used case-control design to measure grey matter volume, cortical thickness, surface area and gyrification differences in individuals with ASD relative to controls. However, growing evidence suggests that autistic traits lie as a continuum across the general population, whilst the extreme end of the distribution is diagnosed as clinical ASD (Robinson et al., 2011; Ruzich et al., 2015; Whitehouse et al., 2011). Case-control studies may be useful in measuring the brain structural differences in individuals with ASD, however it may not help us to understand the relationship between cortical morphometry and higher autistic traits. To date, there are many studies with only a small sample size (Hollander et al., 2005; McAlonan et al., 2005; Mueller et al., 2013a; Rojas et al., 2006; Sato, et al., 2017). Further, there are limited studies available with a structural MRI dataset from one site with a large sample size (Ecker et al., 2012b; von dem Hagen et al., 2011). Therefore, this current study will attempt to address this key issue by investigating the relationship between the regional grey matter and autistic traits. The main aim of this study is to examine the relationship between grey matter volume, cortical thickness, surface, gyrification and autistic traits in the cortical and subcortical brain regions across a combined sample of neurotypicals and individuals with ASD using a dimensional approach. To achieve this, we used voxel-based morphometry and surface-based morphometry to analyse the structural brain MRI images, and the Autism Spectrum Quotient (AQ, can be validated to replace ASD diagnosis) (Ashwood et al., 2016) to measure the autistic traits across the diagnostic divide. We predicted

widespread regional grey matter differences in the cortical and subcortical structures which would lead to higher autistic traits.

2.2 Methods and materials

2.2.1 Participants

Ninety-one adults, consists of 66 neurotypicals and 25 High Functioning Autism (HFA) (52 males, 39 females, aged 18-60 years), participated in this study. All of the neurotypical individuals were recruited from the University of Reading campus and individuals with HFA were recruited from a registered clinic. Participants with symptoms of HFA were assessed using the Autism Diagnostic Observation Schedule (ADOS) module-4 and diagnosed using the diagnostic and statistical manual (DSM IV) of mental disorders criteria. However, participants who failed to meet the cut-off for ADOS scores for ASD did not lead to their exclusion. Subjects with any neurological conditions or head injuries as well as those who did not satisfy the requirements for the specified age limit were excluded from the study. Autism spectrum quotient (AQ) (Baron-Cohen et al., 2001) scores were also collected from all participants through online survey. AQ is a 50-item questionnaire used to measure the autistic traits from the five different subscales including social skills, communication, attention switching, attention to detail and imagination in both clinical and non-clinical population. This dataset came from two separate phases of data collection (53 and 38; but used the same protocol for collecting the structural MRI). This study was approved by the University Research Ethics Committee (UREC), University of Reading.

Table 2.1 Participant characteristics

Characteristics	**Neurotypicals (N=66)**		**ASD (N=25)**		**P-values**
	Mean	**SD**	**Mean**	**SD**	
Age	25.74	8.003	34.48	12.952	0.004***
Gender (m/f)	37/29	-	15/10	-	0.735
AQ	14.86	6.919	36.32	7.809	<0.001***
ADOS (Soc+Comm)	-	-	10.08	4.924	

N= Number of participants, SD-standard deviation, m-male; f-female, AQ-Autism Spectrum Quotient, Soc- Social interaction, Comm- Communication, *p < .05. ***p < .001.

2.2.2 MRI Data collection

Siemens 3T Tim Trio MRI scanner was used to acquire the high resolution T1-Weighted structural whole brain images using Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence with 32-channel head coil from all participants. This structural MRI pulse sequence included the following parameters: repetition time, T_R = 2020ms; echo time, T_E = 2ms; voxel size = 1 x 1 x 1 mm; matrix =256 x 256; flip angle=9 degrees, slice thickness = 0.70 mm using a radiological convention at the Centre for Integrative Neurosciences and Neurodynamics (CINN).

2.2.3 VBM preprocessing

Voxel-based Morphometry (VBM) (Mechelli et al., 2005) using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) incorporated in SPM12 toolbox (Ashburner et al., 2014) supported Matlab R2017a version was applied for preprocessing and analysis. The standard DARTEL preprocessing pipelines included segmentation, template creation, registration, normalisation and smoothing as follows: Initially the T1-weighted structural images were reoriented for anterior and posterior commissure alignment and corrected for head motion. In this method, images were segmented into grey matter, white matter and CSF. Then, a study-specific template was created by aligning and averaging the inter-subject grey matter volumes iteratively. The segmented individual grey matter volumes were registered to the template using non-linear registration and normalised to MNI standard space. These normalised images were smoothed using Gaussian kernel (Full Width at Half Maximum, FWHM=8mm) for the cortical structures and subcortical structures (FWHM=4mm) by averaging the spatial intensity of the local neighbouring voxels. Different levels of smoothing depend on several factors such as the level of accuracy of spatial normalisation and variability of voxels in the whole brain. Since DARTEL provides a high level of spatial normalisation and the variability of voxels in the cortical regions is higher relative to the subcortical structures (Ashburner, 2010; Coalson et al., 2018), different levels of optimal smoothing were applied.

2.2.4 Surface-based morphometry

The surface-based morphometry measurements of the brain include cortical thickness, surface area and cortical volume. The cortical thickness is measured by the shortest distance between the pial and white surface (Fig. 2.1). The pial surface is defined as a boundary between the grey matter and cerebrospinal fluid, whereas the white surface is a boundary between the white matter and grey

matter. The surface area is measured as an area assigned to each vertex equal to the average of the vertex forming triangles in the white surface. The cortical volume is defined as a product of the cortical thickness and surface area. In other words, it is a measure of grey matter volume bounded between the pial and white surface. The local gyrification index is measured as the amount of cortical foldings buried into sulci compared to the foldings visible on the gyri projections (Ecker, et al., 2013; Yang et al., 2016).

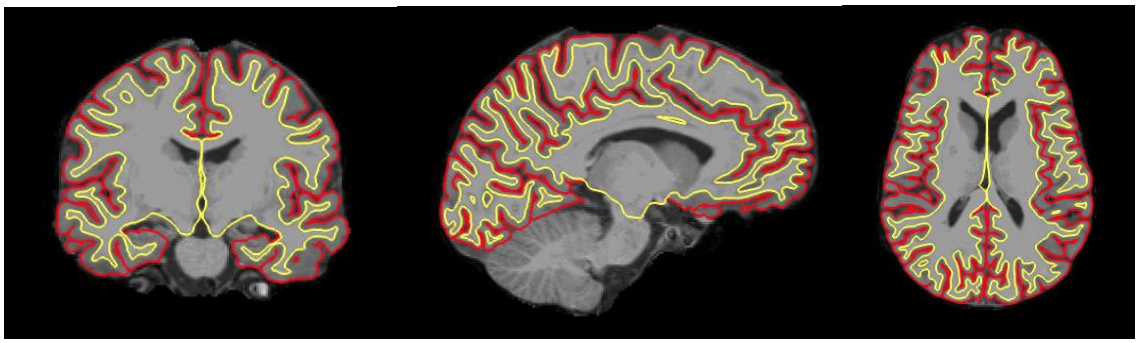


Fig. 2.1 T1-weighted structural brain image displaying the pial surface (red) and white surface (yellow) in the coronal, sagittal and axial planes (from left to right).

2.2.5 SBM preprocessing

FreeSurfer analysis suite (http://surfer.nmr.mgh.harvard.edu/) was used to perform the surface-based morphometry which reconstructs the cortical surface. High resolution T1-weighted structural brain images were preprocessed and corrected for head motion, bias field correction, skull-stripping, segmentation, registration, spatial normalisation and smoothing (Fischl, 2012). The skull-stripping was done using a deformable template to discard the non-brain tissues in the cortical surface. Bias field correction was performed to limit the magnetic field inhomogeneity in the brain images. The individual structural images were computed to determine the transformation matrix and co-registered to the Talairach space to maximise the possibility that individual images overlap with the average brain template coordinates. The structural brain images are segmented into pial and white surface. The pial surface refers to the grey matter and CSF interface, whereas the white surface refers to the grey and white matter interface. The inflated cortical surfaces from the individual images were spatially normalised to the spherical average template, such that each vertex forming multiple triangles across the surface were aligned closely to the corresponding anatomical locations. In the final step, default smoothing was applied to normalise the local neighbourhood voxels across the entire brain. As a result of all the preprocessing steps, cortical tessellations were generated for each hemisphere in which the vertices forming triangular meshes

were mapped closely to the spherical template and connected across the surface (Dale et al., 1999; Fischl et al., 1999). The pial surfaces of each hemisphere were preprocessed to create an outer smoothed pial surface to account for the local gyrification index (LGI).

All the individual subjects' cortical thickness, surface area, cortical volume and local gyrification index maps were concatenated together for measuring each metric separately in the group level analysis. Additionally, different levels of smoothing (FWHM= 0,10,15,20 mm) were applied to average the close neighbourhood voxels. However, we decided to select the smoothing (10mm) for cortical thickness, surface area, cortical volume, while no additional smoothing (FWHM= 00 mm) was used for measuring the local gyrification index in this analysis based on its compatibility of the cluster-forming threshold (0.05). Different levels of optimal smoothing were applied for all these four surface-based metrics (Liem et al., 2015) and tested for statistical significance.

2.2.6 Statistical analysis

2.2.6.1 VBM group-level analysis

The general linear model was used to test the relationship between the regional grey matter volume and AQ scores across the combined sample of ASD and neurotypicals after controlling for the effects of age, gender and total brain volume. The covariates including the age and gender were demeaned for the whole sample. We used Family Wise Error (FWE) rate testing for multiple comparisons.

2.2.6.2 SBM group-level analysis

In the whole brain group level analysis, the Different Offset Same Slope (DOSS) model was used to test the relationship between cortical thickness, surface area, cortical volume, local gyrification index (separately for each dependent variable at a time) and autistic traits, including age and gender as covariates. The FreeSurfer Group Descriptor (FSGD) format was used to construct the design matrix. In our statistical model, we used one whole sample without the group factor with gender being the only discrete factor, and age (demeaned) and AQ as continuous measures. Then, the precomputed Monte-Carlo Simulation was used to run the tests for multiple comparisons with a cluster-forming threshold (0.05) and the threshold for significance (p=0.05, two-tailed).

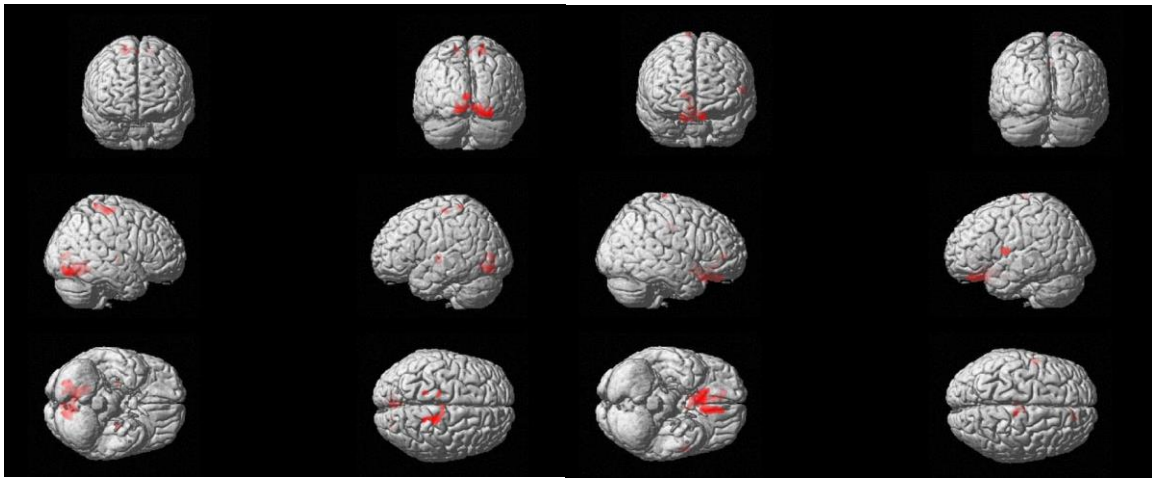
2.3 Results

2.3.1 VBM results

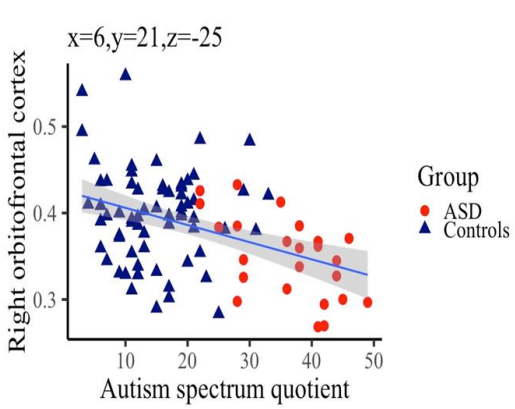
2.3.1.1 Relationship between cortical grey matter volume and AQ

We found significant positive association between regional GMV and AQ scores in cortical brain regions including the clusters of right lingual gyrus and precentral gyrus. We also found significant negative association between regional GMV and AQ in the bilateral orbitofrontal cortex which also extends to the anterior cingulate gyrus (Figure 2.2, Table 2.2).

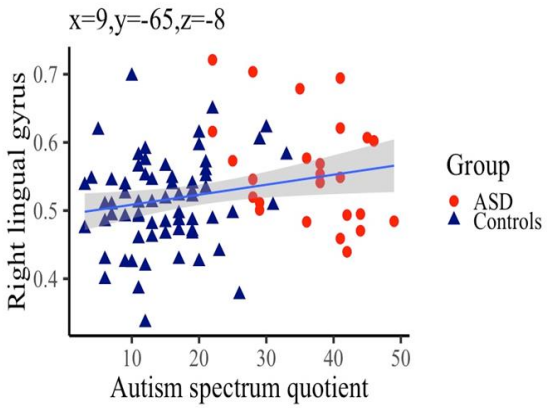
Figure 2.2: Association between regional GMV in the cortical structures and AQ



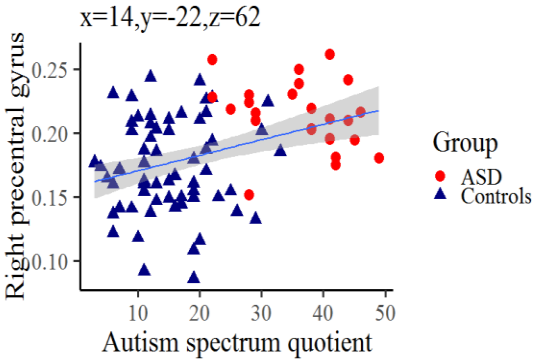
(a) **(b)**



(c)



(d)



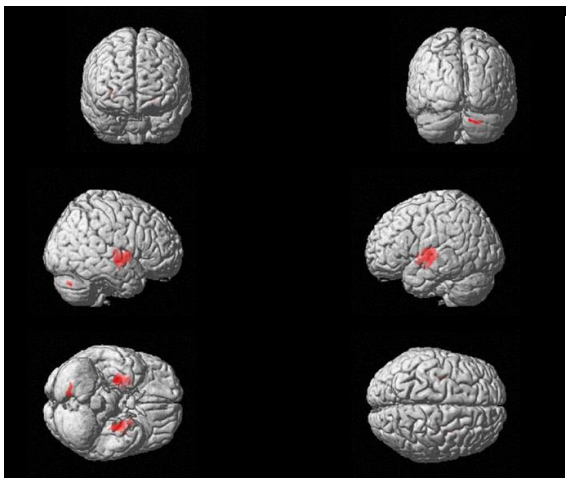
(e)

Fig. 2.2 (a) Clusters showing significant positive association between the regional GMV of right lingual gyrus, precentral gyrus and AQ scores, **(b)** clusters showing significant negative association between the regional GMV of right orbitofrontal cortex and AQ scores. The following scatterplots are provided only for visualisation, since the clusters were identified on the basis of the significant correlation. **(c)** Scatterplot showing negative association between right orbitofrontal cortex and AQ scores, **(d)** scatterplot showing positive association between right lingual gyrus and AQ scores, **(e)** scatterplot showing positive association between right precentral gyrus and AQ scores.

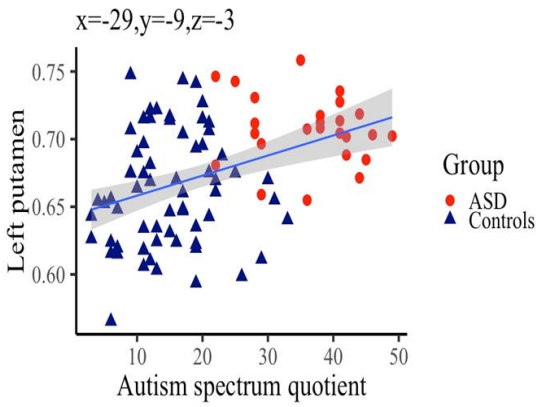
2.3.1.2 Relationship between subcortical grey matter volume and autism spectrum quotient

In addition, we also found significant positive association between regional GMV and AQ scores in subcortical brain regions including the left putamen and right putamen (Fig. 2.3, Table 2.2).

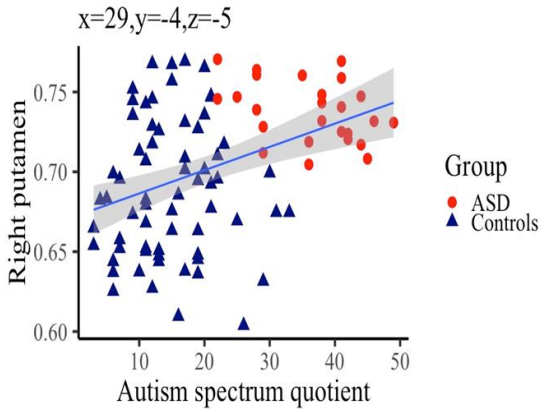
Figure 2.3: Association between regional GMV in the subcortical structures and AQ



(f)



(g)



(h)

Fig. 2.3. (f) significant clusters showing positive association between the regional GMV and AQ scores in the left putamen and right putamen. Scatterplots showing the relationship between the left **(g)** and right **(h)** putamen and AQ, respectively. The unit of regional GMV is cubic millimetre (mm^3).

Table 2.2 Association between regional grey matter volume and AQ

Cortical brain regions	**MNI-Coordinates**			**K_E**	**P_{FWE}**
	x	**y**	**z**		
Positive association					
Right lingual gyrus	9	-65	-8	8010	<0.001***
Right precentral gyrus	14	-22	62	6918	0.012**
Negative association					
Right orbitofrontal cortex	6	21	-25	7888	<0.001***
Subcortical brain regions					
Positive association					
Left putamen	-29	-9	-3	2837	<0.001***
Right putamen	29	-4	-5	2459	<0.001***

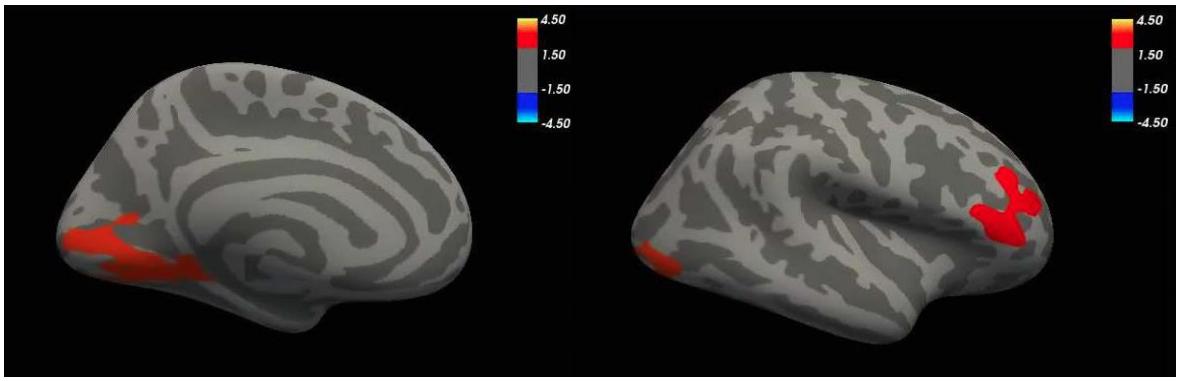
Abbreviations: Level of significance *p < .05, **p < .01, ***p < .001 FWE- Family Wise Error and K_E- Cluster size.

2.3.4 SBM results

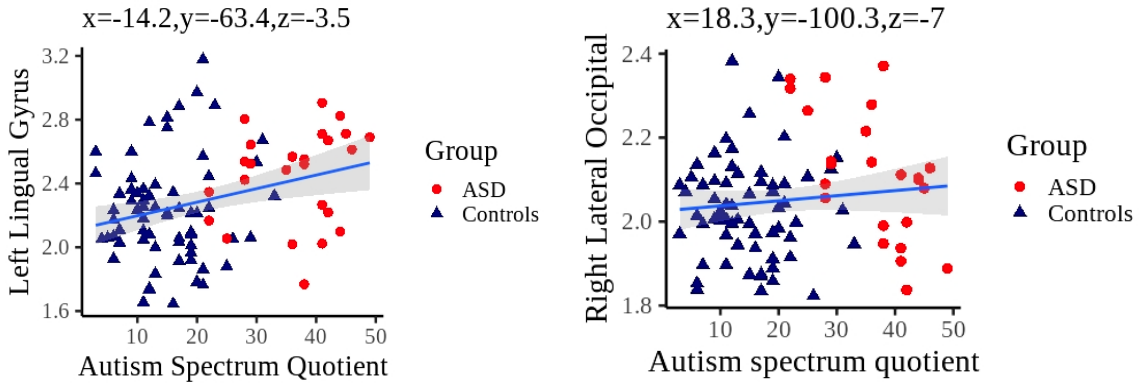
Our analysis focused on the relationship between surface-based morphometrics and autistic traits, revealed significant positive association between all four metrics including cortical thickness, surface area, cortical volume, local gyrification index and autistic traits across the combined sample of neurotypicals and individuals with ASD. The regional differences in cortical thickness (Fig. 2.4) were observed in the left lingual gyrus, right lateral occipital cortex and right pars triangularis, whereas the regional differences in surface area were observed only in the right lateral occipital cortex (Fig. 2.5). The regional differences in cortical volume (Fig. 2.6) were observed in the left lingual gyrus, right lateral occipital cortex and right pars triangularis. In addition, the clusters in the local gyrification index were observed only in the right lingual gyrus (Fig. 2.7) (Table 2.3).

2.3.4.1 Cortical thickness

(A) **(B)**



(C) **(D)**



E)

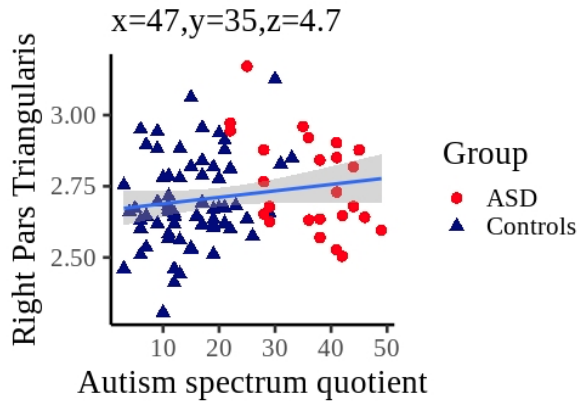


Fig. **2.4**: Cortical thickness: (A) Clusters showing significant brain regions of lingual Gyrus (left), (B) lateral occipital (Right) and pars triangularis (right) and its scatterplots (C), (D) and (E), respectively. Cortical thickness is measured in millimetres (mm).

2.3.4.2 Surface Area

(A) **(B)**

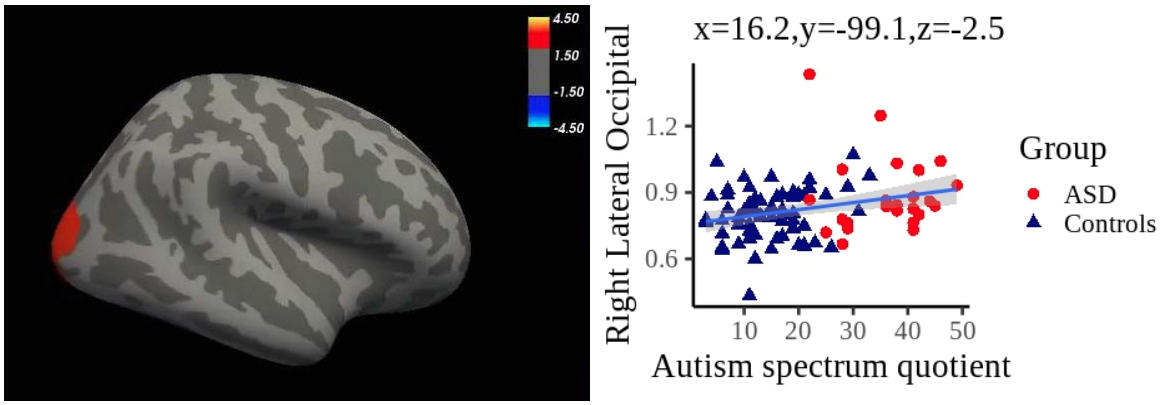


Fig 2.5: Surface area: (A) Clusters showing significant brain regions of lateral occipital (right) and its scatterplot (B). The unit of cortical surface area is measured in square millimetre (mm^2).

2.3.4.3 Cortical Volume

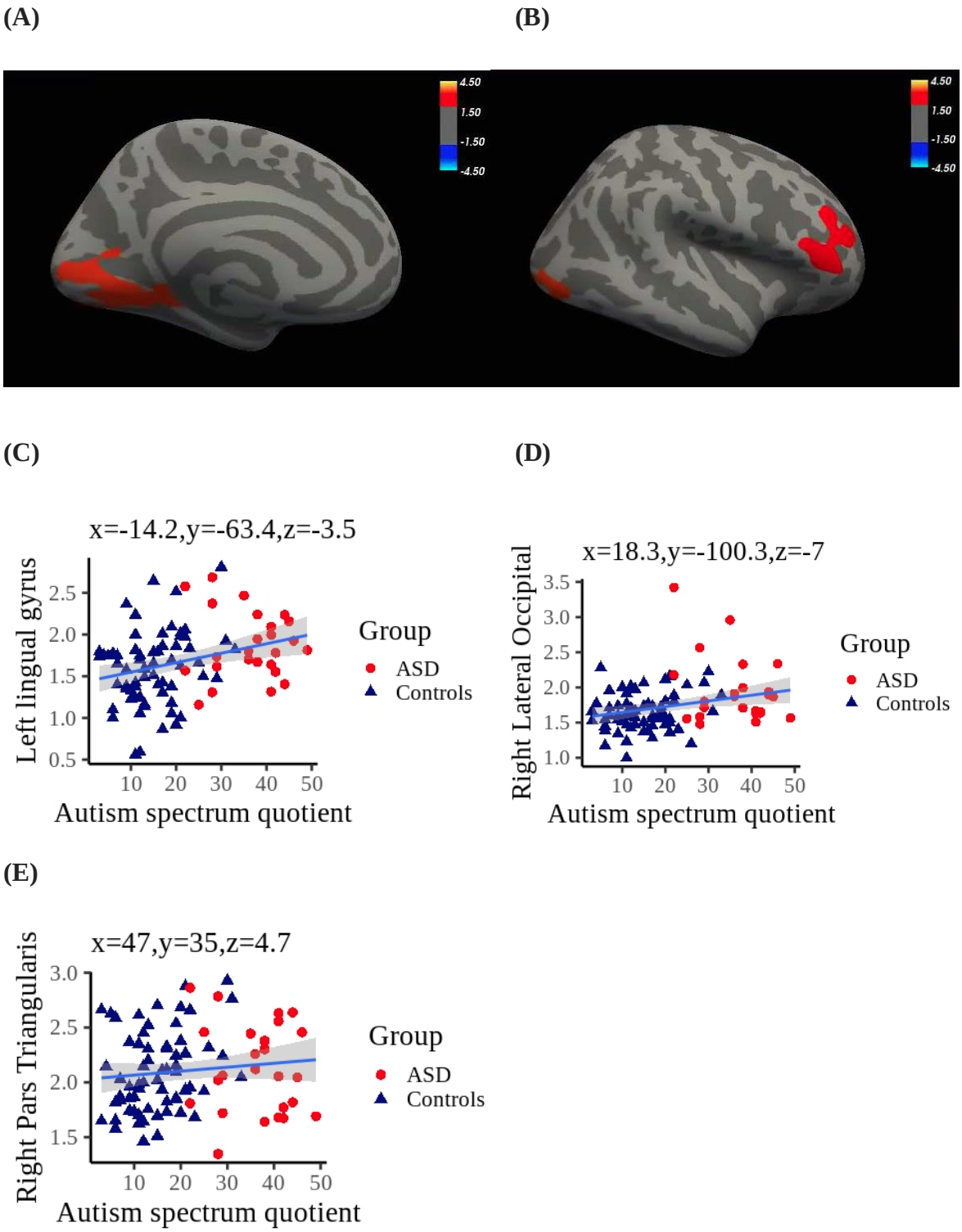


Fig. 2.6: Cortical volume: (A) Clusters showing significant brain regions of lingual gyrus (left), (B) lateral occipital (right) and pars triangularis (right) and its scatterplots (C), (D) and (E), respectively. Cortical volume is measured in cubic millimetres (mm^3).

2.3.4.4 Local gyrification index (LGI)

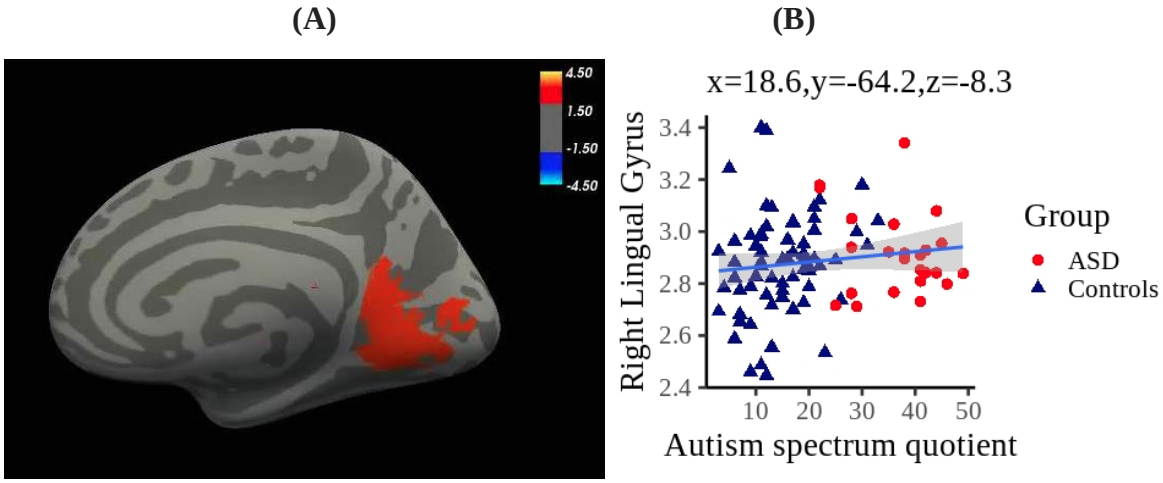


Fig. 2.7: LGI: (A) Clusters showing significant brain regions of lingual gyrus (right) and (B) its scatterplot. Local gyrification index has no units.

Table 2.3 Association between cortical thickness, surface area, cortical volume and AQ

Brain regions	Side	Talairach coordinates			t-value	K_E
		x	y	z		
Cortical thickness						
Lingual gyrus	L	-14.2	-63.4	-3.5	3.642	2386.74
Lateral Occipital	R	18.3	-100.3	-7	4.255	4388.31
Pars triangularis	R	47	35	4.7	3.679	1480.64
Surface area						
Lateral Occipital	R	16.2	-99.1	-2.5	3.434	4042.26
Cortical volume						
Lingual gyrus	L	-14.2	-63.4	-3.5	3.642	2386.74
Lateral Occipital	R	18.3	-100.3	-7	4.255	4388.31
Pars triangularis	R	47	35	4.7	3.679	1480.64
Local gyrification index						
Lingual gyrus	R	18.6	-64.2	-8.3	2.493	2392.50

Abbreviations: L- Left, R- Right, K_E- cluster size, t-value - test statistics, p-threshold = 0.05.

2.4 Discussion

Several reports showed regional differences in grey matter volume, cortical thickness, surface area, and gyrification between individuals with ASD and neurotypicals. However, very few studies have investigated the relationship between these grey matter properties and autistic traits. Considering this gap in the literature, we decided to test the relationship between regional GMV, cortical thickness, surface area and gyrification and autistic traits in a dimensional approach using VBM and SBM, respectively. The present study showed the relationship between regional grey matter volume, cortical thickness, surface area, gyrification and autistic traits across the diagnostic divide. Our findings were consistent with previous reports using cross-sectional studies between individuals with ASD and neurotypicals.

We used VBM (DARTEL) to demonstrate the regional GMV differences at the whole brain level. Our regional GMV findings determined using VBM were consistent with previous VBM studies on ASD. We chose DARTEL over classical VBM as it was more likely to provide us with high dimensional spatial registration. The brains of different individuals may vary in size and therefore whole brain volume. In fact, global brain measurements such as total brain volume may have a direct impact on grey matter volume. Considering this, the total brain volume was included as a covariate of no interest in the GLM to avoid bias in presuming differences in the global measures between neurotypicals and individuals with ASD.

Our results revealed significant positive association between the regional grey matter volume and autistic traits in the brain regions including the right lingual gyrus, right precentral gyrus and bilateral putamen, whereas negative association was found between the grey matter volume and autistic traits in the right orbitofrontal cortex. The current study used a dimensional approach to demonstrate the association between GMV and autistic traits and found results that were consistent with previous studies that used case-control design (Ecker et al., 2012a; Sato, et al., 2017).

The reduced regional GMV in the orbitofrontal cortex extended to the anterior cingulate gyrus may be associated with the reduced number of minicolumns in the frontal lobe related to autism risk genes (Buxhoeveden et al., 2006). Previous studies have found that the differences in regional GMV of orbitofrontal cortices/ventromedial prefrontal cortex are involved in the Theory Of Mind (TOM) deficits in individuals with ASD (Frith, 2001; Lewis et al., 2011; Sabbagh, 2004). The anterior cingulate gyrus is one of the most consistently reported brain regions in the literature on individuals with ASD; specifically, the structural brain abnormalities in the anterior cingulate

gyrus are associated with declined goal-oriented behaviour in individuals with ASD. Some studies have proposed that the anterior cingulate gyrus adjacent to the medial prefrontal cortex may sometimes underlie the implications in ACC (Frith, 1999). The reduced GMV in the orbitofrontal cortex and anterior cingulate gyrus is related to higher autistic traits and may underlie social skill deficits and atypical executive function, respectively (Girgis et al., 2007; Mundy, 2003).

In our study, another important finding was the positive association between bilateral precentral gyrus, lingual gyrus and the AQ. This result is consistent with previous findings of regional grey matter volume differences in ASD (Bonilha et al., 2008b; Ecker et al., 2012a; Rojas et al., 2006). The precentral gyrus is believed to be an integral part of the mirror neuron system (Hadjikhani et al., 2006). The increased grey matter volume in the precentral gyrus may underlie atypical visuomotor learning in individuals with higher autistic traits (Mahajan et al., 2016). The increased grey matter volume in the lingual gyrus has been reported consistently in individuals with ASD/higher autistic traits (Peterson et al., 2006). Another assumption is that this brain region may constitute a part of the network, which also includes other brain regions (calcarine cortex, fusiform gyrus and posterior superior temporal sulcus) playing a significant role in object/face recognition and following biological motion cues in ASD. The enhanced sensory inputs to the lingual gyrus may influence the atypical visual processing in individuals with higher autistic traits (Keehn et al., 2008).

Another interesting finding in our study was the positive association between the bilateral putamen and higher autistic traits. The putamen, an integral part of the dorsal striatum, plays a key role in restricted and repetitive behaviour in ASD (Langen et al., 2012; Sato et al., 2014a). Individuals with ASD may overreact/obsess and form object attachments (narrow range of interests). This may be because they are likely to benefit from non-social reward processing and therefore continue to form these attachments. This suggests that the striatum may also be associated with a reward circuit in individuals with ASD (Kohls et al., 2014). The striatum may be involved in understanding others' preferences and predict other individuals' actions leading to their own social reward (Báez-Mendoza & Schultz, 2013). This also raises the question of whether or not the lack of social motivation and skills leads to increased circumscribed interests (may also be vice-versa) in individuals with higher autistic traits.

As stated in the method section above, the product of cortical thickness and surface area is cortical volume. This is the formula used for measuring the cortical volume in SBM. Our findings include cortical thickness (lingual gyrus, lateral occipital, pars triangularis), surface area (lateral occipital),

volume (lingual gyrus, lateral occipital, pars triangularis). In this case, the cortical thickness, surface area and gyrification affect the cortical volume, however the opposite is possible.

From the literature review on methods in SBM, we found some studies that included TBV as a covariate of no interest in GLM (Ecker, et al., 2013), as well as some other studies that did not do the same (Gebauer et al., 2015). This remains inconsistent and unclear across different studies. In order to address this inconsistency, we performed group differences for measuring the TBV separately, although this is not our primary approach. After finding no significant differences between the individuals with ASD and neurotypicals, we preferred not to include TBV as a covariate of no interest in our model as it would not warrant avoiding the differences in our analysis (Yang et al., 2016).

Using SBM, we demonstrated increased cortical thickness (lingual gyrus, lateral occipital, pars triangularis), surface area (lateral occipital), volume (lingual gyrus, lateral occipital, pars triangularis) and gyrification (lingual gyrus) in association with higher autistic traits. The increased surface-based metrics including cortical thickness, surface area, volume and gyrification in the frontal and occipital brain regions were in line with previous study findings on ASD (Ecker et al., 2013; Yang et al., 2016).

We found increased cortical thickness and volume in the pars triangularis (inferior frontal gyrus) in individuals with higher autistic traits. The atypical cortical morphometry in the pars triangularis may be associated with expressive language deficits in individuals with ASD (Knaus et al., 2018), which may also be seen in individuals with higher autistic traits. On the other hand, the pars triangularis may cross-talk with the other social brain region (pars orbitalis) closely located in the frontal lobe, which may also account for the atypical social behavioural manifestations in individuals with higher autistic traits (Fishman et al., 2014). Individuals with high-functioning autism exhibit language impairments from childhood and continuing on into adulthood. This language impairment may be specifically related to Broca's area (which also includes pars triangularis) in individuals with ASD. In this case, the increased cortical thickness in the pars triangularis may also reflect the differences in the cortical volume (Van Rooij et al., 2018). Therefore, these regional differences in the cortical morphometry in the pars triangularis may be associated with language deficits in individuals with higher autistic traits. In light of this, the atypical cortical morphometry in the pars triangularis may serve as a neural basis underlying social communication deficits in individuals with higher autistic traits (Yamagata et al., 2019).

We also found an increased surface area in the lateral occipital cortex, in association with higher autistic traits. The lateral occipital cortex is believed to play a significant role in visuospatial attention in individuals with ASD (Ecker et al., 2013). This increased surface area in the lateral occipital cortex may result in difficulty when modulating the visual perceptual abilities in individuals with higher autistic traits. Supporting evidence from a previous study, our study found that the lateral occipital cortex (mid-level visual cortex) exhibited increased functional connectivity, associated with atypical superior local and inferior global visual processing in individuals with ASD (Kana et al., 2013). This is also seen in individuals with higher autistic traits. It is understood that the cortical thickness and surface area influence the grey matter volume; however, the former metrics may be associated with independent neurobiological pathways which in turn affect the cortical morphometry in ASD. Taking this into consideration, the right pars triangularis, right lateral occipital and left lingual gyrus showed increased cortical volume associated with higher autistic traits. We observed increased gyrification in the right lingual gyrus in individuals with higher autistic traits. This evidence is consistent with previous reports of structural atypicalities, with greater local gyrification in lingual gyrus in individuals with ASD (Libero et al., 2019). The lingual gyrus may underlie the atypical visual processing in ASD (Ecker et al., 2010b). This behavioural manifestation is also seen in individuals with higher autistic traits.

The abnormal intrinsic grey matter properties may arise as a result of genetic and epigenetic factors in ASD. The abnormal neuronal migration within the microcircuits of radial minicolumns associated with the pyramidal neurons may be altered in ASD. This aberrant cortical cytoarchitecture may influence the increased number of minicolumns, reduced alignment and increased volume density of pyramidal neuronal cells during the developmental phase, and may be a key factor associated with the atypical cortico-cortical connectivity in ASD (Casanova & Trippe, 2009). This may be the case with the brain regions including the pars triangularis, lateral occipital and lingual gyrus showing altered cortical morphometry in those with higher autistic traits. Our findings from the SBM study supports the atypical cortico-cortical connectivity hypothesis in ASD.

VBM versus SBM

In general, there are some methodological differences between VBM and SBM in measuring cortical morphometry. VBM uses whole brain voxel-wise comparison to measure grey matter volume abnormalities, whereas the SBM uses intrinsic topology of the cerebral cortex (2-D like sheet) to measure the cortical foldings, unlike VBM. In terms of measuring the regional grey matter

volume, VBM accounts for a number of voxels in the brain structure, whilst SBM calculates the volume as a product of cortical thickness and surface area. However, the grey matter volume findings (lingual gyrus) from our study in both approaches are reasonably comparable. These two analytical approaches (VBM and SBM) are incomparable when measuring the cortical thickness, surface area and gyrification because they both apply different ways of implementation. SBM provides us with a higher reliability in measuring the cortical thickness, surface and gyrification, whereas the VBM (DARTEL) provides us with a high dimensional spatial registration for measuring cortical and subcortical regional grey matter volume in ASD. But the limitation with SBM is that it helps us to measure the grey matter properties only in the cortical structures and not in the subcortical structures unlike VBM. Therefore, both VBM and SBM are the two complementary approaches that contribute to the efforts in identifying a neuroimaging biomarker for ASD (Jiao et al., 2010b).

There are certain limitations in this study: The study sample was matched only for gender, but not for age between individuals with ASD and neurotypicals. However, the effects of age and gender were controlled by including them as covariates in our group level analysis. In this study, we used a univariate analytical approach to assess the relationship between regional grey matter volume and AQ in the combined sample of neurotypicals and individuals with ASD. However, it is possible to explore the network level grey matter volume in the same dataset using multivariate approaches (source-based morphometry). This may help us to understand whether the brain structures implicated in ASD constitute a network in which they are functionally connected.

To summarise, our pattern of results suggest that the orbitofrontal cortex and the lingual gyrus may underlie the social skill deficits and atypical visuospatial skills, respectively, seen in individuals with ASD (Ecker et al., 2012a; Sato, et al., 2017). The reduced GMV in the anterior cingulate gyrus may underlie the atypical executive control function (Thakkar et al., 2008) associated with higher autistic traits. The regional brain volume differences in the precentral gyrus may be associated with the atypical visuomotor learning observed in individuals with ASD (Rojas et al., 2006). The increased GMV volume in the bilateral putamen may underlie repetitive and stereotyped behavioural features seen in individuals with ASD (Ecker et al., 2012a; Sato et al., 2014b). Therefore, our study findings provide insight into the atypical cortical morphometry which may affect the cortico-cortical connectivity in individuals with higher autistic traits.

Chapter 3: Investigating the relationship between white matter microstructure and autistic traits across the diagnostic divide

This chapter is mainly focused on the study of the white matter microstructure properties related to autistic traits. In light of this, we discussed the white matter microstructure integrity and reviewed the DTI findings related to Autism Spectrum Disorders and autistic traits. The main aim of the current study is to investigate the relationship between the white matter microstructure properties and higher autistic traits. To achieve this, we used skeleton-based tracts of interest (hypothesis-driven) and tract-based spatial statistics (data-driven) approaches to address our primary research question.

3.1 Introduction

3.1.1 Principles of Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique used to measure the white matter microstructure properties in the brain. DTI works based on the principle of random motion of water molecules that occur due to thermal agitation in the medium (Brownian motion). The white matter is composed of axons and glial cells, more specifically the oligodendrocytes which form myelin covering the axons. Certain studies have indicated that the anisotropic properties in the axons and myelin are not similar (Assaf & Pasternak, 2008). The diffusion of water molecules is restricted along the walls of axons, such that the diffusion of water in the white matter is anisotropic, whereas the movement of water molecules are unrestricted in the grey matter and therefore the diffusion of water is isotropic in nature. The diffusion properties parallel to the axonal orientation (axial diffusivity) are highly anisotropic and less anisotropic in the perpendicular direction of the fibre orientation (radial diffusivity). DTI is measured in terms of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). The relationship between these four metrics are as follows: the fractional anisotropy is directly proportional to axial diffusivity and the mean diffusivity is directly proportional to radial diffusivity. However, we will mainly focus on the FA and MD in the interest of examining the white matter microstructure in our study. The fractional anisotropy is used to measure the white matter microstructure integrity and directionality of water diffusion, whereas the mean diffusivity is used to measure the magnitude of water diffusion regardless of direction in the axons. The fractional anisotropy values range from 0 to 1, where 0 indicates lower FA and 1 indicates higher FA. The decrease in the FA and increase in the MD values are considered as markers of white matter microstructure abnormalities (thinning of axons and reduced myelination) in the brain (Johansen-Berg & Behrens, 2013).

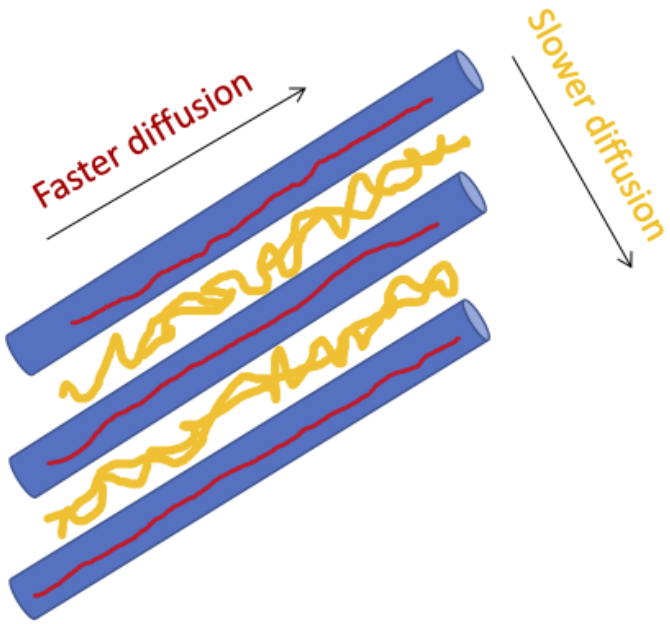


Fig. 3.1: Schematics of the principle of diffusion of water (a) Diffusion of water is faster in the direction parallel to the axons indicating more anisotropic nature (red) (b) diffusion of water is slower in the direction perpendicular to axons indicating more isotropic nature (yellow)

3.1.2 Connectivity hypothesis in ASD

It has been hypothesised that the core symptoms of Autism Spectrum Disorder, including reciprocal social interaction and communication, and increased narrow range of interests and stereotyped behaviour, are associated with atypical brain connectivity (Müller & Fishman, 2018). In light of the connectivity hypothesis, it has been suggested that the atypical brain connectivity may be characterised by long-range hypoconnectivity and short-range hyperconnectivity in ASD. In this context, the distant brain regions communicate together to a lesser extent, while the local brain regions communicate to a greater extent (Belmonte et al., 2004). Several lines of evidence suggest that atypical structural brain connectivity in individuals with ASD occurs due to abnormal axonal outgrowth/synaptic pruning and migration of neurons forming cortical connections, underlying the genetic basis of ASD throughout the course of development (Kana et al., 2014). Previous studies termed ASD as a disconnection syndrome, which means that the cortical connections between the higher order association areas in the brain are unestablished through underlying white matter structural connectivity during brain development (Frith, 2004; Geschwind & Levitt, 2007a; Hoppenbrouwers et al., 2014). It was further suggested that this may arise due to varying complex cortical neuropathology including the atypical regional grey and white matter volume, cortical thickness and surface area across the different developmental trajectories in ASD

(Ecker et al., 2015). These brain structural metrics may also influence brain connectivity and enlargement during early childhood. In a longitudinal study, it was demonstrated that the children (aged between 2 and 5 years) with ASD exhibited a rapid increase in early brain overgrowth, while such significant differences were not observed in their middle childhood (aged between 6 and 8 years). Brain overgrowth continued to decline from their later childhood through to adolescence and adulthood. The same study propounded that the age-specific structural brain abnormalities in ASD may underlie the atypical neurobiological phenomena including synaptogenesis, molecular and gene expression (Courchesne et al., 2011b).

The concept of atypical structural connectivity in ASD is further supported by the post-mortem studies. A systematic review of the histopathological brain studies on autism suggests that the myelinated axons in the white matter in the frontal lobe (below the anterior cingulate cortex, orbitofrontal cortex and medial and lateral prefrontal cortex) were increased in absolute numbers and density, which may be strong evidence for the atypical structural brain connectivity associated with the primary deficits in ASD (McFadden & Minshew, 2013). Another post-mortem brain study on ASD suggested that declined axonal properties (proliferation, migration, organisation) and reduced myelin thickness in the white matter tracts connecting the prefrontal and temporoparietal brain regions is an indication of atypical brain connectivity associated with the socio-emotional deficits in ASD (Ameis & Catani, 2015). Moreover, the gene expression between the prefrontal cortex and superior temporal cortex exhibited a diminished variability in the ASD post-mortem brains, suggesting further evidence that autism-specific candidate genes may underlie the aberrant brain connectivity in ASD (Voineagu et al., 2011).

To summarise, there are several lines of evidence suggesting atypical brain connectivity in ASD. The multidisciplinary studies on ASD involving different brain imaging techniques, genetics and post-mortem brains also contributed to emerging ideas that these structural brain abnormalities may underpin the hereditary characteristics reflecting the behavioural phenotype in ASD.

3.1.3 DTI studies of ASD - evidence review

Several studies have reported different white matter microstructure abnormalities including superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus in individuals with ASD (Barnea-Goraly et al., 2010; Kleinhans et al., 2012; Libero et al., 2016). The Superior Longitudinal Fasciculus (SLF) is a major association white matter tract which connects the fronto-parietal cortices in the brain (Kamali et al., 2014).

SLF plays an important role in integrating higher-order brain regions involved in social communication skills. However, the disruption in SLF may impose difficulties in maintaining attention and developing language skills in individuals with ASD (Fitzgerald et al., 2018). The Uncinate Fasciculus (UF), a U-shaped WM fibre tract, connects the fronto-temporal lobes and limbic areas in the brain. UF mainly connects the amygdala to the lateral orbitofrontal cortices in the brain. Any sort of damage to the UF may result in impairments in acquiring and implementing socio-emotional skills in individuals with ASD (Olson et al., 2015). Studies investigating group differences of different white matter microstructures showed significantly reduced FA and increased MD in adults with ASD compared to controls (Catani et al., 2016). The Inferior Longitudinal Fasciculus (ILF) is a major association white matter fibre tract which connects the occipital lobe (brain regions including cuneus and lingual gyrus) to the anterior temporal lobe (including amygdala and fusiform gyrus) of the brain (Ashtari, 2012; M. Catani, 2003). The disruption in the ILF may result in atypical visual information processing in individuals with ASD (Boets et al., 2018). The Inferior Fronto-Occipital Fasciculus (IFOF) is a long association white matter fibre tract which directly connects the frontal, temporal and occipital lobes of the brain (Sarubbo et al., 2013). The disruption in the IFOF may result in the impaired social communication as well as socio-emotional processing deficits in individuals with ASD (Ameis et al., 2011). Overall, the damages in all these four major association fibres (SLF, UF, ILF and IFOF) may underlie the core symptoms associated with ASD.

Many studies have shown atypical white matter microstructure associated with social skill deficits in individuals with ASD (Im et al., 2018; Jou et al., 2011; Vogan et al., 2016). Previous studies on ASD have reported white matter microstructure abnormalities (reduced fractional anisotropy and increased mean diffusivity) in the fibre tracts including bilateral superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF) (Boets et al., 2018; Catani et al., 2016; Itahashi et al., 2015). These findings suggested that the major association white matter tracts including SLF, UF, ILF and IFOF reflect the atypical language function, socio-emotional characteristics and visual processing deficits respectively in individuals with ASD. The white matter microstructure differences in ASD are characterised by lower long-range and greater short-range connectivity (Hoppenbrouwers et al., 2014). Some previous studies on diffusion tensor imaging (DTI) using a whole-brain voxel-wise analysis showed reduced fractional anisotropy in the different white matter tracts connecting the brain regions including the ventrolateral medial prefrontal cortex (VMPFC), superior temporal sulci (STS), amygdala and fusiform gyri in individuals with ASD (Barnea-Goraly et al., 2004;

Groen et al., 2011; Lee et al., 2007; Lisiecka et al., 2015). Cortical brain regions including VMPFC and STS (temporoparietal junction) constitute a main portion of the default mode network and also play a significant role in the theory of mind skills, whereas the amygdala and fusiform gyri are involved in emotional judgements and facial expression recognition, respectively. As such, the impairments in these white matter microstructures which integrate the higher-order brain association areas may underlie the social skill deficits in ASD.

Earlier studies using whole-brain white matter voxel-wise analysis showed reduced fractional anisotropy in white matter tracts including the right SLF, left ILF, bilateral corpus callosum, anterior and posterior corona radiata and anterior thalamic radiation in individuals with ASD compared to controls, suggesting widespread white matter microstructure abnormalities are associated with the social deficits and stereotyped behaviours in ASD (Fitzgerald et al., 2019). In line with this, another white matter microstructure study showed reduced fractional anisotropy, and increased mean diffusivity and radial diffusivity in white matter fibre tracts including the SLF, ILF, IFOF, cingulum, corpus callosum and anterior thalamic radiation in individuals with ASD (Shukla et al., 2011). These white matter microstructure differences in individuals with ASD may underlie atypical socio-communication, socio-emotional and visual information processing skills. These whole-brain white matter microstructure study findings further suggested that individuals with ASD may exhibit widespread disruptions in the white matter microstructure, rather than in a specific tract related to the core symptoms of ASD.

Many previous studies used case-control designs to examine the white matter microstructure differences associated with ASD (Catani et al., 2016; Fletcher et al., 2010; Mueller et al., 2013b). However, growing evidence suggests that autistic traits lie on a continuum in the general population, whilst clinical ASD lies at the extreme end of the distribution (Robinson et al., 2011; Ruzich et al., 2015; Whitehouse et al., 2011). In line with this, a previous study that used tract-based spatial statistics and probabilistic tractography demonstrated reduced fractional anisotropy in the inferior fronto-occipital fasciculus related to higher autistic traits in the neurotypicals. This finding suggested that IFOF may be associated with socio-emotional processing difficulties in the general population (Hirose et al., 2014). In an investigation testing the relationship between white matter connectivity and autistic traits in the general population, it was found that increased white matter connectivity between the superior temporal sulcus and amygdala may be related to higher autistic traits (Iidaka et al., 2012). Similarly, another study found a significant positive correlation between the left inferior longitudinal fasciculus (fractional anisotropy) and AQ scores in the

general population (Bradstreet et al., 2017). The white matter microstructure findings in the ILF and IFOF suggested that individuals with higher autistic traits showed atypical behavioural manifestations associated with face and emotion processing difficulties, which is also seen in individuals with ASD (Bradstreet et al., 2017; Iidaka et al., 2012). In a previous whole-brain white matter microstructure study, it was demonstrated that reduced fractional anisotropy and increased mean diffusivity related to higher autistic traits, suggesting that the severity of autistic traits may reflect social skill difficulties across the clinical and non-clinical population (Gibbard et al., 2013). A recent white matter microstructure study using TBSS analysis showed reduced fractional anisotropy in the left superior longitudinal fasciculus related to autistic traits in the neurotypicals, suggesting that the atypical white matter microstructure in the SLF may be associated with the continuum of autistic traits in the general population (Blanken et al., 2017). A previous study found a negative relationship between regional fractional anisotropy and autistic traits in the white matter microstructures connecting the right temporal fusiform and parahippocampal gyri in the general population. This study indicated that this localised atypical white matter microstructure may be related to certain autistic traits which have been observed in individuals with high-functioning autism (Jakab et al., 2013).

In contrast, unlike the majority of the previous white matter microstructure studies related to autistic traits, a white matter microstructure study using an exploratory and validation sample showed no significant relationship between white matter microstructure and autistic traits in the general population (Koolschijn et al., 2015). The conflicting findings from some previous studies bring up the research question of whether the white matter microstructure abnormalities are associated with the autistic traits in the general population (Gibbard et al., 2013; Iidaka et al., 2012; Jakab et al., 2013) or only in those with clinical ASD. The other question is, does the association between autistic traits and white matter microstructure affect the whole white matter pathway in the brain or does it relate to the specific white matter tracts? A large number of studies have reported atypical white matter microstructure exhibiting reduced FA and increased MD values in the SLF, ILF, UF and genu of the corpus callosum using case-control design (Catani et al., 2016; Nickel et al., 2017; Perkins et al., 2014). A moderate number of studies using a dimensional approach to analyse symptoms of autism/traits across a diagnostic divide found evidence for a relationship between white matter microstructure and autistic traits (Gibbard et al., 2013; Iidaka et al., 2012; Jakab et al., 2013). However, an abundance of inconsistent findings in the published literature on white matter microstructure across neurotypicals and individuals with ASD might

reflect the differences in the study population, such as age, heterogeneity, comorbidities, data quality and various analytical approaches.

To date, there are few studies that have aimed to identify the white matter microstructural correlates of autistic traits in a sample that includes both neurotypicals and individuals with ASD (Blanken et al., 2017; Gibbard et al., 2013). However, according to previous research, focusing on apriori TOI from the white matter skeleton may help us to study and better understand the abnormalities in the individual white matter tracts specific to the behavioural manifestations of ASD. In addition, it may also improve the statistical significance of the results and perhaps replicate findings from previous studies. On the other hand, TBSS may help us to study and explore the whole white matter microstructure abnormalities, whereas it is possible that one may miss out the probability of measuring other white matter tracts which may have had an effect while using a TOI approach. In attempting to address the limitations of prior studies, we sought to investigate the white matter microstructure related to autistic traits across the combined sample of neurotypicals and individuals with ASD.

In summary, we sought to examine the relationship between white matter microstructural properties (regional and whole white matter structure) and autistic traits in the combined sample of neurotypicals and individuals with ASD. To achieve this aim, this proposed study will measure the white matter microstructural properties using DTI and assess the relationship between fractional anisotropy, mean diffusivity and autism spectrum quotient (AQ) using a dimensional approach. Based on the existing literature, the following hypothesis was put forward: reduced fractional anisotropy and increased mean diffusivity will be observed in individuals with higher autistic traits in specific white matter tracts, including bilateral superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum across the combined sample of neurotypicals and individuals with ASD.

3.2 Methods and materials

3.2.1 Participants

Twenty-eight neurotypical adults (age: 18-57 years, gender: 16 males and 12 females) and twenty-five adults with High Functioning Autism (HFA) (age: 18-60 years, gender: 15 males and 10 females) matched for age, gender and IQ were recruited in this study (Neufeld et al., 2019). All the neurotypical individuals were recruited from the University of Reading and the individuals with HFA from the registered clinic. The performance IQ was measured using Raven's progressive

matrices (Raven, 2000). Participants with symptoms of ASD were assessed with the Autism Diagnostic Observation Schedule (ADOS) module-4 and diagnosed using the diagnostic and statistical manual (DSM IV). Subjects with any neurological conditions or head injuries were excluded from the study. Autism Spectrum Quotient (AQ) scores were also collected from all the participants. This study was approved by the University Research Ethics Committee (UREC), University of Reading.

Table 3.1 Participant characteristics

Characteristics	**Neurotypicals (N=28)**		**ASD (N=25)**		**P-values**
	Mean	**SD**	**Mean**	**SD**	
Age	29.93	9.63	34.48	12.95	0.150
Gender (m/f)	16/12	-	15/10	-	0.833
AQ	15.29	5.06	36.32	7.80	<0.001*
Raven's percentile	48.46	23.07	55.92	26.76	0.281
ADOS (Soc+Comm)	-	-	10.08	4.924	-

Abbreviations and signs: N- Number of subjects, SD-Standard deviation, m-male, f-female, Soc- Social interaction, Comm- Communication, ***p < .001

3.2.2 MRI data collection

Siemens Trio MRI 3T scanner (32-channel head coil) was used to acquire the diffusion tensor images and T1-weighted structural images at the Centre for Integrative Neurosciences and Neurodynamics (CINN), University of Reading. The diffusion tensor imaging protocol used single-shot spin echo, Echo Planar Imaging (EPI) with 32-gradients including 60 diffusion weighted (b=1000 sec/mm^2) and 2 non-diffusion weighted images (b=0 sec/mm^2), repetition time = 7200 ms; echo time = 10 ms, matrix =128 x 128, voxel size = 2 x 2 x 2 mm (isotropic). High resolution T1-weighted structural whole brain images with parameters (repetition time = 2020 ms, echo time = 2 ms; matrix =256 x 256, voxel size = 1 x 1 x 1 mm (isotropic) were acquired to inspect the brain anatomical landmarks corresponding to individual diffusion weighted images.

3.2.3 DTI analytical approaches

In the present study, we used two diffusion tensor imaging analytical approaches: (i) Skeleton-based tracts of interest and (ii) Tract-based spatial statistics (TBSS). These two analytical approaches provide us with a unique methodological direction to investigate the white matter microstructures in the brain.

3.2.3.1 Skeleton-based tracts of interest (TOI) analysis

Skeleton-based tracts of interest (TOI) analysis (Nguyen et al., 2011) was used to derive all the skeletonised fractional anisotropy (FA) and mean diffusivity (MD) maps with standard tract-based spatial statistics (TBSS) pipeline incorporated in the FSL FMRIB software package (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). All the DTI dataset were pre-processed for eddy current correction, non-brain tissue removal using the brain extraction tool (BET) (Smith, 2002) and the diffusion tensor models were derived using DTIFIT (Behrens et al., 2003). The FA and MD maps were organised systematically in order to register the scalar maps to the FA FMRIB template using non-linear registration. Then the 4D concatenated multi-subject skeletonised FA and MD maps were derived and transformed to the MNI standard space. Fractional anisotropy threshold 0.2 was applied to confine the major white matter fibres and prevent partial volume effects of grey matter. The ROI masks of bilateral superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus extracted using JHU white matter atlas (Mori et al., 2005) were projected over all the skeletonised FA and MD maps. Using these diffusion maps, the FA and MD values across the respective TOI masks were extracted using 'fslstats' (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils).

3.2.3.2 Tract-based Spatial Statistics

Tract-based Spatial Statistics (TBSS), a whole-brain voxel-wise analytical approach incorporated in the FSL software library version 5.0 (Smith et al., 2006) was used for the data analysis. The standard TBSS pipeline was used for eddy current correction, non-brain tissue removal, diffusion tensor modelling, registration, normalisation, thresholding and randomisation as follows: The DTI images were preprocessed for eddy current correction and removal of non-brain tissues, and the Diffusion tensor models (FA and MD maps) were derived from all the images. In the first step, the fractional anisotropy (FA) and mean diffusivity (MD) maps were organised into two separate subdirectories. In the second step, the FA and MD maps were non-linearly registered and transformed to the *FA FMRIB (1mm^3)* standard space. In the third step, the mean FA skeleton, all

skeletonised FA and MD 4D concatenated multi-subject were derived and transformed using non-linear registration to the MNI152 *(1mm^3)* standard space. In the fourth step, a white matter thresholding (0.2) was used on the mean FA skeleton to restrict the grey matter partial volume effects.

3.2.4 Statistical analysis

3.2.4.1 Skeleton-based ROI analysis

To test the relationship between the diffusion indices and AQ, the Statistical Package for the Social Sciences (SPSS) (George & Mallery, 2019; Nie et al., 1975) was used for statistical analysis. Pearson partial correlation (one-tailed) was performed between FA, MD values and AQ scores after controlling for age, gender and IQ in the whole sample. We preferred a one-tailed test over two-tailed because the FA and MD are unidirectional, and it will also help us to improve the statistical power.

3.2.4.2 Tract-based spatial statistics

The General Linear Model was used to test the relationship between fractional anisotropy and AQ. In addition, the relationship between the mean diffusivity and AQ was also tested, while controlling for age, gender and IQ. This was performed using permutation-based testing (N=5000) and Threshold-Free Cluster Enhancement (TFCE) (Smith & Nichols, 2009) for multiple comparisons. The cluster-forming threshold is usually arbitrary. In addition, the cluster forming threshold also varies depending upon the level of smoothing (FWHM) applied. Sometimes defining an uncertain cluster threshold may mislead to false positive findings. So as to avoid such cluster threshold defining problems, TFCE approach was used. TFCE uses a raw statistic image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial extent.

3.3 Results

3.3.1 Skeleton-based TOI analysis

We found a negative correlation between FA and AQ in the right inferior longitudinal fasciculus ($r = -0.275$, $p = 0.027$, uncorrected) (Fig. 3.2, Table: 2). However, it was not significant after correcting for multiple comparisons using the Bonferroni method ($p < 0.05$). There was no

significant correlation between MD and AQ scores in the combined sample of neurotypicals and individuals with ASD (Table: 3.2).

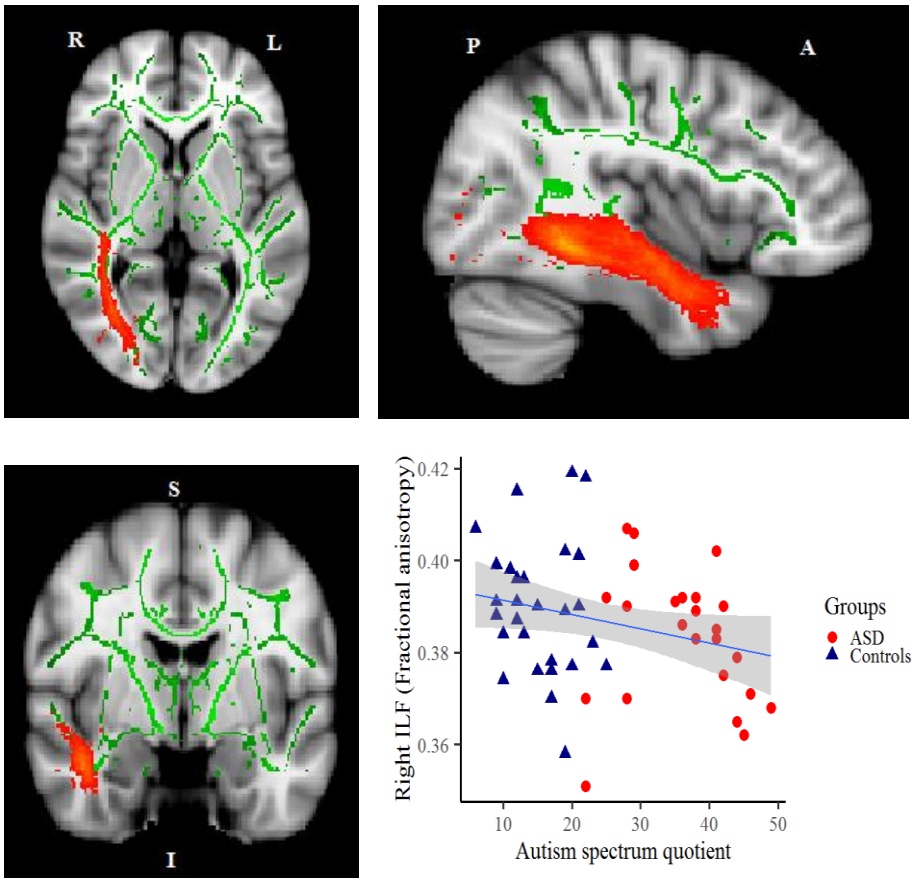


Fig. 3.2: Right ILF mask projected over the mean FA skeleton and the scatterplot showing negative correlation between FA in this tract and AQ.

Table 3.2 Correlation between fractional anisotropy and mean diffusivity and AQ

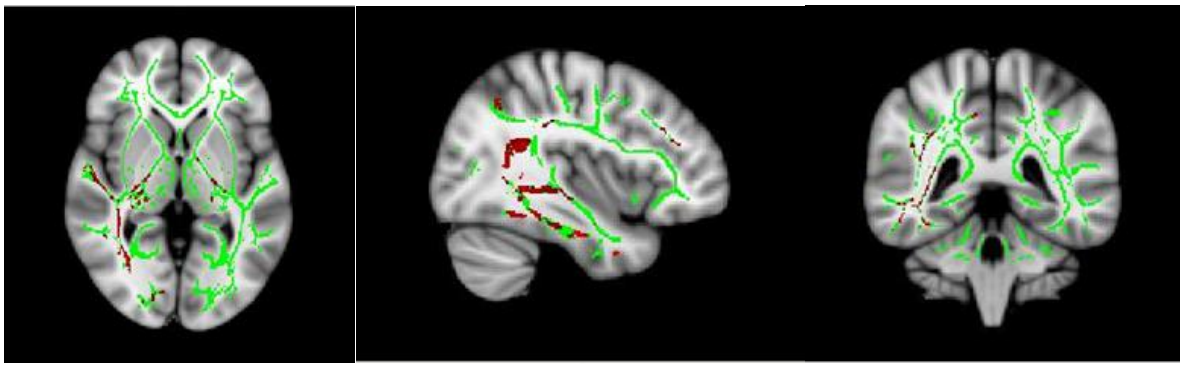
	Side	Fractional Anisotropy		Mean Diffusivity	
Brain regions		**r-values**	**P-values**	**r-values**	**P-values**
Superior longitudinal fasciculus	L	-0.019	0.447	0.158	0.137
Superior longitudinal fasciculus	R	-0.183	0.102	0.185	0.100
Uncinate fasciculus	L	-0.038	0.396	0.072	0.309
Uncinate fasciculus	R	-0.065	0.327	0.171	0.117
Inferior longitudinal fasciculus	L	-0.037	0.400	0.193	0.090
Inferior longitudinal fasciculus	R	-0.275	0.027 *	0.217	0.065
Inferior fronto-occipital fasciculus	L	-0.052	0.360	0.150	0.150
Inferior fronto-occipital fasciculus	R	-0.208	0.074	0.203	0.078

Abbreviations: r - Correlation coefficient, *p < .05, uncorrected.

3.3.2 Tract-based Spatial Statistics

We found a positive association between MD and AQ in the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum (forceps major and splenium). We also found a negative association between FA and AQ in the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corticospinal tract in the combined sample of neurotypicals and individuals with ASD (Fig. 3.3, Table: 3.3). However, no clusters survived after correcting for multiple comparisons using threshold-free cluster enhancement (TFCE) ($p < 0.05$).

(a)



(b)

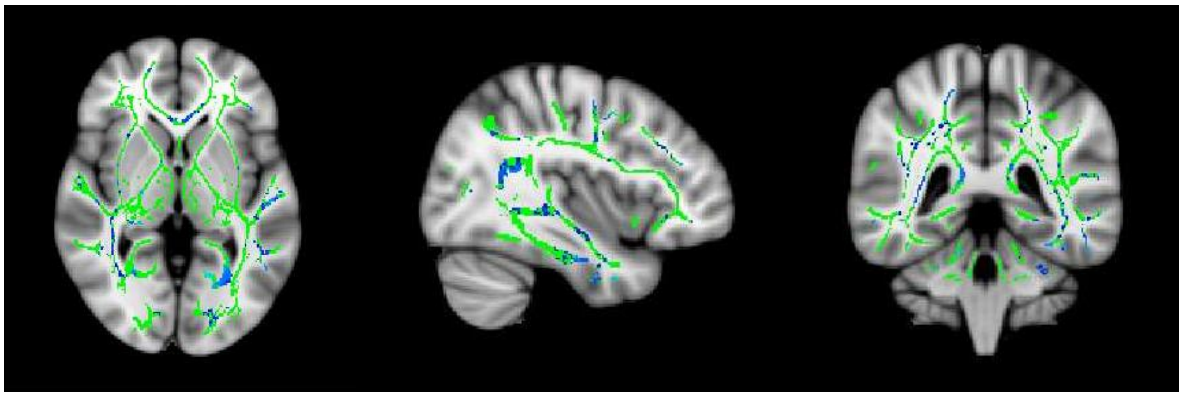


Fig. 3.3: Whole white matter skeleton (green) display, (a) negative association (red) between fractional anisotropy and AQ and (b) positive association (blue) between mean diffusivity and AQ in the specific tracts listed in the table (3.3).

Table 3.3 Association between fractional anisotropy and mean diffusivity and AQ

White matter tracts	Side	MNI coordinates			K_E	P-values
		x	y	z		
Fractional anisotropy						
Superior longitudinal fasciculus	R	40	-48	8	266	0.04
Inferior longitudinal fasciculus	R	49	-24	-22	2837	0.04
Inferior fronto-occipital fasciculus	R	26	-24	-5	118	0.03
Corticospinal tract	L	-17	-12	-4	300	0.05
Mean diffusivity						
Superior longitudinal fasciculus	R	57	-42	-7	135	0.05
Inferior longitudinal fasciculus	R	38	5	-36	105	0.03
Inferior fronto-occipital fasciculus	R	36	-54	4	129	0.03
Corpus callosum (Forceps major)		6	-37	13	473	0.03

Abbreviations: K_E- Cluster size, L- Left, R- Right, FA- Fractional Anisotropy, MD- Mean Diffusivity, P-values - uncorrected.

3.4 Discussion

In the current study, we used a dimensional approach to test the relationship between white matter microstructures and autistic traits across a combined sample of neurotypicals and individuals with ASD. Our results demonstrated the relationship between major association fibres (superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus), commissural fibre (corpus callosum) and projection fibre (cortico-spinal tract) and higher autistic traits. However, our clusters did not survive correction after multiple comparisons in both TBSS and skeleton-based TOI analysis. Despite the level of non-significance, the white matter tract right ILF finding using the TOI-based approach and a large cluster size in the same tract using TBSS were consistent in terms of its directionality as measured by fractional anisotropy related to higher autistic traits. Our results were consistent with previous findings (Boets et al., 2018; Koldewyn et al., 2014) using case-control design which showed reduced fractional anisotropy in the right inferior longitudinal fasciculus (ILF) in individuals with ASD.

In this study, we used two different analytical approaches: (i) skeleton-based TOI analysis and (ii) tract-based spatial statistics. First, we applied skeleton-based TOI analysis, a hypothesis-driven method to focus on the specific white matter tracts associated with ASD based on the literature. Second, we used tract-based spatial statistics, a data-driven method to measure the diffusion indices in the whole mean white matter skeleton to explore all WM microstructure. The first analytical approach used a similar preprocessing pipeline to the second approach before thresholding the whole mean white matter skeleton. The major difference in this skeleton-based TOI approach was that specific tracts of interest were used based on the prior hypothesis, whereas the TBSS used the whole white matter skeleton to study the fractional anisotropy and mean diffusivity indices in the white matter structure.

Previous studies have used a similar dimensional approach to examine how the different white matter microstructures are related to autistic traits in the general population (Iidaka et al., 2012; Koolschijn et al., 2015). However, few studies have demonstrated white matter microstructure differences in the right inferior longitudinal fasciculus across the combined sample of neurotypicals and individuals with ASD (Gibbard et al., 2013). Our findings can be explained by the fact that the reduced long-range connectivity (Vissers et al., 2012) in the right ILF (connecting the brain regions including amygdala, fusiform gyrus and lingual gyrus) may be related to autistic traits in the combined sample of neurotypicals and ASD. The converging evidence suggests that the co-occurrence of weaker integration of these distant brain regions and atypical white matter microstructure integrity of ILF and IFOF may underlie the deficits in social skills in individuals with ASD (Itahashi et al., 2015). Another possible explanation for this is that, these white matter microstructure abnormalities may be underpinned by axonal thinning/reduced myelination, which may have led to reduced fractional anisotropy and increased mean diffusivity measures in individuals with higher autistic traits. As discussed earlier, ILF partially overlaps with the IFOF, which also extends its connections to the prefrontal cortex (Catani & Thiebautdeschotten, 2008). In line with this, the atypical WM connectivity in the right ILF may have influenced the higher autistic traits across the whole sample. Thus, our study findings indicate that the reduced fractional anisotropy in the right ILF may be associated with higher autistic traits across the diagnostic divide.

The limitations in this study include having a moderate sample size (N=53) with the best of its MRI protocol in both neurotypicals and individuals with ASD, which might have influenced the statistical power of the analysis. The other major association white matter tracts, including the

bilateral superior longitudinal fasciculus, uncinate fasciculus and inferior fronto-occipital fasciculus, did not show a strong correlation with AQ in the skeleton-based TOI approach; however, these same WM tracts only exhibited a weaker relationship (small cluster size) with autistic traits using TBSS. This may be due to the specific inclusion of individuals with high-functioning autism (HFA), which helped us to reduce the head motion artefacts. Some previous studies suggested that widespread white matter microstructure differences in ASD may be specifically associated with the sample characteristics of the broader autism phenotype (Cheung et al., 2009; Weinstein et al., 2011). In the future, it may also be interesting to test the relationship between neural connectivity and specific gene variants related to autistic traits in the clinical and non-clinical population.

To summarise, we explored the possible relationship between the white matter microstructure and autistic traits in the right inferior longitudinal fasciculus across the combined sample of neurotypicals and individuals with ASD. More importantly, we understand that the right inferior longitudinal fasciculus may be associated with atypical visuospatial skills (Latini et al., 2017) in individuals with higher autistic traits. These white matter findings used skeleton-based TOI and tract-based spatial statistics to provide scientific evidence and shed light on the advantages of a dimensional approach in testing the association between white matter microstructure and autistic traits across the diagnostic divide, as suggested in the previous study (Boets et al., 2018).

Chapter 4: Investigating the relationship between resting state networks and autistic traits in the general population: a resting state functional Magnetic Resonance Imaging study

In this chapter, we begin by explaining how the differences in resting state functional connectivity modulate the social behaviour in individuals with ASD and autistic traits in the general population. The main aim of this study is to investigate the relationship between the intrinsic resting state networks and autistic traits in the general population.

4.1 Introduction

4.1.1 Principles of BOLD signal

Functional magnetic resonance imaging (fMRI) is a brain imaging technique used to measure the physiological origin of Blood Oxygenation Level Dependent (BOLD) signals associated with neural activity. The relationship between the BOLD signal associated with the neuronal activity can be explained by the hemodynamic response function (HRF) (Lindquist et al., 2009). HRF helps us to better characterise and understand the onset, amplitude, delay and duration of the BOLD signal corresponding to the neuronal activity. The variability in the HRF is subjected to the differences in the BOLD signal reflecting the neuronal activity. BOLD signals were conceptualised based on the principle of haemodynamics associated with oxygenated and deoxygenated haemoglobin present in the blood of the human brain. To explain briefly, when water molecules composed of protons in the blood are excited using the high magnetic field strength with a T2* weighted gradient echo sequence, the deoxygenated blood attains paramagnetic properties, while the oxygenated blood attains diamagnetic properties. Subsequently, this deoxygenated blood produces phase dispersion of the water proton signal. This dispersion reduces the proton signal intensity at high magnetic fields extending beyond the boundary of the blood vessels resulting in a BOLD contrast signal (Ogawa et al., 1990). The BOLD signal identified was associated with the neuronal activity indexed by the local field potential as the result of neurophysiological phenomena (Rosazza et al., 2012). This discovery of BOLD signals enabled great strides in the application of functional magnetic resonance imaging in the brain imaging research.

4.1.2 Principles of resting state functional MRI and underlying networks

Resting state functional magnetic resonance imaging is a paradigm used to examine the low frequency (0.01-0.1 Hz) fluctuations associated with BOLD signals, which reflect the functional architecture of the brain when an individual is at rest and does not require any complex tasks that require complex cognition (Lee et al., 2013). These low frequency fluctuations associated with BOLD signals are believed to reflect the differences in resting state functional connectivity. Resting state fMRI can be used to acquire data with eyes opened/closed. There are differences between these two types of paradigms conceptually. However, there is no clear evidence suggesting that one is better than the other. Some researchers prefer the eyes opened condition over the eyes being closed to ensure that an individual is awake and not falling asleep.

Resting state functional connectivity is used to examine the differences in the intrinsic/extrinsic network connectivity of different resting state networks when an individual is at rest in both clinical and non-clinical populations. Intrinsic network connectivity is defined as different brain regions integrated together within a network to function without the interaction of brain regions from other resting state networks. By contrast, the extrinsic network may constitute different brain regions across different resting state networks. This principle was conceptualised in order to examine large-scale brain networks using the rs-fMRI in various healthy populations and neuropsychiatric conditions (Menon, 2011). Biswal and colleagues were the first to use rs-fMRI to demonstrate that the motor cortex and other closely associated brain regions in the sensorimotor cortex were synchronously active. The voxels within the latter brain regions were positively correlated with the voxels of other regions in the whole brain at rest, while the seed region in the same motor cortex was found to be negatively correlated during the finger-tapping task. This finding suggested that low frequency fluctuations associated with the BOLD signal in the baseline at rest is the manifestation of functional connectivity in the brain (Biswal et al., 1995).

Functional connectivity is defined as the temporal correlation of BOLD signals associated with neuronal activity in different brain regions when an individual is at rest (Cordes et al., 2000; Lin et al., 2008; van den Heuvel & Hulshoff Pol, 2010). This helps us to understand how different brain regions communicate with each other as a network and functionally integrated to achieve specific tasks or at rest. The functional connectivity was tested and supported by different studies (Doria et al., 2010; Greicius et al., 2003; Picci et al., 2016) investigating the resting state networks (RSN). Amongst all RSN, the Default Mode Network (DMN) is a widely investigated network of interest in different clinical conditions. The DMN consists of the medial prefrontal cortex, posterior cingulate cortex and precuneus. It was observed in a Positron Emission Tomography (PET) study that the DMN was relatively more active at rest, but less active during cognitive tasks, which is believed to reflect the different patterns of activations in the default mode brain regions at baseline resting state (Raichle et al., 2001). The DMN is commonly known as a ‘task-negative network’, which means that it may exhibit an increased BOLD signal indicating increased neural activity at rest but reduced while performing complex cognitive tasks. These brain regions are believed to constitute a default mode network which may be involved in higher order brain functions when the brain is at resting state (Greicius et al., 2003). Existing research recognises the critical role played by DMN, indicating that the differences in functional connectivity associated with this specific RSN may be involved in self-awareness (mentalizing and self-interpreting one’s own thoughts) (Raichle, 2015). Following this, a number of resting state networks have been

investigated including medial and lateral occipital visual network, auditory, sensorimotor, default mode, executive control, right and left-lateralised fronto-parietal networks across different studies. These RSNs have been commonly investigated to understand the physiological responses of low frequency fluctuations associated with BOLD signals underlying neuronal activity (Beckmann et al., 2005) in various neuropsychiatric and neurodevelopmental conditions. This revolutionary finding in the field of functional magnetic resonance imaging paved the way for further investigation of functional connectivity, based on several cognitive theories on neurodevelopmental conditions like Autism Spectrum Disorders.

4.1.3 Resting state fMRI protocol and artefacts

Optimised resting state fMRI protocol for data acquisition is important for attaining good data quality. Resting state fMRI protocol requires a large number of volumes (~ 200-300 volumes/per subject) which may take a long period of time. In addition, an individual has to stay awake without moving the body while lying down in the MRI scanner. This was a major challenge for many researchers to acquire images of high data quality without subject motion artefacts. In modern day scanners, this can be achieved by using echo planar imaging (EPI) with a repetition time (2000-3000 milliseconds) in a very short period of time (10-15 mins). In terms of spatial resolution, voxel size (2-3 cubic mm) will help us to acquire data of good quality (Friedman & Glover, 2006). Therefore, a longer repetition time and good voxel resolution without subject motion will yield a data of high standards. Despite this, there may be a possibility of having signal dropout and slice timing differences while applying fast EPI sequence to acquire rs-fMRI data. The other major challenges are subjective to nuisance signals in the rs-fMRI images as it is sensitive to subject motion and physiological signal artefacts. Therefore, an efficient preprocessing and clean-up procedure is required to minimise the impact of the subject motion artefacts, slice timing correction, magnetic field inhomogeneity and high frequency physiological noise signals before performing the data analysis (Smith et al., 2013).

Functional connectivity can be examined using various analytical approaches, including independent component analysis, seed-based analysis, regional homogeneity, amplitude of low frequency fluctuations and graph theory. Each of these approaches serves a different purpose in measuring functional connectivity. However, the most commonly used approach amongst these is independent component analysis.

Independent Component Analysis (ICA) is a data-driven analytical approach which can be used to measure the intrinsic and extrinsic network connectivity. ICA primarily identifies the primary source of BOLD signals associated with the spatiotemporal patterns and separates the noisy signals (scanner and physiological artefacts) from the fMRI dataset (Beckmann et al., 2009). However, some manual interpretation and prior knowledge may be required for ICA to select the significant components associated with BOLD activity. Nowadays, automated tools (FIX and AROMA) (Griffanti et al., 2017) are available to train the algorithm to label the noisy components and discard it from the analysis. This is because the spatial and temporal components showing BOLD activations may be mixed up with the noisy signals. Therefore, it is crucial to pick up the appropriate components to avoid bias in the data analysis.

4.1.4 Connectivity hypothesis in ASD

The phenomenon of synaptic pruning is essential for establishing connections between neurons in the brain and brain connectivity. The abnormalities associated with synaptic pruning may disrupt neural connectivity (atypical brain connectivity) and this could lead to deficits in information processing. Therefore, atypical brain connectivity can be defined as disconnections between different brain regions which may underlie abnormalities in synapse formation/elimination (Geschwind, 2011). Atypical brain connectivity is characterised by hypo-connectivity and hyper-connectivity underlying pathophysiological mechanisms. It was also hypothesised that short-range hyper-connectivity and long-range hypo-connectivity may arise as a result of dependencies of local and distant neural assembly (number and density of neurons) respectively in individuals with ASD (Belmonte et al., 2004). In light of this, Cherkassky and colleagues demonstrated reduced functional connectivity in the anterior and posterior regions of the default mode network (medial prefrontal cortex, anterior cingulate cortex and posterior cingulate cortex) in individuals with ASD (at rest) compared to controls. This finding suggested that functional hypo-connectivity in the DMN may underlie the atypical social behaviours (theory of mind deficits) in individuals with ASD (Cherkassky et al., 2006). Our main focus in this section is to explain the broader perspective of the functional connectivity hypothesis in ASD.

The brain structure is represented by cortical and subcortical regions, and white matter connections. To compose a fully functional system, different cortical and subcortical regions are integrated by white matter fibres. Although these white matter fibres integrate different brain regions and facilitate structural connectivity, the grey matter largely accounts for functional connectivity. It has been suggested that white matter microstructure abnormalities may underlie

axonal and myelin deficits, whereas the grey matter abnormalities may be associated with atypical functional connectivity (Damoiseaux & Greicius, 2009). In light of this, using rs-fMRI and diffusion tensor imaging correlations between functional and structural connectivity was demonstrated along the neural pathway including default brain regions. This suggested that differences in functional connectivity may also reflect structural connectivity (Honey et al., 2009) in individuals with ASD. For instance, the differences in the average time series of voxels from different grey matter brain regions may also occur as a result of white matter microstructure abnormalities, which could manifest functional uncoupling between two brain regions in a resting state network. Therefore, these neural components may be functionally disintegrated/developed poorly (abnormal brain overgrowth) in young children with ASD (Minshew & Keller, 2010).

Different brain regions are believed to be functionally active when an individual is at rest. However, the higher order brain regions constituting different resting state networks may exhibit functional hypo-connectivity and hyper-connectivity in ASD (Hull et al., 2017). Considering this, the intrinsic functional connectivity of crucial resting state networks, including the default mode network (DMN), executive control network and salience network, is widely assessed because of its high relevance to the theory of mind deficits, goal-oriented and emotional behaviours in ASD, respectively (Abbott et al., 2016). On the other hand, the aberrant functional connectivity (hypo-connectivity and hyper-connectivity) may vary across children, adolescents and adults which suggests that different stages of brain maturation may also account for differences in behavioural patterns in ASD (Uddin et al., 2013). Some assumptions have been made that abnormal structural and functional integration of brain circuits together may underlie atypical brain connectivity in ASD.

New evidence is emerging on altered functional connectivity related to atypical behaviours in ASD. However, these are complicated by some methodological constraints, such as sample characteristics, motion and physiological artefacts, global signal regression, variations in the protocols of multisite MRI dataset, different analytical approaches (such as whole brain connectivity, local overconnectivity/distant underconnectivity). These factors may reflect the conflicting findings of hypo-connectivity and hyper-connectivity and therefore hinder the development of neuroimaging biomarkers (Kana et al., 2014). There is also growing evidence that using multimodal brain imaging techniques (resting state fMRI, magnetoencephalography, electroencephalography and functional Near Infrared Spectroscopy (fNIRS) supports the atypical functional connectivity hypothesis in ASD (Mash et al., 2018). However, there may be challenges

present in integrating/comparing findings because of the variation in sources of measuring functional connectivity as the spatial and temporal characteristics across these modalities are not the same. For instance, the spatial resolution of the data acquired using fMRI may be better than the fNIRS and the temporal resolution of EEG data may be better than the fMRI in measuring functional connectivity. Therefore, a unified framework may be required to avoid such inconsistencies in measuring functional connectivity in ASD.

Taken together, some neurobiological factors suggest that pathophysiology of synaptic pruning could influence the atypical brain connectivity in ASD. Despite this, emerging evidence from brain imaging studies suggests that atypical brain connectivity of the resting state networks may be associated with social behavioural deficits in individuals with ASD, which may also be seen in individuals with autistics traits in the general population. However, several methodological factors must be considered carefully in measuring the functional connectivity of the resting state networks.

4.1.5 Resting state fMRI studies of ASD - evidence review

Several resting state functional MRI studies have demonstrated atypical functional connectivity in different resting state networks/specific brain regions related to social and behavioural abnormalities in individuals with ASD. However, some studies showed functional hypo-connectivity while other studies showed functional hyper-connectivity in different brain regions in individuals with ASD (Lau et al., 2019, 2020; Uddin et al., 2013; Wang et al., 2018). Many studies reported atypical functional connectivity in some common brain regions including the orbito-prefrontal cortex, amygdala, fusiform face area and posterior superior temporal sulcus which are known as social brain regions in ASD. Other studies reported atypical functional connectivity between different RSN including the default mode, fronto-parietal, sensory motor and primary visual networks in ASD. Therefore, we will review the atypical functional connectivity findings associated with a wide range of social behavioural atypicalities in individuals with ASD from previous studies in this section.

Previous studies have shown a particular interest in studying the default mode network because of implications in theory of mind deficits in individuals with ASD. The default mode network comprises the medial prefrontal cortex, posterior cingulate cortex and precuneus. These brain regions are believed to underlie difficulties in interpreting one's own thoughts and judging others' intentions in individuals with ASD (Joshi et al., 2017; Nielsen et al., 2014). Considering this, Maximo and colleagues studied local functional over-connectivity using regional homogeneity in

the calcarine gyrus and fusiform gyrus, and under-connectivity between the medial prefrontal cortex and anterior and posterior cingulate gyrus in children and adolescents with ASD compared to age-matched controls (Maximo et al., 2013). This study suggested that atypical functional connectivity in the brain regions involved in the default mode network and occipital and posterior-temporal regions may be associated with impaired social cognition and local versus global visual processing difficulties, respectively, in individuals with ASD. Another important point is that differences in functional connectivity in specific brain regions may also vary depending upon the age of the cohort.

One study using seed-based correlation showed reduced functional connectivity between the dentate nucleus and the other cortical brain regions including the middle frontal gyrus, superior temporal gyrus, precentral gyrus, supramarginal gyrus and angular gyrus in adults with high-functioning autism relative to controls. This finding suggested that the aberrant functional connectivity in some social brain regions associated with social processing may also underlie the differences in heterogeneous conditions of ASD (Olivito et al., 2017). In an attempt to test the relationship between the functional connectivity of specific brain regions and theory of mind and mirror neuron deficits, Fishman and colleagues found increased (medial prefrontal cortex and posterior cingulate cortex) and reduced (temporo-parietal junction) patterns of altered functional connectivity using the extrinsic network connectivity in the fronto-parietal regions in individuals with ASD, related to the social interaction and communication domains (Fishman et al., 2014). In another study, Monk and colleagues used regions of interest-based analysis to assess the differences in intrinsic functional connectivity of default mode brain regions between individuals with ASD and controls (Monk et al., 2009). This study showed stronger connectivity between the posterior cingulate cortex and temporal lobe, posterior cingulate cortex and parahippocampal gyrus in individuals with ASD relative to controls, which suggested a different pattern of altered functional connectivity in ASD. These empirical findings of atypical functional connectivity in the default mode network support the idea that the theory of mind deficits may be more pronounced in individuals with ASD compared to controls.

Some previous studies have reported atypical functional connectivity (reduced and increased) limited to the resting state networks including the default mode network, salience network including the insula, and medial temporal lobe including the amygdala (Assaf et al., 2010; von dem Hagen et al., 2013) associated with higher autistic traits. The functional connectivity of these resting state networks and their relationship to autistic traits are being examined increasingly in an

attempt to identify potential neuroimaging biomarkers. A recent study showed that the large-scale brain networks including the anterior salience network, medial motor network and orbitofrontal cortex network are implicated with-in network connectivity and higher autistic traits across neurotypicals and individuals with ASD (Oldehinkel et al., 2019). In addition, there are a number of resting state fMRI studies that have demonstrated the relationship between atypical functional connectivity and higher autistic traits using various methodological approaches, such as seed-based analysis and graph theory (Di Martino et al., 2009; Itahashi et al., 2014; von dem Hagen et al., 2011). One previous study using a graph theory approach showed differences in path length characteristics and network efficiencies (metrics used to measure connectivity based on the distance between different brain regions), reflecting reduced functional connectivity between the anterior cingulate cortex and posterior cingulate cortex related to autistic traits in the general population (Jakab et al., 2013). In another study, Di Martino and colleagues found increased functional connectivity between the pregenual anterior cingulate cortex, anterior insula, posterior cingulate cortex and precuneus, whereas reduced functional connectivity in the dorsal attention networks and supplementary motor cortex, associated with autistic traits in typical adults (Di Martino et al., 2009). Previous studies suggest that these differences in functional connectivity may arise as a result of using different analytical approaches, sample characteristics (age group and sample size) and heterogeneous conditions in ASD (PDD-NOS, Asperger's syndrome, high-functioning autism and classic autism) as well as different fMRI paradigms.

From the literature, we understand that ASD may be associated with atypical functional connectivity in different resting state networks related to theory of mind (Padmanabhan et al., 2017), execution of goal-oriented behaviour (Uddin, 2015), visuomotor coordination (Chen et al., 2018), visual attention (Just et al., 2012; Watanabe & Rees, 2016a), sensory and communication deficits (Hitoglou et al., 2010) and visual processing difficulties (Chen et al., 2015). There is evidence showing that the majority of the resting state networks included in our study have atypical functional connectivity in individuals with ASD compared to controls (Bi et al., 2018). However, none of the studies in the literature have examined the relationship between the intrinsic network connectivity of these eight resting state networks in relation to autistic traits in the general population.

There is a key gap in the literature: the altered functional connectivity has been primarily investigated in the default mode, salience and medial temporal lobe network because of their close relationship with the broader autism phenotype (von dem Hagen et al., 2013; Elizabeth Redcay et

al., 2013). However, there is evidence suggesting atypical functional connectivity in the other networks including fronto-parietal network (Redcay et al., 2013), medial and lateral visual network, auditory, sensorimotor network (Cerliani et al., 2015) in individuals with ASD relative to controls. To address these issues, we aimed to investigate the relationship between the intrinsic functional connectivity of the eight resting state networks (Fig. 4.1) including the medial visual network (MVN), lateral occipital visual network, auditory, sensorimotor, default mode network (DMN), executive control network (ECN), and right and left-lateralised fronto-parietal networks (RFPN and LFPN) (Beckmann et al., 2005) related to the autistic traits in the general population. We hypothesised that differences in intrinsic network connectivity in these eight RSN observed in individuals with ASD may also be seen in individuals with autistic traits in the general population.

Table 4.1 List of Beckmann's resting state networks

	Beckmann's RSN	Brain regions
a.)	Medial occipital visual network	Mainly includes calcarine sulcus
b.)	Lateral occipital visual network	Mainly includes occipital pole
c.)	Auditory network	Heschl's gyrus and superior temporal gyrus
d.)	Sensory motor network	Motor cortex, Precentral and postcentral gyri
e.)	Default mode network	Medial prefrontal, posterior cingulate cortex and precuneus
f.)	Executive control network	Anterior cingulate and ventrolateral prefrontal cortex
g.)	Right fronto-parietal network	Superior and middle frontal gyri, inferior parietal cortex and intraparietal sulcus (Right)
h.)	Left fronto-parietal network	Superior and middle frontal gyri, inferior parietal cortex and intraparietal sulcus (Left)

Beckmann's resting state networks including different brain regions (Beckmann et al., 2005).

4.2 Methods and materials

4.2.1 Participants

The second phase of the data collection included fifty-six neurotypical adults (aged 18-60 years, 28 males and 28 females) recruited from the university campus and local areas in Reading. Participants were screened for any head injuries, neuropsychiatric and neurological conditions,

and only the participants meeting the inclusion criteria were included in the study. As a requirement, autism spectrum quotient (AQ) scores were also collected from all the participants. This study was approved by the University Research Ethics Committee (UREC), University of Reading.

Table 4.2 Participant characteristics

Characteristics	**Neurotypicals (N=56)**	
	Mean	**SD**
Age	33.357	8.704
Gender (m/f)	28/28	
AQ	16.536	7.336

N-Number of subjects, Standard deviation

4.2.2 MRI data collection

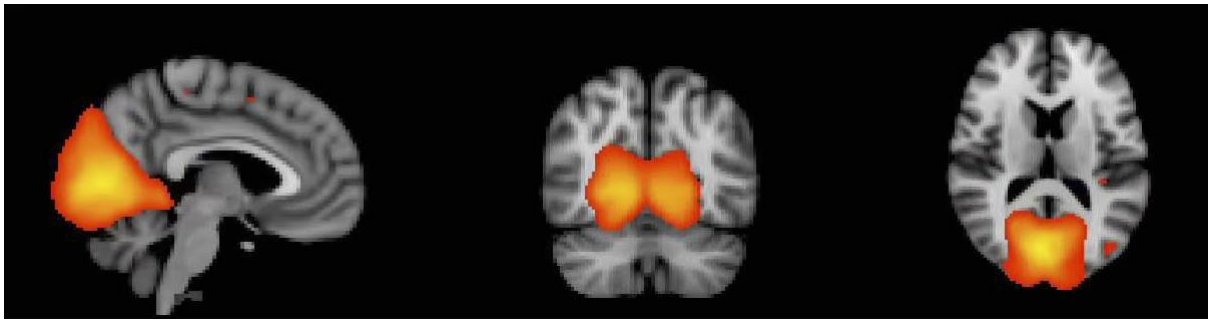
Siemens Trio 3T MRI scanner with 32-channel head coil was used to acquire the resting state functional magnetic resonance imaging (rs-fMRI) dataset in an opened eyes condition at the Centre for Integrative Neurosciences and Neurodynamics (CINN). The rs-fMRI protocol included T2* -weighted gradient echo, echo planar imaging sequence with the following parameters: (T_R = 1500 ms; T_E = 30 ms, voxel size = 2 x 2 x 2 mm, field of view = 192 x 192 mm, flip angle = 66 degrees, number of volumes = 300). High resolution T1-weighted structural MRI (MPRAGE) dataset was acquired including (T_R = 2400 ms, T_E = 2.41 ms, voxel size = 0.7 x 0.7 x 0.7 mm, field of view = 224 x 224 mm, matrix = 256 x 298 mm, flip angle = 8 degrees).

4.2.3 ICA preprocessing

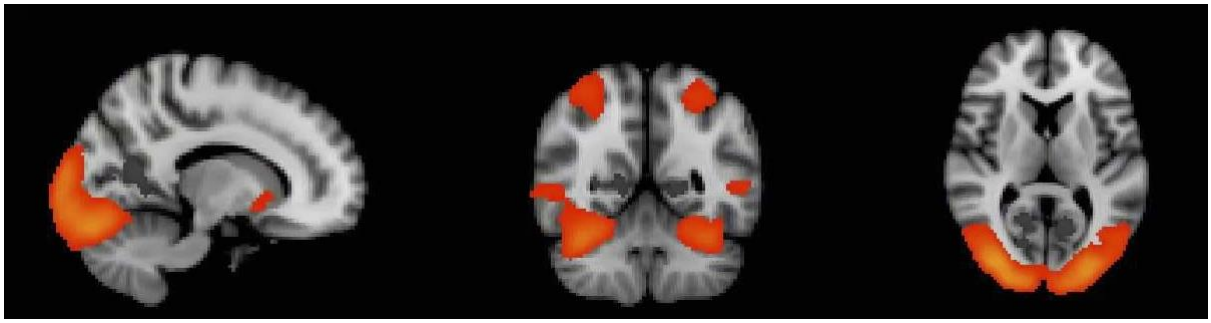
The resting state functional MRI images were preprocessed using Multivariate Exploratory Linear Optimised Decomposition into Independent Components (MELODIC) incorporated in the FSL FMRIB data analysis package and analysed using standard dual regression pipeline (Beckmann et al., 2009; Filippini et al., 2009). The first five volumes from the individual fMRI dataset were discarded. Then, all the rs-fMRI images were corrected for slice timing, magnetic field susceptibility and head motion (MCFLIRT) and the non-brain tissues were removed using the brain extraction tool (BET). Subsequently, these rs-fMRI images were co-registered to the native T1-weighted structural image space using linear registration (FLIRT) and further registering it to

the MNI152 standard template using non-linear registration (FNIRT). The intensity normalisation was applied to all the fMRI images to maintain a consistent mean signal across all the volumes. Temporal filtering was applied on the normalised fMRI data by using the default high pass filter (100 secs) to eliminate high frequency noise signals caused by physiological motion artefacts. Spatial filtering was applied by a Gaussian smoothing kernel with full width at half maximum (FWHM=5mm) to average the signal intensity of local neighbourhood voxels. These preprocessed individual fMRI dataset were denoised using ICA-based cleaning to remove possible confounding signals (WM, CSF, subject motion and other physiological artifacts). All the subjects' cleaned fMRI datasets were used to create a 4D concatenated group-ICA template (melodic_IC.nii.gz). Based on the eight resting state networks (Beckmann et al., 2005), we carefully extracted the corresponding eight independent components of interest by using cross-correlation from the group ICA output for the dual regression analysis and discarded the rest of them.

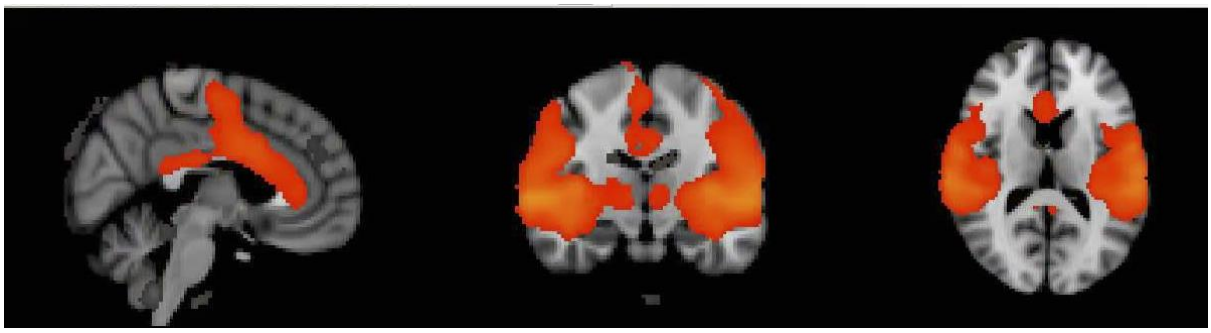
(a) Medial occipital visual network



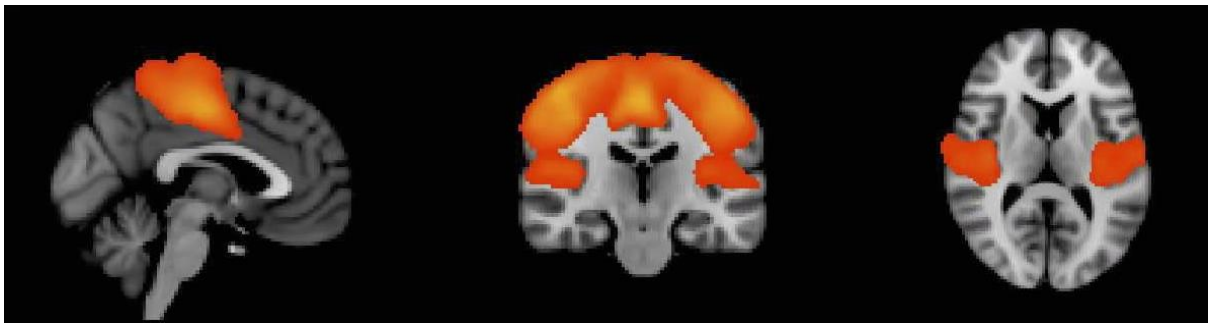
(b) Lateral occipital visual network



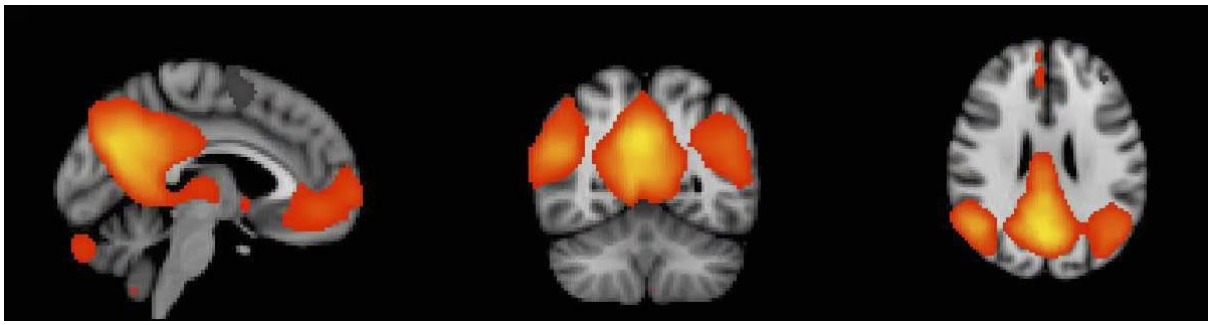
(c) Auditory network



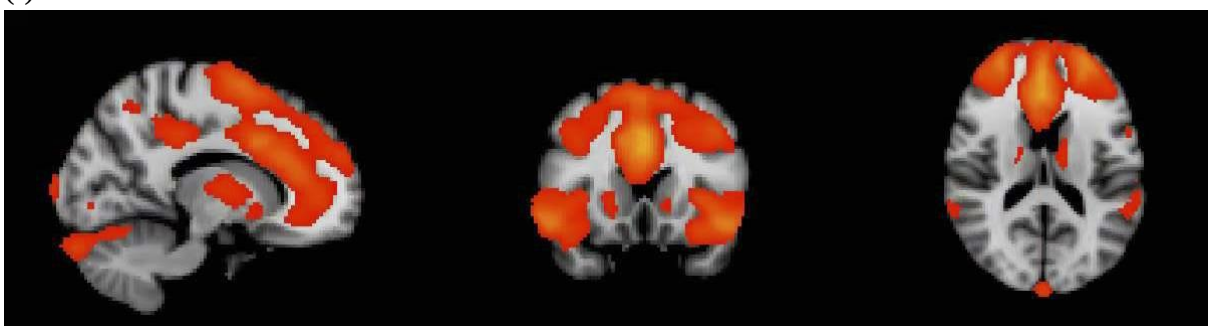
(d) Sensory motor network



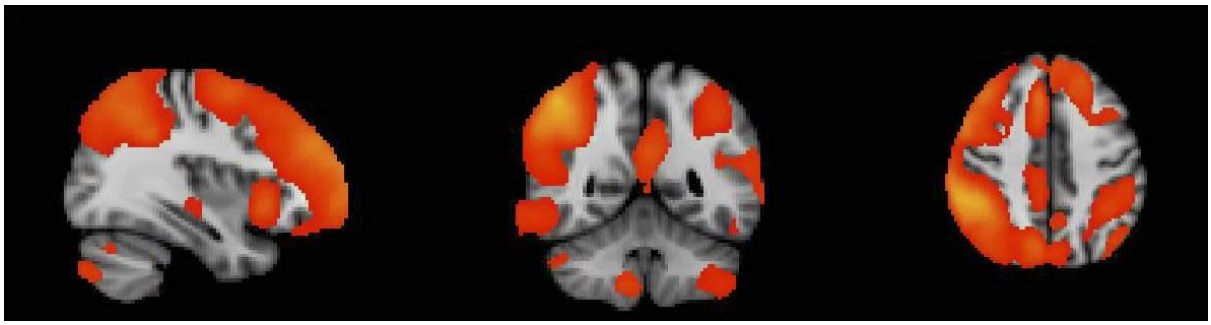
(e) Default mode network



(f) Executive control network



(g) Right fronto-parietal network



(h) Left fronto-parietal network

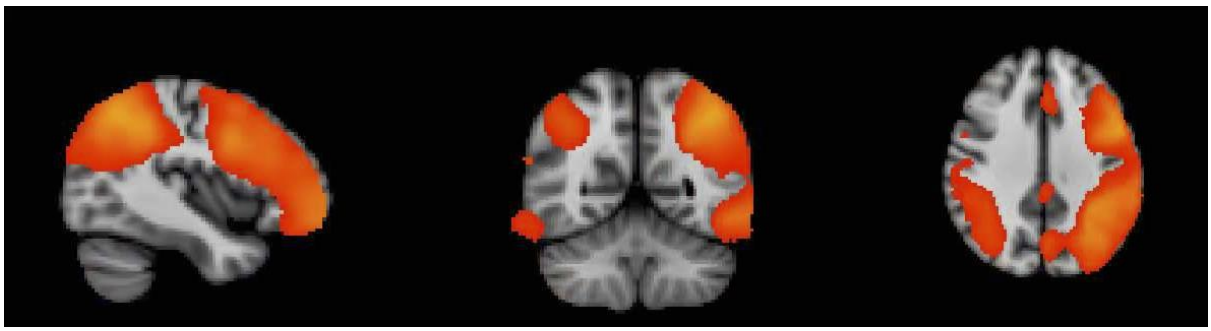


Fig. 4.1: Functional representation of Beckmann's eight resting state networks.

4.2.4 Dual regression

To determine the relationship between the intrinsic functional connectivity of Beckmann's RSN and AQ, we used dual regression analysis in this study. We applied dual regression using the 4D concatenated group ICA (8 components), the design and contrast matrix, and randomisation with (n=5000) permutations based on Threshold Free Cluster Enhancement (TFCE) (Smith & Nichols, 2009). The dual regression analysis consisted of two stages (Fig. 4.2). The first stage was the spatial regression and the second stage was temporal regression. The spatial regression was used to estimate the subject-specific time series by linearly regressing the eight component maps against the individual resting state fMRI data. The temporal regression used these subject-specific time series regressing against the individual rs-fMRI data resulting in the subject-specific spatial maps for all the eight components of interest. Using a general linear model, a design and contrast matrix was constructed by including the eight RSN as dependent variable and Autism Spectrum Quotient as a predictor variable, and age and gender as covariates of no interest.

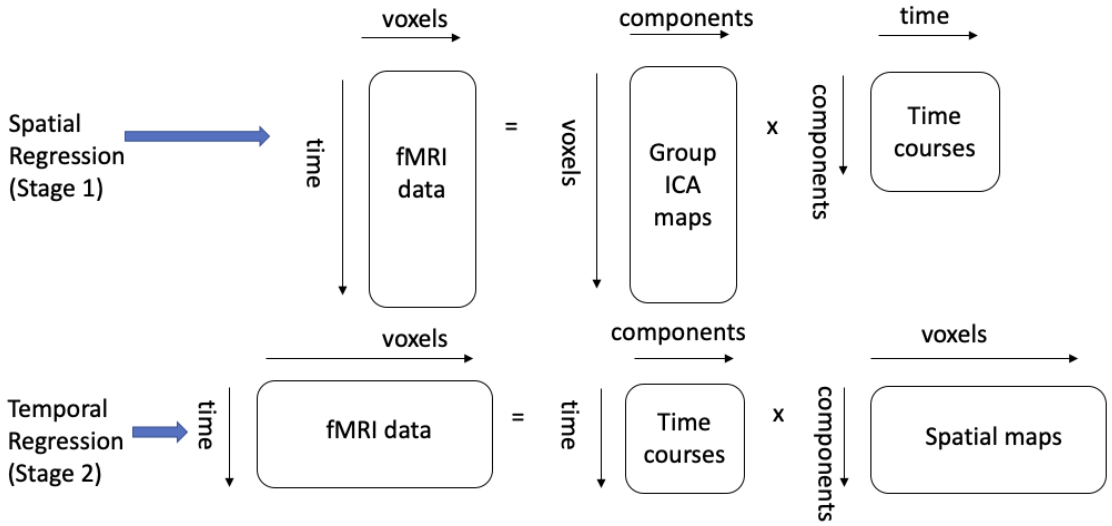
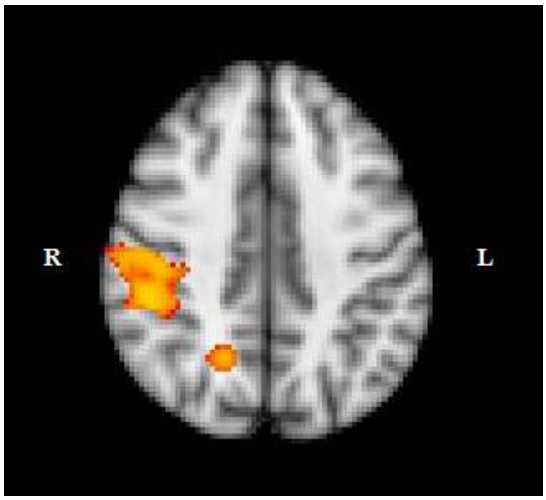


Fig. 4.2: Schematic representation of dual regression analysis: stage (1) Spatial regression and stage (2) Temporal regression (Image courtesy: Beckmann et al., 2009)

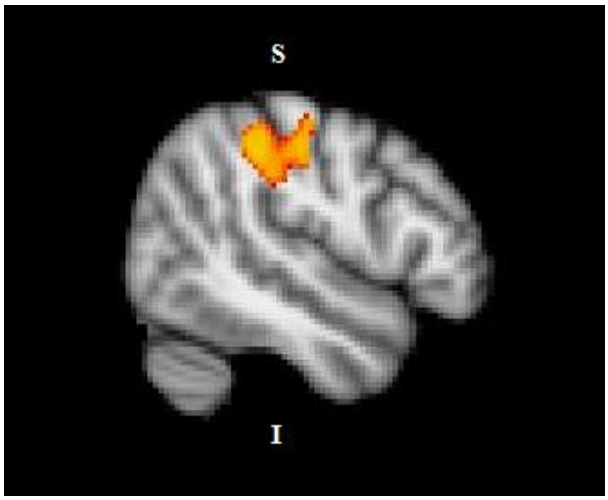
4.3 Results

4.3.1 Dual regression

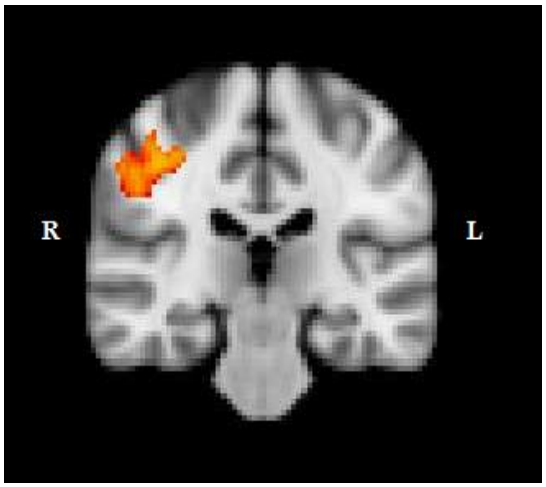
The regression analysis testing the relationship between the intrinsic resting state networks and AQ showed significantly increased functional activation associated with autistic traits within the right fronto-parietal network (supramarginal gyrus, superior parietal lobule, precuneus) across neurotypical individuals (Fig. 4.3, Table 4.3). There were no other significant positive or negative associations between any other resting state networks and autistic traits across subjects.



(a)



(b)



(c)

Fig. 4.3: Clusters (red-yellow colour) showing increased functional activation within the right Frontoparietal network (FPN) in the (a) Supramarginal gyrus (axial plane), (b) Superior parietal lobule (sagittal plane) and (c) Precuneus (coronal section).

Table 4.3 Brain regions within the frontoparietal network representing increased functional activation associated with AQ

Brain regions	Side	MNI coordinates			K_E	t-value	P-values
		x	y	z			
Supramarginal gyrus	R	46	-34	40	1191	3.4	0.007**
Superior parietal lobule	R	30	-52	62	698	3.64	0.007**
Precuneus	R	28	-56	26	33	4.27	0.03**

P-values-level of significance *p < .05, **p < .01, K_E- Cluster size, t-value - mean activation of voxels within each cluster, Threshold Free Cluster Enhancement (TFCE) corrected.

4.4 Discussion

The current study demonstrated increased functional activation associated with autistic traits within the parietal regions of the frontoparietal network in the general population. Our findings showed increased functional activation in the frontoparietal network, consistent with the findings of previous studies (Just et al., 2012; Redcay et al., 2013) in the literature.

The increased functional activation in the parietal brain regions of the frontoparietal network was seen in the supramarginal gyrus, superior parietal lobule and precuneus. However, no significant functional activations were observed in the prefrontal brain regions. First, the supramarginal gyrus, an integral part of the inferior parietal lobule, plays a crucial role in the spatial location of the objects (Samson et al., 2012). In this case, increased functional activation in this parietal cortex may be associated with disrupted dorsal (object location) and ventral (object recognition) visual pathways in individuals with ASD. Some theories have suggested that the atypical brain connectivity may arise as a result of the asynchronous temporal correlation of brain regions which are less functionally integrated in individuals with ASD (DeRamus et al., 2014). The supramarginal gyrus is an action observation network that may influence the temporoparietal junction, which also serves as a hub for social information processing deficits in individuals with ASD (Alaerts et al., 2014). The increased functional activation in the superior parietal lobule may account for the abnormal enhanced perceptual functioning in individuals with autistic traits in the neurotypical population (Kana et al., 2013). The superior parietal lobule may underlie the atypical visuospatial attention in individuals with ASD (Belmonte & Yurgelun-Todd, 2003). The increased functional activation in the superior parietal lobule may represent difficulties in attention control in individuals with ASD (Anderson et al., 2011) which may also be observed in individuals with higher autistic traits. The precuneus located in the parietal cortex is a component of the default mode network and fronto-parietal network and plays an important role in processing visuospatial cues and autobiographical memory in adults with ASD (Crane & Goddard, 2008; Utevsky et al., 2014). It is possible that the precuneus, a common brain region across different networks including DMN and FPN communicate together, which have shown increased functional activation in individuals with higher autistic traits. As such, individuals with ASD may experience more difficulty when recalling their autobiographical memory than controls (Kristen et al., 2014).

The weak central coherence theory suggests that low-level enhanced perceptual abilities co-occur with difficulties in complex information processing, which may underlie the local overconnectivity in the visual brain regions in individuals with ASD (McGrath et al., 2012). The increased intrinsic

functional connectivity in the fronto-parietal network may underlie the difficulties in top-down modulation of visual attention associated with higher autistic traits (Neumann et al., 2006; Watanabe & Rees, 2016b). The cortical overconnectivity theory suggests that the stronger functional connections of different brain regions including parietal brain regions may be associated with enhanced low-level perceptual abilities in individuals with ASD. The altered functional connectivity in the fronto-parietal networks may underlie the disrupted anatomical connectivity (Kana et al., 2011) related to autistic traits, which has also been observed in individuals with ASD. Essentially, the functional integration of these cortices may be overconnected as a result of low-level increased perceptual abilities, while receiving large sensory inputs may reflect the increased functional connectivity in individuals with ASD. This is also observed in individuals with higher autistic traits. Since this was a resting state fMRI under the eyes opened condition, it is possible that the study participants were unintentionally exposed to random visual stimuli around the scanner environment. It is likely that this would have modulated their visual attention, which may account for the increased functional activations in the fronto-parietal network, specifically the parietal brain regions related to enhanced perceptual functioning in the neurotypical population. Further analytical approaches such as extrinsic network connectivity across other different resting state networks may be useful in examining the functional connectivity of the common brain regions overlapping across different resting state networks. This may provide insight into the atypical brain connectivity associated with autistic traits.

Collectively, the current study's findings suggest that increased functional activations in the fronto-parietal networks may underlie top-down modulation of visual attention related to autistic traits, which has also been observed in individuals with ASD. Our findings provide support for and shed light on the theory of atypical brain connectivity in association with autistic traits in the general population.

Chapter 5: General discussion

General discussion

5.1 Brief summary

The majority of the previous studies used a case-control design to investigate the differences in neuroanatomical and functional brain abnormalities between individuals with ASD and neurotypicals. However, growing evidence suggests that autistic traits are distributed continuously across the general population, whilst the extreme end of the distribution is diagnosed as clinical ASD (Colvert et al., 2015). Indeed, the structural and functional brain differences reported in individuals with clinical ASD have also been observed in individuals with higher autistic traits, even if they did not have a clinical diagnosis. Further evidence suggests that the brain abnormalities associated with higher autistic traits are not limited to one brain region or metric. Taking this into account, the neuropathology in grey matter can be indexed using measures of grey matter volume, cortical thickness, surface area and gyrification. Similarly, atypicalities in WM microstructure can be captured using measures of fractional anisotropy and mean diffusivity. Considering this, the atypical structural connectivity may underlie the aberrant functional connectivity in individuals with higher autistic traits. In addition, several reports concluded with inconsistent findings, thereby reflecting the heterogeneity of brain imaging data quality and various analytical approaches (Brun et al., 2009; Kazeminejad & Sotero, 2018; Koolschijn et al., 2015). Taking these factors into consideration, structural MRI, DTI and rs-fMRI were used to address our research question. As such, we sought to examine the relationship between the brain structure and function and autistic traits across the combined sample of individuals with ASD and neurotypicals/neurotypicals.

The main aim of our study was to examine the relationship between the structural and functional brain connectivity associated with higher autistic traits using a dimensional approach. To accomplish this, with respect to our first research question, we used voxel-based morphometry and surface-based morphometry to assess the different metrics of grey matter including grey matter volume, cortical thickness, surface area and gyrification. In our second research question, we used diffusion tensor imaging to examine the white matter microstructure with two different analytical approaches: skeleton-based tracts of interest and tract-based spatial statistics. In our third research question, we used resting state functional MRI to assess the intrinsic functional connectivity within eight resting state networks (Beckmann et al., 2005).

Table 5.1: Summary of the structural and functional brain imaging findings related to autistic traits

Research questions	Analytical approaches	Brain imaging findings
Relationship between the regional GMV and cortical folding abnormalities and autistic traits across the diagnostic divide	Voxel-based morphometry	Negative association between the regional GMV and AQ in the right OFC. Positive association between the regional GMV and AQ in the right lingual gyrus, precentral gyrus and bilateral putamen.
	Surface-based morphometry	Positive association between the cortical thickness, cortical volume and AQ in the left lingual gyrus, right lateral occipital and right pars triangularis. Positive association between the surface area and AQ in the right lateral occipital cortex. Positive association between the gyrification and AQ in the right lingual gyrus.
Relationship between the white matter microstructure and autistic traits across the diagnostic divide	Skeleton-based tracts of interest	Negative association between the fractional anisotropy and AQ in the right inferior longitudinal fasciculus.
	Tract-based spatial statistics	Negative association between fractional anisotropy and AQ in the right superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and left corticospinal tract. Positive association between MD and AQ in the right superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum.

Relationship between functional connectivity and autistic traits in the general population	Dual regression analysis	Positive association between the intrinsic right fronto-parietal network (in the parietal regions) and AQ.

5.2 Discussion of grey matter metrics

Based on our primary research questions, we sought to identify the neural correlates of autistic traits across the clinical and non-clinical population. Our study findings were consistent with previous reports on structural (grey and white matter) and functional connectivity in ASD. We found widespread grey matter differences, specifically in some of the social brain regions, which suggested that the neuropathology underlying grey matter may play a significant role in the development of higher autistic traits. The orbitofrontal cortex constitutes a part of the social brain regions (Pelphrey et al., 2011), whereas the pars triangularis located in the inferior frontal gyrus is involved in acquiring language function and may be impaired in individuals with higher autistic traits (Knaus et al., 2009). Other studies have found that the frontal lobe brain regions, including the orbitofrontal cortex and pars triangularis, play an important role in acquiring socio-communication skills. These grey matter differences in the frontal lobe brain areas are consistently affected in individuals with ASD.

The VBM and SBM results showed a relationship between the lingual gyrus and higher autistic traits. The lateral occipital cortex and bilateral putamen were revealed to have a positive association in the SBM and VBM, respectively. These occipital brain regions are believed to play an important role in the visual information processing, whereas the putamen plays an important role in the stereotyped behaviours in individuals with higher autistic traits. Previous studies have suggested that these grey matter differences may underlie the early abnormal brain enlargement in individuals with ASD (Carper et al., 2002; Carper & Courchesne, 2005).

Early abnormal brain overgrowth in individuals with ASD is a multistage process which may start in the prenatal or postnatal stages of human life. The neuropathology of ASD brains may involve abnormal cell proliferation, neurogenesis, neuronal migration and synaptogenesis, which may vary at different stages of infanthood, childhood, adolescence and adulthood (Courchesne et al., 2020). These brain abnormalities may be widespread/localised in the specific brain regions depending

upon the heterogeneity, severity and the occurrence of comorbid conditions. One possible explanation for the increase in cortical thickness in the pars triangularis and reduced grey matter volume in the orbitofrontal cortex may be alterations in the size and number of pyramidal neurons in minicolumns of the inferior frontal gyrus, which may be associated with social communication difficulties (Varghese et al., 2017) in individuals with higher autistic traits. These grey matter differences in the social brain regions may reflect the atypical social behaviour in individuals with ASD/higher autistic traits.

The most interesting finding was the reduced regional GMV in the orbitofrontal cortex related to higher autistic traits. This finding broadly supports the work of previous studies linking the neural model of the social brain (Brothers, 1990) with the theory of mind deficits hypothesis in autism (Baron-Cohen et al., 1999). The OFC is believed to play a significant role in learning and developing abilities of social intelligence (Jonker et al., 2015). The dysfunction of OFC may underlie the TOM deficits in individuals with ASD. Therefore, the grey matter differences in the OFC may hinder the ability to judge one's own and others' thoughts in individuals with ASD. The reduced regional GMV in the medial prefrontal cortex has been consistently reported in individuals with ASD and has also been observed in individuals with higher autistic traits (Umeda et al., 2010). The disruptions in the frontal lobe social brain regions may be related to variation in specific ASD risk genes. In light of this, the reduced GMV may occur as a result of aberrant CNTNAP2 (neurexin family) which may underlie the TOM deficits in individuals with ASD (Tan et al., 2010).

Another important finding was the increased regional GMV of the bilateral putamen related to higher autistic traits. This finding also corresponds with the findings of previous studies (Langen et al., 2009, 2014) showing increased regional GMV of the putamen in individuals with ASD. The putamen (part of striatum) plays a significant role in restricted and stereotyped behaviour in individuals with ASD. Individuals with ASD are found to be more obsessed with a narrow range of interests/stereotyped behaviours. Previous evidence suggests that disrupted brain structures in the striatum are associated with restricted and repetitive behaviours in individuals with ASD. This increased regional GMV in the putamen may be related to the overexpression of the dopamine 3-receptor gene, which may lead to stereotyped behaviours in individuals with ASD (Staal et al., 2015). The aberrations in DRD3 gene may underlie the shared behavioural abnormalities associated with the stereotyped behaviours in ASD, ADHD and OCD (de Krom et al., 2009). Therefore, the dopamine regulation implications in the fronto-striatal brain regions may

predominantly influence repetitive and stereotyped behaviours (Staal et al., 2015) as seen in individuals with ASD/higher autistic traits.

The orbitofrontal cortex and putamen together are believed to play a crucial role in reward processing. However, implications in the later brain regions may underlie reward processing difficulties in individuals with ASD. This evidence suggests that individuals with higher autistic traits may fail to respond to reward processing associated with impairments in the fronto-striatal system (Langen et al., 2012). This involves a liking/wanting feedback mechanism between the OFC and striatum (Kohls et al., 2012), which may enhance motivation for social interaction and communication. The OFC is believed to be involved in liking, whereas the striatum is involved in wanting. However, the grey matter differences in this fronto-striatal system may be associated with atypical reward processing (Kohls et al., 2014) in individuals with higher autistic traits.

In chapter 2, both VBM and SBM findings showed increased grey matter volume, cortical thickness and gyrification in the lingual gyrus associated with higher autistic traits. This finding is consistent with previous reports of structural atypicalities in this region in ASD individuals, including greater GMV (Ecker et al., 2010a) and greater local gyrification (Libero et al., 2019). The lingual gyrus plays an important role in the visual information processing in individuals with ASD. Increasing evidence suggests neuroanatomical alterations in the lingual gyrus in individuals with ASD (Caeyenberghs et al., 2016; Ecker et al., 2013; Hyde et al., 2010; Levman et al., 2019; Libero et al., 2019; Van Rooij et al., 2018). However, the neurobiology underlying the alterations in this specific brain region in ASD has not been thoroughly examined. This can be explained by the fact that the other crucial neighbouring brain region, the fusiform gyrus located in the posterior temporo-occipital area, has received more attention than the lingual gyrus which is believed to serve a similar purpose of information processing about the face identity in individuals with ASD.

VBM and SBM were used to measure the differences in regional GMV and surface curvature, and the degree of cortical foldings, respectively. Fundamentally, cortical volume, thickness, surface area and gyrification are different metrics of grey matter. By definition, we know that cortical volume is a product of cortical thickness and surface area (Yang et al., 2016). In light of this, our SBM findings (lingual gyrus, lateral occipital cortex and pars triangularis) also concord with the previous definition of cortical volume and the distinct aetiology related to cortical thickness and surface area in individuals with higher autistic traits. However, the cortical volume and other three surface-based measurements follow a different developmental trajectory throughout the course of brain development (Li et al., 2017; Mahajan & Mostofsky, 2015) in individuals with ASD/higher

autistic traits. Our regional GMV findings as measured by VBM are different from SBM which measured cortical thickness, surface area, volume and gyrification. This indicates the existence of some methodological differences (measuring surface curvature and volumetric) between SBM and VBM, which might account for the observed differences in the grey matter findings. Having said this, some important brain regions from our study were also widely reported in the previous studies on autism. According to the radial unit hypothesis, the cortical surface area is related to the number of minicolumns, whereas the cortical thickness is related to the number of cells within the columns. In fact, the cortical volume is more driven by the cortical surface area than the cortical thickness (Panizzon et al., 2009). Most importantly, the cortical thickness and surface area may underpin a dissociable genetic basis, especially in neurodevelopmental conditions like ASD (Li et al., 2017). Therefore, it is highly advantageous to use both VBM and SBM to explore the grey matter properties in individuals with ASD/higher autistic traits.

It has been established in previous studies that whole/regional structural brain differences in individuals with ASD may also vary across different age groups (Carper & Courchesne, 2005; Courchesne, 2002; Courchesne et al., 2011a; Zielinski et al., 2014). Abnormal brain overgrowth is found to be higher in young children followed by growth arrest in later childhood, declining from adolescence to adulthood. These age-related structural brain differences may be driven by the differences in genetic factors associated with cortical morphology in individuals with ASD (Courchesne et al., 2011a; Geschwind & Levitt, 2007b). On the other hand, previous studies have shown differences in sex that indicate autism is biased in favour of males rather than the females (Ferri et al., 2018; McCarthy & Wright, 2017). Indeed, structural brain differences in the frontal and temporal cortices have been found in males, but not in females with ASD (Lai et al., 2017). Further, the elevated levels of testosterone interacting with different neurotransmitters may underlie the differences in neurogenesis and synaptic pruning in males, which could possibly lead to higher autistic traits. Some evidence also supports neuroanatomical alterations in the key social brain regions including the orbitofrontal cortex and amygdala. These alterations reflect the differences in empathising and systemising abilities associated with the extreme brain theory hypothesis and are suggestive of higher autistic traits (Focquaert & Vanneste, 2015).

One common critique of studies that have identified sex differences in autism is that some studies recruit a lower number of females as they may be less interested/anxious to participate in research. However, since our focus was the relationship between brain structure and autistic traits, we co-variated out the effects of age and gender in our analysis.

In summary, the regional grey matter differences may reflect the atypical social and stereotyped behaviours in individuals with ASD, also seen in individuals with higher autistic traits. These grey matter differences may also influence the regional brain volume alterations which may be age-dependent in individuals with ASD. The neuroanatomical alterations associated with sex differences, especially in high-risk ASD males, may be an indication of higher autistic traits. These structural brain differences may underlie the genetic factors in individuals with ASD. Based on the evidence from this study, atypical structural and functional brain networks may be associated with higher autistic traits.

5.3 Discussion of white matter microstructure

With respect to the second research question, using skeleton-based TOI, our results revealed a negative association between the fractional anisotropy of the right inferior longitudinal fasciculus and higher autistic traits. Using TBSS, our results revealed a negative association between fractional anisotropy and higher autistic traits in the right superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and left corticospinal tract. A positive association was observed between MD and higher autistic traits in the right superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and corpus callosum. However, the right inferior longitudinal fasciculus had a larger set of clusters compared to the other major white matter fibre tracts from both the skeleton-based TOI and TBSS analysis. This finding is in line with previous case-control studies in individuals with ASD (Jou et al., 2011; Shukla et al., 2011).

In general, white matter microstructures have increased fractional anisotropy and reduced mean diffusivity, representing normality in neurotypicals. On the contrary, our findings identified reduced fractional anisotropy and increased mean diffusivity in the major white matter microstructures in individuals with higher autistic traits. These differences in fractional anisotropy and mean diffusivity may reflect abnormal axonal thinning and reduced myelination, representing atypical white matter microstructures which are seen in individuals with ASD. The disruption in the ILF also overlaps with IFOF. In fact, these latter adjacent major WM association fibres connect the ventral part of the social brain regions, extending across the frontal, temporal and occipital lobes. Certainly, the white matter microstructure abnormalities in the ILF and IFOF may possibly reflect the differences in connectivity as reported in individuals with ASD. These white matter microstructure differences in the inferior longitudinal fasciculus may play an important role in atypical visual information processing in individuals with higher autistic traits.

Although the ILF showed a negative association between FA and autistic traits in both skeleton-based TOI and TBSS, the clusters did not survive after multiple comparison correction. Surprisingly, this study was unable to demonstrate the relationship between the other association fibres (SLF, UF) (Catani et al., 2016; Libero et al., 2016; Shukla et al., 2011), commissural fibre (corpus callosum) and the projection fibre (CST) (Fitzgerald et al., 2019; Vogan et al., 2016) and autistic traits. This inconsistency may underlie the differences in several methodological factors. For instance, significant grey matter differences were observed in the VBM and SBM study (relatively large sample size), but the skeleton-based TOI and TBSS did not show major differences in the other major white matter microstructures, which may reflect the differences in sample size of our study.

To summarise, white matter microstructure abnormalities in the right inferior longitudinal fasciculus may be related to atypical visual information processing in individuals with higher autistic traits. However, the absence of association in other white matter tracts may be due to the inadequate sample size.

5.4 Intrinsic network connectivity

The third research question in our study sought to determine the relationship between the intrinsic network connectivity of eight resting state networks and autistic traits in the general population. Our intrinsic network connectivity findings revealed a positive association only in the fronto-parietal network (FPN). The significant clusters were found in the superior parietal lobule, supramarginal gyrus and precuneus in the parietal regions of right FPN. The relationship between increased functional activation and autistic traits in the parietal brain regions of FPN in this study corroborates earlier findings (Plitt et al., 2015). These brain regions constitute a network which is believed to be involved in atypical visual attention in individuals with ASD (Keehn et al., 2013; Minshew & Keller, 2010; Riedel et al., 2017). This finding also emphasises the crucial importance of the BOLD activation in the SPL, SMG and precuneus related to autistic traits in the general population.

Increasing evidence has suggested that atypical functional connectivity in the fronto-posterior brain regions may be related to difficulties in complex perceptual processing in individuals with ASD. Previous studies have investigated the functional connectivity of the FPN, considering it as a task-related network in individuals with ASD. However, other studies (Kennedy & Courchesne, 2008), have incorporated FPN as one of the more important resting state networks by

hypothesising that this network could also influence different patterns of activation without task-related paradigms in individuals with autistic traits (Oldehinkel et al., 2019). In agreement with this, our study demonstrated increased activations at rest in the parietal regions of FPN related to autistic traits. This finding suggested that this pattern of increased activations in the resting state networks does not only occur during task-related paradigms but can also occur without task-related paradigms.

Contrary to our expectations, this study did not find a significant association between the functional connectivity of the other seven RSNs (medial visual network (MVN), lateral occipital visual network, auditory, sensorimotor, default mode network (DMN), executive control network (ECN), left-lateralized FPN) and autistic traits. These other seven RSN findings were not consistent with findings from previous studies (Di Martino et al., 2009; Oldehinkel et al., 2019; von dem Hagen et al., 2011). Our findings also challenge the relationship between intrinsic functional networks and autistic traits in the general population. It is little difficult to explain this, nevertheless autistic traits may only modulate certain RSN or there may exist unknown patterns of age effects interaction (Plitt et al., 2015). One factor that could have contributed to the absence of significant differences in intrinsic network connectivity may be the absence of individuals with clinical ASD. This could also have been due to the inadequacy of the sample size of the general population, which may have affected the statistical power for all the other RSN. Considering this, further research should be undertaken to investigate the relationship between the functional connectivity hypothesis and autistic traits across the diagnostic divide.

5.5 Commonalities and differences across grey matter, white matter and functional connectivity

The findings from this study make reasonable contributions in understanding the differences in brain structure and functional networks and provide a basis for neural correlates of autistic traits across the clinical and non-clinical population. The regional grey matter findings from VBM and SBM are partially consistent with the white matter microstructure findings according to the literature review. However, the differences in intrinsic network connectivity from the resting state fMRI study did not comply with the findings from the grey and white matter microstructure study. This could be accounted for by the samples being from different sources. This work especially contributes to the existing knowledge of the social brain hypothesis by providing empirical evidence for the association between regional grey matter and higher autistic traits.

5.6 Neurobiological factors driving the ASD and autistic traits

ASD is highly genetic and the neurobiological factors associated with brain development still remain unclear. As stated earlier, the grey/white matter differences may account for the abnormal brain development in ASD. In this case, the white matter microstructures may be susceptible to certain gene variants (FMR1 and NRXN1) in individuals with ASD (Rowley et al., 2019). The fragile X mental retardation protein plays an important role in synaptic development, axonal growth and myelin synthesis in oligodendrocytes, whereas the precursor of neurexin is crucial for the formation of the Neurexin/neuroligin complex at synapses. The reduced FMR1 and NRXN1 proteins may underpin the axonal growth dysregulation which may reflect the differences in white matter microstructure (ILF) reported in individuals with FXS and ASD (Green et al., 2015). The similarity in genetic aetiology shared between FXS and ASD may implicate the white matter microstructures in individuals with higher autistic traits. Although many previous studies have shown high reliability to the AQ, it may be worth using the SRS questionnaire in addition to assess the autistic traits and validate our findings with both questionnaire measures.

Many twin-, family- and population-based studies support the evidence that hereditary characteristics underlying genetic factors are highly prevalent in ASD. Although there are a number of autism risk genes reported in the literature on idiopathic ASD, only 20% of genetic factors account for de novo mutations in individuals with ASD. The abnormalities in the specific brain regions (social brain) may be associated with specific ASD risk genes. Some human post-mortem brain studies have suggested that the minicolumnopathy (associated with an increase in number of neurons and density) may underlie the cortical disorganisation in individuals with ASD. This aberrancy in the cerebral cortex may be influenced by autism risk candidate genes in ASD (M. F. Casanova, 2006). Further the genetically modified animal model also supports the evidence that the ASD risk genes (Neurxin, neuroligin, contactin associated protein 2 (CNTNAP2), SHANK3, Fragile X and MECP2) and deletion and duplication of copy number variants (15q11-13) may play a crucial role in the neuropathology of ASD (Varghese et al., 2017). Another possible explanation for this is that the GABAergic and glutamatergic interneurons in the neocortex synthesise neurotransmitters, which play a crucial role in facilitating neural migration and synaptogenesis. It is possible that glutamate/GABA ratio imbalance may account for the neuropathology of the grey matter, which may in turn disturb the cortical connectivity in individuals with ASD. Therefore, all these neurobiological factors, including the differences in

minicolumn cytoarchitecture, genetics and neurotransmitters, may affect the aetiology associated with ASD and higher autistic traits.

5.7 Limitations and future directions

Since the study was limited to the adult population, it was not possible to assess the differences in age interaction effects across children and adolescents. In addition, the MRI data collection in multiple phases (for structural MRI and DTI) and different data sources (resting state fMRI) with varied protocols was another limitation in this study. The sample size for the white matter microstructure study (chapter 3) was limited to the best of its DTI data acquisition protocol. Another limitation was lack of clinical ASD samples to assess the resting state networks (chapter 4), which may have influenced the statistical power in the data analysis. The scope of this study was limited to autistic traits and lacked other behavioural data like Autism Diagnostic Interview-Revised (ADI-R).

Till date, Autism spectrum Quotient (AQ) is used to measure the autism-like traits in the clinical and non-clinical population for research purposes, but not for clinical purposes. It is now certainly understood that ASD is driven by shared neurobiological differences (Casanova, 2006; Varghese et al., 2017). However, AQ provides us with different subscale measures of autistic traits, but it does not provide biologically meaningful information related to autistic symptoms and therefore not a greater predictor for Autism diagnosis. Alternatively, Research Domain Criteria (RDoC) developed by National Institute for Mental Health (NIMH) suggests that treating the neurodevelopmental conditions like autism spectrum disorders as a category based on the unitary behavioural diagnostic outcome are heterogeneous and it is not very much helpful in developing novel target treatments (Insel et al., 2010). According to the RDoC, to address this key issue, future researches should highly focus on understanding the neuroimaging and other neurobiological mechanisms underlying ASD (Insel, 2014). In light of this, our future research will pay more attention to the application of neuroimaging, genetics, neurophysiology, biochemistry study to understand the neurobiological underpinnings of autism. This could potentially provide us insights towards understanding the pathophysiology of autism and lead to the development of novel target therapeutic interventions for autism.

5.8 Conclusion

In this thesis, we used different brain imaging techniques (structural MRI, diffusion tensor imaging, resting state functional MRI) and various analytical approaches to examine the relationship between regional grey matter properties, white matter microstructure and intrinsic network connectivity and higher autistic traits, using a dimensional approach. Our results demonstrated clear differences in regional grey matter, white matter microstructure properties and functional connectivity related to autistic traits.

The widespread grey matter differences (including the right orbitofrontal cortex, pars triangularis, precentral gyrus, lingual gyrus, lateral occipital cortex and bilateral putamen) as measured by regional GMV, cortical thickness, surface area and gyrification may underlie the atypical cortical laminar and columnar cytoarchitecture properties associated with higher autistic traits. The complex neuropathology underlying the latter grey matter properties provided us with greater insight into the neurobiology of cortical and subcortical grey matter influencing social behavioural abnormalities in individuals with higher autistic traits. In the diffusion tensor imaging study, we explored the possible relationship between the white matter microstructural properties in the right inferior longitudinal fasciculus and higher autistic traits across the diagnostic divide. This study contributes to our understanding that reduced white matter microstructure integrity in the ILF may manifest the atypical visual information processing associated with higher autistic traits across neurotypicals and individuals with ASD. In the resting state fMRI study, the increased functional activations in the parietal regions (superior parietal lobule, supramarginal gyrus and precuneus) of fronto-parietal networks may underlie difficulties in top-down modulation of visual attention associated with autistic traits in the general population, also seen in individuals with ASD.

Thus, this converging evidence provides great support for and sheds light on the long-standing structural and functional connectivity hypothesis underlying higher autistic traits. In the future, a more multidisciplinary research project (combining multimodal brain imaging techniques, genetics, biochemistry and neurophysiology) with a large sample size on the same subjects at one site will need to be undertaken – this could provide insight into the aetiology for the neural basis of higher autistic traits.

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APPENDIX I

The Adult Autism Spectrum Quotient (AQ)

The Autism Spectrum Quotient (AQ) questionnaire shown below was uploaded onto Bristol online survey (https://reading.onlinesurveys.ac.uk/personality_questionnaires-3) for participants to complete online:

Below is a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer.

1. I prefer to do things with others rather than on my own.	definitely agree	slightly agree	slightly disagree	definitely disagree
2. I prefer to do things the same way over and over again.	definitely agree	slightly agree	slightly disagree	definitely disagree
3. If I try to imagine something, I find it very easy to create a picture in my mind.	definitely agree	slightly agree	slightly disagree	definitely disagree
4. I frequently get so strongly absorbed in one thing that I lose sight of other things.	definitely agree	slightly agree	slightly disagree	definitely disagree
5. I often notice small sounds when others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree
6. I usually notice car number plates or similar strings of information.	definitely agree	slightly agree	slightly disagree	definitely disagree
7. Other people frequently tell me that what I've said is impolite, even though I think it is polite.	definitely agree	slightly agree	slightly disagree	definitely disagree
8. When I'm reading a story, I can easily imagine what the characters might look like.	definitely agree	slightly agree	slightly disagree	definitely disagree

9. I am fascinated by dates.	definitely agree	slightly agree	slightly disagree	definitely disagree
10. In a social group, I can easily keep track of several different people's conversations.	definitely agree	slightly agree	slightly disagree	definitely disagree
11. I find social situations easy.	definitely agree	slightly agree	slightly disagree	definitely disagree
12. I tend to notice details that others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree
13. I would rather go to a library than a party.	definitely agree	slightly agree	slightly disagree	definitely disagree
14. I find making up stories easy.	definitely agree	slightly agree	slightly disagree	definitely Disagree
15. I find myself drawn more strongly to people than to things.	definitely agree	slightly agree	slightly disagree	definitely disagree
16. I tend to have very strong interests which I get upset about if I can't pursue.	definitely agree	slightly agree	slightly disagree	definitely disagree
17. I enjoy social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree
18. When I talk, it isn't always easy for others to get a word in edgeways.	definitely agree	slightly agree	slightly disagree	definitely disagree
19. I am fascinated by numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree

21. I don't particularly enjoy reading fiction.	definitely agree	slightly agree	slightly disagree	definitely disagree
22. I find it hard to make new friends.	definitely agree	slightly agree	slightly disagree	definitely disagree
23. I notice patterns in things all the time.	definitely agree	slightly agree	slightly disagree	definitely disagree
24. I would rather go to the theatre than a museum.	definitely agree	slightly agree	slightly disagree	definitely disagree
25. It does not upset me if my daily routine is disturbed.	definitely agree	slightly agree	slightly disagree	definitely disagree
26. I frequently find that I don't know how to keep a conversation going.	definitely agree	slightly agree	slightly disagree	definitely disagree
27. I find it easy to "read between the lines" when someone is talking to me.	definitely agree	slightly agree	slightly disagree	definitely disagree
28. I usually concentrate more on the whole picture, rather than the small details.	definitely agree	slightly agree	slightly disagree	definitely disagree
29. I am not very good at remembering phone numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree
30. I don't usually notice small changes in a situation, or a person's appearance.	definitely agree	slightly agree	slightly disagree	definitely disagree
31. I know how to tell if someone listening to me is getting bored.	definitely agree	slightly agree	slightly disagree	definitely disagree

33. When I talk on the phone, I'm not sure when it's my turn to speak.	definitely agree	slightly agree	slightly disagree	definitely disagree
34. I enjoy doing things spontaneously.	definitely agree	slightly agree	slightly disagree	definitely disagree
35. I am often the last to understand the point of a joke.	definitely agree	slightly agree	slightly disagree	definitely disagree
36. I find it easy to work out what someone is thinking or feeling just by looking at their face.	definitely agree	slightly agree	slightly disagree	definitely disagree
37. If there is an interruption, I can switch back to what I was doing very quickly.	definitely agree	slightly agree	slightly disagree	definitely disagree
38. I am good at social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree
39. People often tell me that I keep going on and on about the same thing.	definitely agree	slightly agree	slightly disagree	definitely disagree
40. When I was young, I used to enjoy playing games involving pretending with other children.	definitely agree	slightly agree	slightly disagree	definitely disagree
42. I find it difficult to imagine what it would be like to be someone else.	definitely agree	slightly agree	slightly disagree	definitely disagree
43. I like to plan any activities I participate in carefully.	definitely agree	slightly agree	slightly disagree	definitely disagree
44. I enjoy social occasions.	definitely agree	slightly agree	slightly disagree	definitely disagree

45. I find it difficult to work out people's intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
46. New situations make me anxious.	definitely agree	slightly agree	slightly disagree	definitely disagree
47. I enjoy meeting new people.	definitely agree	slightly agree	slightly disagree	definitely disagree
48. I am a good diplomat.	definitely agree	slightly agree	slightly disagree	definitely disagree
49. I am not very good at remembering people's date of birth.	definitely agree	slightly agree	slightly disagree	definitely disagree
50. I find it very easy to play games with children that involve pretending.	definitely agree	slightly agree	slightly disagree	definitely disagree

Information sheet

Dear participant,

You might recall taking part in our research study last year on 'Investigating the impact of bilingualism on neural structure and cognition'. We thank you for your help with our research, and would like to request another favour that will take no more than ten minutes of your time. We are embarking on a new analysis to test how certain personality traits map onto individual differences in brain structure. For this purpose, we would request you to fill in an online personality questionnaire on this link. https://reading.onlinesurveys.ac.uk/personality_questionnaires-3 Please fill in your participant number in the appropriate space provided when you open the link.

All data will be anonymised prior to the analysis. If you need further information/clarification with regards to this study, please feel free to contact us at any time. If you are interested in the results of this study once we complete the analysis, please email us at v.arunachalamchandran@pgr.reading.ac.uk

Needless to say, we will be extremely grateful for your help!

best,

Varun Arunachalam Chandran
PhD in Neurosciences (Second year)
School of Psychology and Clinical language sciences
University of Reading, Reading - RG66AL
United Kingdom

Information sheet

Dear participant,

Your contribution in filling out this personality questionnaire online will be of great importance for our research in understanding the complex brain structural differences associated with certain personality traits. In doing so, you are helping our neuroscience research community to find solutions and improve the quality of day-to-day life in human behaviour. Please use your participant number when you open the link. https://reading.onlinesurveys.ac.uk/personality_questionnaires-3

We will be extremely grateful for your help!

best,

Varun Arunachalam Chandran
PhD scholar in Neurosciences
School of Psychology and Clinical language sciences
University of Reading, Reading - RG66AL
United Kingdom

List of abbreviations

ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorders
AQ	Autism Spectrum Quotient
BAP	Broader Autism Phenotype
BOLD	Blood Oxygenation Level Dependent
CDC	Centres for Disease Control and Prevention
CINN	Centre for Neurosciences and Neurodynamics
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual
DTI	Diffusion Tensor Imaging
EEG	ElectroEncephaloGram
EPI	Echo Planar Imaging
E-S	Empathising-Systemising
EQ	Empathy Quotient
FA	Fractional Anisotropy
fNIRS	functional Near Infrared Spectroscopy
FPN	Fronto Parietal Network
FSGD	FreeSurfer Group Descriptor
FWHM	Full Width at Half Maximum
GABA	Gamma Amino Butyric Acid
GLM	General Linear Model
GMV	Grey Matter Volume
HFA	High Functioning Autism
ICA	Independent Component Analysis
IFOF	Inferior Fronto-Occipital Fasciculus
ILF	Inferior Longitudinal Fasciculus
IQ	Intelligent Quotient
MD	Mean Diffusivity
MECP2	Methyl-CpG-Binding protein 2

MEG	MagnetoEncephaloGram
MPRAGE	Magnetization-Prepared Rapid Gradient-Echo
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAS	National Autistic Society
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
RF	Radio Frequency
rs-fMRI	resting state functional Magnetic Resonance Imaging
RRBI	Restricted and Repetitive patterns of Behaviours and Interests
RSN	Resting State Networks
SBM	Surface Based Morphometry
SLF	Superior Longitudinal Fasciculus
SPM	Statistical Parametric Mapping
SQ	Systemizing Quotient
SRS	Social Responsiveness Scale
TBSS	Tract Based Spatial Statistics
TFCE	Threshold-Free Cluster Enhancement
TOI	Tracts Of Interest
TOM	Theory Of Mind
UF	Uncinate Fasciculus
UREC	University Research Ethics Committee
VBM	Voxel Based Morphometry
WM	White Matter

APPENDIX II: Conference poster presentations

Association of regional brain volumes with autistic traits across the diagnostic divide: A VBM study

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Affiliations: 1 Centre for Autism, School of Psychology and Clinical Language Sciences (SPCLS), University of Reading, UK.
2 Centre for Literacy and Multilingualism, SPCLS, University of Reading, UK.
3 KIND lab, Karolinska institute, Sweden.
4 School of Mind and Brain, Humboldt University, Berlin, Germany.

University of Reading | CINN Centre for Integrative Neuroscience and Neurodynamics | CENTRE for AUTISM

BACKGROUND

- Autism spectrum Disorders (ASD) are complex neurodevelopmental conditions associated with difficulties in social interaction and communication skills, as well as stereotypic behaviour and restricted range of interests (APA, 2013).
- Some previous studies have shown group differences in volume in specific brain regions (Ecker et al., 2012, Sato et al., 2017).
- Some of these brain regions (including orbitofrontal cortex, amygdala, fusiform gyrus, lingual gyrus, cuneus and putamen) play a significant role in acquiring and influencing socio-communication, emotional judgement, visuospatial skills and stereotyped behaviours in individuals with ASD.
- Autistic traits (AT) lie on a continuum in the general population, with clinical ASD representing the extreme end of the distribution (Whitehouse et al., 2011).
- We sought to investigate the association of regional GMV with autistic traits (AT) across the diagnostic divide.

OBJECTIVE

- The main objective of this study is to examine the association between regional GMV and autistic traits in a combined sample of neurotypicals and ASD participants.
- To achieve this aim, brain volumes were computed from structural MRI scans from neurotypicals and ASD adult participants. All participants also filled in the Autism spectrum Quotient (AQ).

METHODS AND MATERIALS

Participants

- Ninety one adults (66 neurotypicals and 25 ASD).
- Age (18-60 years old) and gender (52 males and 39 females).

Data collection

- Siemens 3T MRI using 32-channel head coil.
- High resolution T1-Weighted structural images were collected.
- Autism Spectrum Quotient (AQ) scores were collected from all the participants.

Preprocessing

- Voxel based morphometry (VBM) analysis was performed using DARTEL incorporated in the Statistical parametric mapping (SPM12) toolbox.
- All the images were pre-processed, and segmented into grey matter (GM), white matter (WM) and CSF.
- Subsequently, a study specific GM template was generated and transformed to the MNI standard space.
- Then the individual segmented GM images were normalized to the study specific template to generate a modulated GM normalized images.
- These resulting GM images were smoothed using the Gaussian kernel for cortical structures (FWHM = 8mm) and subcortical structures (FWHM = 4mm).

Participant characteristics

Parameters	Neurotypicals	ASD	P values
Age	25.74 ± 8.003	34.48 ± 12.952	0.004
Gender (m/f)	37/29	15/10	0.735
AQ	14.86 ± 6.919	36.32 ± 7.809	<0.001

RESULTS

- General linear model was used to test the association between the regional grey matter volumes (GMV) and the AQ scores after controlling for age, gender and total brain volume.

Cortical structures

- We found significant positive association between AQ and a cluster in right lingual gyrus (X= 9; Y= -65; Z= -8; $P_{FWE} < 0.001$; K_E= 8010, Z_{stats}= 4.58) (Fig. a).
- Significant negative association between AQ and a cluster in right orbitofrontal cortex (X= 16; Y= 21; Z= -25; $P_{FWE} < 0.001$; K_E= 7888, Z_{stats}= 4.09) (Fig. b).

Sub-cortical structures

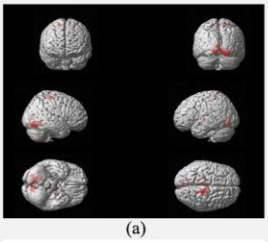
- We found a significant positive association between AQ and a cluster in the left putamen (X= -29; Y= -9; Z= -3; $P_{FWE} < 0.001$; K_E= 2837, Z_{stats}= 4.64) and right putamen (X= 29; Y= -4; Z= -5; $P_{FWE} < 0.001$; K_E= 2459, Z_{stats}= 4.45) (Fig. e).

DISCUSSION

- These findings are consistent with previous reports of case-control differences using partial least square (PLS) analysis characterized by higher regional GMV in right lingual gyrus and bilateral putamen, and lower regional GMV in the lateral orbitofrontal cortex in adults with ASD (Ecker et al., 2012, Sato et al., 2017).
- This supports the previous evidence for the relationship between the regional grey matter volume and autistic traits in the combined sample of neurotypicals and ASD.

KEY FINDINGS

Cortical regional GMV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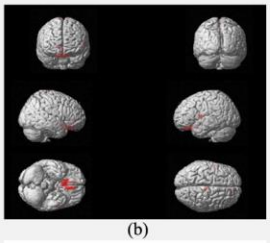
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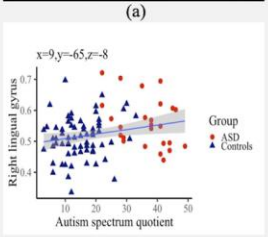
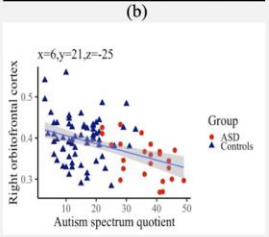
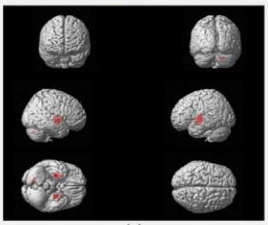


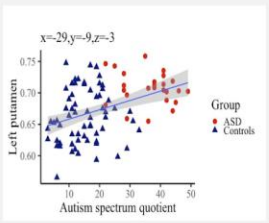
(c)



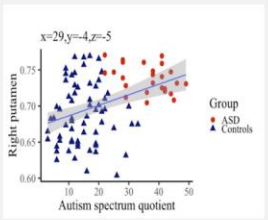
(d)

Subcortical regional GMV


(e)



(f)



(g)

Fig. (a) Clusters showing significant positive association between AQ and a cluster centred on the right lingual gyrus (X= 9; Y= -65; Z=-8; $P_{FWE} < 0.001$; K_E= 8010), **(b)** clusters showing significant negative association between a cluster centred on the right orbitofrontal cortex (X= 16; Y= 21; Z= -25; $P_{FWE} < 0.001$; K_E= 7888) and AQ scores, **(c)** scatterplot showing positive association between right lingual gyrus and AQ scores, **(d)** scatterplot showing negative association between right orbitofrontal cortex and AQ scores, **(e)** significant positive association between the cluster centred on the left putamen (X= -29; Y= -9; Z= -3; $P_{FWE} < 0.001$; K_E= 2837) and right putamen (X= 29; Y= -4; Z= -5; $P_{FWE} < 0.001$; K_E= 2459) and, **(f)** and **(g)** are the scatterplots for left and right putamen respectively.

CONCLUSION

- Our results demonstrate clear differences in how different brain region volumes relate to autistic traits.
- Higher autistic traits were associated with reduced volumes in the right orbitofrontal cortex, and increased volumes in right lingual gyrus and bilateral putamen.
- The pattern of results observed for the orbitofrontal cortex and the lingual gyrus may underlie social skill deficits and atypical visuospatial skills respectively in ASD individuals (Ecker et al., 2012, Sato et al., 2017).
- Increased volume in bilateral putamen may underlie repetitive and stereotyped behavioural features seen in ASD individuals (Ecker et al., 2012, Sato et al., 2014).

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Poster 1 was presented in the conference of Organization for Human brain mapping in June 2019

Poster 2 was presented in the conference of International Society for Autism Research in May 2019.

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Association between white matter microstructure and autistic traits across the diagnostic divide

University of Reading

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Introduction

- Autistic traits (AT) lie on a continuum in the general population, with clinical ASD representing the extreme end of the distribution (Whitehouse et al., 2011).
- Some previous studies have reported associations between white matter (WM) microstructural properties (particularly in superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) and AT (Lidaka et al., 2012, Gibbard et al., 2013), but these findings have not been consistently replicated (Cedric et al., 2015).
- These WM tracts are believed to play a significant role in acquiring socio-communication, emotion recognition and visual processing skills.
- The discrepancies in the results of previous studies led us to investigate whether the AT are associated with WM properties in a combined sample of individuals with and without a clinical diagnosis.
- We hypothesized that AT will be associated with WM microstructural integrity across the diagnostic divide, in line with similar previous studies.

Objective

- To examine the white matter microstructural integrity and its relationship with AT in a combined sample of neurotypicals and ASD.

Methods and materials

Participants

- Fifty three adults (28 neurotypicals and 25 ASD)
- Age, gender and IQ matched for ASD and controls

Methods and materials

	Typicals	ASD	P-value
Age	23.93 ± 9.63	34.48 ± 12.95	0.150
Gender	16 m/12 f	15 m/10 f	0.833
IQ	48.46 ± 23.07	55.92 ± 26.76	0.281
AQ	15.29 ± 5.06	36.32 ± 7.80	<0.001

Data collection

- Siemens 3T MRI using 32-channel head coil.
- Diffusion Tensor Imaging (DTI) was acquired using the following parameters: 32-gradient directions, b=1000 and b=0, along with high resolution T1-Weighted images (MPRAGE).
- Autism Spectrum Quotient (AQ) scores were collected from all the participants.

Preprocessing

- Tract based spatial statistics (TBSS) incorporated in the FSL FMRIB toolbox was employed.
- Standard space masks were applied on the output of TBSS.
- Mean Fractional Anisotropy (FA) and Mean Diffusivity (MD) values from the bilateral superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus and inferior fronto-occipital fasciculus were extracted.

Results

- Pearson's partial correlation (one-tailed) was used to find the associations between FA, MD values and AQ scores in the combined sample of neurotypicals and ASD while controlling for age, gender and IQ.
- Negative correlation was found between FA and AQ scores in right inferior longitudinal fasciculus ($r = -0.275$, $P = 0.027$).

Results

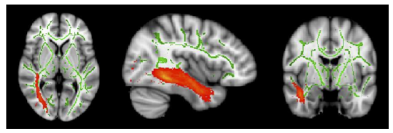

Fig.1 Standard space mask of right inferior longitudinal fasciculus over skeletonized FA projected on std. MNI template

WM tracts	FA- r_{AQ} (P)	MD- r_{AQ} (P)
L SLF	-0.019 (0.447)	0.158 (0.137)
R SLF	-0.183 (0.102)	0.185 (0.100)
L UNCF	-0.038 (0.396)	0.072 (0.309)
R UNCF	-0.065 (0.327)	0.171 (0.117)
L ILF	-0.037 (0.400)	0.193 (0.090)
RILF	-0.275 (0.027)	0.217 (0.065)
L IFOF	-0.052 (0.360)	0.150 (0.150)
R IFOF	-0.208 (0.074)	0.203 (0.078)

Table 2: Correlation values between FA, MD and AQ scores

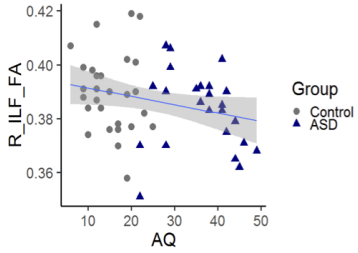

Fig. 2 Scatterplot for negative correlation between FA values and AQ scores in the right inferior longitudinal fasciculus.

Discussion

- This finding is consistent with previous reports of case-control differences in this tract (Gibbard et al., 2013) and supports previous evidence for the relationship between the white matter microstructural properties and autistic traits in the combined samples of neurotypicals and ASD.

Conclusion

- In this study, we explored the possible relationship between the white matter microstructural properties in the right inferior longitudinal fasciculus and autistic traits across the diagnostic divide.
- The right inferior longitudinal fasciculus may be associated with atypical visual processing skills (Boets et al., 2018) in both neurotypicals with higher autistic traits and individuals with ASD.

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APPENDIX III: Different phases of data collection and individual contribution

In all the three empirical chapters including (chapter 2, 3 and 4), I used a secondary dataset which was available in our Centre for Neurosciences and Neurodynamics (CINN) database. This provided me a great opportunity to make use of the valuable secondary dataset and explore different methodological approaches in my research. This dataset consisted of two separate cohorts. The sample dataset used in the chapter 2 and 3 were from one cohort, whereas the sample dataset used in the chapter 4 was from a different cohort.

In the chapter 2, all ninety-one participants (thirty-eight and fifty-three participants) (Neufeld et al., 2019; Hsu et al., 2018) MPRAGE dataset acquired for the voxel based morphometry and surface based morphometry analysis consisted of the same structural MRI data acquisition protocol. In the chapter 3 amongst ninety-one participants dataset, I included only the fifty-three participants DTI dataset which was acquired with the same diffusion MRI protocol and excluded the remaining thirty-eight participants DTI dataset to avoid bias in the skeleton based TOI and TBSS analysis.

In the chapter 4, the fifty-six participants resting state functional MRI dataset was collected from a different cohort from another study (Deluca et al., 2019). I recontacted all these participants individually by email and collected the Autism Spectrum Quotient (AQ) scores through Bristol online survey. In addition to these fifty-six participants, my actual plan was to collect some more rs-fMRI from the participants with clinical ASD, but couldn’t materialize it due to unprecedented COVID-19 restrictions.

From the previous information about data collection for the ninety-one participants, the thirty-eight participants dataset were collected from the student population in the University of Reading, Whiteknights campus. Since this was a student population, all the thirty-eight participants' IQ was assumed to be above average intelligence. Therefore, it was decided not to collect the participant’s IQ scores. The other fifty-three participants including the twenty-five participants with clinical ASD were collected from the local general public and NHS registered clinic from Reading, Berkshire.

My significant contribution in this thesis were literature review, application of various methodologies including different brain imaging techniques (structural MRI, DTI and rs-fMRI) to assess the grey matter, white matter microstructure and resting state networks with different

analytical approaches (VBM, SBM, skeleton based TOI, TBSS, and dual regression analysis) in relation to autistic traits. Based on the results from this study, I interpreted how these brain imaging findings related to autistic traits concord with previous studies on ASD and interpreted how the differences in the neural underpinnings may underlie the autistic traits. In addition, comparison between the different analytical approaches facilitated validation of our results and suggested future directions. Finally, I concluded that the association between the grey matter, white matter microstructure and resting state networks related to autistic traits using a dimensional approach shed light on the long-standing hypothesis of differences in brain structure and function.