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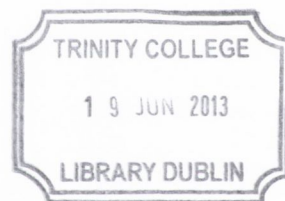
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The Neural Basis of Reward Processing in Autism

Spectrum Disorder:

Brain Function, Structure and Connectivity.

Sonja Delmonte



Thesis 10120

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Summary

Autism spectrum disorder (ASD) is a pervasive developmental disorder defined by impairments in reciprocal social interaction and communication, as well as stereotyped behaviour and repetitive interests (Lord et al., 2011). The theory of social motivation proposes that impairments in social interaction in ASD are due to failure to associate social stimuli with emotional rewards (Dawson, Bernier, & Ring, 2012; Dawson, Webb, & McPartland, 2005a). The aim of this thesis was to examine the reward responses to social and non-social stimuli in ASD using functional magnetic resonance imaging (fMRI), to investigate the structure and connectivity of frontostriatal circuitry – which sub-serves reward processing – and to use model free analyses to examine group differences in reward circuitry function and structure in the light of other neuroanatomical differences in ASD.

In the first experimental chapter I examined social and non-social reward processing in ASD using fMRI. The ASD group showed reduced activity in the dorsal striatum (DS) compared to controls during the receipt of social rewards but not monetary rewards. The ASD group also showed decreased activation for social rewards compared to monetary rewards whereas controls showed no significant difference between the two reward types. These results support the social motivation theory of ASD and suggest that interventions that seek to promote social motivation could improve social skills among people with ASD (Dawson et al., 2012).

The second experimental chapter examined the structure and connectivity of frontostriatal circuitry in ASD. The ASD group showed increased functional connectivity

between the striatum and regions of the prefrontal cortex including the anterior cingulate, the middle frontal gyrus and the paracingulate gyrus. Increased connectivity was primarily lateralised to the right hemisphere. There were no significant group differences in the structure of the striatum in terms of shape or volume, and there were no group differences in white matter connectivity between frontostriatal regions, as indexed by fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) or axial diffusivity (AD) values. The lack of significant structural alterations in frontostriatal circuitry, suggest that abnormal functional activation and connectivity within these regions are unlikely to be due to structural abnormalities within this circuitry, but may be secondary to other pathological mechanisms.

In the final experimental chapter model-free analyses were conducted to examine structural integrity, as well as functional connectivity, at the whole-brain level. There were subtle group differences in grey matter volume between groups, with the ASD group showing increased grey matter volume in temporal and parietal lobes and reductions in the frontal lobe and thalamus. In terms of white matter integrity, there were significant group differences in a number of major white matter fibre bundles including the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), the anterior thalamic radiation (ATR) and the inferior fronto-occipital fasciculus (IFOF). There was also evidence of abnormal maturation of functional connectivity in the ASD group, as indexed by developmental differences in spectral power properties in the default mode network (DMN). These results indicate that there are important functional and neuroanatomical differences in regions outside reward circuitry in ASD, which should be taken into account when developing theoretical models of ASD symptoms.

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1 General Introduction

1.1 Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a pervasive developmental disorder defined by impairments in reciprocal social interaction and communication, as well as the presence of stereotyped behaviour and repetitive interests (APA, 2000; Lord et al., 2011). Whereas the core deficits were previously regarded as a triad of impairments, in terms of social interaction, communication and restricted interests and repetitive behaviour, recent conceptualisations have emphasised two core features; social communication deficits and restricted and repetitive behaviour (Lord et al., 2011) – see figure 1.1. ASD is frequently accompanied by cognitive and language impairments as well as other mental health and behavioural co-morbidities (see figure 1.1. and section 1.1.3). ASD is more common in males than females, with males approximately four and a half times more likely to be diagnosed with the condition than females (Centers for Disease Control and Prevention, 2012). Estimates of ASD prevalence in the United States indicate that it affects approximately 1 in 88 individuals (1.13% of the population), representing a 78% increase in the six-year period between 2002 and 2008, and a 23% increase for the 2-year period 2006 and 2008 (Centers for Disease Control and Prevention, 2012). This increase may reflect a true increase in prevalence but may also reflect other factors such as changes in diagnostic criteria, better ascertainment and greater awareness of the disorder. Though there are no published data on the prevalence of ASD in Ireland, estimates from the UK range from between 1% (Baird et al., 2006) and 1.5% (Baron-Cohen et al., 2009).

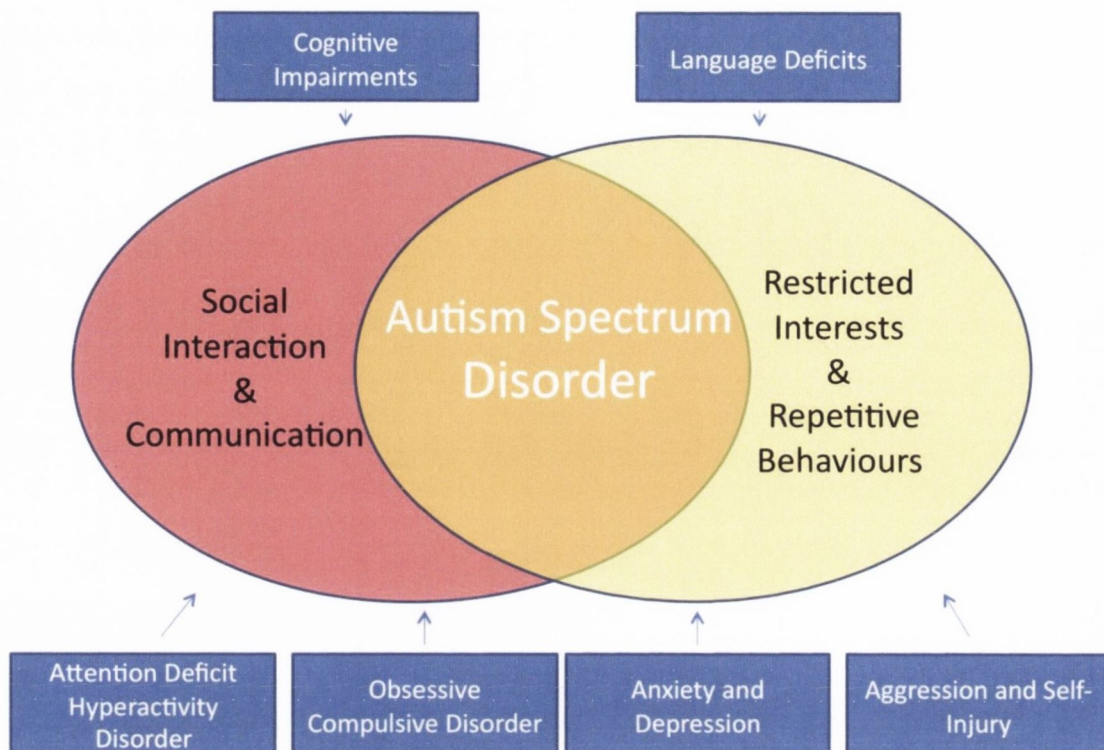


Figure 1.1. Core Deficits in ASD.

ASD is characterised by impaired Social Interaction and Communication and Restricted interests and Repetitive Behaviour. Associated impairments can include cognitive and language deficits and other mental health and behavioural co-morbidities.

1.1.1 Historical Background

Autism was first described by Leo Kanner (1943) who noticed a group of children who had a profound lack of affective contact with other people, intense insistence on sameness in their chosen repetitive routines, muteness or a marked abnormality of speech, fascination with objects, high levels of visuo-spatial skills and good rote memory with learning difficulties in other areas. Kanner suggested that the first two of these features were sufficient for diagnosis. Kanner's contemporary, Hans Asperger (1944) identified a similar group of children and adolescents who displayed naive, inappropriate social approaches, intense circumscribed interests, good grammar and

vocabulary but unusual use of speech and a level of ability in the borderline, average or superior range, but some specific learning difficulties. The importance of the diversity in these descriptions is that Kanner described individuals with more severe deficits and greater intellectual impairment while Asperger's descriptions were of individuals who were less impaired. These descriptions represented the range of impairments that is now regarded on a continuum of deficits, i.e. the autistic spectrum, which are incorporated in future revisions of classification systems (see below, section 1.1.2).

1.1.2 Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) (APA, 2000) places Autism Spectrum Disorders in the category of Pervasive Developmental Disorders. These include Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS). The diagnosis of autism, as specified by the DSM-IV, depends upon the presence of at least six deficits from each of three domains; i) social interaction, ii) communication and iii) repetitive behaviour, with symptoms present before three years of age. Asperger's syndrome, on the other hand, is diagnosed based on the presence of a qualitative impairment in social interaction and restricted, repetitive and stereotyped patterns of behaviour, interests and activities. Unlike Autism, Asperger's syndrome is not diagnosed in cases where there is a language delay or cognitive impairment. Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS or Atypical Autism) may be diagnosed in cases that do not meet the criteria for Autism because of late age at onset or due to atypical or sub-threshold symptoms. Two important changes in the

diagnosis of ASD are due to be made in the fifth edition of the DSM (DSM-5) by representing the deficits along a continuum as referenced above. Firstly, the formal diagnoses of Autistic Disorder, Asperger's Disorder, and PDD-NOS will be removed and these disorders will come under the umbrella term Autism Spectrum Disorder (ASD). Rather than distinguishing between ASD sub-types there will be a coding system in place for describing the severity of symptoms. Secondly, the triad of symptom domains, as seen in the DSM-IV, will be replaced by two domains. Social and communication symptom domains are to come under a single symptom domain – social and communicative deficits – and the second category will refer to restricted and repetitive behaviours, interests, or activities (McPartland, Reichow, & Volkmar, 2012).

1.1.3 Co-morbidities

ASD is associated with a number of co-occurring developmental, behavioural, psychiatric and medical conditions. Intellectual disability (ID – I.Q. less than 70) has historically been associated with diagnosis in 70 to 75% of children with ASD, though recent estimates are substantially lower indicating that 38% of those with ASD are now classified as having an ID (Newschaffer et al., 2007), due to increased recognition of ASD in higher functioning individuals. Aggression and self-injury are common behavioural difficulties and psychiatric co-morbidities include obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), specific phobia, anxiety and depression (Leyfer et al., 2006; Mazefsky, Folstein, & Lainhart, 2008; Skokauskas & Gallagher, 2012; Skokauskas & Gallagher, 2010). Neurological co-

morbidities include motor impairments, epilepsy, and sleep dysfunction (Maski et al., 2011) .

1.2 The Aetiology of ASD

In approximately 10% of cases, the aetiology of ASD can be attributed to known medical conditions, most of which are cytogenetic or known genetic disorders such as Angelman Syndrome, Prader-Willi Syndrome, Fragile-X Syndrome and Tuberous Sclerosis (Fombonne, 2003; Freitag, 2007). Both genetic and environmental factors confer risk to the development of idiopathic ASD. Early studies estimated the heritability of Autism at approximately 90% (Bailey et al., 1998; Folstein & Rutter, 1977; Steffenburg et al., 1989), though this may be an over-estimation with recent evidence suggesting that genetic and environmental factors could contribute to 37% and 58% risk for ASD respectively (Hallmayer et al., 2011). Methodological issues, including whether the data were acquired from a population-based sample and whether contemporary standards for diagnosis of ASD were used, may contribute to disparities in these estimates (Hallmayer et al., 2011). In addition, epigenetic factors are likely to further contribute to the multi-factorial aetiology of ASD (Grafodatskaya et al., 2010).

1.2.1 Environmental and Prenatal Risk Factors

A number of environmental risk factors have been associated with ASD. Meta-analytic findings show that maternal migration and maternal medication use increase risk for ASD (Gardener et al., 2009). Potential mechanisms by which maternal migration may increase risk for ASD include increased maternal stress and/or lower immunity to

common infections. In terms of medication use, prenatal exposure to valproate, used in the treatment of epilepsy, is associated with an eight-fold increase in risk for ASD (Rasalam et al., 2005) and the evidence suggests that maternal use of the selective serotonin reuptake inhibitors (SSRIs), used in the treatment of depression, present a two-fold increase in risk for ASD (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011). Other prenatal risk factors include maternal bleeding, gestational diabetes, advanced parental age at birth and being firstborn versus third or later born (Gardener et al., 2009). Exposure to obstetrical complications is associated with increased risk, though it may be that complications occur as a result of ASD, or as a consequence of other factors, such as genetic factors, that also confer risk for ASD. The mechanisms via which these factors may increase risk for ASD have not yet been delineated, a possible suggestion being that some of these factors – including migration, birth order, gestational diabetes, obstetric complications and advanced parental age – could mediate risk via their impact on intrauterine androgen levels (James, 2012).

1.2.2 Genetic Risk Factors: Common and Rare variants

Genetic studies suggest that both common and rare variants confer risk for idiopathic ASD (State & Levitt, 2011). Genetic studies investigating rearrangements in chromosomal structure and sequence variations have implicated variants involved in synaptic assembly and functioning in ASD pathology. These included Neuroligin 4 (NLGN4), Neurexin 1 (NRXN1), SHANK3, SHANK2, Contactin 4 (CNTN4) and Contactin-associated protein 2 (CNTNAP2) (State & Levitt, 2011). *De Novo* Copy Number Variants (CNVs), sporadic rather than inherited rearrangements in chromosomal structure, are reported in approximately 7-10% of simplex ASD families, 2-3% of multiplex families

and 1% of controls (Abrahams & Geschwind, 2008). *De Novo* CNVs associated with ASD include deletions and duplications at 16p11.2, duplications at 15q11–13, deletions and duplications combined at 22q11.2, deletions at the Neurexin 1 locus, and duplications at 7q11.23 (Sanders et al., 2011). However, some of these CNVs are not specific to ASD and also confer risk for other disorders. For example, 16p11.2 duplications confer risk for schizophrenia (McCarthy et al., 2009) and deletions at this locus are associated with intellectual disability and obesity, as well as ASD (Bochukova et al., 2010). Network based analyses of CNVs implicated in ASD provide evidence that genes impacting genes involved in neuronal development appear to be impacted with greater frequency by large CNV deletions in syndromic forms of autism, lending further support for aberrant functioning of these genes in the underlying pathophysiology (Pinto et al., 2010).

According to the common variant hypothesis, the majority of risk for neuropsychiatric disorders such as ASD is due to multiple alleles each conferring modest risk for the overall phenotype or for sub-components of the disorder. A number of common variants have been associated with ASD in several studies but replications have been ambiguous. The strongest supported findings from candidate gene studies include arginine vasopressin receptor 1A (AVPR1A); contactin associated protein-like 2 (CNTNAP2); disrupted in schizophrenia 1 (DISC1); engrailed homeobox 2 (EN2); gamma-aminobutyric acid (GABA) A receptor beta 3 (GABRB3); glutamate receptor ionotropic kainite 2 precursor (GRIK2); integrin beta 3 (ITGB3); met proto-oncogene (MET); oxytocin receptor (OXTR); reelin (RELN); solute carrier family 25 (mitochondrial carrier, Aralar) member 12 (SLC25A12) and solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 (SLC6A4) (Abrahams & Geschwind, 2008). These

genes are associated with a variety of functions. AVPR1A and OXTR are associated with affiliative behaviours (Hammock & Young, 2006), EN2 with cerebellar development (Cheh et al., 2006), ITGB3 and SLC6A4 with serotonin regulation (Coutinho et al., 2004; Weiss et al., 2006), MET with neuronal growth and cell migration (Judson, Eagleson, Wang, & Levitt, 2010), GABRB3 with GABA inhibitory (Buxbaum et al., 2002), and GRIK2 with glutamate excitatory (Jamain et al., 2002) neurotransmission. As in the case with *de Novo* CNVs, a number of these variants also confer risk for other neuropsychiatric disorders. For example, DISC1 is associated with schizophrenia and bipolar disorder risk (Hennah et al., 2009; Millar et al., 2000). Moreover no marked support for common variants within specific candidate genes that confer risk for autism has emerged from a number of large scale Genome-wide Association Studies (GWAS) (Anney et al., 2010, 2012; Ma et al., 2009; Wang et al., 2009; Weiss, Arking, Daly, & Chakravarti, 2009).

1.2.3 Gene Expression Studies

Post-mortem gene-expression studies have provided insight into how genetic and environmental factors disrupt typical brain development in ASD. For example, Voineagu et al. (2011) identified two synaptic modules implicated in ASD pathology. The first was a synaptic module, A2BP1 which showed decreased expression in frontal and temporal cortices in ASD. A2BP1 dependent deficits were apparent in RNA-splicing assembly in a number of genes, suggesting that reduced expression of a single gene could have a cascading effect on other genes. The second finding concerned an immune module which is thought to reflect adaptive, environmental rather than genetic processes (Korade & Mirnics, 2011). Taken together, these findings suggest

that specific rare variants can work in combination with common variants, environmental inputs, epigenetic factors and perhaps also stochastic events, to alter neural brain development in ASD – see figure 1.2 (State & Levitt, 2011).

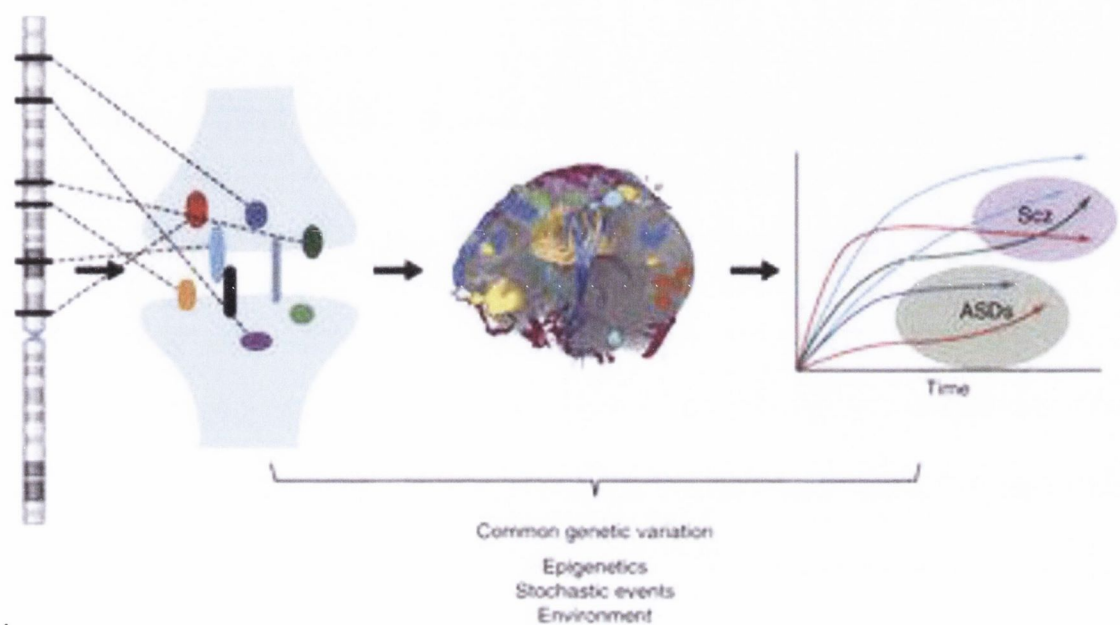


Figure 1.2 Genetic Risk Factors for Neuropsychiatric Disorders, figure from State and Levitt (2011).

This figure illustrates the interaction of different risk factors to the development of neurodevelopmental disorders. A human chromosome is represented on the left with the black bars indicating the sites of rare mutations, thought to lead to alterations in basic cellular and molecular processes. These in turn influence cortical organization and connections, represented in the figure by the diffusion tensor image showing neural pathways. These processes are likely to be influenced by a variety of factors, including common functional genetic variation, stochastic effects, environmental inputs and epigenetic phenomena. The graph on the right illustrates that genetic variations may influence diverse developmental trajectories (lines of similar colours reflect rare mutations in the same CNV or gene) leading to distinct clinical phenomena (ASD and schizophrenia in this example) or to typical development (State & Levitt, 2011).

1.3 Neuroanatomical Abnormalities in ASD

It is thought that early genetic and environmental risk factors for ASD lead to abnormalities in brain development, which alter a child's perception of, and response to, his or her environment. These altered interactions between the child and his or her environment are hypothesised to disrupt critical input influencing the development, specialisation and integration of brain circuitry (Dawson et al., 2009). The following section outlines evidence of abnormal brain development in ASD.

1.3.1 Macrocephaly and Head Circumference

Macrocephaly, as defined by head circumference above the 97th percentile, is found in approximately 20% of subjects with autism (Fombonne, 2000). ASD is characterised by atypical patterns of head circumference growth, with small to normal head size at birth followed by accelerated growth in infancy between 1-2 months and 6-14 months (Courchesne, 2004). MRI and post-mortem studies indicate that on average, brain size is 13% smaller in ASD than controls at birth, but by one year brain size in ASD is 10% greater than controls. Brain over-growth diminishes during childhood, and by adolescence it is only 2% larger than in controls (Redcay & Courchesne, 2005). The results of these studies are compounded by the inclusion of a large number of participants with ID and medical complications and therefore should be treated with some degree of caution. A longitudinal study of 28 children from birth to 36 months, which excluded subjects with medical disorders including genetic syndromes, significant sensory or motor impairments, premature birth or serious birth complications, head trauma or neurological disorders, indicated that those who were diagnosed with ASD at 3-4 years, showed no difference in head circumference at birth.

Head circumference increased by almost 1 standard deviation (SD) by 12 months but there were no differences detected between groups after 1 year of age. Though I.Q. data were not reported in this study, the results suggest that accelerated head growth may be confined to the first year of life in ASD, in cases where there are no known medical co-morbidities (Dawson et al., 2007). However, accelerated brain growth in infancy is likely to be due to abnormal growth factors that also contribute to increased overall body growth in ASD during the first year of life, with head circumference comparable to controls when body length and weight are controlled (Mraz, Green, Dumont-Mathieu, Makin, & Fein, 2007).

1.3.2 Atypical Neural Development

Neuropathological studies suggest that brain overgrowth in ASD may be due to excessive numbers of neurons resulting from prenatal dysregulation of proliferation and/or apoptosis (Courchesne et al., 2001). Courchesne et al. (2011) reported a 67% increase in neuron number in the prefrontal cortex (PFC) of 7 ASD children compared to controls, with no difference detected in the number of glial cells. The excess was greater within dorsolateral PFC (dlPFC) than in the medial PFC (mPFC), and may extend to other cortical regions, though this study confined examination to the PFC. There was also a disruption in the normal linear relationship between neuron number and brain weight in ASD, with the ASD group also showing an increase in brain weight by 17%, which was lower than might have been expected given the increased number of neurons in the PFC. There have been consistent reports of smaller, more densely packed neurons in limbic system including the hippocampus, subiculum and amygdala as well as reduced Purkinje cell density in the cerebellum (Bailey et al., 1998; Bauman

& Kemper, 1985; Palmen et al., 2004; Whitney et al., 2008). These studies provide important insight into neuropathological processes in ASD, however, the results of these post-mortem studies should be interpreted in the light of small sample sizes, and the inclusion of cases with ID and seizures, and other cortical abnormalities such as dysplasia.

1.4 Neuroimaging Studies of Brain Structure, Development, Function and Connectivity in ASD

1.4.1 Brain Structure in ASD: Volumetric Studies

Structural neuroimaging studies have shown abnormal grey and white matter volumes in a number of brain regions in ASD. A meta-analysis of volumetric studies indicated that ASD is characterised by increased intracranial and total brain volume and enlargements in the cerebellar and cerebral hemispheres as well as the caudate nucleus in ASD (Stanfield et al., 2008). Reductions in volume were reported in the corpus callosum, midbrain and the cerebellar vermal lobules VI–VII and VIII–X, and reductions in amygdala volume were age-dependent, such that increased age was associated with reduced amygdala volume in autistic subjects relative to controls (Stanfield et al., 2008).

The use of whole brain voxel based morphology (VBM) techniques, which do not require a priori hypotheses regarding the location of structural differences, have provided further insight into the neuroanatomical basis of ASD. Several meta-analyses of VBM studies have been reported to date. Nickl-Jockschat et al. (2011) reported differences in grey and white matter volume in the lateral occipital lobe, the

pericentral region, the medial temporal lobe, right caudate and proximate to the right parietal operculum. A second meta-analysis, which focused on grey matter abnormalities indicated volumetric increases bilaterally in the cerebellum, in the right middle temporal gyrus, the right anterior cingulate cortex, right caudate head, right insula, right fusiform gyrus, right precuneus and right posterior cingulate cortex and left lingual gyrus. Grey Matter decreases were observed bilaterally in the cerebellar tonsil and inferior parietal lobule, in the right amygdala, right insula, right middle temporal gyrus, right caudate tail, right precuneus and in the left precentral gyrus (Cauda et al., 2011).

1.4.2 Developmental Differences in Brain Structure in ASD

Longitudinal and cross-sectional MRI studies have shown that the brain undergoes a protracted period of development that extends beyond childhood to adolescence and young adulthood (Pfefferbaum et al., 2012). During typical development, FA and grey matter density change according to an inverted U-Shape (Giedd et al., 1999; Kochunov et al., 2012). Longitudinal data indicates that grey matter volume peaks at approximately 12 years of age in the frontal and parietal lobes, at about age 16 in the temporal lobe and about 20 in the occipital lobe (Giedd et al., 1999). Cross-sectional data indicates that white matter FA values peak at approximately 32 years of age, with phylogenetically older brain regions (sensory and motor regions) maturing first (Kochunov et al., 2012).

ASD is characterised by abnormal changes in grey matter volume as a function of age (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012). Cross-sectional data of ASD subjects aged between eight and fifty suggests that ASD subjects show reduced grey matter

volume in the anterior cingulate cortex, posterior superior temporal sulcus and middle temporal gyrus, regardless of age. Age-related changes in grey matter volume in the amygdala, temporoparietal junction, septal nucleus and middle cingulate cortex follow an inverted U-shaped trajectory in both ASD participants and controls, but this trajectory is shifted to the left in ASD such that grey matter volumes in these regions peak at an earlier age (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012). Similarly, the evidence suggests that white matter FA undergoes an abnormal developmental trajectory in ASD. Kleinhans et al. (2012) reported reduced FA in a number of major white matter tracts in a group of adolescence and young adults with ASD. However, whereas FA values decreased over time among controls, FA increased in the ASD group. This suggests that FA values were normalising in ASD over time to typical levels. These results indicate that ASD is characterised by complex changes the developmental trajectories of both grey matter volume and white matter FA but that there may be some normalisation over time.

1.4.3 Brain Function in ASD during Cognitive Tasks

fMRI studies have provided important insights into the neural processes that underlie deficits in social perception and interaction, language and communication and restricted interests and repetitive behaviours in ASD. A number of studies have shown that ASD subjects show hypoactivation of the fusiform gyrus (Critchley et al., 2000; Pierce, Müller, Ambrose, Allen, & Courchesne, 2001; Piggot et al., 2004; Schultz, 2000; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004) and amygdala (S. Baron-Cohen et al., 1999; Critchley et al., 2000; Pierce et al., 2001) during face processing. Amygdala hypoactivation has also been reported during theory of mind and emotion processing

tasks (Ashwin, Chapman, Colle, & Baron-Cohen, 2006; Baron-Cohen, 2001; Critchley et al., 2000) and it has been suggested that amygdala deficits may have downstream effects on face perception deficits associated with the fusiform gyrus (Schultz, 2005). However, these findings have not been replicated by all studies (Nouchine Hadjikhani et al., 2004; Kleinhans et al., 2008; Pierce, Haist, Sedaghat, & Courchesne, 2004), perhaps reflecting methodological considerations such as the familiarity of the face presented and whether the participants were told to fixate on a cross-hair – which is thought to mediate attention to the faces. The superior temporal sulcus (STS), which is involved in interpreting intentions associated with actions (Pelphrey, Shultz, Hudac, & Vander Wyk, 2011), shows abnormal activation in ASD during eye gaze perception (Pelphrey, Morris, & McCarthy, 2005), intention attribution (Castelli, Frith, Happé, & Frith, 2002) and theory of mind tasks (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011).

Functional MRI studies of language processing in ASD indicate that ASD subjects show reduced activation in the inferior frontal gyrus (Broca's area) and increased activation in parietal and temporal areas during language processing tasks (Harris et al., 2006; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006). Few studies have directly examined the neuroanatomical basis of repetitive behaviours in ASD. Repetitive behaviours are associated with certain executive function deficits in ASD, such as cognitive flexibility and response inhibition (Lopez, Lincoln, Ozonoff, & Lai, 2005). In one study, individuals with ASD show reduced activation in the frontal eye fields and the dorsal anterior cingulate cortex during inhibition of pre-potent responses (Agam, Joseph, Barton, & Manoach, 2010). BOLD activation in both of these regions was associated with repetitive behaviour

symptoms. These results suggest that regions involved in cognitive control play a role in repetitive behaviours in ASD.

1.4.4 Structural and Functional Connectivity in ASD

Given the distributed nature of neuroanatomical abnormalities in ASD it has been hypothesised that ASD is characterised by abnormalities in neural circuitry rather than a dysfunction in specific brain regions. 'Developmental-disconnection' models of ASD propose that ASD arises from the failure in the typical development of connections between brain regions, which may arise as a result of diverse aetiologies (Geschwind & Levitt, 2007; Hughes, 2007; Just et al., 2004; Just, Keller, Malave, Kana, & Varma, 2012). Accordingly, it is proposed that complex cognitive and neurological functions, that require the integration of diverse brain regions, are particularly susceptible to disruption in ASD (Keller et al., 2007). A prominent model proposes that ASD is characterised by long-range over-connectivity and short-range under-connectivity (Barttfeld et al., 2010; Belmonte et al., 2004; Wass, 2011). However, mounting evidence suggests that ASD is characterised by abnormal connectivity rather than under-connectivity as implied by developmental disconnection models (Wass, 2011).

Genetic, as well as structural and functional neuroimaging studies have provided support for models of abnormal connectivity in ASD. For example, a number of genes involved in synaptogenesis (Neuroligins and Neurexins), dendrite development (SHANK genes) and cortical inter-neuron development (MET) have been implicated in ASD pathology (Campbell et al., 2006; Geschwind & Levitt, 2007; Scott-Van Zeeland et al., 2010; Wang et al., 2009). A review of diffusion tensor imaging studies of ASD indicates that white matter structural abnormalities have been recorded in a number of major

white matter tracts including the corpus callosum (CC), cingulum, arcuate fasciculus, superior longitudinal fasciculus and uncinate fasciculus, with more consistent evidence of reductions in FA in the corpus callosum, cingulum and white matter tracts within the temporal lobe (Travers et al., 2012). However, there are inconsistencies in the literature, with a number of studies reporting increased FA (Bode et al., 2011; Cheng et al., 2010; Weinstein et al., 2011). Increased FA in disorders such as ASD may reflect microstructural abnormalities or methodological issues (Jones, 2010).

Functional connectivity analyses of MRI data indicate abnormal connectivity between brain regions during rest (Cherkassky, Kana, Keller, & Just, 2006; Di Martino et al., 2010; Weng et al., 2010; Von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2012), as well as during task performance in ASD. Both increased and decreased functional connectivity have been reported in tasks sub-serving visuomotor performance, face processing, social cognition, executive function and language processing (Just et al., 2004; Kana, Libero, Hu, Deshpande, & Colburn, 2012; Kleinhans et al., 2008; Sato, Toichi, Uono, & Kochiyama, 2012; Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005; Solomon et al., 2009). Taken together, these findings suggest that functional and structural differences in neural connectivity may provide a link between aetiological risk factors and the behavioural impairments that characterise ASD (see figure 1.2).

1.5 Cognitive Theories of Impairment in ASD

Three prominent cognitive theories have sought to explain ASD symptoms; the theory of 'Executive Dysfunction', 'Weak Central Coherence Theory' and 'Theory of Mind'(ToM) (Rajendran & Mitchell, 2007). Executive Function (EF) refers to cognitive functions necessary for problem-solving to attain a future goal, which include planning,

impulse control, inhibition, set maintenance and cognitive flexibility (Ozonoff et al., 1991). EF deficits could potentially explain a range of cognitive and motor symptoms that characterise ASD from 'insistence for sameness,' repetitive hand flapping, rocking, difficulty switching attention and poor inhibition (Rajendran & Mitchell, 2007), as well as social difficulties as measured by ToM tasks (Russell et al., 1991). Deficits in planning ability, mental flexibility (set shifting) and inhibition have been recorded in some but not all studies of EF in ASD (Hill, 2004). This account has been criticised as some children with ASD have normal EF abilities, and EF deficits are not specific to ASD with ADHD, schizophrenia, OCD and Tourette syndrome also characterised by deficits in EF (Pellicano et al., 2006).

According to the Weak Central Coherence Theory (WCT) ASD symptoms may be due to atypical information processing characterised by a preference for processing information in a detail-focused way, examining constituent parts, rather than the global whole (Frith, 2003). Support for this account comes primarily from studies showing that ASD participants perform better than controls on 'Embedded Figures Tasks' in which hidden shapes in drawings have to be found as quickly as possible (Shah & Frith, 1993), and from studies showing that people with ASD do not benefit as much as controls from the context of meaning in sentences when learning the pronunciation of words (Frith & Snowling, 1983; Happé, 1997; López & Leekam, 2003). WCT has been called into question by studies showing that language impairment may account for weak central coherence on verbal tasks (Norbury, 2005), that these deficits do not necessarily generalise to visual domain (López & Leekam, 2003; Ropar & Mitchell, 2001), and that they may be accounted for by deficits in EF (Mann & Walker, 2003; Rinehart et al., 2000). As such, the theory of weak central coherence has been

revised and is now considered a cognitive style characterised by superior local processing, rather than an account of cognitive deficits in ASD (Happé, 1999).

The 'Theory of Mind' (ToM) hypothesis proposes that social impairments in ASD are due to a deficit in representing the mental states of others (Baron-Cohen et al., 1985). A number of studies have indicated that children and adults with ASD show significant impairments on tests of ToM (Lind & Bowler, 2009; Pilowsky, Yirmiya, Arbelle, & Mozes, 2000; White, Coniston, Rogers, & Frith, 2011). However, ToM deficits are not universal in ASD with approximately 20-70% of subjects being able to pass ToM tests (Bowler, 1992; Happé, 1994). Deficits are not specific to ASD, having been reported in other disorders such as schizophrenia and fronto-temporal dementia (Ang & Pridmore, 2009; Gregory et al., 2002). In addition, the ToM hypothesis does not account for basic face perception or emotion recognition deficits in ASD (Dawson et al., 2005a; Law Smith et al., 2010). A further criticism of this account is that it cannot explain early social dysfunction, as recorded in the first year of life in ASD (Werner et al., 2000; Zwaigenbaum et al., 2005), as ToM does not develop until approximately three years of age in typical development (Lewis & Osborne, 1990). Though the ToM hypothesis has been useful in understanding some of the social difficulties experienced by people with ASD, the issues raised above pose challenges for this theory as an aetiological account of social deficits characteristic of ASD.

1.6 The Social Motivation Theory of ASD

The 'Social Motivation' account proposes that motivational, as opposed to cognitive deficits underlie social impairments in ASD (Dawson et al., 2005a). According to this account motivational factors reduce attention to social stimuli, which in turn has a

downstream effect on the development of face perception and social cognition (Chevallier, Kohls, Troiani, Brodtkin, & Schultz, 2012; Dawson et al., 2005a; Dawson et al., 2012). Figure 1.3 illustrates the model of social motivation provided by Chevallier et al. (2012). It describes how social motivation functions at a 'proximate level' (i.e. behavioural manifestations and biological mechanisms) and at the 'ultimate level' (i.e. its' evolutionary purpose).

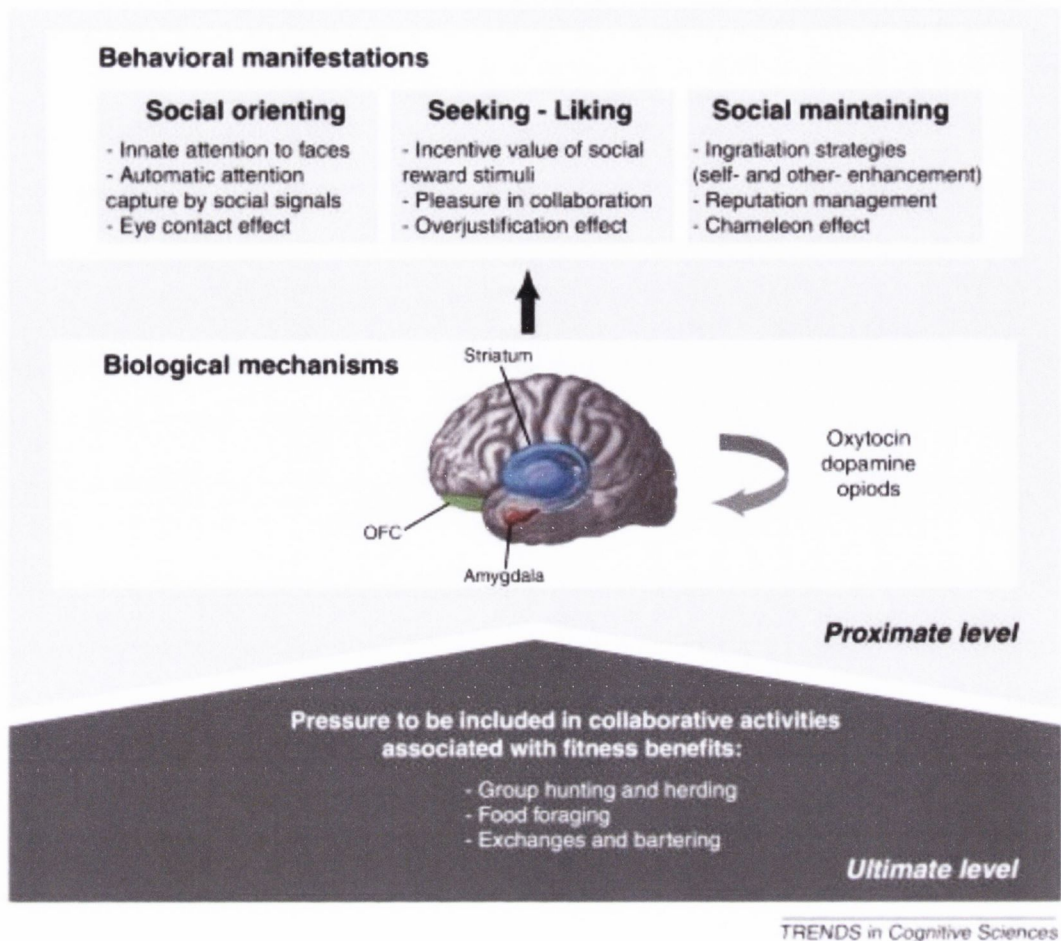


Figure 1.3 The Social Motivation Theory of ASD, figure from Chevallier et al (2012).

Figure 1.3 depicts the model of social motivation proposed by Chevallier et al. (2012). At the proximate level, social motivation underlies a range of behaviours including orientating to social stimuli and seeking social interaction. It is sub-served by neural mechanisms in orbitofrontal-striatal-amygdala circuitry and regulated by neuropeptides such as oxytocin, neurotransmitters such as dopamine and the endogenous opioid system. At the ultimate level social motivation is regarded as an evolutionary adaptation to enhance individuals' ability to act collaboratively in their environments.

1.6.1 Behavioural Manifestations

Social orientating is the phenomenon whereby social signals are given attentional priority over non-social signals. This is apparent from birth with neonates preferring faces to non-face images and speech to non-speech sounds (Farroni et al., 2005; Rosa Salva et al., 2011; Vouloumanos et al., 2010). Adults also show a preference for social stimuli, rapidly orientating to human faces and bodies in naturalistic scenes (Fletcher-Watson et al., 2008). Highly salient social signals such as direct eye contact facilitate cognitive processes such as memory for facial identity among both adults and infants (Senju & Johnson, 2009). Both adults and children take pleasure in collaboration (Rekers et al., 2011; Rilling et al., 2002) and find pro-social behaviour intrinsically rewarding, with pro-social behaviour decreasing when material rewards are given in exchange for helpful behaviour – a phenomenon known as the over-justification effect (Falkinger et al., 2000; Warneken & Tomasello, 2008). Behavioural economic studies show that social stimuli have a strong incentive value and obey some of the same economic principles as non-social rewarding stimuli. For example, people will exert effort for the opportunity to see an attractive face and, as in the case of monetary rewards, these social rewards are discounted as a function of time (Hayden et al., 2007). People have the tendency to seek to engage in long-term social relationships (Chevallier, Kohls, et al., 2012) and seek to establish and maintain these relationships by engaging in ingratiating behaviours which can vary in their manifestation from unconscious mimicry (Heyes, 2001; Lakin & Chartrand, 2003) to overt flattery (Fu & Lee, 2007; Gordon, 1996; Higgins et al., 2003).

Reduced social orientating is one of the earliest signs of ASD. Retrospective videotape studies show that children who are later diagnosed with ASD, show reduced social orientating during the first six months of life, with normal spontaneous attention shifts to non-social stimuli (Maestro et al., 2002). Orientating to information conveyed by the eyes is particularly impaired in ASD. Impaired eye contact has been recorded in the first 12 months of life (Werner et al., 2000) and is listed among the DSM-IV-TR (APA, 2000) and DSM-5 (McPartland, Reichow, et al., 2012) diagnostic criteria for ASD. Poor 'gaze-monitoring' is among three items on the Checklist for Autism in Toddlers (CHAT), in addition to 'proto-declarative pointing' and 'pretend play,' which confers a specific risk for ASD compared to other forms of developmental delay (Baron-Cohen et al., 1996). Poor gaze monitoring is thought to be a particularly good indicator of ASD. A prospective study, of children at high familial risk for developing ASD showed that ERP components evoked in response to dynamic eye-gaze shifts at six to ten months were associated with autism diagnoses at 36 months (Elsabbagh et al., 2012). Social orientating deficits in ASD have also been recorded in the auditory modality. For example, children with ASD fail to show normal preferences for speech sounds and unlike typically developing children and children with ID, they do not show a preference for their mother's voice (Klin, 1991; Kuhl et al., 2005).

As noted above, Kanner (1943) observed that children with autism demonstrated a profound lack of affective contact with others. A lack of social enjoyment features among the diagnostic criteria for autism, which includes 'a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people' in the DSM-IV (APA, 2000) and a 'lack of social or emotional reciprocity' in the DSM-IV and DSM-5 (McPartland, Reichow, et al., 2012). Children with ASD are less likely to smile when

interacting with their mothers (Dawson et al., 1990), show less responsiveness to social rewards such as verbal praise (Demurie et al., 2011) and are less likely to seek cooperative engagement with others (Liebal et al., 2007). The evidence suggests that ASD is characterised by selective social anhedonia, with reduced self-reported pleasure in social activities, such as being in the company of others, talking and exchanging expressions of feelings. Enjoyment of physical pleasures, such as eating, movement, smells and sounds, and non-physical pleasures, such as intellectual pleasure and the pleasure of achievement, is reportedly normal in ASD (Chevallier et al., 2012).

Adults and children with ASD are less likely to engage behaviours that are used by their typically developing peers to maintain social relationships. Clinical and parental descriptions indicate that people with ASD often come across as honest and very direct, as well as 'blunt' (Chevallier et al., 2012). Experimental evidence suggests that adults with ASD may pay less regard to their 'social reputation' than controls. Unlike controls, adults with ASD do not increase charitable donations in the presence of an observer, (Izuma, et al., 2011). Similarly, children with ASD are less likely to flatter others. For example, they do not enhance their ratings of a picture in the presence of the picture's drawer (Chevallier, Molesworth, et al., 2012). Chevallier et al. (2012) reported that flattery behaviour among the ASD and control children in their study was correlated with self-reported social enjoyment, suggesting that social motivation may underlie the lack of ingratiating behaviour seen in ASD. However, this lack of reputation management could be due to poor theory of mind abilities (Tennie et al., 2010) rather than diminished social motivation.

1.6.2 Biological Mechanisms

Social Motivation involves a well characterised network of brain regions including the amygdala, striatum, orbitofrontal (OFC) and ventromedial (vmPFC) prefrontal cortex (Chevallier, Kohls, et al., 2012; Skuse & Gallagher, 2009). The amygdala plays a key role in mediating vigilance towards salient environmental stimuli (Adolphs, 2009), guiding attention towards important social signals such as information conveyed by the eyes (Adolphs et al., 2005). The frontostriatal regions within this circuit are important for mediating the motivational, hedonic and cognitive aspects of rewards (Berridge et al., 2009). The ventral striatum is typically associated with incentive motivation whereas the dorsal striatum is important for monitoring action outcomes to maximise reward consumption (Balleine et al., 2007). Both the ventral and dorsal striatum have been implicated in social reward processing, with the ventral striatum involved in the anticipation of social rewards (Spreckelmeyer et al., 2009) and the dorsal striatum involved in the receipt of more complex social rewards (Balleine et al., 2007). Within the PFC, the OFC and vmPFC are important for coding the reward value of primary and secondary rewards such as food, money and positive social feedback (Lin, et al., 2011; O'Doherty, 2004).

The neural circuit involved in social motivation is influenced by the neuropeptides oxytocin (OT) and vasopressin (AVP), which work in concert with the neurotransmitters dopamine (DA), serotonin (5HT), acetylcholine (Ach) and norepinephrine (NE), as well as endogenous opioids and cannabinoids (Skuse & Gallagher, 2009; Trezza et al., 2010). Human and rodent studies indicate that both OT and AVP play an important role in social motivation and are involved in a number of other key social behaviours

such as pair-bonding and social recognition (Bora, Yucel, & Allen, 2009; Gordon, Martin, Feldman, & Leckman, 2011; Stevenson & Caldwell, 2012; Wersinger et al., 2004). OT and AVP synthesis is regulated by the sex steroids oestrogen and androgen respectively, with AVP receptor sensitivity further influenced by 5HT (Skuse & Gallagher, 2009). These neuropeptides are thought to modulate social motivation via interactions with the DA reward circuits in the striatum and associated regions; OT receptors interact with DA in the nucleus accumbens (NAcc) shell and the ventral tegmental area (VTA), and AVP interacts with similar circuits in the NAcc shell, lateral septal nucleus and dorsal striatum (Skuse & Gallagher, 2009). In addition to DA, opioids and cannabinoids play an important role in regulating motivational, hedonic and cognitive components of social rewards with the cognitive elements of socially rewarding behaviours further regulated by norepinephrine and acetylcholine (Avale et al., 2011; Trezza et al., 2010).

The evidence suggests that the neural circuit involved in the processing of social rewards may be abnormal in ASD. For example, fMRI studies indicate that people with ASD show abnormal activation in the amygdala, striatum and temporal lobe during social cognitive tasks such as emotion processing and theory of mind (Baron-Cohen et al., 1999; Castelli, Frith, Happé, & Frith, 2002; Critchley et al., 2000) as well as abnormal activity in the vmPFC during mentalising tasks (Kennedy & Courchesne, 2008). In addition, recent evidence suggests that activity within these regions is abnormal during processing of social and non-social rewards (see chapter 4). Structural neuroimaging studies also suggest that these regions are abnormal in ASD, with structural abnormalities having been reported in the amygdala and frontostriatal

regions (Cauda et al., 2011). These findings provide potential neurological basis for disrupted social reward processing in ASD.

It is hypothesised that disrupted oxytocin and vasopressin signalling plays a role in social reward processing deficits in ASD, impacting upon DA function in the context of social interactions (Dawson et al., 2009). There are a number of lines of evidence that lend support to this conjecture. In terms of genetic evidence, polymorphisms on the oxytocin (OXTR) and vasopressin (AVPR1a) receptor genes have been associated with ASD (Jacob et al., 2007; Lerer et al., 2007; Modahl, Fein, Waterhouse, & Newton, 1992; Yirmiya et al., 2006) although these have been inconsistently reported (Tansey et al., 2010, 2011). Evidence from fMRI studies suggest OXT and AVP may mediate risk for ASD via their influence on amygdala activation (Kirsch et al., 2005; Meyer-Lindenberg et al., 2009). Variation in genes encoding proteins involved in the function of OXT and AVP also provide a potential mechanism whereby social reward processing deficits could emerge in ASD. For example, allelic variants on the CD38 gene, which encodes a protein involved in OT secretion, have been reported in ASD and are associated with reduced plasma OT levels (Munesue et al., 2010). Abnormal peripheral OXT and AVP levels have also been recorded in ASD, with decreased plasma OT associated with higher levels of social impairment in ASD (Green et al., 2001; Modahl et al., 1992) and increased plasma AVP levels also observed in ASD (Boso et al., 2007).

1.6.3 Evolutionary Perspective

Modern humans' ancestors lived in hunter-gatherer societies and evolved from primates who mostly lived in groups (Lancaster, 1975). Though there are certain costs associated with living in groups, such as competition for resources and exploitation by

others, there are also important benefits, such as sharing of food, knowledge and parenting responsibilities (Kenrick et al., 2010). Social affiliation, referring to the 'need for belongingness,' is thought to underlie a number of collaborative activities and can be distinguished from other socially motivated behaviours such as mating, parenting or dominance (Kenrick et al., 2010). Social affiliative behaviours that are intrinsically reinforcing are conserved across evolution, with behaviours such as social play observed across mammalian species from rodents, to non-human primates and human children (Trezza et al., 2010). What is more, these behaviours are sub-served by similar neurobiological processes, with neuropeptides similar to OT and AVP found in diverse species (Skuse & Gallagher, 2009).

Chevallier et al. (2012) propose that ASD is characterised by a specific deficit in the motivation for social affiliation, as opposed to other socially motivated behaviours including familial attachments and sexual drives. Studies have shown that attachment behaviours are preserved in ASD, when intellectual disability is taken into account (Rutgers et al., 2004) and that people with ASD often report desire for romantic relationships (Mehzabin & Stokes, 2011) suggesting that these social drives are preserved in ASD.

1.6.4 Treatment Implications of the Social Motivation Theory for ASD

Dawson (2008) proposes that social motivation deficits in ASD could be addressed through early interventions that target parent-infant interactions. Such interventions would need to take into account that relationships are transactional, i.e. that the infant exerts an effect on the parent, which influences the sensitivity of the parent's

response. Interventions that seek to improve synchronisation between parents and their children, such as the 'Early Start Denver Model,' have been shown to be associated with long-term improvements in adaptive behaviour and communicative development in ASD (Dawson et al., 2010; Siller & Sigman, 2002). Alternatively a classical conditioning approach could be used, pairing social stimuli with other positive reinforcers, such that the social stimulus gains a reinforcing value (Dawson et al., 2005a). There are currently no pharmacological interventions for treating the core deficits in ASD. Stimulants, selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics are commonly used for treating associated symptoms in ASD, but not the core symptoms. Evidence suggests that the oxytocin system provides a potential avenue for the pharmacological treatment of social impairments (Andari et al., 2010; Chadman, Guariglia, & Yoo, 2012; Hollander et al., 2007) as well as repetitive behaviours in ASD (Hollander et al., 2003).

1.7 Frontostriatal Circuitry in ASD

Damasio and Maurer (1978) proposed that autism is caused by problems in the mesolimbic-cortex, striatum and thalamus. They observed that damage to these regions was associated with autistic like impairments in terms of motor abnormalities, social and communication deficits, ritualistic and compulsive behaviours and problems with attention and perception. Since these original neuropsychological observations were made, over thirty years ago, the structure and function of the frontostriatal system and associated limbic regions has been clearly delineated.

1.7.1 The Structure and Functions of Frontostriatal Circuitry

Multiple parallel loops connect the striatum to distinct cortical regions. These can be broadly categorised into sensorimotor, associative and limbic circuits, each associated with specific functions – movement, cognition and emotion/motivation respectively - see figure 1.4 (Groenewegen et al., 2003). These circuits are crucial for the implementation of goal-directed behaviours and are responsible for the execution of motor plans as well as the motivational and cognitive functions necessary for such behaviours. They play a cardinal role reward and reinforcement, habit formation, cognitive functions such as procedural learning and working memory, as well as the control of movement (Haber & Knutson, 2009; Haber, 2003).

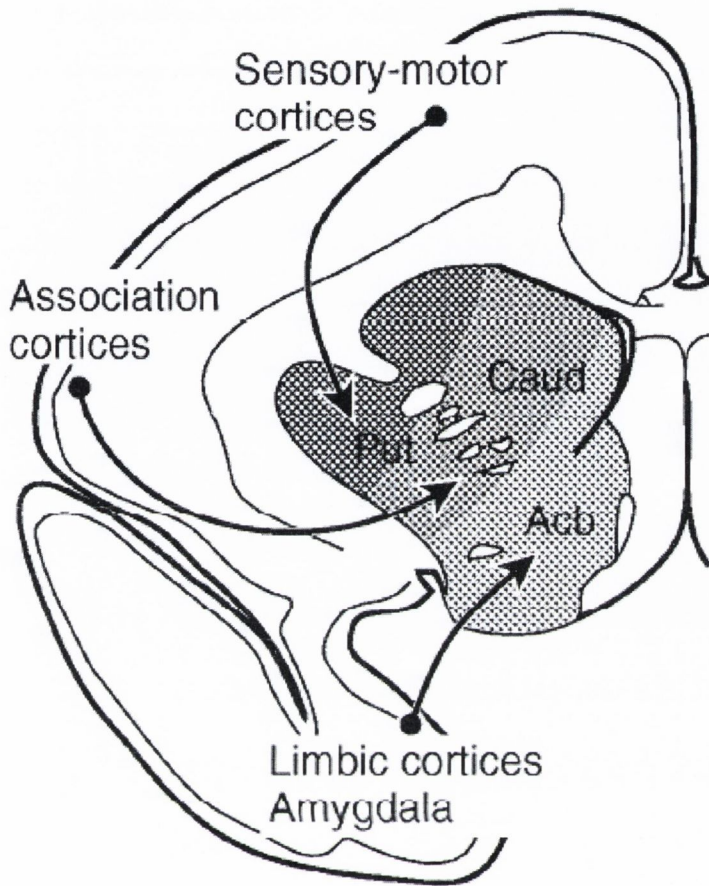


Figure 1.4 Functionally Distinct Corticostriatal Projections, figure from Groenewegen et al. (2003).

Corticostriatal connections can be broadly defined in terms dorsolateral 'sensorimotor,' medial 'cognitive' and ventrolateral 'motivation/emotion' loops. Caudate nucleus (Caud), Putamen (Put) and nucleus accumbens (Acb) (Groenewegen et al., 2003).

1.7.2 The Functions of the Frontostriatal Circuitry and their relevance to ASD

Abnormal functioning of frontostriatal circuitry is potentially involved in the two core deficits in ASD – social interaction difficulties and repetitive behaviours problems

(Dichter & Adolphs, 2012), and may also underlie other associated difficulties in ASD, such as executive function problems (Langen, , et al., 2011). The following sections shall specifically examine the potential role of frontostriatal circuitry in social impairments and repetitive behaviours in ASD.

1.7.2.1 Reward Processing and Social Impairments

Reward processing involves a network of frontostriatal and limbic regions including the striatum, amygdala, OFC and vmPFC (Haber & Knutson, 2009; O'Doherty, 2004). 'Social Motivation Theory,' proposes that deficits in social interaction in ASD are due to a difficulty in forming reward representations of social stimuli, which results in reduced social attention and contributes to further difficulties in terms of social interaction and communication (Dawson et al., 2005a, 2005b; 2012). Neuropsychological studies provided the first evidence that ASD may be characterised by impaired reward processing. Simple fear conditioning, which relies primarily on the subcortical amygdala system, is preserved in ASD, whereas differential fear conditioning, which relies on frontostriatal-amygdala circuitry is impaired (Bernier et al., 2005; Gaigg & Bowler, 2007), suggesting that tasks that rely on corticostriatal connections are impaired in ASD. Additionally, poor performance on 'hot' executive function tasks, that involve delayed gratification, but not 'cold' executive function tasks, which do not have a rewarding element, has been found in ASD – unpublished data see Dawson et al. (2012). Therefore reward processing abnormalities in the frontostriatal system could underlie social motivation deficits and social impairments more generally in ASD (Dawson et al., 2005b).

1.7.2.2 Repetitive Behaviours

The basal ganglia are probably best known for the role they play in motor control (Haber, 2003). Understanding of the function of corticostriatal circuitry has been largely informed by clinical descriptions of basal ganglia disorders, such as Huntington's and Parkinson's disease, which result in profound motor disturbances (Langen et al., 2011) and repetitive and preservative behaviours (Cools et al., 2001; Lawrence et al., 1996). Like ASD, Tourette syndrome and OCD are associated with repetitive behaviours. Tourette syndrome is a neurodevelopmental disorder characterised by phonic and motor tics and OCD is an anxiety disorder characterised by intrusive, recurrent thoughts (obsessions) and repetitive and ritualistic behaviours (compulsions). Both of these disorders are associated with abnormalities in the basal ganglia and frontostriatal circuitry (Brem et al., 2012; Frey & Albin, 2006; Graybiel & Rauch, 2000; Worbe et al., 2012). Repetitive behaviours are a core feature of ASD and typically include repetitive non-functional manipulation of objects, stereotypies, restricted and repetitive motor or vocal responses, narrow or circumscribed interests, compulsions, and severe problem behaviours, such as self-injury (Gabriels et al., 2005; Hattier et al., 2012). Repetitive behaviours are associated with deficits in inhibitory control and set shifting (Lopez et al., 2005; Mosconi et al., 2009; South et al., 2007) and it has been suggested that abnormalities in frontostriatal circuitry could underlie repetitive behaviours and EF deficits in ASD (Langen, et al., 2011; Langen, Durston, et al., 2011).

1.8 Thesis Rational and Objectives

The 'Social Motivation Theory' predicts that people with ASD will show reduced responsiveness to social rewards in frontostriatal circuitry (Dawson et al., 2005b). As outlined above, a deficit in social reward processing in ASD would imply that social difficulties in ASD could be ameliorated through interventions that seek to improve social motivation. Behavioural interventions that are based on the principles of operant conditioning, such as Applied Behavioural Analysis (ABA), are often the treatment of choice in ASD, and have been shown to be effective for treating some aspects of the disorder, though not all children respond to treatment (Reichow & Wolery, 2009). Understanding how people with ASD respond to non-social rewards is therefore also important. In addition to sub-serving reward processing, frontostriatal circuitry is implicated in repetitive behaviours (Langen, , et al., 2011; Langen, Durston, et al., 2011). Improved understanding of the structure and function of frontostriatal circuitry could therefore improve understanding of the two core deficits in ASD – deficits in social interaction and communication and restricted interests and repetitive behaviours, could potentially inform interventions, and could be useful in developing suitable biomarkers for evaluating treatment efficacy.

Neuroimaging studies also suggest that there may be diffuse differences in brain function, structure and connectivity in ASD, which are not confined to the frontostriatal regions. Additionally, abnormal developmental processes may underlie differences in brain function and structure in ASD. Therefore differences in frontostriatal function, structure and connectivity, will be examined in the light of potentially more diffuse differences in neuroanatomy in ASD.

1.9 Summary of Thesis Aims:

1. To examine if there is a deficit in social reward processing in ASD and whether abnormalities in reward processing generalise to other classes of rewarding stimuli.
2. To examine the structure and connectivity of frontostriatal circuitry in ASD.
3. To use model-free functional and structural whole-brain analyses to evaluate potential abnormalities in frontostriatal circuitry in the context of other brain anomalies in ASD, and to explore potential convergence across neuroimaging modalities.
4. To examine potential differences in developmental trajectories underlying group differences in brain function and structure in ASD.
5. To investigate the way in which abnormalities in function and structure relate to symptom severity in ASD.

2 Methods

2.1 Introduction

This section describes diagnostic and screening instruments used for participant selection, methods used for recruitment, sample characteristics, behavioural data analysis, basic principles of magnetic resonance imaging (MRI) and methods used for MRI data acquisition and preprocessing. A brief overview of the methods used for data analysis in the experimental chapters of this thesis (chapters 3-5) is also provided.

Detailed descriptions of data analysis are given in chapters three to five.

2.2 Diagnostic, Screening and Cognitive Assessments

Autistic traits are known to vary on a spectrum that extends into the typically developing population (Skuse, 2007). High functioning ASD can be difficult to diagnose as people with high-functioning ASD may use compensatory strategies to overcome some of their social difficulties and often have good expressive language skills, which lead to an over-estimation of their abilities. It is therefore important to use standardised instruments with appropriate cut-off points to dissociate autistic traits that are in the normal range from those which are characteristic of ASD.

2.2.1 The Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview

The Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1994) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 2000), when used together and in conjunction with detailed clinical assessments, are described as the ‘gold standard’

assessments for ASD. Clinical diagnosis of ASD, which was established prior to recruitment to the study for all ASD participants, was confirmed using the ADOS-G the ADI-R, and clinical consensus diagnosis carried out by an expert clinician (Prof. Gallagher) in accordance with DSM-IV-TR criteria.

The ADOS-G is a semi-structured assessment, involving various activities, which allow the assessor to observe and rate social, communication and repetitive behaviours related to ASD diagnosis. The ADOS-G is divided into four modules depending on the individual's chronological age and expressive language level. All ASD participants in the present study were assessed using module four, which is appropriate for adolescents and adults with fluent speech. ASD and Autism cut-off points are based on scores of communication, reciprocal social interaction and the combination of communication and reciprocal social interaction. I carried out ADOS-G assessments except in cases where they had already been carried out in a clinical setting or for research in the Department of Psychiatry. In order to carry out these assessments, I attended training in the Department of Psychiatry at Trinity College Dublin and had reached a research reliable standard, i.e. I had coded at least three assessments from modules 1 and 2 and three assessments from modules 3 and 4 with greater than 80% agreement with another research reliable assessor.

The Autism Diagnostic Interview–Revised (ADI-R) is a structured interview, carried out with parents or caregivers, which focuses on the developmental history and current behaviour of the individual being evaluated. The interview focuses on the three functional domains, social interaction, communication and restricted interests and repetitive behaviours, and also examines other clinically relevant behaviours. As such

the interview enables the assessor to screen for ASD and distinguish ASD from other developmental disorders, such as Rett Syndrome. Autism cut-off levels are based on reciprocal social interaction, communication, repetitive/stereotyped behaviour scores and evidence of abnormal development before 36 months of age. Having completed ADI training (with over 90% agreement for scoring of training videos), I interviewed either one or both of the participant's parents, except in cases where the ADI* or ADI-R had been completed as part of a prior research study in the Department of Psychiatry. *Four cases had been assessed using the ADI (Couteur et al., 1989), a pre-publication version of the ADI-R.

2.2.2 The Social Responsiveness Scale and the Social Communication Questionnaire

The social responsiveness scale (SRS) is a clinically validated, informant based questionnaire for measuring current autistic traits (Constantino et al., 2003). The SRS can also be used to quantify social deficits characteristic of autism in the general population. Autistic traits measured by the SRS are continuously distributed and moderately to highly heritable (Constantino & Todd, 2003). In the current study, the adult pre-publication version of the SRS was used with permission in cases 18 years or older (Constantino & Todd, 2005). Child and adult versions of the SRS scales differ only in the questions posed with the questions in the adult version more appropriate for young adults. Though there is no published data on the clinical validity of the adult SRS, a recent study combined the child and adult versions showing that these scales measure a quantitative, heritable trait supporting their genetic validity (Coon et al., 2010). T-scores above 60 (corresponding to a raw score of above 79 for males) on the

SRS are indicative of ASD. In the present study the SRS was completed by one of the participant's parents, for both cases and controls. The SRS was used to screen controls for features of ASD – with a raw-score cut-off of above 50 set as an exclusion criterion for the control group – and as quantitative measure to correlate neuroimaging findings with autistic traits in both ASD and control groups.

The Social Communication Questionnaire (SCQ) is a brief informant based questionnaire which is based on the ADI-R. Scores of above 15 on the SCQ are indicative of an ASD. The lifetime version, which focuses on an individual's developmental history, was completed by parents of both cases and controls. This was used to screen controls for features of ASD and a cut-off above 10 was set as an exclusion criterion for the control group.

2.2.3 The Intelligence Quotient

Full scale IQ (FSIQ) was measured using the four-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or the Wechsler Intelligence scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003). Performance IQ (PIQ) score was based on the Matrix Reasoning and Block Design subtests and Verbal IQ (VIQ) score on the Vocabulary and Similarities subtests. I carried out all WASI assessments, except in cases where the WASI or WISC-IV had been carried out for clinical, research (in the Department of Psychiatry) or educational assessments within the last two years.

2.3 Participant Recruitment and Selection

Twenty-eight right-handed male participants with high functioning ASD and twenty-seven right-handed male, age and IQ matched controls took part in the MRI study. In addition to these fifty-five participants, assessments were carried out on other potential participants and only those who met diagnostic criteria, but not any of the exclusion criteria, were included. Six ASD participants were recruited through an associated genetics research programme. The remainder were recruited through clinical services, schools and advocacy groups. Controls were recruited through schools, the university, local volunteer websites and in local businesses. Ethical approval was obtained from the St. James's Hospital/AMNCH (ref: 2010/09/07) and the HSE Linn Dara Child and Adolescent Psychiatry Ethics Committees (ref: 2010/12/07). Written informed consents/assents were obtained from all participants and their parents (where under 18 years of age).

In terms of inclusion criteria all participants were right-handed males aged between 12 and 25. Exclusion criteria for both ASD and control participants included a FSIQ <70, a known neurological or genetic disorder, a history of a loss of consciousness for more than five minutes and current use of psychoactive medication. Exclusion criteria specific to MRI scanning included metal in the body, wearing dental braces, claustrophobia and fear of loud noises. Due to well-recognised high levels of co-morbidity of ASD and Attention Deficit Disorder (ADD) or ADHD symptoms (Leyfer et al., 2006), four subjects in the ASD group with ADD or ADHD symptoms were included in the study. None of the participants were taking psychoactive medication at the time of testing. One of the subjects with ADHD symptoms was taking methylphenidate

(Concerta) prior to taking part in the study but was given a two-week wash-out period, during school holidays, before scanning. Controls were excluded if they had a first degree relative with an ASD, had a raw score of above 50 on the SRS (Constantino et al., 2003) or above 10 on the SCQ (Rutter et al., 2003). All participants had normal, or corrected to normal, vision.

2.4 Sample Characteristics and Demographics

All ASD participants met criteria for Autism or ASD on the ADOS and Autism on the ADI-R. Eleven participants in the ASD group met DSM-IV-TR criteria for Autism, nine met criteria for Asperger syndrome and eight had a diagnosis of PDD-NOS. Of these subjects, one participant with Autism, two with Asperger syndrome and one with PDD-NOS were excluded from further analysis. These subjects were excluded due to excessive motion in the scanner, anxiety in the scanner resulting in the scanning session being terminated early or - in the case of the participant with PDD-NOS - due to the discovery of agenesis of the corpus callosum during the scanning session. Age, IQ, SRS, SCQ, ADOS-G, ADI-R and demographic information for the 24 ASD and 27 control participants included in the study are provided in tables 2.1 to 2.3 below. There were no significant group differences in age or IQ (table 2.1) or years of education for participants or their parents (table 2.2). As expected, groups differed significantly in terms of SRS and SCQ scores (table 2.1). ADOS-G and ADI-R scores for the ASD group are provided in table 2.3.

Table 2.1 Age, IQ, SRS and SCQ scores.

	Mean (SD)	P Value
Age	ASD=17.28 (3.57) Control=17.15 (3.64)	.899
FSIQ	ASD= 109.25 (15.04) Control=111.85 (12.32)	.500
VIQ	ASD= 108.54 (14.42) Control=110.52 (13.59)	.617
PIQ	ASD= 107.42 (14.68) Control=110.81 (11.11)	.307
SRS	ASD= 94.5 (27.57) Control=13.26 (10.35(	<.0001
SCQ	ASD= 20.85 (6.44) Control=2.91 (3.08)	<.0001

Table 2.2 Years of Education

	Mean (SD)	P Value
Participant Years of Education	ASD= 12.17 (3.16) Control=13.04 (3.79)	.386
Mother's Years of Education	ASD= 15.41 (4.06) Control=15.56 (2.66)	.251
Father's Years of Education	ASD=16.58 (3.89) Control=15.75 (2.29)	.388

Table 2.3 ADOS-G and ADI-R scores

	Mean (SD)
ADOS: Communication	3.88 (1.19)
ADOS: Reciprocal social interaction	6.71 (2.22)
ADOS: Social and Communication	10.54 (2.87)
ADOS: Stereotyped behaviours and restricted interests	0.75 (1.07)
ADI: Qualitative Impairment in reciprocal social interaction	20.29 (6.06)
ADI: Qualitative Abnormalities in communication	16.00 (4.98)
ADI: Restricted, Repetitive and Stereotyped Patterns of Behaviour	5.42 (2.69)

2.5 Behavioural Data Analysis

Behavioural Data were analysed in SPSSv16 (SPSS Inc., Chicago), PASW statistics (IBM Corp., Armonk, NY) and Matlab 2009, 2011 (MathWorks Inc., United Kingdom). Group differences in neural function, structure and connectivity were correlated with behavioural measures (ADOS-G, ADI-R and SRS). Non-parametric Spearman’s correlations were carried out for the three ADOS-G subscales and the three ADI-R subscales for the ASD group, and SRS total scores for both ASD and control groups (see table F.1, appendix F, for tests of normality of the distributions). Correlations with behavioural measures were corrected for multiple comparisons using a bonferroni correction for the number of behavioural measures including their subscales ($p(.05/7)=.0071$). In addition, given that the DSM-5 is to use two dimensions for ASD diagnosis – social and communicative deficits (SCD) and restricted interests and repetitive behaviours (RRB) – and that recent findings support two factor models of

ASD symptoms (Boomsma et al., 2008; Frazier, Youngstrom, Kubu, Sinclair, & Rezai, 2008; Georgiades et al., 2012; Mandy, Charman, & Skuse, 2012), correlation analyses were repeated using scores from a two-factor model of ADI scores as reported by (Georgiades et al., 2012). Total SCD and RRB scores were calculated for ASD participants using the 20 SCD and the six RRB items described by Georgiades et al. (2012) (see appendix H).

2.6 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) allows detailed in vivo examination of brain anatomy and function. Studies using MRI have the advantage of being able to recruit large samples and are hampered by fewer confounding factors than post-mortem studies. The following section shall provide a brief introduction to the principles and applications of MRI.

2.6.1 Basic Principles of Magnetic Resonance Imaging (MRI)

MRI is a non-invasive medical imaging technique for imaging soft tissues in the body including the brain, heart and other muscles. It is based on the principle of nuclear magnetic resonance (NMR) which makes use of the positive charge of the spinning nucleus of hydrogen atoms that are present in tissues containing water, proteins, lipids and other macromolecules (Edelman & Warach, 1993). The proton has a small magnetic field which aligns in a parallel or anti-parallel direction with respect to a larger magnetic field when placed inside it. The majority of protons align in the parallel direction as this is the lower energy state, creating net magnetisation in the direction of the larger magnetic field. When a radiofrequency pulse is applied at the appropriate

frequency (called the resonance frequency), the protons absorb the energy and reverse their direction, giving rise to net polarisation in the transverse plane, perpendicular to the external magnetic field. They then release this energy ('relaxation') producing a small current in the receiver coil called free induction decay (FID). Relaxation gives rise to the MR signal and is composed of two components: 1) longitudinal relaxation whereby spins reorientate to the external field (T_1), and 2) transverse relaxation which occurs due to the spins getting out of phase (T_2) - see figure 2.1. FID decays approximately exponentially with the time constant T_2 . However, human tissue produces inhomogeneities which cause the resonance frequency to vary across the body and shortens the FID. The time constant for the observed decay is T_2^* , which is faster than T_2 .

An MR image is a display of localised signal intensities which appear as points of relative brightness or darkness (Edelman & Warach, 1993). The signal strength depends on the strength of the magnetic field, the imaging technique (pulse sequence), tissue characteristics and other factors such as magnetic susceptibility and blood flow. Information about the origin of the signal is acquired by applying additional magnetic gradients to the external magnetic field during the radio frequency pulse. This makes it possible to acquire one slice at a time. Multiple 2D slices are usually acquired in the axial plane. The signal from each slice is received from the receiver coil in frequency space, or k-space. Spatial frequency information in each k-space image is reconstructed into image space using an inverse fourier transform (Huettel, Song, & McCarthy, 2009). The resulting 3D image, compiled from multiple 2D images can be viewed in any plane (i.e. axial, coronal or sagittal). The basic units of these images are voxels, or three dimensional volume elements, which vary in size from 1 to 2mm for

structural MRI (high spatial resolution) and 3 to 5 mm for functional MRI (low spatial resolution).

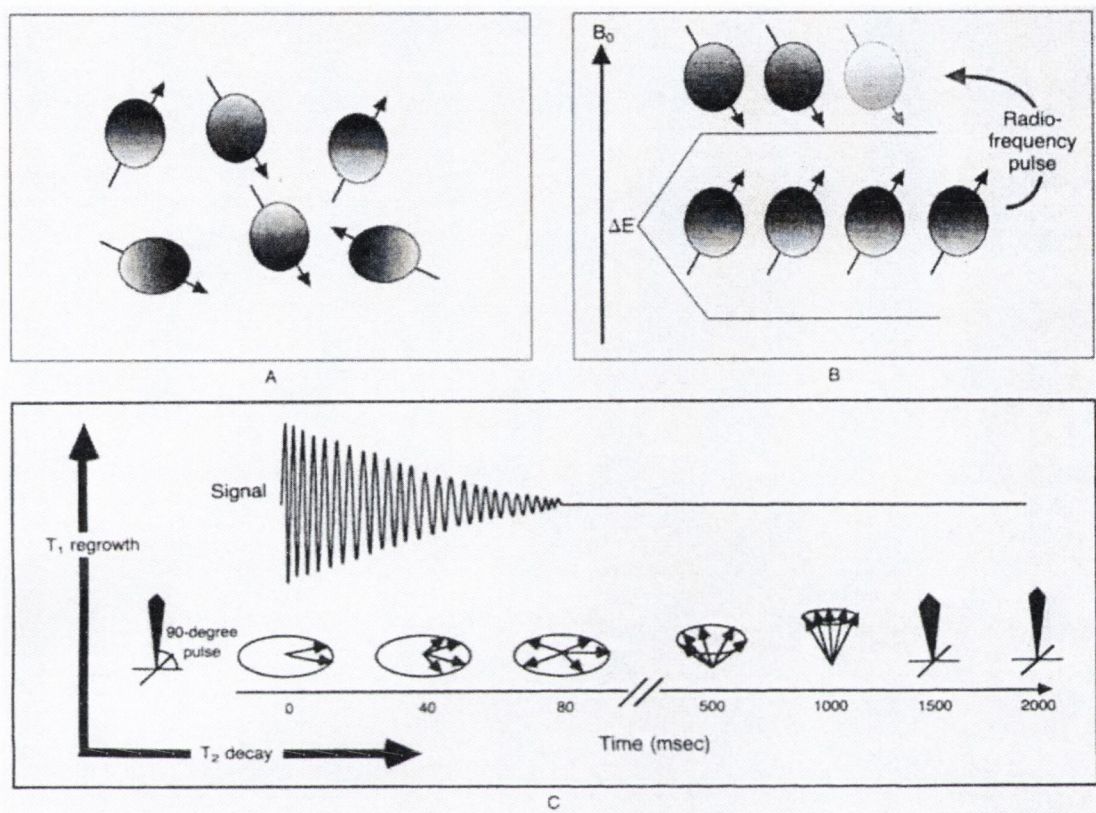


Figure 2.1 Basic Principles of Magnetic Resonance Imaging, figure from Edelman and Warach (1993).

In the absence of a magnetic field the magnetic axes of a group of protons is randomly orientated (Panel A). The presence of a strong magnetic field causes the protons to align both with and against the field. There is an excess of protons aligned to the field as this is the lower energy (ΔE) state (Panel B). A 90° radiofrequency pulse applied at the resonance frequency causes the protons to flip and align with the higher energy state, from which they 'relax' back to their original alignment at a rate determined by T_1 and T_2 relaxation times producing the magnetic resonance signal (Panel C). T_1 relaxation represents the 're-growth' of the net alignment in the direction of the magnetic field (longitudinal magnetisation), occurring over several hundred milliseconds to several seconds depending on the tissue. T_2 relaxation is much shorter (tens of milliseconds) and represents the disappearance of transverse magnetisation (Edelman & Warach, 1993).

2.6.2 MRI Contrast Mechanisms

Different contrasts can be used to generate images providing a wide range of information about tissue properties. Static contrasts, such as T_1 , T_2 and T_2^* , are based on relaxation time, whereas motion contrasts are sensitive to the movement of spins through space, as used in diffusion MRI (Huettel et al., 2009).

2.6.2.1 Structural MRI: T_1 and T_2 images

The most commonly used structural contrast for creating high resolution anatomical images of the brain is the T_1 -contrast. In T_1 -weighted images CSF appears dark, grey matter is grey and white matter is light. These images can be used to provide quantitative information (usually volumetric) about brain structures. Techniques have also been developed to provide other metrics such as shape and cortical thickness.

2.6.2.2 Functional MRI: T_2^* images

Functional MRI (fMRI) allows the study of the neural processes that underlie cognitive processes and how these may be disturbed in conditions such as ASD. fMRI involves the acquisition of a large number of low resolution T_2^* -weighted images. In T_2^* -weighted images CSF is bright, white matter is dark grey and grey matter is light grey. The blood-oxygen-level-dependent (BOLD) contrast provides an index of neural activity by using the difference in signal on T_2^* -weighted images as a function of the amount of deoxygenated haemoglobin. A cognitive, sensory or motor process causes an increase in neural signal within certain regions of the brain. This neural activity requires energy in the form of adenosine triphosphate (ATP) which is created through the oxidation of glucose. Oxygen and glucose are supplied through increased blood flow to active

neurons and deoxyhaemoglobin is replaced with oxygenated haemoglobin. Deoxyhaemoglobin is paramagnetic and therefore reduces MR signal intensity by altering the spins of nearby hydrogen nuclei. The subsequent displacement of deoxyhaemoglobin by oxyhaemoglobin, with increased blood flow to regions involved in the specific cognitive, motor or sensory process, results in localised increases in the MR signal (Huettel et al., 2009). Following preprocessing, to correct for factors such as subject head motion, a statistical model (typically the General Linear Model – GLM) is applied to the data to examine signal intensity at each voxel in the brain. The canonical haemodynamic response function -see figure 2.2 - is typically used to model the BOLD response within the GLM. Therefore the measured signal intensity provides an indirect measure of neuronal activation in a given voxel or set of voxels. Correlational analyses can also be carried out to quantify the amount of co-activation between voxels within regions of the brain.

Functional neuroimaging studies typically use 'stimulation paradigms' to examine task or stimulus dependent changes in brain activity (Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008). Initially fMRI paradigms relied on sequentially presented stimuli within blocked conditions, with subtraction methods used to compare the BOLD response across conditions. The advent of event-related designs (Friston, Frith, Frackowiak, & Turner, 1995a; Friston, Frith, Turner, & Frackowiak, 1995b) enabled the detection of transient variations in the hemodynamic response allowing the temporal characterisation of BOLD signal change, typically using the HRF (Amaro & Barker, 2006). The advantage of this technique is that it allows one to model BOLD changes during several events within a trial. Both block designs and event-related fMRI are used to approximate neural activity during cognitive processes of interest. The BOLD

signal can also be used to measure spontaneous activity in the absence of a task (Fox et al., 2005) – with the brain showing functional organisation during rest that parallels task related activity decreases (Raichle & Snyder, 2007).

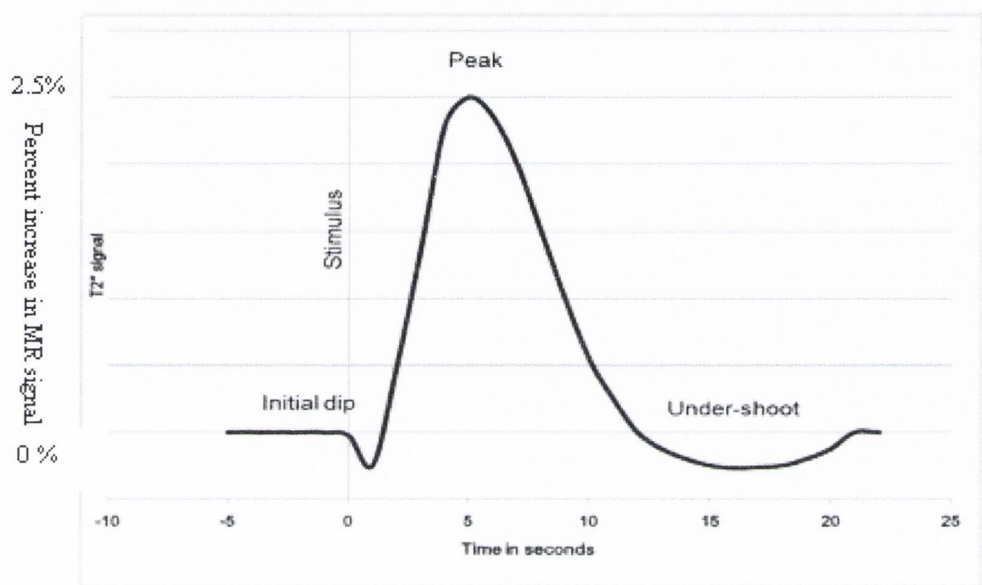


Figure 2.2 The Haemodynamic Response Function, figure from Heijblom (2009).

Neuronal activity results in an initial 'dip' in the BOLD signal, followed by an increase in blood flow, which 'over-compensates' for the increased demand. Blood flow peaks at approximately 6 seconds, after-which it falls back to baseline, or is characterised by a 'post-stimulus undershoot' (figure from (Heijblom, 2009)).

2.6.2.3 Diffusion MRI

T₁-weighted images are not capable of detecting subtle differences in white matter integrity (Büchel et al., 2004). Diffusion MRI, on the other hand is thought to provide more precise information about white matter composition (Basser, 1995). Diffusion MRI exploits the thermodynamic properties of water molecules to create a contrast

based on the mobility of water molecules within a tissue. At temperatures above zero, water molecules undergo constant thermal agitation known as 'Brownian Motion' or 'diffusion' (Jones, 2008). When there are no restrictions water will diffuse equally in all directions (isotropic diffusion). However, when there are restrictions on diffusion, as in the case of neuronal axons, diffusion will occur primarily along one axis (anisotropic diffusion). In diffusion MRI, magnetic gradients are applied to cause changes in the MR signal that are dependent on the amplitude and/or direction of diffusion (Huettel et al., 2009).

As white matter is composed mostly of nerve fibres, diffusion is highly anisotropic as water diffuses in the direction of the fibre. Diffusion Tensor Imaging (DTI) is a non-invasive method for quantifying white matter integrity in-vivo. A 3-by-3 diffusion tensor matrix is generated for each voxel (Basser, Mattiello, & LeBihan, 1994a, 1994b). This comprises three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and corresponding eigenvectors ($\hat{e}_1, \hat{e}_2, \hat{e}_3$) which describe the apparent diffusivities and directions along the principle axes of diffusion respectively (Alexander, Lee, Lazar, & Field, 2007). The eigenvalues can be used to infer white matter integrity in the brain. The first eigenvalue (Axial Diffusivity-AD) reflects diffusion in the direction of the axon, and the mean of the second and third eigenvalues (Radial Diffusivity-RD), indexes diffusivity perpendicular to the axon bundle. Fractional Anisotropy (FA) and Mean Diffusivity (MD) are summary measures based on the eigenvalues. FA measures the fraction of the tensor that can be assigned to anisotropic diffusion with values ranging from 0 (isotropic diffusion,) to 1 (anisotropic diffusion) represented by constrained diffusion along one axis only (Jones, 2008). MD quantifies the average diffusion across the three eigenvalues.

FA and MD are the two most commonly used metrics for characterising white matter structure (Vos, Jones, Jeurissen, Viergever, & Leemans, 2012). White matter neuropathology often causes FA and AD to decrease, and MD and RD to increase (Alexander, Lee, Lazar, & Field, 2007; Beaulieu, 2002; Horsfield & Jones, 2002; Qiu, Tan, Zhou, & Khong, 2008). Changes in FA and MD may be a consequence of changes to AD or RD, or both of these metrics in proportion to one another. Higher FA is thought to reflect increased fibre bundle density and corresponding axonal membranes, which is modulated by the degree of myelination (Beaulieu, 2002). Increased MD is thought to reflect demyelination or axonal damage (Basser, 1995; Basser & Pierpaoli, 1996). AD is thought to index axonal integrity and RD is thought to measure the degree of myelination (Song et al., 2003). These measures can be examined in a voxel-wise fashion across the entire brain, within a volume of interest, or by estimating white matter connection patterns using diffusion tensor tractography (Jones, 2010), which typically uses the major eigenvector (AD) to estimate the tract direction (Conturo et al., 1999). FA, MD, AD and RD values can then be extracted for the tract of interest to compared white matter integrity between groups.

2.7 MRI Data Acquisition

MRI data were collected on a Philips 3T Achieva MRI Scanner at the Centre for Advanced Medical Imaging (CAMI), St. James's Hospital, Dublin. Subjects lay supine in the fMRI scanner during image acquisition and were instructed to remain as still as possible.

2.7.1 T_1 -weighted Structural Scan

A high-resolution 3D T_1 -weighted MPRAGE image was acquired for each participant (FOV = 256 x 256 x 160 mm³; TR = 8.5 ms; TE = 3.9 ms; total acquisition time = 7.3 mins; voxel size = 1x1x1 mm³).

2.7.2 Task Based fMRI

Two hundred and eighty functional images were acquired for each run using a T_2^* weighted gradient echo sequence to visualise changes in the BOLD signal (TR = 2000ms, TE = 28ms; flip angle = 90°; FOV = 256 x 256mm²; voxel size: 3 x 3 x 3.5 mm³, slice gap 0.35 mm; 38 slices; total acquisition time = 9.3 mins). Presentation® software (Version 14.4, www.neurobs.com) was used for stimulus presentation. Subjects lay supine and stimuli were projected onto a screen behind the subject and viewed in a mirror above the subjects' face.

2.7.3 Resting-state Data

One hundred and fifty functional scans were acquired using a T_2^* weighted gradient echo sequence to visualise changes in the BOLD signal (TR = 2000ms, TE = 28ms; flip angle = 90°; FOV = 240 x 240mm²; voxel size: 3 x 3 x 3.5 mm³, slice gap 0.35 mm; 38 slices; total acquisition time = 5.06 mins). Subjects were instructed to keep their eyes shut and to rest for five minutes.

2.7.4 Diffusion Tensor Imaging (DTI)

Diffusion-weighted data were acquired using a single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme (SENSitivity Encoding). Diffusion-

weighted images were encoded along 32 independent directions and one non-diffusion-weighted image was acquired. Data were acquired with the following parameters: TR = 12052 ms; TE 55 ms; B value 1000; slice thickness/gap FOV; slice number=70; voxel dimensions 2mm³ Acquisition time 8.08 mins.

2.8 MRI Data Preprocessing

2.8.1 fMRI Preprocessing

fMRI preprocessing was carried out in SPM8 (www.fil.ion.ucl.ac.uk/spm) in Matlab 2009a (MathWorks Inc., United Kingdom). Before preprocessing, the origin was set to the anterior commissure for both T₁-weighted and EPI Images. Slice-timing correction was then applied to the data, given the recent evidence that this approach is superior to flexible modelling strategies in correcting for differences in image acquisition time between slices (Sladky et al., 2011). The images were then realigned to correct for motion artefacts and co-registered to the skull stripped T₁-weighted image.

Normalization to standard stereotaxic space (Montreal Neurological Institute; MNI) was performed using the ICBM EPI template and the unified segmentation approach (Ashburner & Friston, 2005). The data were then re-sliced to a voxel size of 2 x 2 x 2 mm³. Finally, the images were smoothed using a 5 mm full-width-half-maximum (FWHM) Gaussian kernel to conform to assumptions of statistical inference using Gaussian Random Field Theory (Friston et al., 1995a; Friston et al., 1995b).

Twenty-one ASD subjects and 21 controls were included in the social and monetary reward processing tasks after excluding subjects for excessive head motion (movements > 3mm) or poor behavioural performance (<50% correct trials in any

condition of either task). Twenty-two ASD participants and 24 controls were included in the resting-state data analysis, after excluding subjects for excessive head motion (movements > 3mm). Given recent evidence that resting-state networks are particularly susceptible to head motion (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012) independent samples t-tests were performed to ensure that groups did not differ on rotation or translation parameters (translation: mean ASD=.0401 (SD=.016), mean control =.0331 (SD=.0157) $p=.136$; rotation: mean ASD=.0006(SD=.00002), mean control =.0005 (SD=.00002) $p=.122$).

2.8.2 Diffusion-weighted Data Preprocessing

Preprocessing of diffusion-weighted data was carried out using Explore DTI (Leemans, Jeurissen, Sijbers, & Jones, 2009). The data were first screened by looping through each subjects' image to ensure that there were no gross artefacts such as signal dropout. Data were then corrected for eddy-current distortions and subject motion with B-matrix rotation to preserve orientational information (Leemans & Jones, 2009). First, the diffusion-weighted images were realigned to the non-diffusion weighed (B0) image using a full affine transformation and cubic interpolation. Motion Tensor values were estimated using robust estimation of tensors by outlier rejection (RESTORE; Chang, Jones, & Pierpaoli, 2005)). The RESTORE method improves tensor estimation compared to the linear and nonlinear least squares methods, correcting for distortions due to fat suppression and cardiac pulsation. The final preprocessing step involved correcting for physically implausible signals. The data were then visually inspected to ensure that the gradient components were in the correct orientation. Finally, participants were excluded for excessive motion (>3mm) or poor data quality

(assessed by looping through diffusion weighted images and examining residuals and outlier profiles in ExploreDTI), with 22 ASD and 24 control participants retained for further analysis.

2.9 MRI Data Analysis

This section gives a brief overview of the training undertaken, and tools used, for conducting MRI data analysis. Detailed description of the methods for each analysis is given in the methods section of the experimental chapters (chapters 3-5).

2.9.1 Skills and Training

Dr Joshua Balsters provided training and supervision of MRI data. I also attended a number of workshops at Trinity College Dublin as well as the ‘Statistical Parametric Mapping (SPM)’ workshop at the Institute of Neurology (IoN), Queen Square, London (13-15 May 2010) and the ‘Neuroanatomy and Tractography Workshop’ at the Institute of Psychiatry (IoP), Kings College London (23rd-25th March, 2011). Further advice on MRI data analysis was provided by Dr. Erik O’Hanlon and Dr. Jane Mc Grath.

2.9.1.1 Analysis of Task Based fMRI data

Task based fMRI data were analysed using Statistical Parametric Mapping (SPM) which can be used to test hypotheses about functionally specialised brain responses (Friston, Frith, Liddle, & Frackowiak, 1991).

2.9.1.2 Analysis of Resting-state fMRI data

Two methods were used to examine resting-state data. A seed region approach was used to examine correlated activity between apriori regions of interest (ROIs) in

frontostriatal circuitry (Whitfield-Gabrieli & Nieto-Castanon 2012). Independent Component Analysis (ICA) was used to examine resting-state networks at the whole brain level (Allen et al., 2011).

2.9.1.3 Analysis of Grey Matter Structure

Two methods were used to examine grey matter structure. The shape and volume of specific subcortical structures were analysed using FIRST in the FSL FMRIB Software Library (Smith et al., 2004). Voxel Based Morphometry (VBM) was used to examine differences in grey matter volume across the whole brain (Ashburner & Friston, 2000).

2.9.1.4 Analysis of White Matter Structure

Two methods were used to examine white matter structure. Between group differences in white matter integrity within frontostriatal circuitry were examined using deterministic streamline tractography in Explore DTI (Leemans et al., 2009). Whole brain analysis of white matter structure was examined using Tract Based Spatial Statistics (TBSS), which is more appropriate for the voxel-wise analysis of white matter integrity than VBM (Smith et al., 2006).

2.10 Thresholding and Correction for Multiple Comparisons

The alpha level was set at .05 for all statistical tests and the False Discovery Rate (FDR) was used for thresholding neuroimaging data, except where otherwise specified. Standard Bonferroni correction for controlling the type I error rate can be too conservative for neuroimaging data, especially when voxel-wise hypothesis testing is performed. This is because the Bonferroni correction controls the probability that false positives will be reported by adjusting the significance level in accordance with the

number of tests performed. FDR, on the other hand, is less conservative, correcting for multiple comparisons by controlling the rate of false positives among the tests that show a significant result (Genovese, Lazar, & Nichols, 2002). Small volume corrections (SVC) were used to correct for multiple comparisons where there were *a priori* hypotheses that activation would be localised within a particular brain region. These can be defined anatomically or functionally (using co-ordinates derived from a meta-analysis), and were defined anatomically for the purpose of the studies presented here, as recommended by Poldrack (2007).

2.11 Presentation of Results

Neuroimaging results are shown in neurological convention (left is left), except where results are presented from FSL, which is in radiological convention (left is right), or where other-wise specified.

2.12 Contribution of Resting-state MRI data to the ABIDE Consortium

T₁ structural, resting-state and phenotype data were contributed to the Autism Brain Imaging Data Exchange (ABIDE) consortium. Ethics approval was obtained from the Linn Dara and AMNCH ethics committees. All data were de-faced and encrypted prior to upload.

3 Social and Monetary Reward Processing in ASD

3.1 Introduction

Studying the neural basis of reward processing in ASD provides a promising approach to understanding the two core deficits that characterise ASD (Dichter & Adolphs, 2012), social communication difficulties and restricted interests and repetitive behaviours (Lord et al., 2011). According to the 'Social Motivation Theory,' deficits in social interaction in ASD are due to a difficulty in forming reward representations of social stimuli, which results in reduced social attention and contributes to further difficulties in terms of social interaction and communication (Dawson et al., 2002; Dawson et al., 2012; Dawson, et al., 2005a). Restricted interests and repetitive behaviour may, on the other hand, reflect hyper-responsive activity in reward circuits to certain classes of stimuli (Dichter et al., 2010).

Evidence from behavioural, electrophysiological and pupillometry studies provide support for the social motivation theory of ASD. As discussed in Chapter 1, young infants with ASD show reduced attention to social stimuli (Klin, 1991; Maestro et al., 2002), which has been interpreted as providing evidence for the social motivation hypothesis (Dawson et al., 2012; Dawson et al., 2002, 2005a). Children and adolescents with ASD do not show enhanced pupillary responses to happy faces, as do their typically developing peers (Sepeta et al., 2012). Pupillary responses to other facial expressions such as anger and fear did not differ between the ASD group and controls. The lack of an enhanced pupillary response to happy faces in the ASD group, with normal responses to other facial expressions, suggests there may be a deficit in the reward system rather than a general aversion to faces conveying emotional

expressions. Behavioural evidence also suggests that ASD may be characterised by a specific deficit in reward based learning in response to social, but not monetary stimuli, with ASD participants failing to choose optimal outcomes based on positive social feedback (Lin, Rangel, & Adolphs, 2012). Electrophysiological studies have provided mixed results, with one study reporting typical feedback-related negativity (FRN) in response to monetary rewards, suggesting that reward based deficits in ASD are not pervasive and may be specific to certain classes of stimuli (McPartland, Crowley, et al., 2012), whereas another study reported reduced P3 amplitude to both social and monetary reward cues in ASD (Kohls et al., 2011), suggesting that ASD may be associated with a general deficit in reward processing. One of the limitations of electrophysiological methods is that they cannot examine the function of subcortical structures – which play an important role in reward processing – and can be better examined using fMRI.

Reward processing involves a well-defined, interconnected, network of cortical and subcortical regions including the orbitofrontal (OFC) and ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), striatum, amygdala, and the dopaminergic midbrain (Balleine & O'Doherty, 2009; Delgado, 2007; Haber & Knutson, 2009; O'Doherty, 2004). Neuroimaging techniques allow the dissociation of neural mechanisms involved in 'wanting,' referring to the incentive motivation to seek the reward, and 'liking,' referring to the hedonic value of the reward (Berridge et al., 2009). Anticipation ('wanting') of rewards is typically associated with activity in the ventral striatum (VS) whereas receipt ('liking') is associated with vmPFC activity (Knutson, Fong, Adams, Varner, & Hommer, 2001). The OFC is associated with coding stimulus reward value, the amygdala with tracking emotional salience of stimuli, and

the ACC with conflict monitoring (Haber & Knutson, 2009; O'Doherty, 2004). The striatum is critical to this circuit; the ventral striatum (VS) for the motivational control of action and dorsal striatum (DS) for integrating rewards with executive functions and action control (Balleine & O'Doherty, 2009; Grahn, Parkinson, & Owen, 2008).

Social reward processing involves a number of neural regions associated with primary (e.g. food) and secondary (e.g. monetary) rewards. Social reward paradigms have used attractive faces, positive feedback (e.g. a smiling face), and more complex social situations such as acquiring a good reputation (Aharon et al., 2001; King-Casas et al., 2005; Spreckelmeyer et al., 2009). Beautiful faces activate foci in the VS and OFC (Aharon et al., 2001) and anticipation of positive emotional expressions has been shown to activate the VS (Rademacher et al., 2010; Spreckelmeyer et al., 2009). Common activation during the receipt of social and monetary rewards has been reported in the striatum (Izuma, Saito, & Sadato, 2008) and social and monetary reward learning engage shared regions of vmPFC and striatum (Lin et al., 2011). On the other hand, the amygdala has been associated with the receipt of social but not monetary rewards in one study (Rademacher et al., 2010) and the DS has been implicated in the receipt of complex social rewards (Balleine et al., 2007; de Quervain et al., 2004; Rilling et al., 2002; Strobel et al., 2011), suggesting that some regions may be more involved in processing social rewards than other types of reward.

Findings from fMRI studies suggest that ASD may be characterised by intact neural responses to primary rewards such as food (Cascio et al., 2012), but abnormalities in terms of social and monetary reward processing. Reduced activation in the VS has been reported during social but not monetary reward feedback in children with ASD

(Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010) as well as during the anticipation of monetary but not social rewards (Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2011; Kohls, Schulte-Rüther, et al., 2012). Reduced VS and vmPFC activity has been reported during the receipt of monetary rewards (Dichter et al., 2010) as well as increased activity in the ACC (Dichter et al., 2011; Schmitz et al., 2008) and OFC (Scott-Van Zeeland et al., 2010). Both increases and decreases in amygdala activation have been reported during social reward anticipation and receipt (Dichter et al., 2011; Kohls, Schulte-Rüther, et al., 2012) and decreased amygdala activation has been recorded during the receipt of monetary rewards (Kohls, Schulte-Rüther, et al., 2012). Additionally, increased vmPFC activation has been reported in response to objects of interest in ASD (Dichter et al., 2010). The results of these studies are clearly heterogeneous and suggest that atypical reward processing in ASD may be non-specific extending to classes of stimuli beyond social rewards and involving a number of regions within reward circuitry. However an important confound in a number of previous studies is that the majority of participants were taking psychoactive medication (Dichter et al., 2010; Dichter et al., 2011; Scott-Van Zeeland et al., 2010), which has a known impact on dopamine regulation and by implication reward processing (Schultz, 2007) as well as having a potential influence on the BOLD signal (Iannetti & Wise, 2007).

The primary aim of the present study was to examine whether deficits in reward processing in ASD are specific to social rewards or can be generalised to other classes of stimuli such as monetary rewards, among medication-free participants with high-functioning ASD. To this end, the BOLD response within frontostriatal reward circuitry for both social and monetary reward anticipation and outcome was examined.

Participants performed adapted versions of the Monetary and Social Incentive Delay Tasks (MID and SID) (Knutson et al., 2001; Knutson, Westdorp, Kaiser, & Hommer, 2000; Rademacher et al., 2010; Spreckelmeyer et al., 2009), which allow the dissociation of the BOLD response during the anticipation and receipt of rewards (Knutson et al., 2001; Spreckelmeyer et al., 2009). A factorial design was used to test two hypotheses; 1) that there is a general dysfunction in reward processing in ASD (main effect of group), characterised by abnormal BOLD responses during the anticipation and/or receipt of both monetary and social rewards, as suggested by the results of previous fMRI studies (Dichter et al., 2010; Dichter et al., 2011; Kohls, Schulte-Rüther, et al., 2012; Schmitz et al., 2008); and 2) that there is a specific deficit in social reward processing (group by reward type interaction), characterised by reduced activation during the anticipation and/or receipt of social rewards, in line with the Social Motivation Theory (Dawson et al., 2002). Based on anatomical regions highlighted by the Social Motivation Theory (Chevallier, Kohls, et al., 2012), previous studies of social and monetary reward processing (Izuma et al., 2008; Knutson et al., 2001; Rademacher et al., 2010; Spreckelmeyer et al., 2009) and studies of reward deficits in ASD (Dichter et al., 2010; Dichter et al., 2011; Kohls, Schulte-Rüther, et al., 2012; Schmitz et al., 2008; Scott-Van Zeeland et al., 2010), it was predicted that group differences in reward processing would be localised to the vmPFC, OFC, ACC, amygdala and/or striatum.

Previous studies suggest that high-functioning ASD is characterised by normal cognitive appraisal of basic positive emotional experiences (Bölte et al., 2008) in the presence of abnormal physiological responses to the same stimuli (Wilbarger et al., 2009). Therefore, in addition to examining the BOLD response during reward

processing, self-reported emotional responses to both reward types were collected to examine if abnormal neural responses to rewards are paralleled by abnormal cognitive appraisal of these rewards. Little is known about how abnormalities in reward processing relate to social interaction/communication and repetitive behaviour problems in ASD, therefore BOLD activation to rewards in regions in which there are significant group differences were correlated with behavioural measures. Finally, reward circuitry undergoes maturational changes during adolescence (Bjork et al., 2004; Bjork, Smith, Chen, & Hommer, 2010) and previous studies indicate that ASD is characterised by atypical neurodevelopmental trajectories (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012; Kleinhans et al., 2012) therefore it is possible that abnormal developmental processes underlie group differences in reward processing in ASD. Group-by-age interactions in regions in which there are significant group differences in the BOLD response were therefore investigated.

3.2 Aims

1. To examine the BOLD response to social and non-social rewards in frontostriatal- limbic circuitry.
2. To examine self-reported emotional responses to both reward types.
3. To examine the relationship between abnormal BOLD responses to rewards and behavioural impairments in ASD.
4. To examine potential group-by-age interactions underlying group differences in the BOLD response to social and monetary rewards.

3.3 Methods

3.3.1 Participants

Twenty-one right-handed ASD and 21 right-handed Caucasian control participants were included in the analyses (see section 2.8).

3.3.2 Functional MRI Tasks

Figure 3.1 illustrates the adapted versions of the ‘Monetary Incentive Delay Task’ (MID; (Knutson et al., 2000)) and the ‘Social Incentive Delay Task’ (SID; (Spreckelmeyer et al., 2009)). In both tasks participants had to respond as quickly as possible to a trigger (white square) while it remained on screen. The amount of time the participant had to respond to the trigger depended on the number of correct or incorrect prior responses (see below). Trigger cues were preceded by an instruction cue signalling the level of potential reward. For ‘reward’ trials a circle denoted that participants would be rewarded if they responded quickly enough (n per task = 60) whilst for ‘no reward’ trials a triangle denoted that the participant would not receive a reward, regardless of whether or not they responded quickly enough to the trigger ($n = 30$). Reward magnitude varied on two levels indicated by the number of horizontal lines on a cue stimulus. In the MID the levels of monetary reward were €0.20 ($n = 30$, preceded by a cue depicting a circle with one horizontal line) and €1.00 ($n = 30$, preceded by a cue showing a circle with two horizontal lines). Success was acknowledged by showing a picture of a coin with the money earned on that trial. In the case of a ‘no reward’ trial, or when participants did not respond to the trigger quickly enough, they were shown a coin stimulus of the same size and luminance but with no features. SID instruction cues

were identical to MID instruction cue except in colour. Feedback was a female face from the NimStim set of Facial Expressions (Tottenham et al., 2009) with a happy facial expression at two levels of intensity (small smile and larger smile), as used in previous studies of social reward (Rademacher et al., 2010). This face stimulus was presented as it was rated as the most pleasant and attractive of the Caucasian faces in the NimStim set by a sample of 20 male participants (see appendix A) and was used previously in a study of social reward in children (Kohls, Peltzer, Herpertz-Dahlmann, & Konrad, 2009). Unlike the original SID task, which used 22 different faces, a single female face was used to remove novelty as a confounding difference between tasks. Two levels of social reward, rather than three (as in the original SID task), were used to reduce task duration. The 'no reward' facial stimulus was the same face graphically dysmorphed, with facial features eliminated but size and luminance retained.

Each task consisted of 90 trials (two 45 trial runs each lasting nine minutes) presented in a counterbalanced order across participants. Each trial lasted 12 seconds (6 TRs). A variable delay was introduced between the instruction cue and trigger (1492-6848ms), and trigger and feedback (1417-6569ms) to ensure that BOLD activity time-locked to the instruction cue was specific to reward anticipation and uncontaminated by the subsequent response or feedback. Similarly, activity at the time of feedback was specific to reward receipt and uncontaminated by reward anticipation or motor responses (Balsters & Ramnani, 2008, 2011). This variable delay was achieved by randomly varying the onset time of instruction cues, triggers and feedback across the first 2 TRs (0-4s), second 2 TRs (4-8s) and third 2 TRs (8-12s) respectively from trial to trial. Cues and feedback were each presented for 1000ms. As in previous MID studies, the duration of the trigger was adjusted to maintain an accuracy rate for

approximately two-thirds of trials. Response periods were reduced by 30ms after each correct response, and increased by 90ms when participants failed to respond within the given time frame. Manipulations of the response period were separate for each reward level given that RTs are known to be faster for higher levels of reward (Knutson et al., 2001, 2000; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008). An upper limit was imposed, such that trigger duration could not exceed more than 500ms.

Prior to scanning participants were asked to identify the emotion shown on the face in the social reward task, to ensure that between group differences in emotion recognition would not confound the results. Participants maintained focus on the cross hair in the centre of the screen throughout the fMRI sessions. They were instructed to respond quickly to the trigger using a button in their right hand. For the MID they were told that they could 'win' real money up to a value of €30. All subjects were given €25 at the end of the experiment, regardless of their performance. For the SID they were informed that success would be acknowledged by a smiling face on the screen.

Practice versions of each task (consisting of 30 trials) were performed to familiarise participants with the experiments prior to scanning. At the beginning of each fMRI session, participants were informed which task (MID or SID) would follow next.

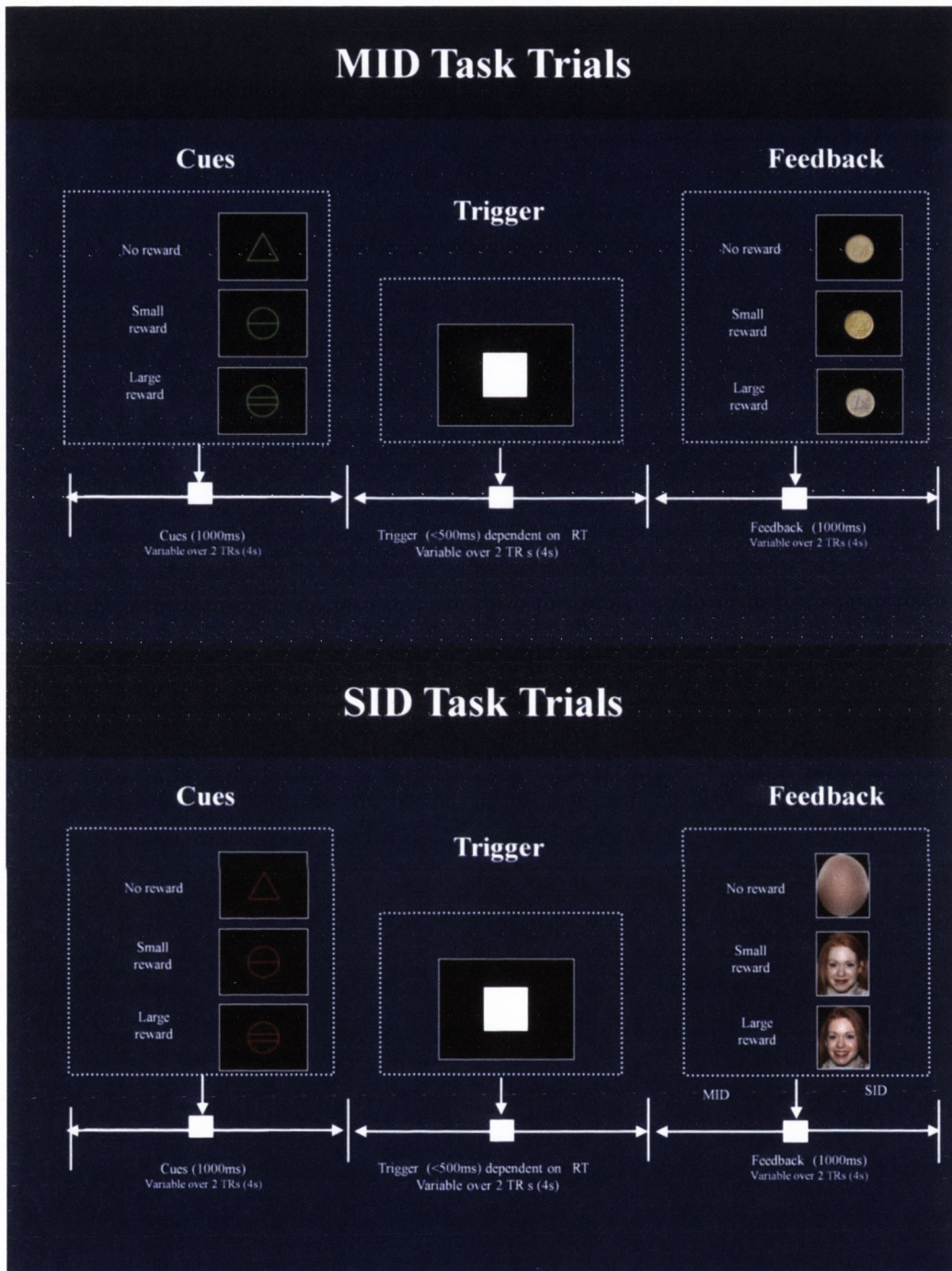


Figure 3.1 MID and SID Task Trials

MID tasks trials are shown on the top panel, SID task trials are shown on the bottom panel. Each trial was divided into three four-second periods; cues occurred in the first period (0-4s), triggers in the second (4-8s) and feedback in the third (8-12s). Cues, triggers and feedback occurred pseudo-randomly within these four-second periods so that activity time-locked to each event type was uncontaminated by preceding or proceeding trial elements

3.3.3 Self-reported ratings of Social and Monetary Rewards

After the experiment, participants were asked to rate how they felt when they received feedback in both tasks using the Self Assessment Manikin (SAM) rating scale (Bradley & Lang, 1994). The SAM is a 9-point visual analogue scale with graphic figures depicting values along the dimensions of valence (unhappy/happy), arousal (calm/excited) and dominance (lack of control/control). The SAM scale has previously been used to test emotional reactivity using a broad range of stimuli in participants of all ages, as well as in several clinical populations including ASD (Ben Shalom et al., 2006; Bölte et al., 2008). For the purpose of this study, the simplified two dimensional model of affective processing which includes only valence and arousal was adopted (Barrett, 1998; Lang et al., 1993). Participants were asked to rate the feedback images for both tasks along the dimensions of valence and arousal by selecting the figure on the scale that best represented how they felt at the time of feedback (see figure 3.2). Prior to rating the images participants received clear instructions, emphasising that the valence scale was a measure of how positive/negative they felt whereas the arousal scale was a measure of the intensity of their emotion regardless of how positive/negative they felt.

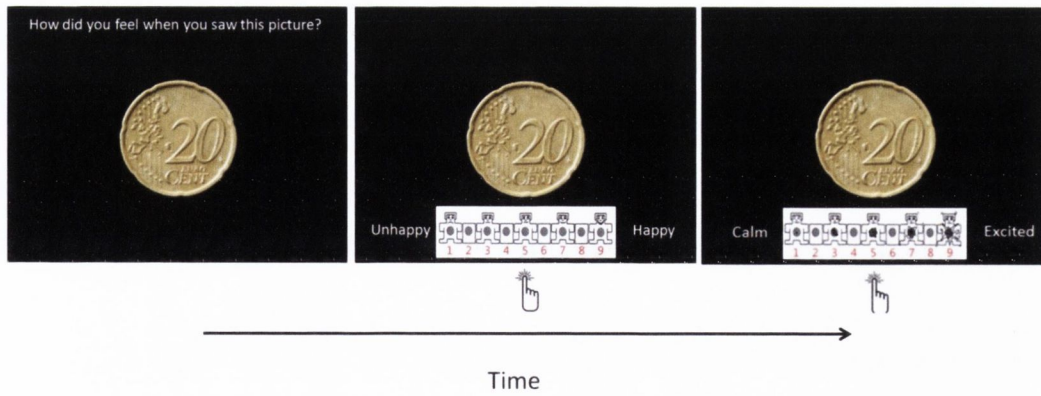


Figure 3.2 Schema of Rating Phase.

Participants rated how they felt along the dimensions of valence and arousal for each feedback image for both tasks. First, they were shown the image on its own and then with valence (unhappy/happy) and arousal (calm/excited) scales beneath the image. Once they had made their selection they were presented with the next image.

3.3.4 Statistical Analysis of Behavioural Data

Mixed model (between/within subjects) ANOVAs were used to examine accuracy and reaction time (RT) data. Pearson’s correlations were conducted to examine the relationship between the BOLD response and RT. Friedman’s Anova and Mann-Whitney tests were used to examine valence and arousal ratings (non-parametric tests were used as rating data are ranked/ordinal).

3.3.5 MRI Data Acquisition and Preprocessing

Details of MRI data acquisition and preprocessing can be seen in section 2.7 and 2.8.

3.3.6 fMRI Data Analysis

fMRI analysis was carried out in SPM8 (www.fil.ion.ucl.ac.uk/spm) in Matlab 2009a (MathWorks Inc., United Kingdom). Nine event types were modelled at the first level for each task: anticipation/cue (‘no reward’, ‘small reward’, ‘large reward’, ‘error’),

feedback ('no reward', 'small reward', 'large reward', 'error') and 'trigger'. 'Cue error' and 'feedback error' comprised reward trials on which participants failed to respond within the given time frame. Nine regressors were created by convolving a delta function of event onset times for each event with the canonical haemodynamic response function (HRF). Given that slice-time correction was used, micro-time onset was set to the middle temporal slice. Covariates of no interest included the six head motion parameters.

Following first level analysis contrast files were created to examine differences in BOLD response between 'no reward' and 'reward' (small and large combined) for both anticipation and feedback. The two levels of reward were combined as behavioural results indicated differences between 'no reward' and 'reward' rather than between the two reward levels. Second level random effects group analyses were used to examine the BOLD response to reward anticipation and feedback. Two two-by-two mixed model ANOVAs [between subjects factor: group; within subjects factor: reward type] were run, to examine main effects and interactions, one for reward anticipation and one for reward feedback. These were followed up using independent and paired sample t-tests. Whole brain analyses were thresholded at $p < .001$ uncorrected (10 contiguous voxels). Finally, age and FSIQ were added as covariates to control for possible effects of these factors.

Key anatomical regions within the reward system (striatum, amygdala, vmPFC, OFC and ACC) were defined *a priori* for small volume correction to correct for multiple comparisons at the family wise error rate (FWE; $p < .05$). Masks for each of these regions were generated in FSL (<http://www.fmrib.ox.ac.uk/fsl/>) using the Harvard

Oxford cortical and subcortical atlases (<http://www.cma.mgh.harvard.edu/>). The caudate nucleus, putamen and nucleus accumbens were combined into a striatal mask (one for each hemisphere) using the image calculator in SPM8. All masks were thresholded at >20% probability. Percent signal change in significant activations was calculated using the Anatomy Toolbox (Eickhoff et al., 2005) in SPM8.

3.4 Results

3.4.1 Reaction Time

Reaction time values are shown in figure 3.3. A mixed model two-by-two-by-three ANOVA [between-subjects factor: group; within subjects factors: reward type and reward magnitude] revealed a significant effect of reward magnitude ($F(1.61, 64.33) = 47.49, p < .0001$; faster responses to 'reward' compared to 'no reward') and a significant interaction between group and reward magnitude, $F(1.61, 64.33) = 4.70, p = .018$. Pair-wise comparisons to examine the main effect of reward magnitude indicated a significant decrease in RT between 'no reward' and 'small reward' levels ($t(41) = 8.660, p < .0001$) as well as 'no reward' and 'large reward' levels ($t(41) = 6.112, p < .001$) but no difference in RT between the 'small' and 'large' rewards ($t(41) = -1.592, p = .119$). Difference scores (RT 'small reward' - RT 'no reward'; RT 'large reward' - RT 'no reward'; RT 'large reward' - RT 'small reward') were calculated to examine the group by magnitude interaction. These indicated that the ASD group showed less of a difference in RT between 'no reward' and 'small reward' ($t(40) = -2.337, p = .025$) and between 'no reward' and 'large reward' than the control group ($t(40) = -2.434, p = .020$) but not between 'large reward' and 'small reward' ($t(40) = -.809, p = .424$). There was no

significant effect of group, group by reward type interaction, magnitude by reward type interaction, or group by reward type by magnitude interaction.

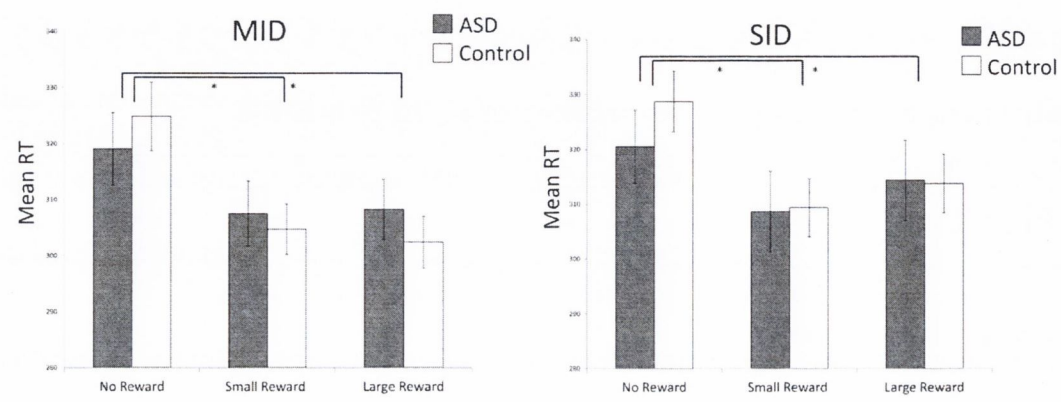


Figure 3.3 Reaction Time for MID and SID tasks.

RT (ms) is shown in grey for the ASD group and in white for the control group. Standard error of the mean is displayed and significant differences in RT between levels of reward magnitude are marked with an asterisk.

3.4.2 Accuracy

As discussed above mean accuracy was maintained for all conditions by adjusting the duration of the trigger from trial to trial. However, a significant effect of reward magnitude was observed ($F(1.65, 66.17) = 21.15, p < .0001$, i.e. greater accuracy for ‘reward’ compared to ‘no reward’), using a mixed model two-by-two-by-three ANOVA [between-subjects factor: group; within subjects factors: reward type and reward magnitude]. Pair-wise comparisons indicated a significant increase in accuracy between ‘no reward’ and ‘small reward’ levels ($t(41) = 5.76, p < .0001$) as well as ‘no reward’ and ‘large reward’ levels ($t(41) = 4.52, p < .0001$) but no difference between the ‘small’ and ‘large’ rewards ($t(41) = -1.00, p = .323$). No other significant effects were observed.

3.4.3 Self-reported Valence and Arousal

There was a significant effect of reward magnitude on valence and arousal ratings for both social and monetary rewards for both groups (Valence SID: $\chi^2(2)=57.306$; $p<.0001$; Arousal SID: $\chi^2(2)=19.527$; $p<.0001$; Valence MID: $\chi^2(2)=70.627$; $p<.0001$; Arousal $\chi^2(2)=19.527$; $p<.0001$). Wilcoxon signed-ranks tests indicated that this was due to significantly higher valence and arousal ratings for increasing levels of reward for both the MID and the SID tasks (see table 1, appendix B). Mann-Witney tests indicated that valence and arousal did not differ between groups for any of the reward levels for either task (see table 2, appendix B).

3.4.4 fMRI results

3.4.4.1 Reward Anticipation

Results for the between groups analyses, carried out using a two-by-two mixed model ANOVA [between subjects factor = group; within subjects factor = reward type] are presented in table 3.1. There were no significant main effects of group, or group by reward type interactions in *a priori* anatomical regions for reward cues. The interaction of group by reward type in the left anterior cingulate did not survive correction for multiple comparisons with anatomical SVC. Within-group results for reward anticipation can be seen in tables 1-4, Appendix C.

Table 3.1 ANOVA for Reward Anticipation.

Two-by-two mixed model ANOVA [group by reward type] for the contrast correct cue>baseline. Results are reported at an uncorrected level of $P<.001$ (extent threshold 10 voxels). Asterisks (*) and crosses (†) indicate regions surviving correction for multiple comparisons (FWE $p<.05$) at the whole-brain cluster or peak level (Asterisk; *) and/or using anatomical small volume correction in *a priori* regions (cross; †).

	Cluster Size (Voxels)	F (Peak)	MNI Co-ordinates (x,y,z)	BA and Probability (%) (if available)
Main Effect of Reward Anticipation (MID>SID):				
Frontal				
Right Middle Frontal Gyrus*	64	27.63	44 -6 58	6 (40%)

Left Inferior Frontal Gyrus p. Orbitalis*†	242	23.95	-36 34 -6	47
Left SMA	60	23.41	0 10 64	6 (40%)
Left Inferior Frontal Gyrus p. Triangularis	33	17.45	-44 34 14	45 (50%)
Right Inferior Frontal Gyrus p. Orbitalis	31	17.05	42 26 -10	47
Temporal				
Right Superior Temporal Gyrus	43	23.42	56 -26 -2	21
Left Middle Temporal Gyrus	52	19.33	-50 -58 -2	37
Left Middle Temporal Gyrus	12	14.44	-56 -24 -12	20
Left Inferior Temporal Gyrus	14	15.95	-34 -6 -23	20

Parietal				
Left Postcentral Gyrus*	90	18.8	-46 -24 48	2 (50%)
Right Precuneus	51	17.99	8 -52 44	7
Left Inferior Parietal Lobule	29	15.16	-28 -50 44	SPL 7PC (10%)
Right Precentral Gyrus	13	15.95	14 -28 64	4a (50%)
Occipital				
Left Superior Occipital Gyrus	33	16.55	-20 -66 38	SPL 7a (10%)
Right Superior Occipital Gyrus	19	18.31	24 -74 44	SPL 7P (10%)

Right Middle Occipital Gyrus *	2951	33.03	36 -90 6	17
Left Middle Occipital Gyrus	484	24.21	-32 -90 12	18 (10%)
Subcortical				
Left Nucleus Accumbens†	228	30.25	-10 2 0	NA
Right Nucleus Accumbens †	199	27.38	8 10 0	NA
Left Amygdala	14	15.95	-34 -6 -28	Amyg (LB) 40%
Cerebellum				
Right Lobule VIIa crus I	49	21.91	32 -76 -30	90%

Right Lobule VIIa crus II	10	17.01	8 -86 -38	74%
Left Lobule VI	36	21.53	-34 -46 -24	20%
Left VIIa Crus 1	32	19.71	-24 -82 -32	99%
Group by Reward Type Interaction:				
Frontal				
Left Anterior Cingulate	38	16.26	-6 8 30	24
Parietal				
Left Inferior Parietal Lobule	26	16.42	-36 -44 46	40; hIP3 (40%)

3.4.4.2 *Reward Feedback*

Results for the two-by-two mixed model ANOVA [group by reward type] are presented in table 3.2. There were no main effects of group within reward circuitry but there was a significant interaction in the left dorsal caudate (see figures 3.4 and 3.5) which was corrected for multiple comparisons using an anatomical SVC of the left striatum (MNI co-ordinates: -18 -2 24; $F = 18.62$; $P_{FWE} < .05$). Independent samples t-tests indicated that the ASD group showed reduced activation, compared to controls, within the same region of left dorsal caudate for the receipt of social rewards (MNI co-ordinates: -16 -2 24; $T=4.24$; $P_{FWE} < .05$). Paired samples t-tests also indicated that the ASD group showed a significant difference in activation between the two tasks (reduced activation for SID compared to MID; MNI co-ordinates: -16 6 22; $T=4.91$; $P_{FWE} < .05$) whereas the control group did not. As aberrant reward processing has previously been reported in ADHD (Scheres, Milham, Knutson, & Castellanos, 2007; Ströhle et al., 2008), the analysis was repeated excluding the four subjects with ADHD/ADD and the interaction effect remained significant in the DS at the uncorrected threshold (MNI= -18 -2 24; $F = 14.88$). The DS activation was overlaid on the striatal connectivity atlas in FSL (Tziortzi et al., 2013), which indicated that group differences were in a region connected to executive and motor regions of cortex. Results suggest that a super-additive interaction within the left DS driven by deactivation to social reward feedback in ASD (see figure C1, Appendix C). This supports the second hypothesis, that reward deficits are specific to social stimuli in ASD, in line with Social Motivation Theory (Dawson et al., 2005a). Within-group results for reward feedback can be seen in tables 5-8, Appendix C.

Table 3.2 ANOVA for Reward Feedback.

Two-by-two mixed model ANOVA [group by reward type] for the contrast correct feedback>baseline. Results are reported at an uncorrected level of $P<.001$ (extent threshold 10 voxels). Asterisks (*) and crosses (†) indicate regions surviving correction for multiple comparisons (FWE $p<.05$) at the whole-brain cluster or peak level (Asterisk; *) and/or using anatomical small volume correction in *a priori* regions (cross).

	Cluster Size (Voxels)	F (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Main Effect of Reward Feedback (MID>SID):				
Frontal				
Right Inferior Frontal Gyrus p. Orbitalis	36	17.96	42 22 -12	45
Right Paracentral Lobule	35	17.51	10 -28 64	4a (50%)

Left Inferior Frontal gyrus p. Opercularis	27	15.79	-54 14 32	44 (60%)
Left Superior Medial Gyrus	20	13.72	-4 46 30	32
Right Anterior Cingulate	23	15.63	4 34 20	24
Right Middle Cingulate	80	15.18	4 -30 34	23
Left Insula lobe	11	14.41	-32 24 4	47
Temporal				
Right Superior Temporal Gyrus*	81	20.44	66 -24 6	22; TE 3 (40%)
Right Superior Temporal Gyrus	29	15.78	54 -14 4	48; TE 1 (70%)
Left Superior Temporal Gyrus	12	14.45	-40 -32 10	41; TE 1.1 (60%)

Right Inferior Temporal Gyrus	17	16.74	52 -62 -12	37; HOC5 (V5) (10%)
Occipital				
Left Middle Occipital Gyrus*	834	42.68	-32 -94 6	18 (20%); hOC3v (V3v) (20%)
Left Calcarine Gyrus*	103	18.49	-16 -74 8	17 (80%)
Right Calcarine Gyrus	37	15.2	16 -70 10	17 (90%)
Right Fusiform Gyrus*	1787	61.63	30 -66 -4	18 (10%)
Right Fusiform Gyrus	16	18.56	42 -46 -16	37
Left Fusiform Gyrus*	95	59.6	-28 -64 -12	19; hOC4 (V4) (10%)

Parietal				
Right Postcentral Gyrus	34	20.58	62 -14 30	3b (30%)
Left Postcentral Gyrus	10	14.4	-46 -24 44	2 (80%); 3b (60%)
Left Inferior Parietal Lobule	52	15.68	-34 -50 56	SPL (7PC) (60%)
Left Inferior Parietal Lobule	13	18.91	-54 -30 38	2; IPC (PFt) (40%)
Left Superior Parietal Lobule	45	17.72	-20 -48 46	SPL (5L) (20%)
Subcortical				
Right Caudate Nucleus†	17	17.14	14 8 20	NA
Right Caudate Nucleus	12	15.24	16 12 0	NA

Left Thalamus	15	13.9	-28 -34 2	Th visual (18%);Temporal (11%)
Cerebellum				
Right Lobule VIIa Crus1	16	14.91	42 -74 -38	72%
Main Effect of Group (ASD>CON):				
Parietal				
Left Rolandic Operculum	11	15.31	-50 0 8	43; OP 4 (30%)
Group by Reward Type Interaction:				

Parietal				
Right Angular Gyrus	21	16.31	32 -64 46	SPL (7P) (10%)
Left Inferior parietal Lobule	25	17.21	-32 -52 44	40; hIP3 (30%)
Right Postcentral Gyrus	16	14.81	32 -64 46	3b (60%)
Temporal				
Right Inferior Temporal Gyrus	47	20.91	52 -62 -14	37; hOC5 (V5) (10%)
Subcortical				
Left Caudate Nucleus†	62	18.62	-18 -2 24	NA

Cerebellum				
Cerebellar Vermis Lobule VI	21	17.74	-2 -76 -16	71%
Right Lobule VIIa Crus 1	17	14.69	46 -66 -32	100%

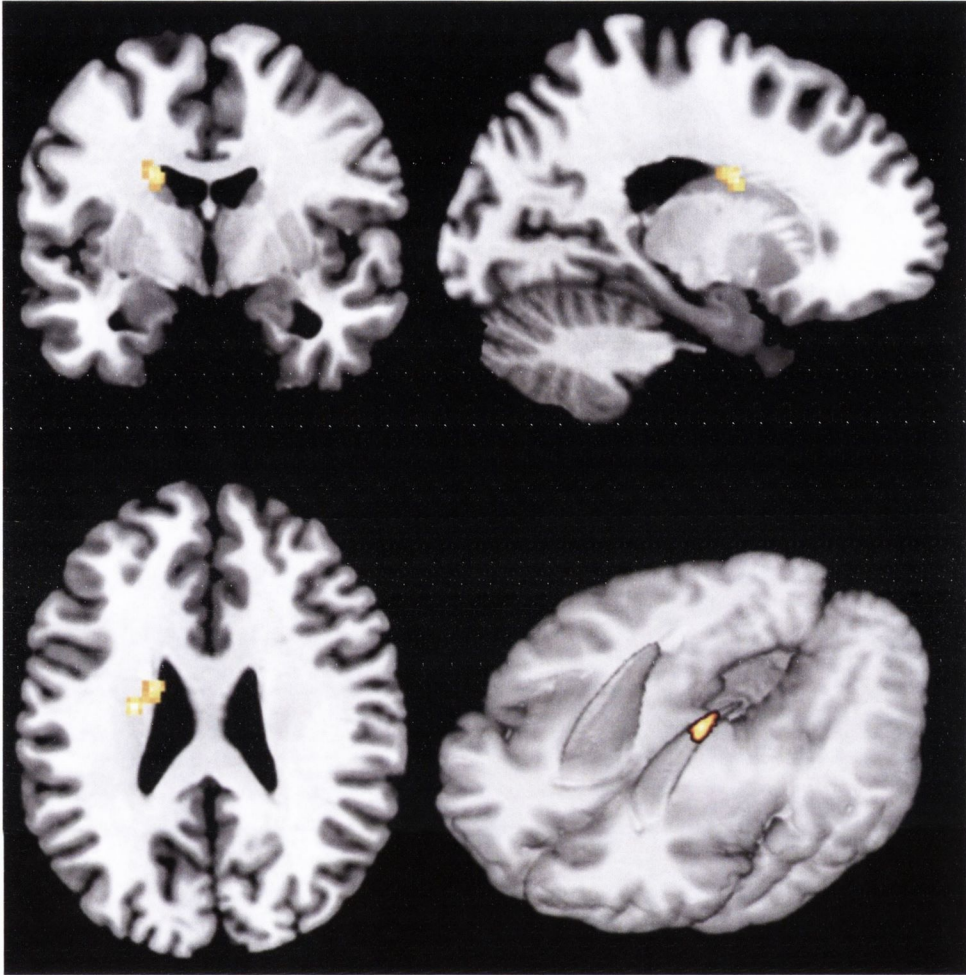


Figure 3.4 Group by Reward Type Interaction for Reward Feedback in the Left Dorsal Caudate

Results are displayed on a standard brain in MNI space (shown in neurological convention-left is left).

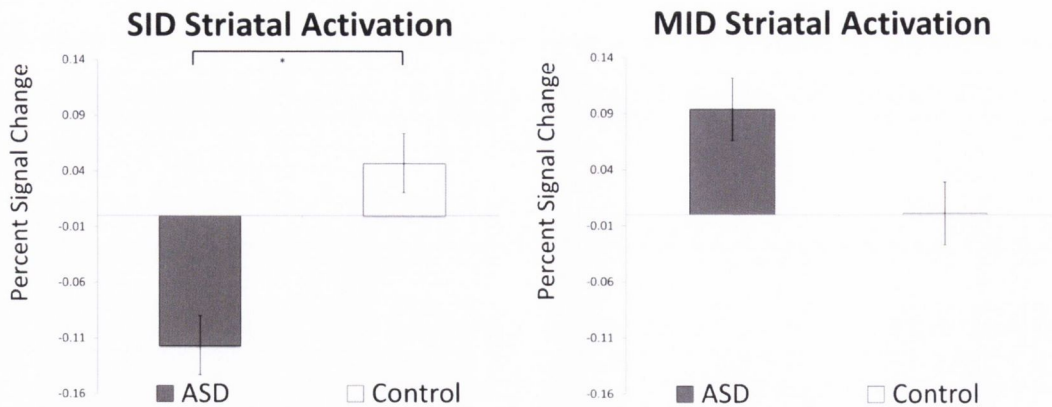


Figure 3.5 BOLD Response in the Left Caudate for Reward Feedback for the SID and MID.

The ASD group is shown in grey and controls in white. The ASD group showed significantly reduced activity compared to controls for the SID. There was no significant group difference for the MID. The ASD group showed significantly decreased activation to social compared to monetary rewards, whereas the controls did not show a significant difference between tasks. Significant between group differences are marked with an asterisk and standard error of the mean is displayed.

3.4.4.3 Age and Group-by-age Interaction Effects

Age was not associated with percent signal change in the left DS for either the ASD (MID: $p=.090$; SID $p=.132$) or control groups (MID: $p=.653$; SID $p=.527$). Using a 3-way ANOVA (factors: age, group, reward type) there were no significant main effects of age ($p=.671$) or interaction effects between age and group ($p=.952$) or age and reward type ($p=.084$) on percent signal change in the left DS.

3.4.4.4 Conjunction Analysis for the Fusiform Gyrus

As previous studies have indicated that ASD is characterised by differences in fusiform activation during face processing under certain conditions (Schultz, 2005), a

conjunction analysis (Friston et al., 2005; Price & Friston, 1997) was used to examine whether the ASD and control groups showed common activation in the fusiform gyrus during the receipt of social rewards. There was a significant conjunction between groups in the right fusiform gyrus during reward feedback in the SID task (MNI: 40 -58 -18; $T=4.54$; $P_{FWE}<.05$). This was corrected for multiple comparisons using a SVC at MNI co-ordinates 38 -55 -20 reported in a recent meta-analysis of emotional face processing (Sabatinelli et al., 2011).

3.4.4.5 Correlations between Significant BOLD Response in the DS and RT

As the DS activation was in a region that is highly connected to regions of cortex implicated in executive functions and motor control (Tziortzi et al., 2013), and the DS has previously been implicated linking rewards to executive functions (Grahn et al., 2008) and in the reinforcement of action (Balleine & O'Doherty, 2009), we investigated whether the BOLD activation (at the co-ordinates described above) was associated with behavioural performance in terms of RT (as accuracy data were held constant). Increased BOLD response for rewards was associated with faster responses for 'rewards' compared to 'no rewards' in both groups for the SID ($r=.367$; $p=.017$), but not the MID ($r=-.033$; $p=.836$), corrected for multiple comparisons (Bonferroni correction, $p=.025$) (see figure 3.6).

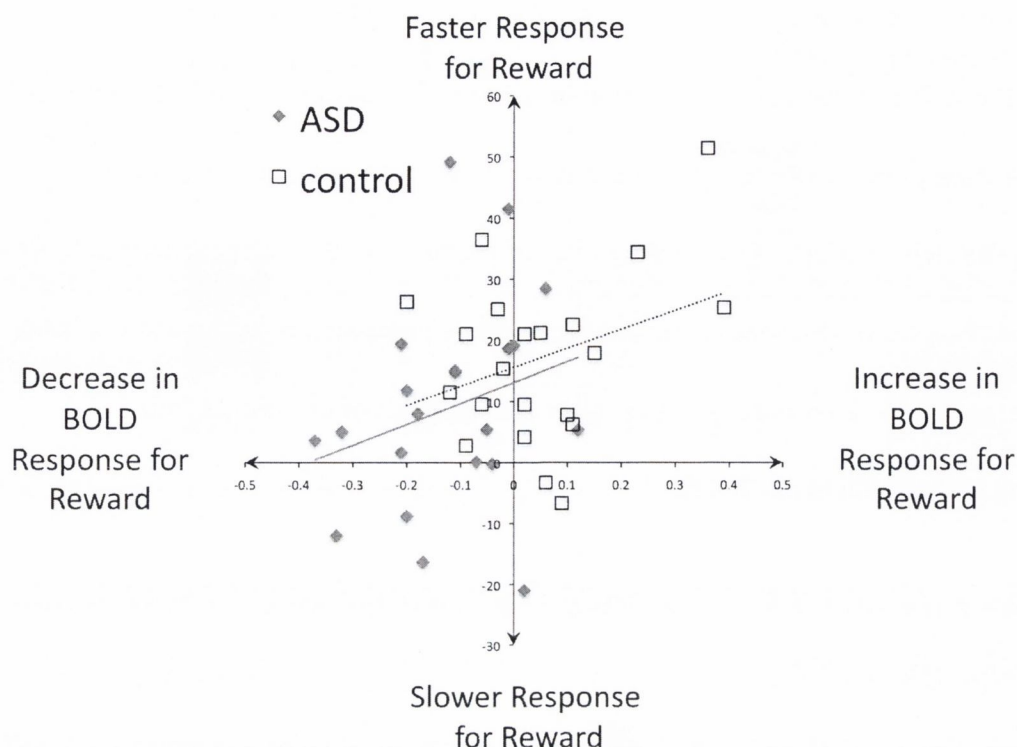


Figure 3.6 BOLD Response and Reaction Time for the SID.

Increase in BOLD response to social rewards was associated with faster responses to social rewards in both groups. The ASD group is shown in grey (with the black trend-line) and the controls are shown in white (with the dashed trend-line).

3.4.4.6 *Correlations between Significant BOLD Response in the DS and Clinical Variables*

There was a significant negative correlation, with higher scores on the ADOS-Stereotyped Behaviours and Restricted Interests scale associated with reduced BOLD signal in the DS region (see co-ordinates above) for social rewards ($r=-.559$; $p=.008$) but not monetary rewards ($r=.50$; $p=.829$) (see figure F 1, Appendix F). The correlation between ADOS-Stereotyped behaviours and Restricted Interests and BOLD signal in the DS to social rewards did not withstand correction for multiple comparisons (Bonferroni correction, $p(.05/7)=.0071$). There were no other significant relationships between ADOS/ADI subscales or the SRS and BOLD signal in the DS. There were no significant

correlations with behavioural measures using the two-factor structure of the ADI-R (see appendix H).

3.5 Discussion

According to the 'Social Motivation Theory' social deficits in ASD are due to a difficulty in forming reward representations of social stimuli (Dawson, Webb, & McPartland, 2005a; Dawson et al., 2002). The purpose of this study was to examine whether impaired reward processing in ASD is specific to social rewards or can be generalised to other classes of stimuli and to interpret results in relation to behavioural deficits in ASD. The results are in line with Social Motivation Theory indicating abnormal processing of social rewards in the left DS during reward receipt in ASD. Specifically, for the feedback condition the ASD group showed reduced activation for social rewards compared to controls in the left DS. The ASD group also showed reduced activation to social rewards compared to monetary rewards in this region (see figures 3.4 and 3.5). Significant results were largely driven by deactivation from the baseline for social rewards in the ASD group. Controls did not show significant activation to social rewards in the DS or a significant difference between the two reward types in this region. In terms of the behavioural results, activation to social rewards in the DS was associated with faster responses to social rewards in both groups which is in line with previous studies showing that the DS is important for linking reward processes with executive function (Tanaka et al., 2006) and action control (O'Doherty et al., 2004). Deactivation to social rewards in the DS was associated with higher restricted interests and repetitive behaviours in the ASD group.

3.5.1 The Role of the Dorsal Striatum in Reward Processing

The DS is involved in the reinforcement of action (Delgado, 2007), playing a fundamental role in goal directed action through the selection of appropriate goals based on the evaluation of action-outcomes (Grahn et al., 2008). Actor-critic models have informed understanding of striatal function, by positing that the ventral striatum (VS) predicts future rewards ('the critic') whereas the DS maintains information about the rewarding outcome of actions ('the actor') (Montague, Dayan, & Sejnowski, 1996). In line with this model, it has been found that the VS supports stimulus-reward learning whereas the DS is necessary for stimulus-response-reward learning (O'Doherty et al., 2004). The DS plays an important role in updating the reward value of chosen actions to guide subsequent behaviour and maximise reward consumption (Kim, Sul, Huh, Lee, & Jung, 2009; Lau & Glimcher, 2008). Representations of chosen actions can be used to aid learning or to modulate behaviour to reflect the value of the action, for example, by modulating RT (Lau & Glimcher, 2008).

In this study, the ASD group had difficulty modulating their RT according to reward level. The ASD group also showed reduced activation compared to controls in the DS for social rewards. Increased BOLD response in the DS to social rewards was associated with faster responses to social rewards in both groups. This suggests that participants with ASD may have difficulty in using social reinforcement to update reward representations and guide subsequent behaviour. DS activation to monetary rewards was not associated with faster responses, implying that the region may be more important for social reward processing. Accumulating evidence implicates the DS in processing of complex social rewards such as trust (King-Casas et al., 2005), mutual

social co-operation (Rilling et al., 2002), receiving positive feedback about one's personality (Izuma et al., 2008) and altruistic punishment (de Quervain et al., 2004; Strobel et al., 2011). Though the task used in the present study was a simple social reward task, the results further implicate the DS in social reward processing and suggest a deficit in ASD evidenced by deactivation to social rewards in this region.

3.5.2 The Striatum in ASD

Structural and functional neuroimaging studies have implicated the striatum, particularly the caudate nucleus, as potentially disrupted in ASD. Meta-analyses and cross-sectional MRI studies have reported enlarged caudate volume generally and across age ranges in ASD (Cauda et al., 2011; Langen et al., 2009; Stanfield et al., 2008; Yu, Cheung, Chua, & McAlonan, 2011). Striatal white matter abnormalities (Langen, et al., 2011; McAlonan et al., 2009) and increased functional connectivity between the dorsal caudate and sensory processing regions (Di Martino et al., 2010) have previously been reported. Functional MRI studies have shown striatal hypo-activation during facial expression imitation and cognitive flexibility tasks (Dapretto et al., 2006; Shafritz, Dichter, Baranek, & Belger, 2008) as well as hyper-activation during sensorimotor tasks (Takarae, Minshew, Luna, & Sweeney, 2007). This suggests that the striatum may be more involved in basic sensorimotor tasks in ASD and less in social, communicative and higher level cognitive tasks. Striatal abnormalities have typically been associated with restricted interests and repetitive behaviours in ASD (Hollander et al., 2005; Langen et al., 2009; Sears et al., 1999), which is in line with the present results whereby striatal deactivation social rewards was associated with increased restricted interests and repetitive behaviours in ASD.

3.5.3 Reward Processing in ASD: Present Findings and Previous Research

Both specific social reward processing deficits (Scott-Van Zeeland et al., 2010) and general abnormalities in reward processing have been reported in ASD (Dichter et al., 2011; Kohls, Schulte-Rüther, et al., 2012). In the present study, the neuroimaging results indicated social but not monetary reward processing deficits, similar to previously reported results (Scott-Van Zeeland et al., 2010). However, behavioural results suggested abnormal processing of monetary rewards as well as social rewards. It is therefore possible that the tasks did not detect subtle between group differences in the neural processing of monetary rewards. Unlike previous studies, we did not detect abnormalities in regions typically associated with incentive motivation (the VS) and the representation of reward value (the OFC and vmPFC). Previous results have been inconsistent (see section 3.1) perhaps reflecting the complex nature of reward processing which involves a network of interacting regions (Haber & Knutson, 2009), or methodological differences between studies. Over half of the participants were taking psychoactive medication in previously reported studies (Dichter et al., 2010; Dichter et al., 2011; Scott-Van Zeeland et al., 2010), with potential impacts on dopamine regulation (Schultz, 2007) and the BOLD signal (Iannetti & Wise, 2007). Matching for IQ and screening for co-morbid psychiatric disorders was not systematically carried out in all studies, introducing other potential confounds. Differences associated with the age and gender of participants may have further contributed to variability between studies as both of these factors are associated with differences in reward processing (Bjork et al., 2004; Spreckelmeyer et al., 2009). Here, we sought to address these

possible confounds, by only including medication-free male subjects, matching groups on age and IQ and by covarying for age and IQ in the fMRI analysis. Subtle differences in task design may further account for some of the discrepancies. For example, for social reward feedback, some studies have contrasted a smiling face with a frowning face (Scott-Van Zeeland et al., 2010), whereas other studies (Dichter et al., 2011) including the present study, contrasted a smiling face and a neutral image. Given that the striatum responds to punishment as well as reward (Delgado, Locke, Stenger, & Fiez, 2003; Ino, Nakai, Azuma, Kimura, & Fukuyama, 2010; Knutson et al., 2000), group differences in the VS may have been affected by the negative social feedback and may not have been specific to social reward.

3.5.4 Subjective Ratings of Rewarding Stimuli

Groups did not differ in terms of explicit ratings of pleasure or arousal for either social or monetary rewards. This replicates previous findings, in which ASD and control groups did not differ in their valence or arousal ratings of social rewards (Dichter et al., 2011; Lin, Rangel, & Adolphs, 2012) and is in line with previous research suggesting that individuals with high functioning ASD show intact cognitive appraisal of basic positive emotional experiences (Bölte et al., 2008). Previous studies have shown that ASD is characterised by poor self-awareness and self-referential cognitive processing (Lombardo et al., 2010; Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007; Toichi et al., 2002), therefore direct measures - physiological, electrophysiological or neuroimaging - may be more appropriate than self-report for recording emotional and hedonic responses in ASD.

3.5.5 Limitations

An important consideration is that the significant group difference during social reward feedback in the DS was largely due to deactivation from the baseline in the ASD group. Though controls showed an increase from the baseline for social rewards this was not significant (see Appendix C). This may be due to a limitation in the task design and future studies may address this issue by using more robust social reward paradigms (see future directions). A second important limitation is that there was a large age range in the sample. There were no significant age effects in the DS (see appendix C), however the large age range invites caution in interpreting negative findings in other regions which undergo pronounced maturational changes (Bjork et al., 2004, 2010). Therefore negative results –for example the lack of group differences in monetary reward processing- may have been due to heterogeneity in the BOLD signal. Additionally, four participants who had ADHD/ADD diagnoses secondary to an ASD diagnosis were included in the study. As ADHD is associated with aberrant reward processing (Scheres et al., 2007; Ströhle et al., 2008), analysis was repeated without these participants. Results remained significant at an uncorrected level suggesting that group differences were not attributable to the presence of these subjects but that their inclusion was necessary to have sufficient statistical power to correct for multiple comparisons. Correlations with behavioural impairments, as measured by the SRS, ADOS and ADI were exploratory. Caution is warranted in interpreting the correlation between ADOS-Stereotyped Behaviours and Restricted Interests and the BOLD signal in the DS as it did not survive correction for multiple comparisons. Numerous studies have previously used the ADOS and ADI to measure behavioural impairments in ASD

(Estes et al., 2011; Langen, et al., 2011; Pierce & Courchesne, 2001) but the interpretation of these findings are limited by the fact that these are diagnostic scales with ordinal values.

3.5.6 Future Directions

These results open several avenues for future research. Reward processing undergoes maturational changes between adolescence and adulthood in typical development (Bjork et al., 2004, 2010), therefore examining developmental factors will be important in future studies of reward in ASD. Gender differences have also been reported in reward processing (Spreckelmeyer et al., 2009), therefore future studies could investigate whether the same gender differences apply to females with ASD. BOLD signal during social reward processing was not significantly correlated with measures of social impairment in ASD. One study reported a correlation between the BOLD signal in the striatum and social functioning in controls but this relationship was not observed in ASD (Scott-Van Zeeland et al., 2010). Therefore further study is needed to evaluate whether deficits in social reward processing are associated with social impairments in ASD. As in previous studies of social reward in ASD, the social stimuli used in the present study were artificial compared to real social encounters. Social reward paradigms with dynamic stimuli (Perino, 2012) and multi-modal information – verbal and auditory – (Lin et al., 2011) may be more ecologically valid and more rewarding for participants, and therefore may be useful in future studies of social reward in ASD. Finally, more complex social decision making tasks may provide a link between reward processing and theory of mind deficits in ASD (Izuma et al., 2011).

I sought to address potential confounds associated with possible group differences in attention to faces, by asking subjects to attend to a cross-hair placed in the middle of the screen during the fMRI session, as intact fusiform activation in ASD participants has been reported when subjects are explicitly instructed to attend to the face (Hadjikhani et al., 2006). Using a conjunction analysis there was significant common activation between the ASD group and controls in the right fusiform gyrus. This suggests that the ASD group did attend to the face in the social reward task and suggests that abnormal activation in the striatum in the ASD group in the current study was not due to perceptual differences. However, future studies may wish to use eye-tracking to control for possible confounds associated with attention to faces.

3.6 Conclusions

The results of the present study are in line with the Social Motivation Theory, indicating that ASD is characterised by abnormal striatal responses to social rewards. Increased activation in the striatum was correlated with faster responses to social rewards in both the ASD group and controls, suggesting that this region plays a role in linking reward responses to behaviour. Additionally, deactivation to social rewards in the striatum was associated with greater restricted interests and repetitive behaviours in ASD. These results are in line with previous findings suggesting that diminished social motivation may underlie deficits in social functioning in ASD and imply that interventions that seek to improve social motivation may be beneficial for improving social functioning in people with ASD.

4 Structure and Connectivity of Frontostriatal Circuitry in ASD

4.1 Introduction

Frontostriatal circuitry plays an important role in social motivation, which is postulated to underlie deficits in social interaction and communication in ASD (Chevallier, Kohls, et al., 2012; Dawson et al., 2012; Dawson et al., 2005a). Aberrant BOLD responses to social rewards have been reported in a number of studies of social reward processing in ASD, providing support for this hypothesis (Delmonte et al., 2012; Dichter et al., 2011; Kohls, Schulte-Rüther, et al., 2012; Scott-Van Zeeland et al., 2010). Studies of reward and executive function also implicate frontostriatal circuitry in repetitive behaviour symptoms (Dichter et al., 2010; Langen, et al., 2011). Additionally, functional abnormalities in frontostriatal circuitry have been reported during higher-order cognitive and sensorimotor tasks (Schmitz et al., 2006; Scott-Van Zeeland et al., 2010; Takarae et al., 2007), suggesting that abnormalities in frontostriatal circuitry may underlie the two core deficits in ASD; social interaction and communication, and restricted interests and repetitive behaviours (Chevallier, et al., 2012; Dichter et al., 2010; Langen, et al., 2011), as well as associated cognitive and motor impairments. Functional abnormalities in frontostriatal regions are potentially due to structural differences in key regions within this network and/or abnormalities in functional or structural connectivity between these regions.

Frontostriatal circuitry plays a key role in emotion, motivation, cognition and the control of movement, which work in tandem to execute goal directed behaviours (Haber, 2003). Cortical inputs to the striatum project from the basal ganglia to the thalamus and back to the cortex (Alexander, Crutcher, & DeLong, 1990; Alexander, DeLong, & Strick, 1986). Primate tracer studies have shown that frontostriatal projections are arranged into a number of parallel, integrative loops, with each loop comprising discrete regions of striatum, cortex, globus pallidus, substantia nigra and thalamus and sub-serving specific motor, cognitive or affective functions (see figure 4.1). Premotor and motor areas project to the central and lateral caudate and the central, dorsal, and lateral putamen, respectively. These pathways mediate the planning, learning, and execution of motor behaviours. The dorsolateral prefrontal cortex (dlPFC) projects to the rostral caudate and putamen, with projections to the caudate involved in working memory and executive function. The orbital and medial prefrontal cortex and anterior cingulate cortex (OFC, mPFC and ACC) project primarily to the ventral striatum (VS) including the nucleus accumbens (NAcc), the medial caudate and the medial and ventral rostral putamen, with VS circuitry primarily involved in motivation and reward (Groenewegen, Wright, Beijer, & Voorn, 1999; Groenewegen et al., 2003; Haber & Knutson, 2009).

Frontostriatal loops are both parallel and integrative (Bevan, Smith, & Bolam, 1996; Haber, 2003; Joel & Weiner, 1994, 1997; McFarland & Haber, 2002; Percheron & Filion, 1991). Information is primarily channeled from ventral-limbic, to more dorsal cognitive and motor loops such that action decision making is influenced by motivation and cognition (Haber, 2003; Middleton & Strick, 2000). Diffusion tensor imaging (DTI) studies indicate that corticostriatal circuitry is similarly organised into segregated and

converging loops in humans (Draganski et al., 2008; Leh, Ptito, Chakravarty, & Strafella, 2007; Lehericy et al., 2004; Verstynen, Badre, Jarbo, & Schneider, 2012) and resting-state functional connectivity analysis of the human striatum has shown functional organisation of corticostriatal loops into affective, cognitive and motor components (Choi, Yeo, & Buckner, 2012; Di Martino et al., 2008).

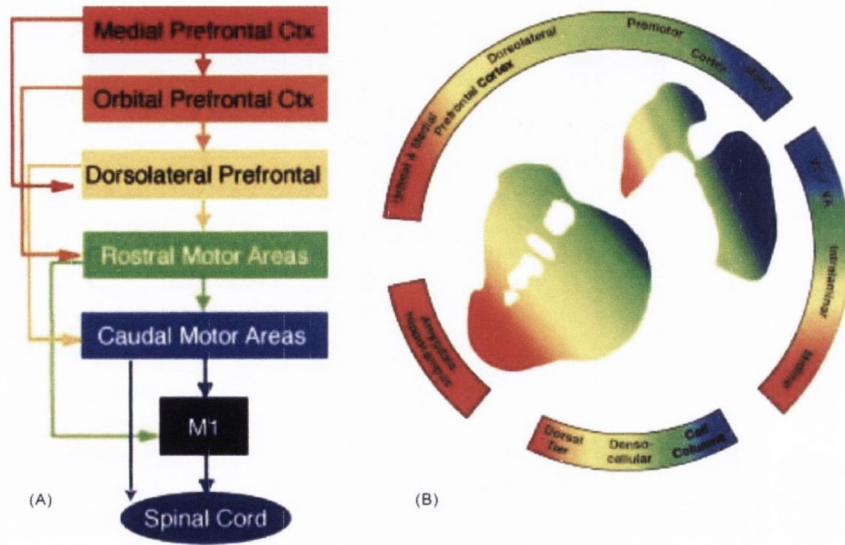


Figure 4.1 The Functional Organisation of the Frontal Cortex (A) and Projections to the Striatum (B), figure from Haber (2003).

(A) Shows the functional connections linking frontal cortical brain regions. (B) Shows the organization of cortical and subcortical inputs to the striatum (projections from cortical, thalamic, midbrain, amygdala/hippocampus are shown in a clockwise fashion). In both (A) and (B), the colours represent functional distinctions. Blue: motor cortex, execution of motor actions; green: pre-motor cortex, planning of movements; yellow: dorsal and lateral prefrontal cortex, cognitive and executive functions; orange: orbital prefrontal cortex, goal-directed behaviours and motivation; red: medial prefrontal cortex, goal-directed behaviours and emotional processing (Haber, 2003).

4.1.1 The Structure of Frontal Cortex, Striatum and Amygdala in ASD

Frontal lobe pathology has been extensively documented in ASD. Early brain overgrowth in ASD is largely due to overgrowth in the frontal lobes (Carper, Moses, Tigue, Courchesne, & others, 2002; Carper & Courchesne, 2005) with excessive neuron numbers in the PFC reported (Courchesne et al., 2011). Increased frontal lobe volume among children (Carper et al., 2002; Carper & Courchesne, 2005), as well as localised differences in cortical thickness and cortical folding in the frontal lobes of both children and adults have been documented in ASD (Ecker et al., 2010; Hardan, Jou, Keshavan, Varma, & Minshew, 2004; Nordahl et al., 2007). Cortical volume and thickness undergo abnormal developmental trajectories in the frontal lobes in ASD, with cortical volume negatively related with age in controls but not in ASD, and reduced cortical thickness in ASD in childhood, but increased thickness in adulthood.

In terms of the striatum, volumetric studies have reported increased caudate volume among children, adolescents and adults with ASD, with caudate volume associated with repetitive behaviour in a number of studies (Estes et al., 2011; Hollander et al., 2005; Langen et al., 2009; Langen, Durston, Staal, Palmen, & van Engeland, 2007; Sears et al., 1999; Stanfield et al., 2008). Increased putamen volume has also been reported bilaterally (Estes et al., 2011) though to a lesser degree than caudate volume abnormalities. The caudate, putamen and accumbens undergo an abnormal developmental trajectory in ASD. The caudate shows the most pronounced developmental differences between ASD subjects and controls with caudate volume

decreasing with age in typical development whereas it increases with age in ASD (Langen et al., 2009).

Volumetric studies of the amygdala have yielded inconsistent results with both increased (Howard et al., 2000; Schumann et al., 2004) and decreased amygdala (Aylward et al., 1999; Cauda et al., 2011) volume reported in ASD. Different developmental trajectories in amygdala volume in ASD may explain some of the inconsistencies in the literature. The amygdala is enlarged in younger subjects with ASD but decreases with age in ASD compared to controls (Schumann et al., 2004; Stanfield et al., 2008). In terms of behavioural implications, amygdala volume is positively associated with emotion recognition and social cognition in controls but not in ASD. On the other hand, amygdala volume is positively associated with restricted interests and repetitive behaviours in ASD, suggesting that the amygdala may be less involved in emotional and social understanding in ASD whilst being implicated in behavioural impairments (Dziobek, Fleck, Rogers, Wolf, & Convit, 2006).

A limitation of volumetric approaches is that they only measure the overall volume of a given structure and therefore cannot identify localised differences within the structure. One previous study has examined localised shape differences in the basal ganglia in ASD, using manual tracing of the striatal structures and in-house software for shape analysis. Surface differences were reported in the caudate, putamen and globus pallidus among children with ASD but these did not withstand correction for multiple comparisons (Qiu, Adler, Crocetti, Miller, & Mostofsky, 2010). No previous study has examined localised shape differences in the striatum or amygdala in adolescents/young adults with ASD. As both the striatum and amygdala are thought to

play an important role in social communication and repetitive behaviours in ASD (Baron-Cohen et al., 2000; Dziobek et al., 2006; Langen, Durston, et al., 2011), further analysis of localised shape differences within these structures is warranted.

4.1.2 Connectivity of Frontostriatal Circuitry in ASD

The theory of ‘under-connectivity’ postulates that ASD symptoms are due to reduced long-range, coupled with increased short-range, connectivity (Hughes, 2007; Marcel Adam Just et al., 2004, 2012). Increased local, and reduced long-range connectivity is associated with immature development (Fair et al., 2009; Vogel, Power, Petersen, & Schlaggar, 2010). Evidence from fMRI and DTI studies suggests that ASD is characterised by abnormal connectivity rather than ‘under-connectivity’ (Alexander, Lee, Lazar, Boudos, et al., 2007; Cherkassky et al., 2006; Di Martino et al., 2010; Just et al., 2004; Keller et al., 2007; Kleinhans et al., 2008; Langen, et al., 2011; Müller et al., 2011, 2011; Sato et al., 2012; Von dem Hagen et al., 2012; Weng et al., 2010).

Despite the growing evidence implicating frontostriatal circuitry in ASD pathology, few studies have specifically examined connectivity within this circuit. In a resting-state study of corticostriatal connectivity, children with ASD showed ectopic connectivity (connectivity present in ASD but not control children) between the caudate and putamen and a number of cortical regions within the frontal cortex, as well as subcortical regions (Di Martino et al., 2010). Interestingly, the results of Di Martino et al. (2010) were suggestive of abnormal connectivity, with the ASD group showing connectivity between a number of corticostriatal regions which were not functionally connected in controls, rather than immature maturational processes, characterised by increased short range and reduced long range connectivity.

Only one previous DTI tractography study has examined frontostriatal structural connectivity. The results suggested that the anatomy of frontostriatal white matter may be different in adults with ASD, who show lower fractional anisotropy (FA) in tracts connecting the putamen to the frontal cortex, and increased mean diffusivity (MD) in tracts connecting the NAcc to the frontal cortex (Langen, et al., 2011).

To date, no previous study has combined functional and structural MRI data to examine the structure and connectivity of frontostriatal circuitry in ASD within the same participants. In the present study, we will examine the structure of the striatum (frontal lobe structural properties have been extensively examined in previous studies (Carper et al., 2002; Carper & Courchesne, 2005; Ecker et al., 2010; Nordahl et al., 2007)), functional connectivity between frontostriatal regions and potential white matter differences underlying group differences in functional connectivity.

4.1.3 Aims

1. To examine the structure of striatum and amygdala in ASD and control subjects using vertex (shape) and volumetric analyses.
2. To examine the functional connectivity of frontostriatal-amygdala circuitry in ASD and to explore possible structural differences underlying differences in functional connectivity using diffusion tensor tractography.
3. To examine group differences in structure and connectivity of the striatum in terms of behavioural impairments and striatal activation to social rewards (see chapter 3).
4. To examine whether significant group differences in structure or function are due to between group differences in developmental trajectories.

4.2 Methods

4.2.1 Participants

Twenty-one ASD and control participants were included in the resting-state fMRI analysis (the same participants as were included in the task based fMRI study reported in chapter 3) and 22 ASD and 24 control participants were included in the DTI analysis after excluding subjects for excessive motion (movements >3mm), poor data quality or technical difficulties (see section 2.8). Twenty-two ASD and 25 control participants were included in the FIRST analysis, after excluding subjects with poor subcortical segmentation (see section 4.2.4).

4.2.2 Statistical analysis of Behavioural Data

Behavioural data were analysed using SPSSv16. Spearman's rank-order correlations were performed in SPSSv16 to examine function-structure relationships. These were carried out on subjects that were included in both analyses, for the group as a whole and for each group separately. Correlations were performed between regions in which there were intra-hemispheric differences in functional connectivity, using Z-transformed r-values, and white matter microstructure (FA, MD, RD and AD) of the appropriate frontostriatal tract, i.e. right caudate or right accumbens (see table 4.1). In addition to performing correlations between ADOS and ADI sub-scale scores (for the ASD group only), SRS total scores (for both groups) and functional connectivity values, Pearson's correlations were used to correlate the BOLD response to social rewards with functional connectivity values. Multivariate analyses were used to examine group-

by-age interaction effects in regions in which there were significant group differences in structure or functional connectivity.

4.2.3 MRI Data Acquisition and Preprocessing

Details of MRI data acquisition and preprocessing can be seen in section 2.7 and 2.8.

4.2.4 Structure of Striatum and Amygdala

FIRST is an automatic segmentation tool for subcortical structures implemented in FSL FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl> (Smith et al., 2004). It uses manually labeled image data to provide anatomical training information. Bayesian constraints are used to calculate the most probable shape instance given the observed intensities in T_1 images (Patenaude, Smith, Kennedy, & Jenkinson, 2011). FIRST can be used to examine average volume differences for each subcortical structure as well as localised shape differences within each structure. FIRST performs vertex analysis to investigate shape differences between groups of subjects. A surface mesh, made up of a set of triangles, is created for each subcortical structure. The apex of adjacent triangles is called a vertex. There are a set number of vertices for each structure and localised shape differences are tested by examining group differences in the spatial location of each vertex.

T_1 -weighted images were re-oriented to match the orientation of the standard (MNI) template image using `fslorient`. Segmentation was then performed on all subcortical structures to produce mesh and volume outputs. Boundary correction was then used to classify the boundary voxels for each structure. Any voxel labeled by two or more structures was re-classified as belonging to only one structure, based on how similar

the intensity is to the intensity distributions of the interior voxels for each of the competing structures. The results of the subcortical segmentation were overlaid on each subject's T_1 image and carefully examined. Four subjects (two ASD and 2 controls) were excluded after visual inspection of the data indicated poor segmentation. For the remaining subjects surfaces were aligned to MNI space in order to investigate group differences and group comparisons were carried out on a per-vertex basis using a multivariate General Linear Model (GLM) to perform statistical analyses (analyses were repeated in native space as this can be more sensitive to changes in shape). The F statistic was calculated in FIRST with age, IQ and Total Intracranial Volume (TIV) included as covariates in the model. Volume information was extracted for each subject for each structure and imported to SPSS as it is not possible to perform volumetric analysis in FIRST. Outliers were removed and MANCOVAs were run to assess group differences while controlling for age, IQ and TIV.

4.2.5 Functional Connectivity Analysis

Functional connectivity analysis was carried out using the CONN toolbox

(<http://www.nitrc.org/projects/conn/>) (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Normalised bias corrected T_1 images were generated in SPM

(<http://www.fil.ion.ucl.ac.uk/spm/>) and segmented into grey matter, white matter and CSF. The principle eigenvariate of the BOLD time-courses from white matter and CSF, as well as the 6 motion correction parameters were included as regressors in the analysis to remove signals associated with these factors. The data were then band pass filtered between 0.008 and 0.2 Hz as has been previously recommended (Baria, Baliki, Parrish, & Apkarian, 2011). A hanning window was used to weight down the initial and

end scans within the resting-state period. Seed regions were defined within the left and right frontal cortex (including the frontal medial and orbital cortices, inferior frontal gyrus -pars opercularis and pars triangularis, frontal pole, middle, superior frontal gyrus, subcallosal cortex, cingulate gyrus-anterior division and paracingulate gyrus, precentral gyrus and juxtapositional lobule cortex/supplementary motor area, see figure 4.2). As the amygdala provides important inputs to the striatum (Groenewegen et al., 2003; Haber & Knutson, 2009; Haber, 2003) and has been implicated in functional and structural MRI studies of ASD (Baron-Cohen et al., 2000; Greimel et al., 2012; Groen, Teluij, Buitelaar, & Tendolkar, 2010; Sato et al., 2012; Schultz, 2005; Verhoeven, De Cock, Lagae, & Sunaert, 2009), the amygdala was also included as a seed region in this analysis (see figure 4.3). Target regions included the left and right caudate, putamen and nucleus accumbens (see figure 4.3). Masks for these regions were generated using the Harvard-Oxford probabilistic atlas in FSL and thresholded at 20%. The ROI time series were defined as the principle eigenvariate of the time series within the ROI voxels using principle component decomposition. ROI-to-ROI correlational analyses were performed between each of the seed regions in the frontal cortex and amygdala and the target regions in the striatum. Second level random effects analyses were computed to examine group differences in connectivity using a T-test with age and IQ included as covariates to control for the effects of these factors. Results were corrected for multiple comparisons for the target regions at the FDR threshold ($p < .05$). Correlations were used to examine relationships with BOLD activation during social reward processing (see chapter 3). Group-by-age interactions were investigated for each pair of regions where there was a significant group

difference. A MANOVA [factors: age and group] was run on Fisher transformed Z-scores of the connectivity (r-values) which were extracted for each subject.

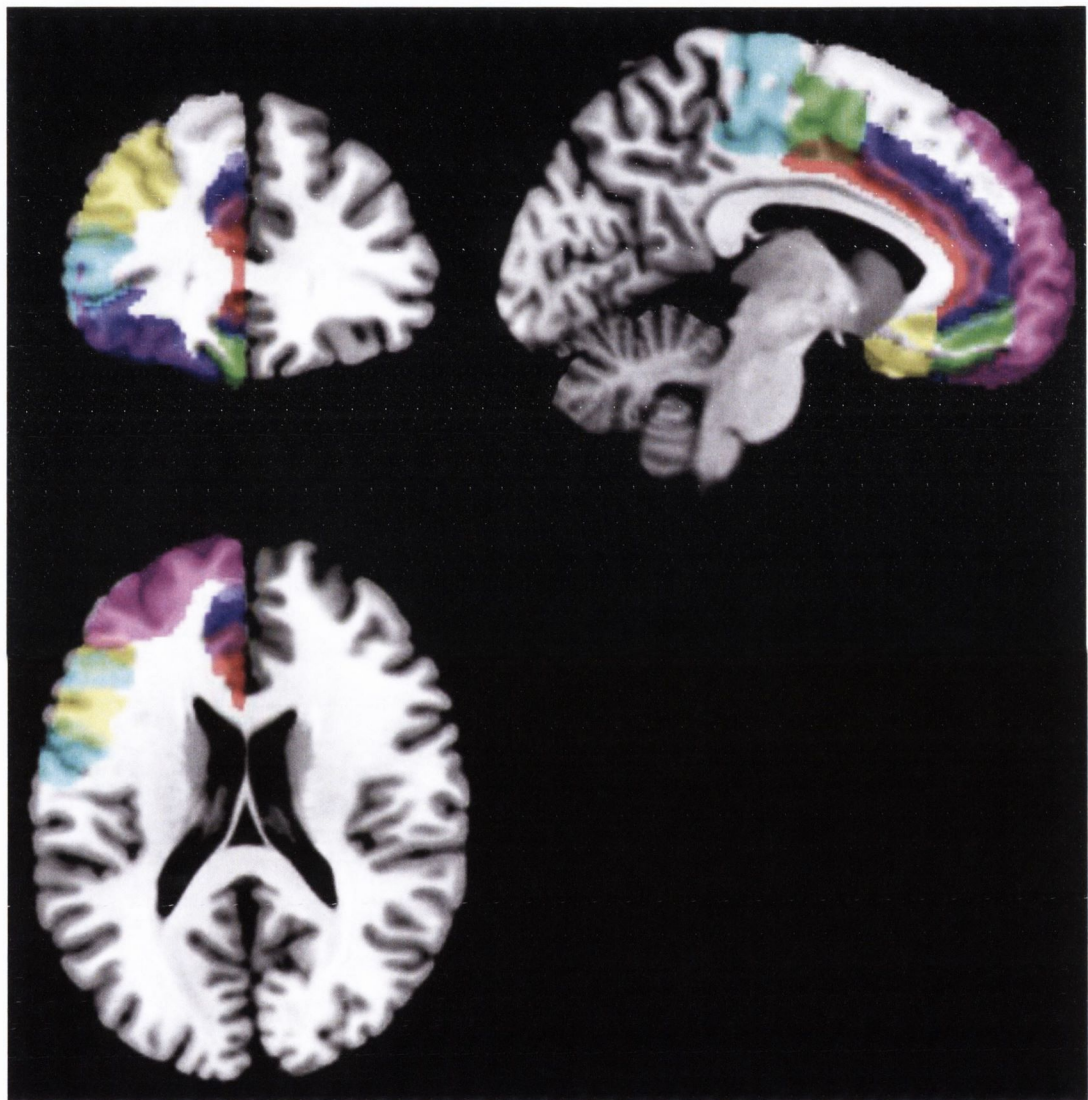


Figure 4.2 Masks for the Frontal Cortex.

The ACC is shown in red, the OFC in blue, the MPFC in green, frontal pole in violet, IFG opercularis in yellow, IFG triangularis in cyan, juxtapositional lobe in green, MFG in yellow, paracingulate in blue, precentral gyrus in light blue, SFG in greyscale and the subcallosal gyrus in yellow, displayed the left hemisphere of a standard brain in neurological convention (left is left and right is right).

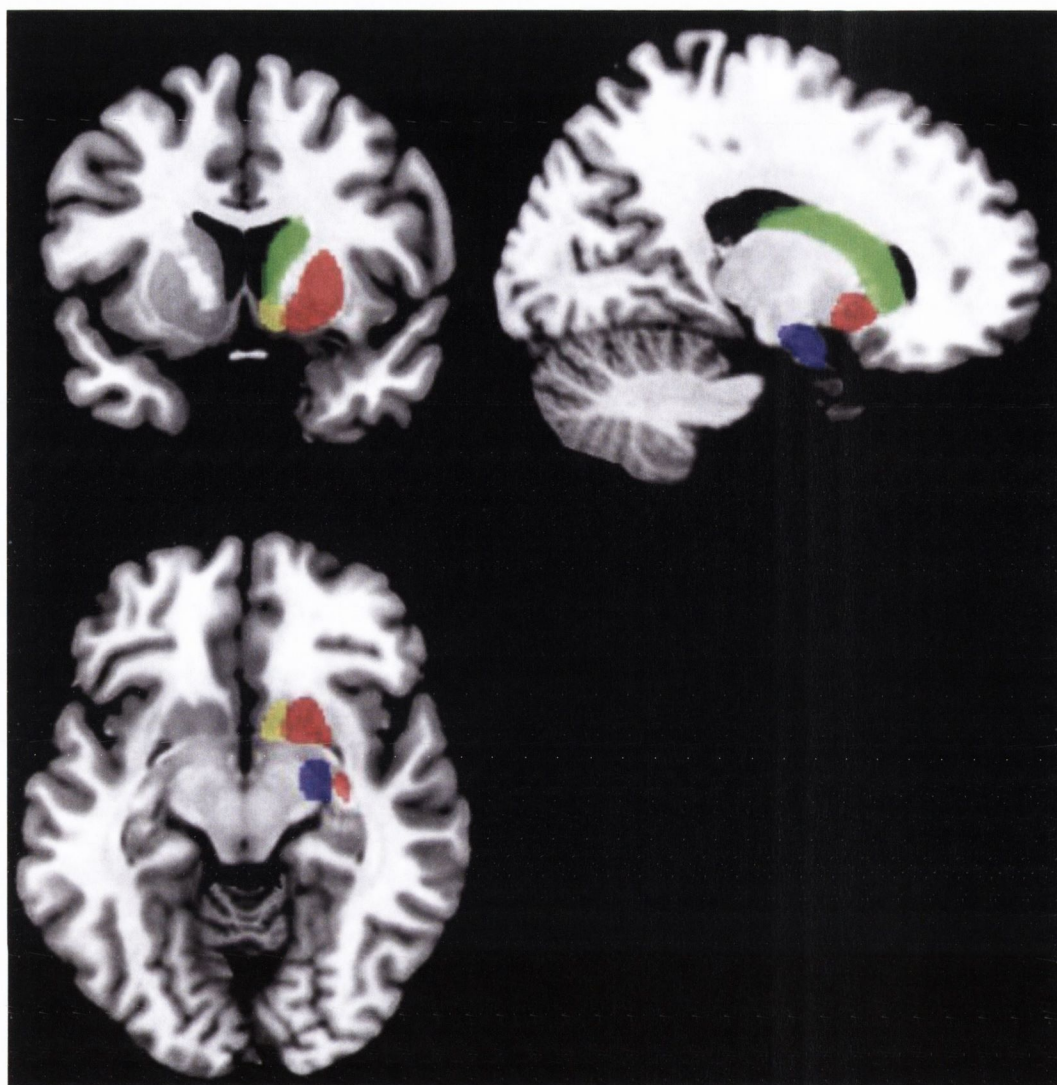


Figure 4.3 Masks for the Striatum and Amygdala:

The accumbens is shown in yellow, the caudate in green, the putamen in red and the amygdala in blue displayed the right hemisphere of a standard brain in neurological convention (left is left).

4.2.6 Diffusion Tensor Tractography

The purpose of this analysis was to examine structural differences underlying differences in functional connectivity. As outlined below (section 4.3.2) differences in functional connectivity were found between the accumbens and caudate and regions in the PFC, thus tractography analyses were confined to intra-hemispheric tracts between these regions. Whole brain tractography was carried out using the

deterministic streamline algorithm (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000) as implemented in Explore DTI (Leemans et al., 2009). Tractography was carried out in each subjects' native space using a 2mm seed point resolution, a 1mm step size, an angle threshold of 30 degrees and an FA tract termination threshold of 0.2. Specific tracts of interest were then isolated using regions of interest (ROIs) with inclusive Boolean logical 'AND' operators used to include tracts passing through a specific regions and 'NOT' operators used to exclude tracts passing through other regions. The atlas based segmentation approach was used to define ROIs in a template subject's native space (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). These ROIs were then transformed to each subjects' native space for tractography analysis. A template subject was chosen at random as in a previously published study (Lebel et al., 2008). Masks of the caudate and accumbens from the Harvard-Oxford atlas, and a mask of the Frontal Cortex from the MNI atlas were created in FSL and thresholded at 20% in SPM8. These masks were then transformed to the template subjects native space by i) co-registering the subjects T_1 image to the subject's motion distortion corrected FA map ii) multiplying the masks by the inverse transform parameters (MNI->Native space) generated using the segmentation option in SPM, iii) re-slicing the masks to the same dimensions as the FA map and binarising them using the 'imcalc' option in SPM. These masks were then visually inspected to ensure that they provided a good fit to the anatomical structure. Tractography analysis was carried out in the template subject using these inclusion masks (see Figure 4.4). 'AND' gates were then drawn at the caudate and accumbens to include only the regions from which tracts projected to the PFC. NOT gates were placed in the planes across the midline and the posterior commissure, and to exclude motor tracts, cortico-spinal tracts, tracts from the corpus

callosum and tracts to the temporal lobe. The atlas based segmentation tool was used to carry out tractography analysis in each subject's native space using the ROIs transformed into the subject specific space for each tract as this method has been successfully applied to improve tract delineation (Verhoeven et al. 2010). An upper limit of 100mm was placed on the tract length to exclude tracts that were greater than this length. Outliers were excluded for each group separately for FA, MD, RD and AD values that were greater than 1.5 box lengths from the inter-quartile range. Mann Whitney-U tests were then computed to compare groups in terms of FA, MD, RD and AD. Diffusion MRI data are not normally distributed (Jones, Symms, Cercignani, & Howard, 2005) therefore non-parametric tests were performed for group comparison.





Figure 4.4 Caudate and Accumbens Tracts for the Template Subject.

Tracts are shown in the sagittal (top) and axial (bottom) planes in neurological convention (left is left). The caudate-prefrontal tracts are shown in yellow and accumbens-prefrontal tracts are shown in red.

4.3 Results

4.3.1 Structure of the Striatum and Amygdala

4.3.1.1 Group-wise Comparisons

Uncorrected results for the vertex analysis can be seen in figure 4.5. Uncorrected results suggest that there may be differences in the shape of the left amygdala in ASD (figures 4.5 and 4.6) with vertex analysis suggesting thinning in the laterobasal nuclei

(Bzdok, Laird, Zilles, Fox, & Eickhoff, 2012). There were no significant group differences in the shape or volume of the left or right caudate or putamen after correction for multiple comparisons (shape analyses for all structures: FDR output = 0 signifying no significant group differences; Volume: Left Caudate $p=.862$; Right Caudate $p=.876$; Left Putamen $p=.858$; Right Putamen $p=.534$; Left Accumbens $p=.812$; Right Accumbens $p=.295$; Left Amygdala $p=.922$; Right Amygdala $p=.782$).

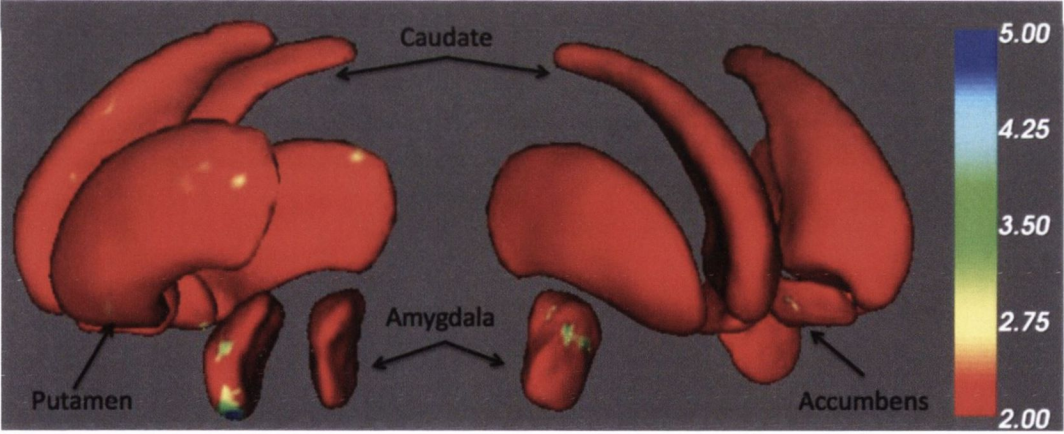
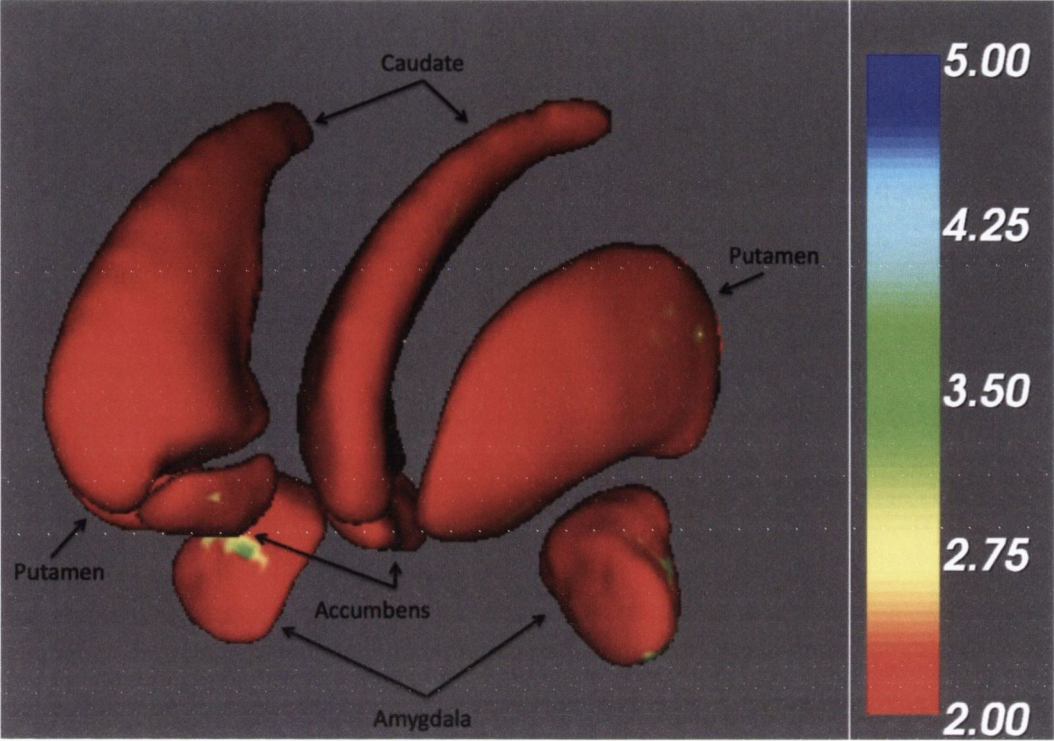


Figure 4.5 Vertex Analysis of the Amygdala and Striatum.

The left hand side of each panel shows the striatum and amygdala. The colour bar shows the f-statistic values with an increase from red (lower) to blue (higher) statistical significance. Uncorrected results($p < .001$) are displayed in radiological convention (left is right and right is left).

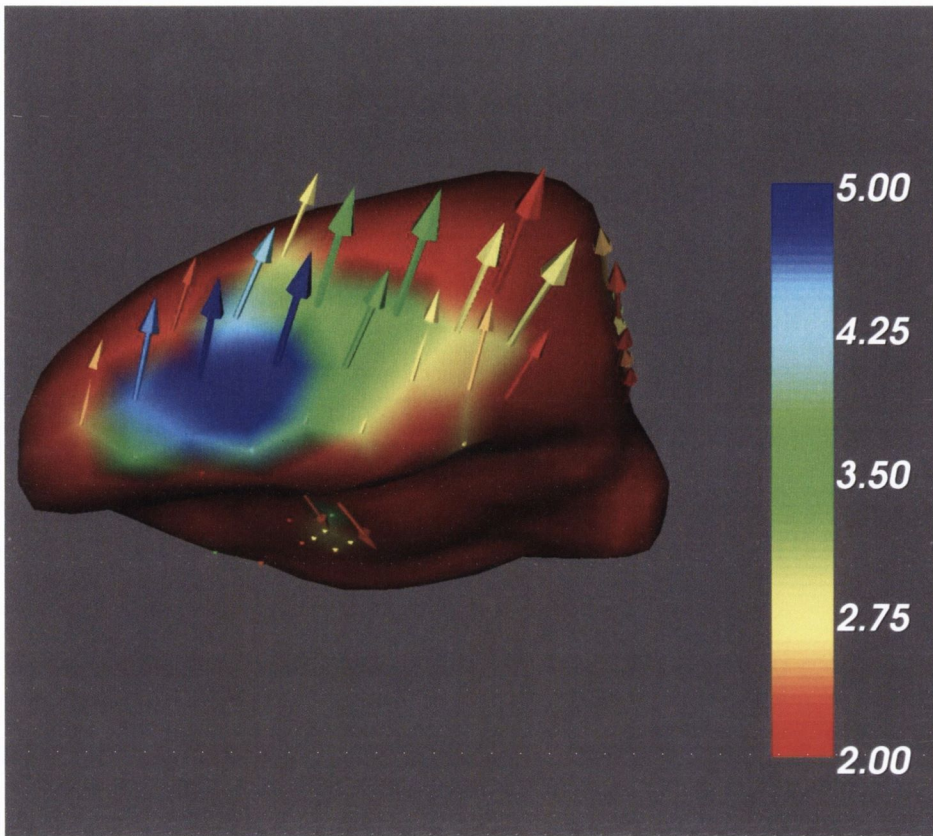


Figure 4.6 Shape Differences in the Left Amygdala.

The amygdala has been rotated so that the ventrolateral region can be viewed. Vectors (surface arrows) point away from the mean surface for the ASD to the control group mean surface. The direction of difference suggests that the left amygdala is smaller/thinner in the ASD group in the laterobasal nuclei.

4.3.2 Striatal Functional Connectivity

4.3.2.1 Group-wise Comparisons

Regions showing significantly increased functional connectivity between the frontal cortex and the striatum in the ASD group are listed in table 4.1 below. There were no regions that showed significantly reduced connectivity between the frontal cortex and the striatum and there were no significant group differences in connectivity between the amygdala and striatum. These results indicate hyper-connectivity between frontal cortical and striatal regions in the ASD group. Z-transformed r-values, adjusted for age

and IQ, for connectivity between each of the regions for which there was a significant group difference can be seen in figure 4.7 below. The ASD groups showed significant positive connectivity between regions for which there were significant connectivity differences between groups whereas controls showed negative connectivity between these regions at rest (see table 4.2). Figure D1 and table D1 in Appendix D show within group connectivity values, and t-scores and p-values for between group comparisons, without age and IQ adjustments. With the exception of right MFG to accumbens connectivity, negative connectivity was no longer apparent between frontostriatal regions in controls when age and IQ adjustments are not included in the analysis, and between group results remained significant.

Table 4.1 T-scores and P-values for Regions Showing Significantly Increased Connectivity in the ASD Group.

Source	Target	T -Value	P-Unc	P-FDR
Right Cingulate Gyrus, anterior division	Right Accumbens	2.61	0.013	0.042
	Left Caudate	2.71	0.010	0.039
Right Middle Frontal Gyrus	Right Accumbens	2.68	0.011	0.044
	Right Caudate	2.89	0.006	0.044
Right Paracingulate Gyrus	Right Accumbens	3.14	0.003	0.010
	Right Caudate	2.58	0.013	0.016

Left Paracingulate Gyrus	Right Accumbens	3.21	0.003	0.016
	Right Caudate	2.68	0.011	0.033

Table 4.2 Within-groups T-scores and P-values for Regions Showing Group Differences in Functional Connectivity

Source	Target	T -Value	P-FDR
Right Cingulate Gyrus, anterior division	Right Accumbens	ASD = 2.64	ASD = .0355
		Control= -2.48	Control=-.0532
	Left Caudate	ASD = 2.95	ASD = .0321
		Control=-2.79	Control=.0481
Right Middle Frontal Gyrus	Right Accumbens	ASD = 2.56	ASD = .0439
		Control=-2.60	Control=.0393
	Right Caudate	ASD = 2.56	ASD = .0439
		Control=-2.65	Control=.0392
Right Paracingulate Gyrus	Right Accumbens	ASD = 3.2	ASD = .0163
		Control=-3.54	Control=.0063
	Right Caudate	ASD =.0065	ASD = .0194
		Control=-3.05	Control=.0012

Left Paracingulate Gyrus	Right Accumbens	ASD = .0165	ASD = .0165
		Control= -3.26	Control=.0138
	Right Caudate	ASD = .0267	ASD = .0267
		Control= -2.56	Control=.0429

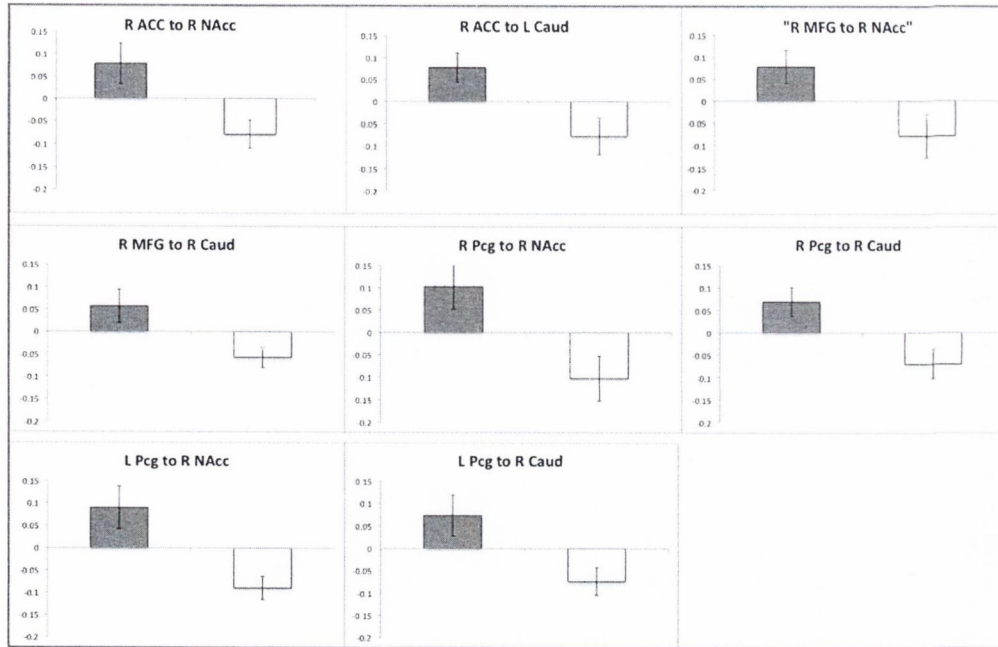


Figure 4.7 Group Differences in Functional Connectivity between the Frontal Cortex and the Striatum.

Bar charts show Z-transformed r-values for connectivity between each of the regions for which there was a significant group difference, while controlling for age and IQ. The ASD group is shown in grey and the controls in white with standard error of the mean displayed. R=Right; L=Left; ACC =Anterior Cingulate Cortex; MFG= Middle Frontal Gyrus; Pcg= Paracingulate Gyrus; NAcc = Nucleus Accumbens; Caud=Caudate.

4.3.2.2 *Group-by-age Interactions*

There was a significant group-by-age interaction effect on connectivity values between the right middle frontal gyrus and the right caudate (see figure 4.8; $F=58.24$ (2,39), $p=.017$), though age related changes were not significant for either group separately (ASD $p= .713$; controls $p=.116$). The group-by-age interaction did not survive correction for multiple comparisons using a Bonferroni correction ($p(.05/8)=0.00625$). There were no other significant group-by-age interactions.

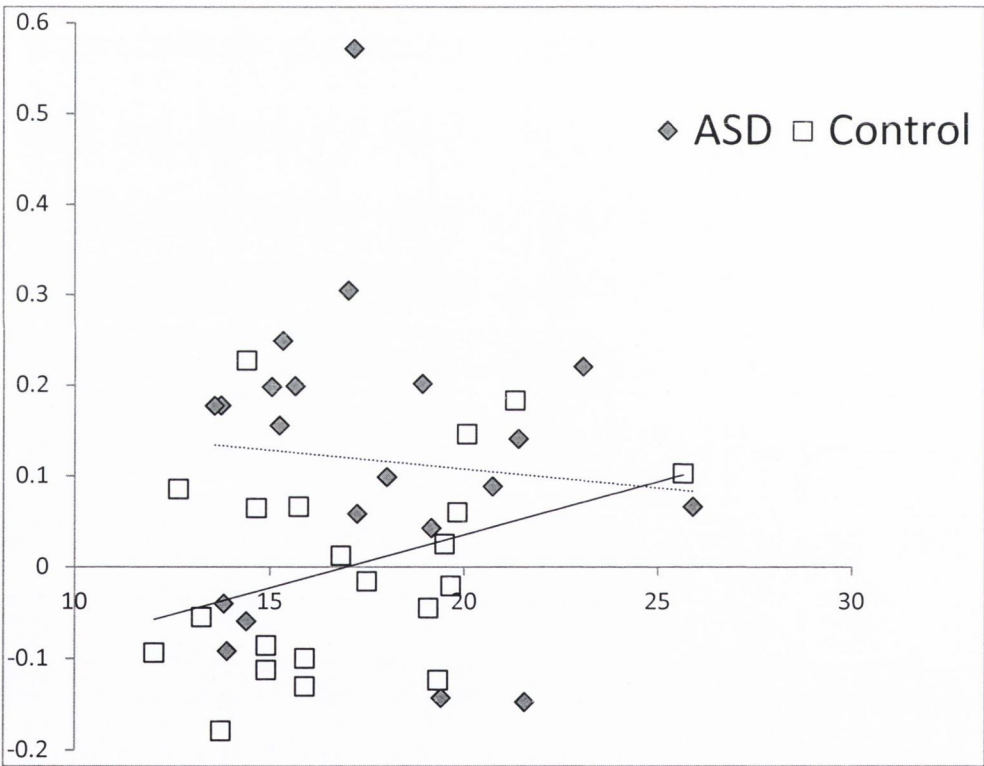


Figure 4.8 Group-by-age Interaction in Functional Connectivity between the Right Middle Frontal Gyrus and Right Caudate.

Age is shown on the X-axis and the Z-transformed raw r-value (i.e. without controlling for age or IQ) is on the y-axis. The ASD group is shown in grey (with dashed trend-line) and the controls in white (with solid black trend-line). Overall the ASD group show increased connectivity between the right MFG and right caudate with a slight decrease with age. The control group showed increased connectivity with age.

4.3.2.3 *Correlations with Social Reward Processing*

In the fMRI study of social and monetary reward processing in the same participants (chapter 3), the ASD group showed deactivation to social rewards in the left caudate. I therefore explored whether increased connectivity between the right anterior cingulate and the left caudate in ASD was associated with deactivation to social rewards. There was a negative correlation between connectivity and SID activation in ASD but not controls (ASD: $r = -.576$, $p = .006$; CON: $r = .234$; $p = .307$) with similar results when controlling for age and IQ with a partial correlation (ASD: $r = -.565$, $p = .012$; CON: $r = .414$; $p = .078$). In the ASD group, deactivation to social rewards in the left caudate was associated with increased connectivity between the left caudate and the anterior cingulate (see figure 4.9).

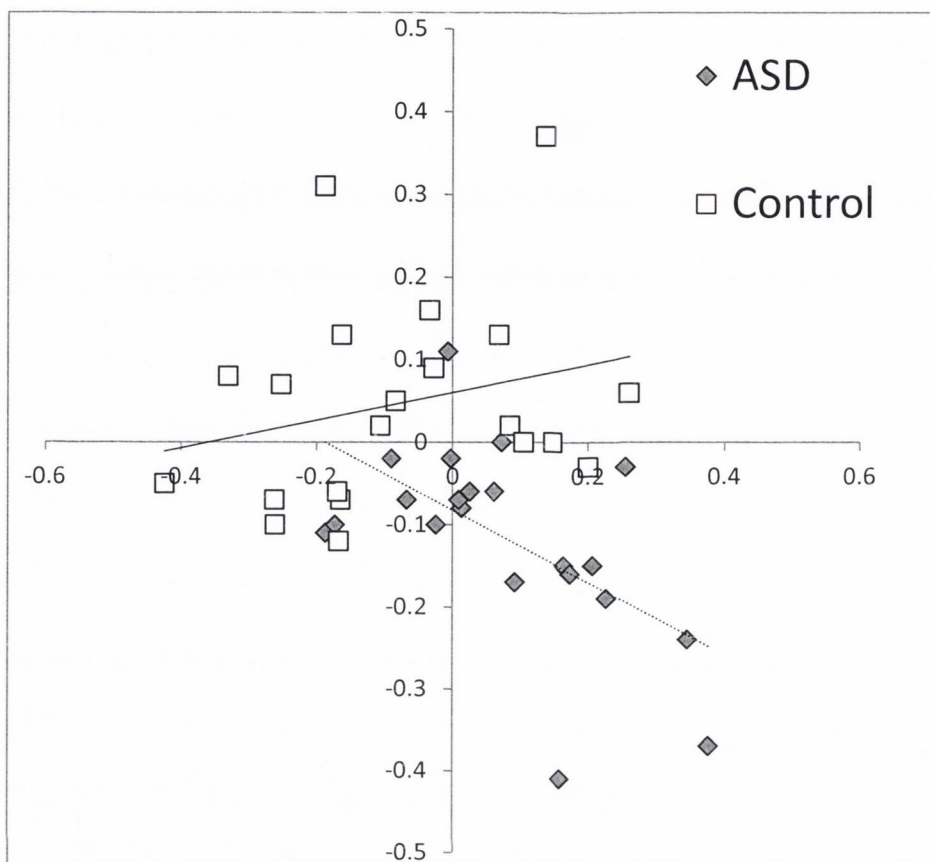


Figure 4.9 Connectivity between the Left Caudate and Right Anterior Cingulate and Activation to Social Rewards in the Left Caudate.

Connectivity values are shown on the x-axis and percent signal change for social reward feedback is shown on the y-axis. The ASD group is shown in grey (with dashed trend-line) and the controls in white (with solid black trend-line).

4.3.2.4 *Correlations with Behaviour*

There was a positive correlation between connectivity in the right MFG and the right caudate and scores on the ADI-R restricted and stereotyped behaviour scale ($r=.524$, $p=.018$); greater connectivity was associated with greater impairment. Connectivity values between the right ACC and right accumbens were negatively correlated with ADI-R communication scores ($r=-.548$, $p=.010$); greater connectivity was associated

with less impairment in terms of communication (see figures F2-F3 in Appendix F). None of these correlations withstood correction for multiple comparisons at the bonferroni level ($p(.05/7)=0.0071$). Correlations with the two-factor structure of the ADI-R (see appendix H) also showed that increased connectivity between the right middle frontal gyrus (MFG) and the right caudate was positively associated with restricted interests and repetitive behaviours (RRB). Correlations with the social communication deficit (SCD) were somewhat different using the two-factor structure of the ADI-R. Connectivity between the bilateral Pcg and the right accumbens was negatively associated with SCD (see appendix H).

4.3.3 Striatal Structural Connectivity

Mann-Whitney tests indicated that there were no significant between group differences in FA, MD, RD or AD (see table D1, Appendix D). Multivariate analyses with age, I.Q. and TIV entered as covariates were also performed but similarly showed no significant group differences (see table D1, Appendix D).

4.3.4 Correlations between Structural and Functional Connectivity

There was a significant positive correlation between AD in the right caudate to prefrontal tract and functional connectivity (raw Z-scores) between the right MFG and the right caudate across the group as a whole ($r=.414$, $p=.010$). There was a trend towards a positive correlation between AD in the right caudate to prefrontal tract and connectivity between the right MFG and the right caudate in the ASD group ($r=.445$, $p=.056$) but not controls participants ($r=.214$, $p=.380$) indicating that the significant

correlation was largely driven by variance in the ASD group. There were no other significant correlations between functional and structural connectivity.

4.4 Discussion

The ASD group showed increased functional connectivity between the cingulate and the MFG in the prefrontal cortex and the caudate and accumbens in the striatum, with group differences primarily in the right hemisphere. There was a significant group-by-age interaction effect on connectivity between the right MFG and the right caudate suggesting that group differences may be due to different developmental trajectories in ASD. Increased functional connectivity between frontostriatal regions in ASD was associated BOLD deactivation to social rewards (see chapter 3) and behavioural measures of social impairment, communication and repetitive behaviour. There were no significant group differences in the structure of the striatum or amygdala or in frontostriatal tracts. This suggests that group differences in functional connectivity, reported in the present study, may not be due to alterations in frontostriatal structures in ASD.

4.4.1 Group Differences in Functional Connectivity

4.4.1.1 Hyperconnectivity between the Cingulate and Striatum in ASD

Neuroanatomical connections between the cingulate and the striatum are organised in functionally distinct loops. The ventral cingulate is connected to the ventral and dorsal striatum (VS and DS) and the dorsal cingulate to the dorsal striatum (Beckmann, Johansen-Berg, & Rushworth, 2009). Cingulate regions connected to the VS are

involved in emotion, reward and pain whereas regions connected to the DS are mostly involved in motor functions, conflict/error detection and reward (Beckmann et al., 2009). The dorsal cognitive division of the cingulate is connected to other regions involved in attention including the dorsolateral Prefrontal Cortex (dlPFC) and parietal attention regions. The rostral-ventral affective division is connected to limbic regions including the OFC, amygdala, and periaqueductal gray (PAG) (Bush, Luu, & Posner, 2000).

Previous findings, together with the present results, suggest that hyperconnectivity between the cingulate and caudate may be specific to adolescents/adults with ASD. Increased bilateral connectivity between the cingulate and caudate has been reported during visuomotor performance among adults with ASD (Turner, Frost, Linsenbardt, McIlroy, & Müller, 2006) but not resting-state among children with ASD (Di Martino et al., 2010). Cingulate pathology has also been implicated more generally in ASD. In a meta-analysis of functional neuroimaging studies, hypoactivation was reported in the perigenual anterior cingulate in ASD during social tasks and in the dorsal anterior cingulate for non-social tasks (Di Martino et al., 2009). Reduced cingulate grey matter volume (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012; Haznedar et al., 2000) and surface area (Doyle-Thomas et al., 2012; Hadjikhani et al., 2006), primarily in the right hemisphere, have also been reported in a number of studies of ASD.

Hyperconnectivity between the right anterior cingulate and the left caudate was associated with deactivation to social rewards in ASD (as seen in chapter 3). This is in keeping with the role of the cingulate in social perception and social cognition deficits in ASD (Di Martino et al., 2009) and with recent evidence of abnormal cingulate

activation during social and non-social reward processing (Dichter et al., 2011; Kohls, Schulte-Rüther, et al., 2012), although this was not observed in the present participant group (see chapter 3). Taken together these results suggest that abnormal activation in the left caudate during social reward feedback could have been due to abnormal top down processes governed by the cingulate. The results of the current study also indicated hyperconnectivity between the right anterior cingulate and the right accumbens was associated with fewer communication deficits in ASD. Previous studies have implicated the anterior cingulate and accumbens abnormalities with increased communication deficits in ASD (Haznedar et al., 2000; Ohnishi et al., 2000; A. Qiu et al., 2010). In contrast, the present results suggest that abnormal connectivity between the right cingulate and accumbens may reflect a compensatory mechanism, in terms of communication in ASD.

4.4.1.2 Hyperconnectivity between the Paracingulate and Striatum in ASD

The paracingulate cortex is often thought of as part of the anterior cingulate cortex (ACC) (Gallagher & Frith, 2003; Walter, Abler, Ciaramidaro, & Erk, 2005), though it is anatomically, and perhaps functionally, distinct from the ACC (Gallagher & Frith, 2003). Diffusion MRI data in humans indicates that it is connected to the ventral and dorsal striatum and the dorsal prefrontal cortex (Beckmann et al., 2009). The paracingulate is involved in emotion, social interaction, reward and decision making, conflict monitoring and error detection (Amodio & Frith, 2006; Beckmann et al., 2009; Vogt, 2005). The anterior paracingulate, along with the superior temporal sulci and the temporal poles, plays an important role in theory of mind (Gallagher & Frith, 2003;

Walter et al., 2005) with activation modulated by the amount of social interaction involved in the task (Walter et al., 2004). The paracingulate and striatum are thought to be involved in separate phases of decision making, with the paracingulate involved in action selection and the ventral striatum responding to positive outcomes (Rogers et al., 2004).

Previous functional connectivity studies of the striatum in ASD, have not implicated the paracingulate (Di Martino et al., 2010; Turner et al., 2006), however reduced connectivity between the paracingulate and the intraparietal sulcus during working memory task performance (Koshino et al., 2005) and reduced connectivity with the IFG during sentence comprehension have been reported in ASD (Just et al., 2004). Additionally, reduced paracingulate activation during theory of mind tasks (Kana, Keller, Cherkassky, Minshew, & Just, 2009) and reduced grey matter volume in the right paracingulate (Abell et al., 1999) have been found in ASD. The results of the present study add to the literature implicating paracingulate abnormalities in ASD, indicating hyperconnectivity between the bilateral paracingulate and the right caudate and accumbens in the absence of task performance.

4.4.1.3 Hyperconnectivity between the MFG and Striatum in ASD

The MFG, along with part of the SFG, comprises the dorsolateral prefrontal cortex (dlPFC) (Badre & D'Esposito, 2009; Barbas & Pandya, 1989; Yeterian, Pandya, Tomaiuolo, & Petrides, 2012), which is connected to the rostral dorsolateral caudate as well as the OFC and mPFC (Draganski et al., 2008; Haber, 2003; Leh et al., 2007; Lehericy et al., 2004). The dlPFC is involved in a host of executive functions including

working memory, set-shifting, rule learning and planning (Badre & D'Esposito, 2009; Goldman-Rakic, Cools, & Srivastava, 1996; Leung, Gore, & Goldman-Rakic, 2002) and is thought to work together with the caudate to mediate these functions (Haber, 2003; Pasupathy & Miller, 2005). In terms of rule-learning, rewarded associations are thought to be identified in the striatum which trains slower learning mechanisms in the dlPFC (Pasupathy & Miller, 2005). The dlPFC is involved in rule-learning via reinforcement; once the rule has been acquired, the dlPFC is no longer required and action execution is controlled by the premotor cortex (Badre & D'Esposito, 2009).

As in previous studies of striatal connectivity (Di Martino et al., 2010; Turner et al., 2006), there was a significant increase in connectivity between the caudate and MFG in ASD. In addition, the ASD group showed hyperconnectivity between the MFG and the accumbens. This is in keeping with a body of evidence implicating the MFG/dlPFC in ASD. Decreased functional connectivity has been reported between the dlPFC and the visuospatial regions in the occipital and parietal lobes during visuospatial processing (Damarla et al., 2010). ASD subjects also show less anti-correlation between the dlPFC and amygdala during passive viewing of emotional facial expressions (Rudie et al., 2011) and increased regional homogeneity (local synchronisation of the BOLD signal) in the right MFG during rest (Paakki et al., 2010). Reduced activation in the dlPFC during social and non-social information processing, including spatial working memory (Luna et al., 2002), sustained attention (Christakou et al., 2012) and memory encoding of social information have been recorded (Greimel, Nehr Korn, Fink, et al., 2012) as well as abnormal involvement in tasks such as gaze perception (Vaidya et al., 2011). In addition, increased grey matter volume (Ecker et al., 2012) and neuronal number (Courchesne et al., 2011) indicate structural abnormalities in the dlPFC in ASD.

There was an age by group interaction for connectivity values between the right MFG and caudate. The ASD group showed increased connectivity between the right MFG and right caudate, compared to controls, with no evidence of change with age. For the control group, connectivity was lower overall but there was evidence of increased connectivity with age. This is in keeping with evidence of progressive functional integration between long range connections with age, and increased frontostriatal connectivity during task performance, during typical development (Rubia,, 2012). Evidence from the present study, along with previous research findings (Di Martino et al., 2010; Turner et al., 2006), suggest that hyperconnectivity between the MFG and the caudate is present across ages and may pervade development in ASD.

Connectivity between the right MFG and right caudate was associated with increased restricted, repetitive and stereotyped behaviours as measured by the ADI-R. This in keeping with previous literature implicating the frontostriatal circuitry, particularly the caudate and MFG/dIPFC, in executive function and repetitive behaviour deficits in ASD (Ecker et al., 2012; Estes et al., 2011; Hollander et al., 2005; Langen, Durston, et al., 2011; Rojas et al., 2006) and suggests that cognitive as opposed to sensorimotor circuitry is implicated in repetitive behaviours in high functioning ASD. It has been proposed that higher-level restricted interests and repetitive behaviours (such as circumscribed interests) may be more characteristic of older individuals and higher functioning ASD, whereas sensorimotor behaviours may be more common in younger individuals and those with intellectual disability (Turner, 1999). Though there is no substantive evidence to support this perspective, such an interpretation would be in line with the present findings showing group differences in cognitive as opposed to sensorimotor circuitry.

4.4.2 Structure of the Striatum, Amygdala and Frontostriatal Connections.

4.4.2.1 Structure of the Striatum and Amygdala

As can be seen in figure 4.5, uncorrected results suggest that there may be localised differences in the shape of the amygdala (and to a lesser extent, the striatum in ASD). The vertex analysis suggested that there may be thinning in the laterobasal nuclei (Bzdok et al., 2012) of the left amygdala in ASD (see figure 4.6). The laterobasal nuclei and are involved in processing emotional stimuli (Ball et al., 2007) and have previously been shown to be enlarged in young children with ASD (Kim, 2010). As amygdala volume decreases with age in ASD (Stanfield et al., 2008), these results suggest that the laterobasal nuclei, may be particularly susceptible to abnormal developmental processes in ASD.

Similar to previous research examining shape differences in the basal ganglia in ASD (Qiu et al., 2010), group differences did not withstand correction for multiple comparisons. Previous volumetric studies have yielded inconsistent results with both increased and decreased caudate and amygdala volumes reported (Cauda et al., 2011; Estes et al., 2011; Howard et al., 2000; Langen, Durston, et al., 2011; McAlonan et al., 2005), as well as no difference in amygdala or caudate volume (Haznedar et al., 2000; Langen , et al., 2011). This suggests that group differences in these subcortical structures are subtle and may be subject to different developmental processes in ASD (Langen et al., 2009; Stanfield et al., 2008), therefore larger samples are necessary to attain necessary statistical power for further inferences to be made.

4.4.2.2 *Frontostriatal Structural Connectivity*

There were no significant group differences in white matter microstructure (FA, MD, RD, AD) in tracts connecting the caudate or accumbens to the prefrontal cortex. Only one previous study has specifically examined microstructural integrity of frontostriatal circuits. Greater MD was reported in projections between the right accumbens and prefrontal cortex but not in projections between the caudate and prefrontal cortex (Langen et al., 2011).

The disparity between structural and functional connectivity findings, with significant group differences for functional data but not structural data, may be due to several factors. Firstly, structural data may be less sensitive to group differences than functional data (Finger et al., 2012). Secondly, with the exception of a significant correlation between functional connectivity between the right caudate and MFG, and AD in the right caudate tract, measures of functional connectivity were unrelated to structural metrics. Greater concordance between functional and structural connectivity metrics may be obtained by examining specific loops (i.e. cingulo-striatal loop or dlPFC-striatal loops) in frontostriatal circuitry rather than connections between the striatum and the entire frontal cortex. It is likely that such analyses would require higher resolution data and advanced modeling techniques such as constrained spherical deconvolution (CSD) rather than the tensor model used in the present study. Resting-state connectivity analysis is not anatomically constrained therefore differences in connections between the striatum and PFC could potentially arise from connectivity differences in another part of the circuit, for example in fibre pathways connecting the striatum and pallidum, pallidum and thalamus or thalamus and to

cortex. DTI tractography analysis was constrained to frontostriatal connections but structural differences may lie in other pathways such as thalamo-cortical connections. Finally, frontostriatal connections may be characterised by topographical re-organisation of fibre pathways in ASD rather than microstructural alterations. Future studies could use connectivity based classification methods (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007) to examine group differences in the topography of frontostriatal connections in ASD.

4.4.3 Limitations and Future Directions

The results of the present study should be interpreted in the light of several methodological issues. We did not replicate previous findings showing positive functional connectivity between frontostriatal regions, for example between the MFG and the caudate, in typical adults in our control group (Di Martino et al. 2008). This is perhaps due to developmental factors related to the age range of the participants in the present study. Indeed negative connectivity between the majority of frontostriatal regions in controls was no longer apparent when age and IQ adjustments were not performed (see figure D.1 and table D.2, Appendix D). Another potential explanation for non-replication of previously published findings is that Di Martino et al. (2008) divided the caudate into ventral and dorsal regions, which showed distinct patterns of connectivity with sub-regions of the ACC and dlPFC. Therefore examining connectivity across entire structures in the current study may have obscured functional relationships between sub-regions of these structures. Recent studies have shed light on the topography of functional and structural connections within the striatum (Robinson et al., 2012; Verstynen et al., 2012) which may be useful in defining seed

regions for future examinations of functional and anatomical connections within frontostriatal circuitry in ASD.

A limitation of functional connectivity methods, as used in the present study, is that one cannot infer the source of differences in functional connectivity. Frontostriatal loops are part of larger circuitry which also involve thalamo-cortical connections that direct feedback from the striatum to the cortex via the pallidum (Alexander et al., 1990, 1986). The thalamus also projects to the striatum, and frontostriatal circuitry is further regulated by projections from the amygdala, hippocampus and brainstem (Haber & Knutson, 2009). Increased connectivity between the thalamus and frontal cortical regions has been reported in ASD (Mizuno, Villalobos, Davies, Dahl, & Müller, 2006) indicating that thalamo-cortical circuitry is also abnormal in ASD, which could impact on frontostriatal circuitry. Given the looped structure of cortico-striatal-thalamo-cortical connections (and various regulatory influence on this circuitry), it is difficult to infer at what point dysregulation occurs, i.e. in the frontal cortex, the thalamus, the striatum, other regulatory subcortical structures, or in specific connections between these structures. Unpublished data from the ABIDE consortium suggests that the thalamus shows increased regional connectivity in ASD.

Hyperconnectivity was limited to subcortical regions (the thalamus and globus pallidus) suggesting that thalamic hyperconnectivity could potentially underlie increased frontostriatal connectivity in ASD, as seen in the present study. Future studies could shed light on the source of hyperconnectivity within frontostriatal circuitry by including additional regions of interest in the thalamus and using effective connectivity modeling techniques, such as dynamic causal modeling.

Two recent studies demonstrate the potential utility of effective connectivity techniques of fronto-basal ganglia pathways in neuroimaging studies of ASD. Results of these studies suggest that response inhibition is mediated by a fast ‘hyper-direct’ pathway connecting the inferior frontal gyrus and the pre-supplementary motor area with the sub-thalamic nucleus, and the more deliberate ‘indirect’ pathway between the same cortical regions and the caudate (Jahfari et al., 2011). Additionally, frontal control of the basal ganglia was strongest in unpredictable environments (potentially explaining why ASD subjects show increased frontostriatal connectivity), but advanced preparation of action plans during response inhibition, reduced the need for top-down control (Jahfari et al., 2012). These results suggest that the ‘hyper-direct – indirect’ model could be useful in understanding response inhibition (Rajendran & Mitchell, 2007), and potentially repetitive behaviour problems in ASD, and that proactively rehearsing action plans could perhaps reduce such behaviours.

There were no significant group differences in striatal volume, shape or white matter connectivity (as measured by DTI tractography). This may reflect a true lack of between group differences or could be due to methodological factors, such as sample size, tractography methods or to heterogeneity in the data owing to ongoing developmental processes in the sample. Previous studies suggest that both grey and white matter undergoes different developmental trajectories in ASD (Carper et al., 2002; Cheng et al., 2010; Keller et al., 2007; Langen et al., 2009; Mak-Fan et al., 2012) . Future studies could use a tighter age range to limit heterogeneity for group-wise comparisons and/or use larger age ranges with larger sample sizes so that between group differences in developmental trajectories can be examined.

Interestingly, hyperconnectivity between the PFC and the striatum was primarily lateralised to the right hemisphere. This is in keeping with evidence that differences in the structure and function of the cingulate are largely lateralised to the right hemisphere (Bejjani et al., 2012; Dichter et al., 2010; Haznedar et al., 2000; Joshi et al., 2012), that increased grey and white matter volume asymmetries are lateralised to the right hemisphere in ASD (Herbert et al., 2005) and that regional homogeneity, a measure of functional connectivity thought to index local synchrony in the BOLD signal, is primarily lateralised to the right hemisphere in ASD, potentially reflecting a compensatory mechanism in ASD (Liu et al., 2008; Paakki et al., 2010). Future studies could examine potential hemispheric asymmetries in functional and structural connectivity.

4.5 Conclusions

The results are in line with previous reports of diffuse patterns of increased functional connectivity between the striatum and frontal, temporal and parietal lobes as well as the pons in ASD (Di Martino et al., 2010; Turner et al., 2006). In the present study, hyperconnectivity was confined to limbic and associative frontostriatal circuits. Unlike previous studies (Di Martino et al., 2010; Turner et al., 2006), there were no group differences in sensorimotor loops, for example between the putamen and precentral gyrus. Similarly, in a separate analysis we found reduced connectivity between cognitive, but not motor regions, of the cerebellum and frontoparietal regions (Balsters, Delmonte, Wenderoth, & Gallagher, 2013). Previous studies did not specifically report accumbens connectivity (Di Martino et al., 2010; Turner et al., 2006)

therefore the results of the present study add to the literature by indicating abnormal connectivity between the accumbens and the ACC, paracingulate cortex and MFG.

These findings add to growing body of literature indicating significant increases as well as decreases in functional connectivity in ASD and do not support general under-connectivity accounts (Just, Cherkassky, Keller, Kana, & Minshew, 2007), but suggest that ASD is characterised by complex functional re-organisation which also involves hyperconnectivity within certain circuits. Increased functional connectivity in frontostriatal circuitry was associated with behavioural characteristics of ASD in terms of communication and restricted interests/repetitive behaviours, as well as deactivation to social rewards in the striatum. There were no differences in the structure of the striatum or in structural connectivity as measured by DTI. This suggests that functional differences in connectivity were not due to structural abnormalities in striatal grey matter, or white matter projections from the frontal cortex.

5 Whole Brain Analyses of Brain Structure and Function in ASD

5.1 Introduction

"Although there is good reason to suppose that infantile autism may well arise on the basis of some type of organic brain disorder ... there are no good grounds for placing the lesion in any one particular area of the brain" (Rutter, 1974, p.138-139).

Michael Rutter proposed, over thirty years ago, that the primary neuropathology in ASD is unlikely to be localised to one brain region. As mentioned in the introduction (section 1.4), neuroanatomical differences in ASD have been reported in a variety of brain regions. Previous chapters in this thesis have focused on the function and structure of frontostriatal circuitry in ASD. In the current chapter, a comprehensive assessment of neural anatomy and function in ASD will be performed using data-driven whole-brain analyses. Voxel-based morphometry (VBM) will be used to examine grey matter volume, Tract-Based Spatial Statistics (TBSS) to examine white matter integrity and Independent Components Analysis (ICA) to examine resting-state functional connectivity. This will provide the opportunity to evaluate the results of localised hypothesis-driven findings in the light of potentially more widespread differences in neuroanatomy and brain function. Additionally, by assessing each of these modalities within the same subjects it will be possible to investigate overlapping differences in function and structure across modalities.

5.1.1 VBM Studies of Grey Matter Volume in ASD

Voxel based morphometry involves a voxel-wise comparison of local differences in grey matter volume and/or density (Ashburner & Friston, 2000). It overcomes the difficulties inherent in traditional volumetric approaches which focus on particular structures, in that it is unbiased and provides an overall assessment of anatomical differences in the brain. Additionally, it is sensitive to localised differences, which may be overlooked when examining average differences within a structure or region (i.e. variations in cytoarchitectonic areas that cannot be visualised in standard anatomical images).

A number of VBM studies have been carried out among children and adults with ASD. The first such study was carried out in a small sample of adults with ASD (Abell et al., 1999). Increased grey matter density in the left amygdala, temporal lobes (left middle temporal gyrus, right inferior temporal gyrus) and bilateral crus 1 of the cerebellum as well as decreased grey matter in the left inferior frontal gyrus and right paracingulate, were reported. Subsequent studies among adults with ASD have shown further localised increases and decreases in grey matter volume and density. Grey matter density increases have been reported bilaterally in frontal regions (inferior, middle and superior frontal gyri) and left anterior cingulate (Schmitz et al., 2006) and increased grey matter volume has been reported extensively in the bilateral temporal lobes, left basal ganglia (caudate and putamen), left insula, bilateral cingulate and in the right dorsolateral prefrontal cortex/middle frontal gyrus, precentral gyrus and postcentral gyrus (Ecker et al., 2012; Toal et al., 2010). Decreased grey matter density has been recorded in the right cerebellum, thalamus and precuneus, bilateral pre- and

postcentral gyri and in the bilaterally in the frontal lobes (superior and medial frontal gyri) (Hyde, Samson, Evans, & Mottron, 2010; Mc Alonan et al., 2002) and decreases in volume have been reported bilaterally in the temporal lobes (inferior, middle and superior temporal gyri), in the cerebellum, the occipital lobes (lingual and fusiform gyri) as well as the parietal lobes (Ecker et al., 2012; Toal et al., 2010).

Findings from studies among children and adolescents have largely mirrored the results obtained from studies with adults, though there are some discrepancies.

Children with ASD show increased grey matter volume in the frontal lobes – primarily in the left hemisphere, bilateral temporal lobes (middle and superior temporal gyri), left parahippocampal gyrus, left inferior occipital gyrus, right fusiform, posterior cingulate and right thalamus. Decreased grey matter volume has been reported in the superior frontal gyrus, precuneus, lateral occipital cortex and left thalamus (Uddin et al., 2011; Waiter et al., 2004).

Recent studies have highlighted important differences in brain maturation in ASD.

Children and adolescents with ASD are more likely than adults to have increased grey matter density in the bilateral fusiform gyri, right cingulate and insula (Duerden, Mak-Fan, Taylor, & Roberts, 2012). In a cross-sectional study of grey matter development in ASD, Greimel et al. (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012) reported that grey matter development curves as a function of age were shifted to the left in ASD, in regions implicated in social and emotional functioning (the left amygdala, right temporoparietal junction and left septal nucleus), suggesting that grey matter peaks earlier in ASD than controls in these regions. Different developmental trajectories were noted for the left and right amygdala, with early overgrowth in both

hemispheres, and only right hemisphere volume converging with controls with increasing age.

Grey matter anatomical differences have been associated with core behavioural deficits in ASD. Ecker et al. (2012) reported that decreased grey matter volume in the occipital lobe was associated with increased social and communicative impairments, and grey matter excesses in the frontal lobe were associated with more severe repetitive symptoms as measured by the ADI-R. In a study of children and adults with ASD, Rojas et al. (2006) reported that increased grey matter volume in the left inferior frontal gyrus, caudate nuclei and right amygdala were positively correlated with repetitive behaviours as measured by the ADI-R, whereas smaller volumes in superior temporal gyri, left postcentral gyrus and cerebellar regions were associated with greater impairment in terms of repetitive behaviours. Increased volumes of the caudate nucleus, left postcentral gyrus, superior temporal gyri and cerebellar regions were associated with greater impairment on terms of social and communication measures of the ADI-R, and reduced volume in the left precuneus, left medial frontal and inferior frontal gyri, and left precentral gyrus were associated with greater impairment on the ADI-R Social and Communication domain. These findings indicate that diffuse grey matter anatomical differences are related to specific behavioural deficits among both children and adults with ASD.

5.1.2 TBSS Studies of White Matter Integrity in ASD

A number of studies have used TBSS to examine white matter integrity among children and young adolescents with ASD. Reduced Fractional Anisotropy (FA) has been recorded in an number of major white matter tracts including the corpus callosum,

cingulum, internal and external capsule, inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), cingulum, anterior thalamic radiation (ATR), forceps minor, uncinate fasciculus inferior cerebellar peduncle and corticospinal tract, comprising regions in frontal, temporal and parietal lobes (Barnea-Goraly, Lotspeich, & Reiss, 2010; Cheng et al., 2010; Jou et al., 2011; Kumar et al., 2009; Shukla, Keehn, & Müller, 2011). Increased FA has also been reported among adolescents with ASD in the optic radiation, IFOF, SLF, corona radiata, bilateral middle cerebellar peduncle cingulate and in regions comprising the bilateral insula, right anterior thalamus, right putamen, right postcentral gyrus, right superior temporal gyrus and right inferior occipital gyrus (Bode et al., 2011; Cheng et al., 2010). Abnormal white matter integrity, as indexed by increased mean diffusivity (MD), as well as changes in axial and radial diffusivity (AD and RD respectively) have also been recorded in a number of these regions (Barnea-Goraly et al., 2010; Cheng et al., 2010; Shukla et al., 2011).

Few studies have used TBSS to examine white matter integrity among older adolescents or adults with ASD, though a recent study has reported widespread decreased FA, and increased RD and MD in young adults with ASD compared to controls (Kleinhans et al., 2012). White matter integrity was compromised in nearly all major white matter tracts including the cingulate gyrus, the IFOF, the SLF, the corpus callosum, the internal capsule and the uncinate fasciculus. Additionally, differences in the developmental trajectories of these tracts were reported. FA decreased with age, from adolescence to adulthood in controls, whereas it increased slightly in ASD in large number of white matter tracts. MD and RD showed a positive age correlation in the TD group and a negative age correlation in the ASD group. Though these age effects are

difficult to interpret – one would expect FA to continue to increase and MD to be decreasing in early adulthood in typically developing controls (Kochunov et al., 2012; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005) – they suggest that ASD may be characterised by abnormal age-related changes in white matter integrity during adulthood.

Little is known about how white matter integrity relates to behavioural symptoms in ASD. Previous studies using the ADOS and ADI (Barnea-Goraly et al., 2010), and the SRS (Jou et al., 2011), did not find any significant correlations between white matter integrity in regions where there were significant group differences, and behavioural symptoms in ASD. This may be due to methodological issues associated with DTI and/or with behavioural measures of ASD symptoms (see section 6.5 for further discussion).

5.1.3 Whole Brain Resting-state Studies of ASD

The majority of studies examining functional connectivity differences in ASD have used seed region approaches. Seed region approaches have identified abnormal functional connectivity during a range of tasks. Reduced functional connectivity between frontal and parietal areas has been recorded during executive functioning tasks (Just et al., 2007), between visual and frontal regions during visuomotor performance (Villalobos et al., 2005) and between the fusiform face area and the amygdala, and the thalamus and posterior cingulate during face processing (Kleinmans et al., 2008), as well as between regions within the default mode network, both during rest and social and introspective tasks (Cheng et al., 2010; Kennedy & Courchesne, 2008a; Kennedy & Courchesne, 2008b). Though these studies have indicated that there are important

differences in connectivity between specific regions in ASD, it is possible that important differences have been overlooked as they depend upon the selection of ROIs based on *a priori* hypotheses. The use of seed region approaches for examining resting-state connectivity is largely due to methodological issues, as measuring connectivity between two or more regions of interest is more easily implemented than examining connectivity between all possible regions within the brain, with the associated challenge of correcting for multiple comparisons.

Recent studies have begun to examine differences during resting-state using whole brain analyses. In a study of adults with ASD, Anderson et al. (2011) obtained pair-wise functional connectivity measurements from a lattice of 7266 regions of interest covering the entire grey matter (26.4 million connections). Abnormal connections in ASD were highlighted in the default mode network, superior parietal lobule, anterior insula and fusiform gyrus. Gotts et al. (2012) carried out a study among adolescents/young adults with ASD, in which whole brain functional connectivity was examined by calculating the correlation of the time series in each voxel with every other voxel. Two sample t-tests were then carried out for each voxel and candidate seeds were selected in regions of significant difference with at least 100 voxels. Reduced connectivity in ASD was identified in social processing regions (the vmPFC, amygdala and middle temporal lobe), regions involved communication (the inferior frontal gyrus, posterior temporal cortex and superior temporal gyrus), and regions involved in visuospatial and somatosensory processing (the postcentral gyrus, precuneus and extrastriate cortex).

ICA is a data-driven method which can be used to identify multiple integrated networks from fMRI time-series, at the whole brain level (Allen et al., 2011). ICA has recently been used to examine functional connectivity in ASD, however, these studies focused on specific networks. Focusing on default-mode sub-networks Assaf et al., (2010) reported reduced connectivity between the precuneus and the medial prefrontal cortex/anterior cingulate cortex. Similarly, Washington et al. (2013) examined DMN activity during rest periods while participants performed a task of executive function. The ASD group showed reduced connectivity between DMN nodes but increased connectivity within nodes. In an analysis of 'social' resting-state networks Von dem Hagen, et al. (2012) reported reduced intra-network functional connectivity in the mPFC of the DMN and reduced inter-network connectivity between the medial temporal lobe network and the salience network in ASD. These studies suggest that ICA is promising tool for examining functional connectivity in ASD.

In the present study group ICA (Calhoun, Adali, Pearlson, & Pekar, 2001) was used to examine whole brain connectivity in ASD and controls using a similar approach to that described previously (Allen et al., 2011). In addition to examining the level of co-activation within and between resting-state networks (RSNs), the spectral properties of the BOLD signal within each network, were analysed. Spectral power reflects the amplitude of the BOLD signal at a particular frequency and therefore provides additional information to measures of functional connectivity. The evidence suggests that spectral information contained in the BOLD signal, at both low (<0.1 Hz) and high (>0.1 Hz) frequencies, relates to underlying neural processes (Baria et al., 2011; He, Zempel, Snyder, & Raichle, 2010) and specific aspects of information processing (Honey et al., 2012), and can be localised to specific anatomical structures (Baria et al.,

2011). Recent studies suggest that spectral information is sensitive to differences between clinical populations (Calhoun et al., 2012; Malinen et al., 2010) as well as subject characteristics, such as age and gender (Allen et al., 2011).

As can be seen from the evidence reviewed above, a myriad of brain regions have been implicated in ASD pathology. The aims of this study were to examine grey and white matter integrity, as well as functional connectivity; across the entire brain to evaluate findings from the previous two chapters of this thesis in the context of other potential differences in neuroanatomy and brain function in ASD. In addition, it was anticipated that by using three different modalities within the same subjects, it would be possible to investigate converging differences across modalities.

5.1.4 Aims

1. To examine whole brain grey matter volume using VBM.
2. To examine whole brain white matter integrity using TBSS. This analysis will primarily focus on FA and MD values. AD and RD will also be examined to complement FA and MD findings.
3. To examine whole brain functional connectivity using ICA, using measures of both functional network connectivity and spectral power.
4. To examine significant group differences in terms of group-by-age interactions.
5. To examine significant group differences in terms of behavioural impairments.

5.2 Methods

5.2.1 Participants

Twenty-three ASD participants and twenty-six controls were included in the VBM analysis after excluding datasets with poor data quality arising from motion and/or other factors (see section 5.2.4). Twenty-two ASD and 24 control participants were included in the DTI and resting-state fMRI analyses after excluding subjects for excessive motion and/or poor data quality (see section 2.8).

5.2.2 Statistical analysis of Behavioural Data

Behavioural data were analysed using SPSSv16. Correlations were carried out between regions in which there were significant group differences in grey or white matter structure, or functional connectivity, and behavioural measures. Non-parametric Spearman's correlations were carried out for the ADOS-G and ADI-R subscales for the ASD group and SRS scores for both ASD and control groups. Multivariate analyses were used to examine group-by-age interaction effects in regions in which there were significant group differences in structure or functional connectivity, except for the resting-state functional connectivity analysis, where group-by-age interactions were tested directly in the MANCOVAN toolbox (see section 5.2.6).

5.2.3 MRI Data Acquisition and Preprocessing

Details of MRI data acquisition and preprocessing can be seen in section 2.7 and 2.8.

5.2.4 Voxel Based Morphology (VBM) of Grey Matter Volume

Voxel Based Morphology (Ashburner & Friston, 2000) was carried out using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm8/>) using the Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL) (Ashburner, 2007) approach as implemented in SPM8 (www.fil.ion.ucl.ac.uk/spm). Image orientation was set to the anterior commissure (AC). T₁-weighted images were then normalised to template space and classified into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the 'new segment' routine. The data were then modulated using Jacobian-transformed tissue probability maps to account for the effect of spatial normalisation by multiplying each voxel value by its relative volume before and after warping. Individual GM images were normalised into Montreal Neurological Institute (MNI) standard space and smoothed using an 8 mm full-width-half-maximum (FWHM) Gaussian kernel. Data quality checks were carried out on the un-smoothed data by displaying one slice for all images and checking sample homogeneity using covariance, to screen for any subjects for whom the variance was greater than 2 standard deviations from the mean. Based on these criteria two subjects, one ASD subject and one control, were subsequently removed from further analysis.

Second level analysis was carried out on modulated grey matter images. Independent samples t-tests were used to examine the effect of group. Age, IQ and total intracranial volume (TIV) were mean centred and included as covariates in all of these analyses, given that these factors are associated with brain structural properties (Barnes et al., 2010; Jung & Haier, 2007). An absolute threshold of 0.1 was used to compute statistics in regions where there was greater than 10% probability that the voxels belonged to

grey matter. As in previous research using small sample sizes and older participants with ASD, an un-corrected threshold of $p < 0.001$, with 10 contiguous voxels was used (Abell et al., 1999; McAlonan et al., 2002; Schmitz et al., 2006). Un-corrected thresholds have previously been recommended for clinical research where a balance between type I and type II errors is sought (Lieberman & Cunningham, 2009; Loring et al., 2002). However, caution is advised when interpreting these findings given the small sample size and use of an un-corrected threshold.

5.2.5 Tract-Based Spatial Statistics (TBSS) of White Matter

Integrity

Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) as implemented in FSL, was used to carry out voxel-wise statistical analysis of the FA data. Firstly, FA images were exported from Explore DTI (see chapter two for preprocessing). A study specific template was generated by aligning every FA image to every other one, identifying the "most representative" image, and using this as the target image. This target image was then affine-aligned into MNI standard space, and every other image was transformed into 1x1x1mm MNI space by combining the nonlinear transform to the target FA image with the affine transform from that target to MNI152 space. The resolution is set to 1mm³ by default as the following steps -skeletonisation and projection - work best at this resolution. In the following step, a mean FA skeleton, representing white matter tracts for the entire group, was created by projecting the thinned mean FA images from each subject onto a single skeleton image. The FA skeleton image was then thresholded at $>.2$, to select regions for subsequent voxel-wise cross-subject statistics.

The non-linear warps and skeleton projection was then applied to the MD, RD and AD images in order to run group-wise statistics on these additional metrics.

Given that diffusion MRI data are not normally distributed (Jones et al., 2005), non-parametric permutation based testing was used to examine group differences in FA, MD, AD and RD. The randomise tool in FSL was used to run two-sample t-tests to examine group differences in FA, MD, AD and RD. Age, IQ and total intracranial volume (TIV) were mean-centred and included as covariates of no interest in randomise. Statistical thresholding was implemented using threshold free cluster enhancement (TFCE, 5000 permutations; $p < .05$) which is sensitive to spatially extensive areas of significant difference. Second, a voxel-based thresholding approach was carried out using the non-parametric toolbox in MRICron (Rorden, Bonilha, & Nichols, 2007), which implements the rank-order Brunner-Munzel test (Brunner & Munzel, 2000) for group comparison, and thresholded using the False-Discovery Rate (Genovese, Lazar, & Nichols, 2002) (FDR $p < .01$; 4000 permutations; 10 or more voxels). This approach is more sensitive to significant group differences with a small spatial extent. As there is no option for including covariates in the npm toolbox, correlations were carried out to examine the potential impact of age, FSIQ and TIV on changes in FA and MD in each group separately.

5.2.6 Independent Component Analysis of Resting-state Data

Group ICA was carried out on the pre-processed fMRI data (see chapter 2) using GIFT software (<http://mialab.mrn.org/software/gift/index.html>). GIFT implements spatial ICA by calculating spatially independent brain sources from the fMRI data. Firstly, the optimal level of components was estimated from the dataset using Minimum

Descriptive Length (MDL) criteria (Li, Adali, & Calhoun, 2006). This determined that the optimal number of independent components (ICs) for group ICA was 38. The data were then compressed for each subject using principal component analysis (PCA) so that the data could be analysed as a single group. Spatial Independent Components Analysis (ICA) was then performed on the reduced data-set using the Infomax algorithm (Bell & Sejnowski, 1995). To ensure a robust decomposition, ICASSO was run with 100 re-runs and random initial conditions (Himberg, Hyvärinen, & Esposito, 2004). Finally, back reconstruction is carried out to compute individual subjects components from the group ICA and the PCA analysis (Calhoun et al., 2001; Erhardt et al., 2011). This resulted in an independent component (IC) map and associated time-course for every component for each subject.

Thirty-eight ICs were initially identified and 24 were included in further analysis. Components were excluded from further analysis if quality (iQ: a measure of intra- and extra- cluster similarity, (Himberg et al., 2004)) was below 0.9 or there was visual evidence of artefacts, e.g. movement artefacts characterised by stereotypical 'ringing' around the edge of the cortex. Resting state networks were categorised as visual, auditory, sensorimotor, subcortical, attention, frontal and default mode. This was done by performing spatial regression using the t-maps of the 28 RSNs identified by Allen et al. (2011) to identify networks that best corresponded to the networks identified in the present study, and by spatial overlap with RSNs presented in other studies (Allen et al., 2011; Cole, Smith, & Beckmann, 2010; Jeong, Choi, & Kim, 2012). Cytoarchitectonic probabilities were established where possible by using the Anatomy toolbox (Eickhoff et al., 2005).

Three outcome variables were examined for the selected RSNs: 1) IC spatial maps (SMs) 2) IC time-course spectra and 3) Functional Network Connectivity (FNC (Jafri, Pearlson, Stevens, & Calhoun, 2008). SMs reflect the level of co-activation within a network by indicating the level of correspondence between a voxel time-course and the ICs time-course. Spectral power reflects the level of coherent activity within a network at given levels of frequency power. FNC indicates the connectivity between RSNs by calculating the temporal correlations between them (Jafri et al., 2008). In addition, the Functional Connectivity toolbox (<http://mialab.mrn.org/software/fnc/index.html>), an extension of GIFT, was used to calculate time lags between components that are correlated with each other. FNC as implemented in GIFT assumes that the time courses of cortical areas within one component are synchronous. The additional step, computes the lag between components and has previously been used to examine differences in time lag in schizophrenia and healthy controls (Jafri et al., 2008).

Second level analysis was performed using the hierarchical approach described by (Allen et al., 2011). Multivariate methods are first used to identify important covariates, which reduces the number of subsequent univariate tests and the potential for spurious findings. The MANCOVAN toolbox was used to examine the effect of group. Age, IQ and head motion parameters (translation and rotation) were included as additional covariates. Multivariate results were inspected and group differences were not reported if there was a significant effect of head motion on the given resting-state measure. Results were corrected for multiple comparisons (FDR, $p < 0.01$).

5.3 Results

5.3.1 VBM Results

Table 5.1 White Matter, Grey Matter, CSF and Intracranial Volumes.

Volumes	Autism	Control	P-Value
Grey Matter (GM)	789.65	781.28	.643
White Matter (WM)	571.23	572.99	.924
Cerebrospinal Fluid (CSF)	226.75	225.61	.888
Total Intracranial Volume (TIV))	1587.63	1579.89	.838

There were no significant differences between groups in terms of overall white matter, grey matter, CSF or intracranial volume (see table 5.1). Uncorrected whole-brain voxel-wise results are reported in table 5.2. There were no significant group differences that survived correction for multiple comparisons using FDR correction. Uncorrected results indicated that the ASD group showed increased grey matter volume in the temporal lobes including the right inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, parahippocampal gyrus and temporal pole and left the fusiform gyrus. The ASD group also showed increased grey matter volume in the right supramarginal gyrus. Decreased grey matter volume was seen in the frontal lobes including the left middle frontal gyrus, right SMA and right paracentral lobule. Results can be seen in figure 5.1.

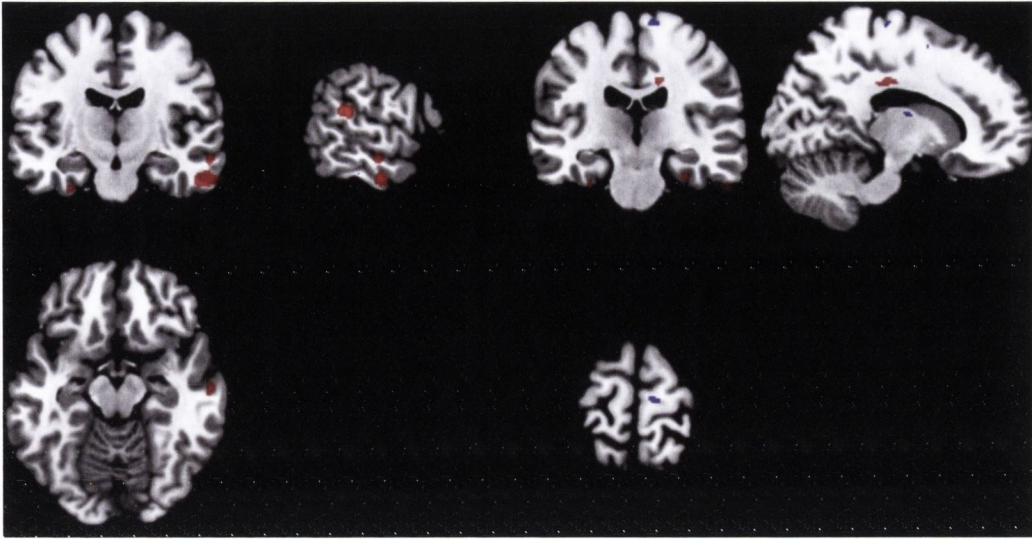


Figure 5.1 Group Differences in Grey Matter Volume.

Greater grey matter volume in the ASD group is shown in red, reduced grey matter volume in ASD is shown in blue.

Table 5.2 Group Differences in Grey Matter Volume.

	Cluster Size	T	MNI	BA and/or Probability (if available)
	Voxels	(Peak)	Co-ordinates (x,y,z)	
ASD>CON				
Temporal				
Right Inferior Temporal Gyrus	389	5.2	59 -11 -27	BA 20
Right Superior Temporal Gyrus	536	4.65	63 -33 16	BA 42; 68.6% right IPC (PF)
Left Fusiform Gyrus	85	3.86	-30 -16 -32	BA 20/36; 60% left Hipp (EC)

Right ParaHippocampal Gyrus	40	3.74	30 -21 -26	BA 20; 37.5% right Hipp (SUB)
Right Middle Temporal Gyrus	74	3.72	60 -15 -15	BA 21
Right Inferior Temporal Gyrus	18	3.7	36 0 -36	BA 36; Amyg LB (10%)
/Fusiform Gyrus				
Temporal Pole	28	3.65	44 12 -20	BA 38
Parietal				BA 40; 33% right IPC (PF); 33%right IPC (PFcn) 27.8%
Right Supramarginal Gyrus	18	3.73	53 -37 34	PFm)
CON>ASD				

Frontal				
Left Middle Frontal Gyrus	56	3.92	-20 20 51	BA 6 (10%)
Right SMA/ Paracentral Lobule	15	3.64	12 5 57	BA 6 (80%)
Right SMA/ Paracentral Lobule	38	3.54	9 -21 73	BA 6 (100%)
Subcortical				
Right Thalamus	17	3.53	14 -7 13	Thalamus-Prefrontal

5.3.2 TBSS Results

There were no significant group differences on measures of FA, MD, RD or AD using TFCE correction in FSL. There were significant group differences in all of these measures using the Brunzel-Munzel test and correction for multiple comparisons using FDR correction in the NPM toolbox. The ASD group showed significantly increased FA in frontal, occipital, cerebellar and subcortical regions comprising the right ILF, left SLF and left ATR. The ASD group showed reduced FA in frontal, temporal and occipital regions, comprising right ILF, the bilateral SLF and bilateral IFOF (see table 5.3 and figure 5.2). The ASD group showed increased MD in occipital and temporal regions in the right ILF. There were no regions where the controls showed increased MD (see table 5.4 and figure 5.2). The ASD group showed increased AD in the temporal and parietal lobes and in the right cerebellum, and decreased AD in frontal, temporal and occipital regions, as well as in the thalamus (see table E1 and figure E1, Appendix E). The ASD group also showed increased RD in frontal, occipital and temporal regions and decreased RD in the middle frontal gyrus and the internal capsule (see table E2 and figure E2, Appendix E).

Table 5.3 FA Differences between Groups.

Asterisks (*), double asterisks (**), triple asterisks (***) indicate correlations with ADI –R Communication score and Social interaction and SRS score respectively. Cross (†) indicates a significant age by group interaction.

White Matter Tract and/or Corresponding Cortical Area	Cluster Size Voxels	Z (Max)	Voxel Co-ordinates (x,y,z)
ASD>CON			
Frontal			
Left superior longitudinal fasciculus, precentral gyrus.***	10	3.53	-53 1 34
Right inferior frontal gyrus, p. opercularis *	19	4.15	49 18 28
Occipital			

Right inferior longitudinal fasciculus, lingual gyrus	11	3.43	28 -45 0
Cerebellum			
Right lobule VI	11	4.51	22 -59 -28
Right lobule VI	14	3.32	20 -63 -25
Subcortical			
Left anterior thalamic radiation, brainstem.	10	3.74	-6 -24 11
CON>ASD			
Frontal			

Left superior longitudinal fasciculus, inferior frontal gyrus, p. opercularis	12	4.01	-49 7 13
Left inferior fronto-occipital fasciculus, inferior frontal gyrus p. opercularis *	12	3.52	-49 19 19
Left inferior fronto-occipital fasciculus, frontal pole	18	3.86	-36 41 3
Right superior longitudinal fasciculus, inferior frontal gyrus, p. triangularis	24	4.87	47 30 3
Temporal			
Left superior longitudinal fasciculus, middle temporal gyrus	15	4.2	-58 -36 -4

Occipital			
Left lingual Gyrus	10	4.5	-22 -49 -3
Left Inferior fronto-occipital fasciculus, lingual gyrus **	17	3.75	-13 -79 4
Right inferior longitudinal fasciculus, cuneus/precuneus	17	4.09	18 -69 49
Right inferior fronto-occipital fasciculus , cuneus/precuneus	19	4.54	22 -79 42

Table 5.4 MD Differences between Groups.

Cross (†) indicates a significant age by group interaction.

White Matter Tract and/or Corresponding Cortical Area	Cluster Size Voxels	Z (Max)	Voxel Co-ordinates (x,y,z)
ASD>CON			
Temporal			
Right inferior longitudinal fasciculus, middle temporal gyrus	24	4.09	57 -7 -20
Right inferior longitudinal fasciculus, superior temporal gyrus	15	3.70	45 -32 7

Right inferior longitudinal fasciculus, planum temporale	11	3.47	53 -25 5
Occipital			
Right Inferior longitudinal fasciculus, lateral occipital lobe/fusiform gyrus †	10	3.70	40 -65 -4

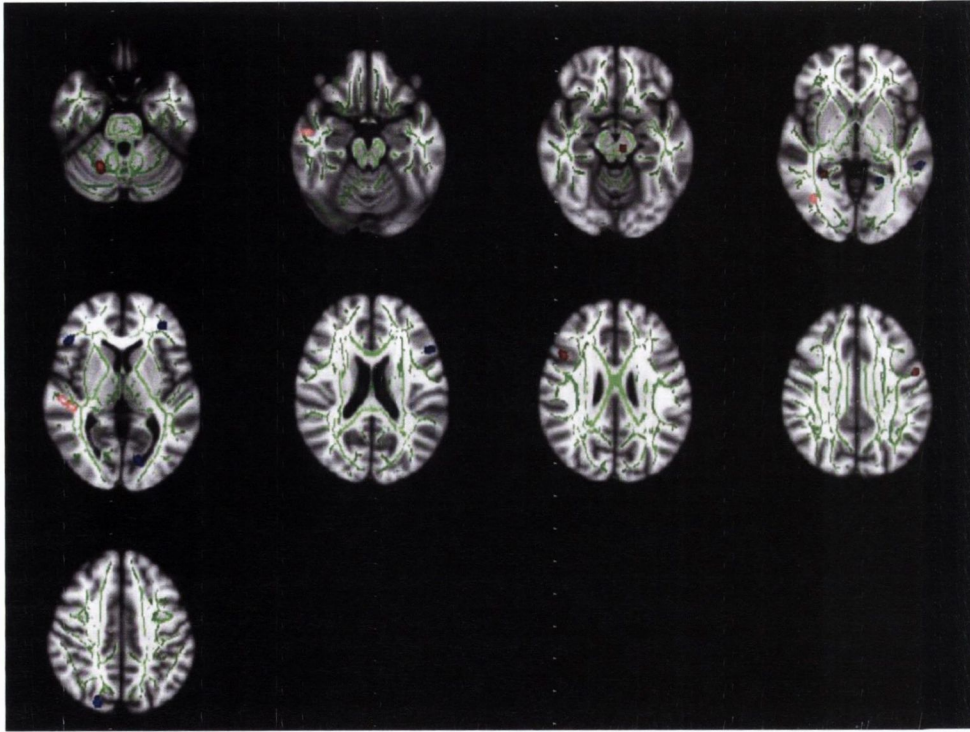


Figure 5.2 Group Differences in FA and MD.

Axial slices show increased FA in the ASD group (red), decreased FA in the ASD group (blue) and increased MD in the ASD group (pink). Images are displayed in radiological convention (left is right) and areas of significant difference have been highlighted using TBSSfill.

5.3.2.1 *Confounding Factors*

Age was positively correlated with FA in the left SLF, middle temporal gyrus (MNI: -58, -36, -4; $r=.469$, $p=.021$) and negatively related to MD in the right ILF, lateral occipital lobe/fusiform gyrus (MNI: 40 -65 -4; $r=-.493$, $p=.014$) in controls. Age was negatively related to MD in the right ILF (planum temporale) in the ASD group (MNI= 53 -25 5; $r=-.599$, $p=.003$). There were no significant correlations between FSIQ and MD or FA in controls. FSIQ was positively related with MD in the right ILF, superior temporal gyrus in the ASD group (MNI 45 -32 7; $r=.426$, $p=.048$). TIV was negatively associated with FA in the right cerebellum (MNI: 20 -63 -25; $r=-.446$; $p=.029$) and positively associated with FA in the right inferior frontal gyrus (MNI: 49 18 28; $r=.466$, $p=.022$) in controls. There were no significant correlations with TIV in the ASD group.

5.3.2.2 *Group-by-age Interactions*

There was a significant group-by-age interaction in MD values in right ILF in the lateral occipital lobe/fusiform gyrus (MNI: 40 -65 -4; $F=4.327$, $p=.044$) (see figure 5.3). The control group showed a significant decrease in MD with age ($r=-.493$; $p=.014$) whereas the ASD group did not show a significant change with age ($r=.055$; $p=.808$).

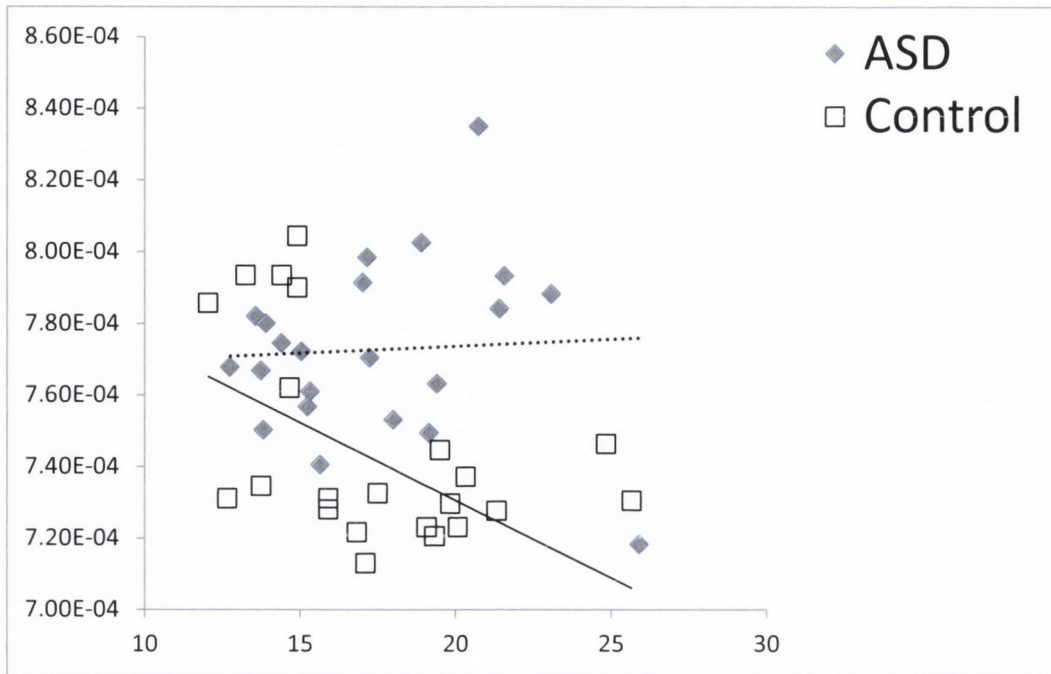


Figure 5.3 Group-by-age Interaction Effects on MD Values in the Right Inferior Longitudinal Fasciculus.

The ASD group is shown in grey (dashed line) and the controls in white (solid black line). The control group show a decrease in MD with age whereas the ASD group do not.

5.3.2.3 Correlations with Behaviour

There was a significant negative correlation between ADI-R communication score and FA in the right IFG in the ASD group (MNI: 49 18 28; $r=-.511$; $p=.015$). The ASD group had significantly greater FA in the right IFG. Higher FA was associated with less impairment in terms of communication. ADI-R social interaction score was negatively related to FA in the right IFOF in the ASD group (MNI: -13 -79 4; $r=-.504$; $p=.017$). The ASD group had reduced FA in this region, with lower FA associated with greater social impairment. SRS total score was positively associated with FA in the left SLF, precentral gyrus (MNI: -53 1 34; $r=.513$; $p=.015$) in the ASD group. The ASD group had greater FA

in this region and higher FA was associated with increased social impairment. Graphs of correlations can be seen in figures F4-F6, Appendix F. Correlations did not survive correction for multiple comparisons with Bonferroni correction ($p(.05/7) = .0071$). There were no significant correlations between FA and impairments as measured by the two-factor symptom domains from the ADI-R, though MD in the right ILF in the occipital cortex was positively correlated with restricted interests and repetitive behaviours (RRB) in the ASD group (see appendix H).

5.3.3 Independent Component Analysis Results

The 24 ICs included in the analysis can be seen in figure 5.4 with details for each network given in table 5.5. There were six attention networks, one frontal network, five sensorimotor networks, four default mode networks, two visual networks, five subcortical networks and one auditory network.

5.3.3.1 Group-wise Comparisons

Uncorrected results ($p < .001$) suggested that there were group differences in spatial maps in components 6 (a sensorimotor network), with controls showing greater connectivity, and 24 (a thalamic/basal ganglia network) with ASD showing greater connectivity. The ASD group also showed less low frequency power and greater high frequency power for both components 16 (a visual network) and 37 (a default mode network).

5.3.3.2 Group-by-age Interactions

Uncorrected ($p < .001$) results also indicated that there were group-by-age interactions in the spatial maps for components 6 (sensorimotor network) and 24 (thalamic/basal

ganglia network) and for spectral power in component 16 (visual network). FDR corrected results showed a significant group-by-age interaction ($p=.0450$) for IC 37, a default mode network IC comprising the bilateral middle and posterior cingulate and precuneus (see figure 5.5). For low frequency power (.0254-.0352 Hz), the controls showed an increase in with age ($r=.587$; $p=.003$), whereas the ASD group showed a decrease with age. ($r=-.427$; $p=.048$). For high frequency power (.1563-.1738 Hz), the ASD group showed an increase with age ($r=.576$; $p=.005$) whereas the controls did not show significant age-related changes ($r=-.334$; $p=.111$). Main effects of age were significant ($p=.0322$) but group effects were not ($p=.0835$). Both multivariate and univariate results were inspected to ensure that the head movement parameters did not have a significant effect on spatial maps for components 6 or 24 or for spectral power for IC 37.

5.3.3.3 *Correlations with Behaviour*

There was a significant positive correlation between high frequency spectral power (.1563-.1738 Hz) and communication difficulties as measured by the ADI ($r=.429$; $p=.046$), and a significant negative correlation between high frequency spectral power and social deficits as measured by the ADOS ($r=-.493$; $p=.020$), in the ASD group (see figures F7-F8, Appendix F). These correlations did not survive correction for multiple comparisons ($p(.05/7)=.0071$). Correlations between spectral power and the two-factor structure of symptom domains on the ADI-R were not significant (see appendix H).

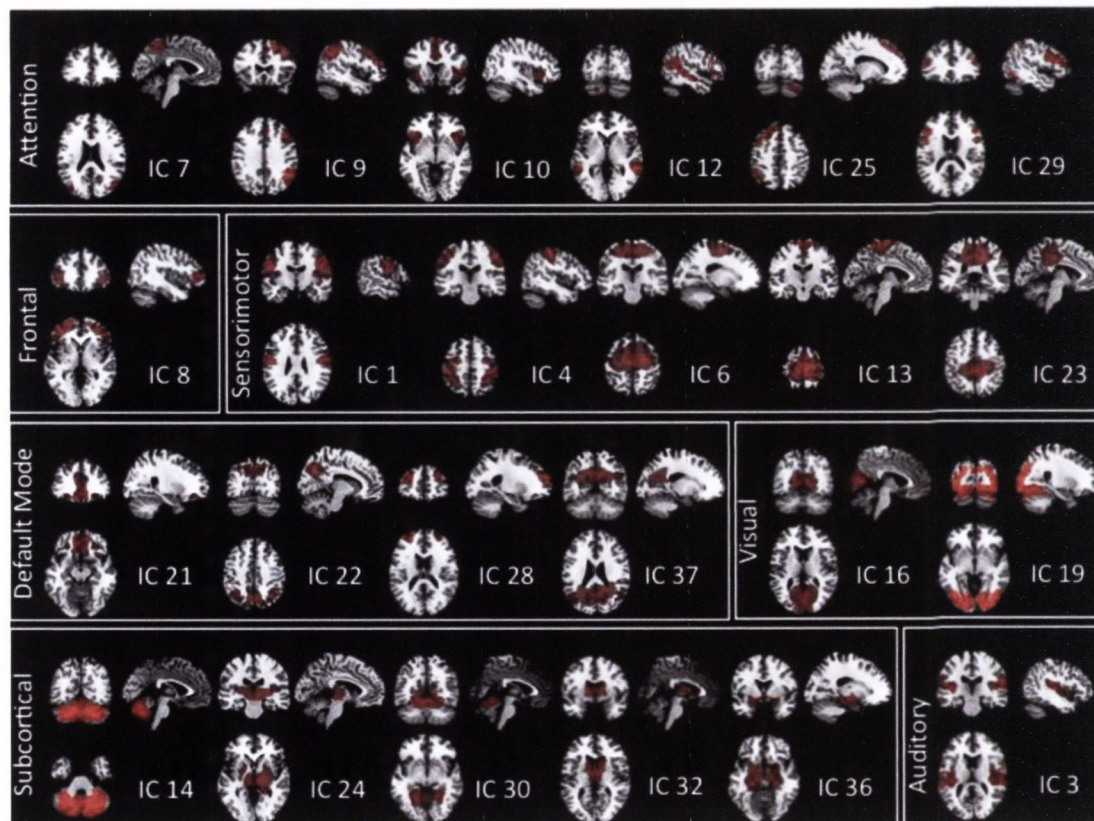


Figure 5.4 Resting-state Independent Components (ICs).

The ICs are displayed according to classification into attention, frontal, sensorimotor, default mode or subcortical networks.

Table 5.5 Peak Activations for Resting-state Independent Components.

IC number is given on the left and networks are classified as attention, frontal, sensorimotor, default mode, visual, subcortical and auditory.

Resting-state Networks							
IC	Brain Region	Cluster Size	T	MNI (X, Y, Z)			BA/Probability if available
Attention							
7	Right Precuneus	4384	24.68	8	-58	54	SPL (5L) (20%)
	Right Middle Occipital Gyrus	569	17.23	38	-78	32	BA 39; IPC (PGp) (40%)
	Left Superior Frontal Gyrus	291	13.21	-24	0	64	BA 6 (40%)
	Left Supramarginal Gyrus	187	11.44	-60	-30	34	BA 2; IPC (PF) (70%)
	Right Superior Frontal Gyrus	153	10.37	24	4	60	BA 6
9	Right Superior Frontal Gyrus	4268	18.29	26	22	52	BA 8
	Right Angular Gyrus	2292	22.17	50	-52	36	BA 39; IPC (PGa) (50%)
	Left Cerebellum	1206	19.40	-38	-76	-44	Lobule VIIa Crus II (Hem)(86%)

	Left Inferior Parietal Lobule	314	13.77	-48	-48	50	BA 40; IPC (PF) (50%)
	Right Middle Temporal Gyrus	119	11.86	62	-50	-6	BA 37
	Right Precuneus	56	11.26	4	-68	44	BA 7A (SPL) (40%)
10	Left Middle Cingulate Cortex	2894	25.78	0	26	34	BA 24
	Right Anterior Cingulate Cortex		17.86	2	32	22	BA 24
	Right Inferior Frontal Gyrus (p. Orbitalis)	1453	20.18	34	22	-12	BA 47
	Left Inferior Frontal Gyrus (p. Orbitalis)	1331	23.62	-42	20	-8	BA 47
12	Right Middle Temporal Gyrus	3399	21.30	58	-40	2	BA 22
	Left Middle Temporal Gyrus	2125	16.72	-54	-54	10	BA 21
	Right Inferior Frontal Gyrus (p. Orbitalis)	649	15.09	52	24	-4	BA 45(40%)
	Left Inferior Frontal Gyrus (p. Orbitalis)	303	12.20	-52	34	-4	BA 45
	Left Cerebellum	188	12.55	-20	-82	-36	Lobule VIIa Crus II (Hem)(94%)
	Right Precentral Gyrus	46	9.78	44	4	50	BA 6

	Right Superior Medial Gyrus	41	10.89	6	26	60	BA 8
25	Left Superior Medial Gyrus	3364	19.00	-2	42	44	BA 9
	Left Angular Gyrus	2097	20.56	-50	-60	24	BA 39; IPC (PGa)(40%)
	Right Cerebellum	819	12.51	40	-82	-36	Lobule VIIa Crus I (Hem) (96%)
	Left Middle Temporal Gyrus	574	16.14	-62	-38	-6	BA 21
	Left Posterior Cingulate Cortex	374	14.45	-4	-52	32	BA 23
	Right Angular Gyrus	151	13.24	52	-62	36	BA 39; IPC (PGa) (70%)
	Left Inferior Frontal Gyrus (p. Orbitalis)	109	10.57	-46	24	-6	BA 47
	Left Inferior Frontal Gyrus (p. Triangularis)	101	10.20	-54	22	22	BA 45 (70%)
29	Left Inferior Frontal Gyrus (p. Triangularis)	1438	18.02	-48	30	22	BA 45 (70%)
	Left Inferior Parietal Lobule	1200	16.76	-36	-50	48	BA 37; hIP1 (30%)
	Right Inferior Frontal Gyrus (p. Opercularis)	1053	19.20	48	14	26	BA 45 (20%); BA 44 (20%)
	Right Superior Occipital Gyrus	709	18.47	30	-70	42	BA 7P (SPL) (20%)

	Right Inferior Temporal Gyrus	328	15.76	54	-60	-12	BA 37
	Left Inferior Temporal Gyrus	289	16.42	-50	-62	-12	BA 37
	Right Cerebellum	86	16.09	10	-78	-26	Lobule VIIa Crus I (Hem) (62%)
	Left Caudate Nucleus	19	11.95	-10	-2	16	NA
Frontal							
8	Left Middle Frontal Gyrus	3421	23.15	-30	60	2	BA11
	Right Middle Frontal Gyrus	2629	19.29	42	46	0	BA 47
	Left Putamen	166	6.31	-24	0	2	NA
	Right Putamen	136	7.70	34	6	0	NA
Sensorimotor							
1	Right Postcentral Gyrus	3199	26.26	50	-8	28	BA 3a (60%)
	Left Postcentral Gyrus	2262	24.60	-58	-8	30	BA 3b (60%)
	Right Cerebellum	309	13.36	20	-64	-18	Lobule VI (Hem) (99%)
	Left Cerebellum	199	10.63	-18	-64	-22	Lobule VI (Hem) (95%)
	Left Amygdala	46	7.63	-24	-2	-10	Amyg (SF) (70%)
4	Right Postcentral Gyrus	4390	22.97	38	-32	54	BA 3b (80%)
	Left Postcentral Gyrus	4237	23.20	-40	-32	44	BA 2 (50%)
	Right Inferior Temporal Gyrus	145	9.69	52	-68	-8	BA 37; hOC5 (V5) (20%)

	Left Precentral Gyrus	89	8.76	-54	8	26	BA 44 (40%)
	Right Precentral Gyrus	87	10.30	58	10	30	BA 44 (40%)
	Left Cerebellum	51	8.01	-22	-50	-28	Lobule VI (Hem) (75%)
	Right Cerebellum	41	7.93	28	-52	-26	Lobule VI (Hem) (100%)
6	Left SMA	10394	33.64	-4	-18	58	BA 6 (80%)
	Right Middle Frontal Gyrus	28	9.10	48	28	38	BA 44
	Right Rolandic Operculum	19	8.83	36	-24	20	BA 48; OP 2 (80%)
13	Left Paracentral Lobule	6261	19.42	-4	-20	70	BA 6 (60%)
	Right Lingual Gyrus	126	8.89	34	-88	-18	BA 19; hOC3v (V3v)(50%)
23	Right Middle Cingulate Cortex	9068	29.74	2	-36	42	BA 23
	Left Middle Cingulate Cortex		29.70	-2	-32	46	BA 23
	Right Supramarginal Gyrus	309	9.63	60	-44	36	BA 40; IPC (PFm)(90%)
Default Mode							
21	Left Superior Medial Gyrus	9610	25.79	0	58	0	BA 10
	Right Mid Orbital Gyrus		25.64	4	56	-2	BA 10
	Left Anterior Cingulate		23.99	-10	42	8	BA 32

	Cortex						
	Right Precuneus	854	14.80	4	-52	26	BA 23
	Cerebellar Vermis	113	9.82	2	-50	-40	Lobule IX (Vermis) (65%)
22	Right Precuneus	6951	27.35	8	-64	34	BA 7
	Left Precuneus		26.61	2	-68	44	BA 7P (SPL) (20%)
28	Left Superior Frontal Gyrus	1154	16.02	-24	54	24	BA 46
	Right Middle Frontal Gyrus	588	17.36	24	50	26	BA 46
	Left Anterior Cingulate Cortex	290	12.62	-2	28	26	BA 24
	Left Thalamus	21	10.83	-12	-4	14	Th-Prefronta (34%)
37	Left Posterior Cingulate Cortex/Precuneus	9538	34.04	0	-54	32	BA 23
	Left Middle Cingulate Cortex	305	12.30	0	6	40	BA 24
Visual							
16	Right Calcarine Gyrus	9213	26.92	4	-74	8	BA 17(90%)
	Left Calcarine Gyrus		24.28	2	-70	10	BA 17(40%)

19	Right Inferior Occipital Gyrus	12895	19.34	32	-84	-10	BA 19;hOC3v (V3v)(50%)
	Left Middle Occipital Gyrus		18.55	-38	-90	-2	BA 19
Subcortical							
24	Right Thalamus	7168	35.50	8	-18	2	Th-Prefrontal(90%)
	Cerebellar Vermis	58	8.74	0	-54	-6	Lobule V (55%)
	Right Caudate	15	6.77	8	8	-12	NA
14	Right Cerebellum	14068	27.91	14	-78	-38	Lobule VIIa Crus II (Hem)(63%)
30	Left Cerebellum	7794	21.89	-8	-52	-14	Lobule V (81%)
	Right Fusiform Gyrus		20.30	-22	-46	-16	BA 37
	Left Hippocampus	16	9.80	-22	-10	-20	Hipp (CA) (80%)
32	Left Caudate Nucleus	4580	30.98	-10	-4	14	NA
	Right Caudate Nucleus		29.53	10	4	10	NA
36	Left Hippocampus	6228	24.90	-20	-20	-16	Hipp (SUB)(90%)
	Right Hippocampus		19.79	14	-30	-10	Hipp (SUB)(70%)
	Left Thalamus	104	10.05	0	-12	8	Th-Temporal(36%)
	Left Cerebellum	24	7.50	-40	-64	-24	Lobule VIIa Crus I (Hem) (34%)

Auditory							
3	Right Superior Temporal Gyrus	4023	21.57	56	-22	16	BA 48; OP 1 (90%)
	Left Superior Temporal Gyrus	3300	19.35	-62	-30	16	BA 42; OP 1 (50%)
	Left Middle Cingulate Cortex	355	17.80	0	4	44	BA 24; BA 6 (30%)
	Right Middle Cingulate Cortex		10.84	2	-8	44	BA 23; BA 6 (40%)
	Right SMA	67	12.09	2	-8	66	BA 6 (100%)

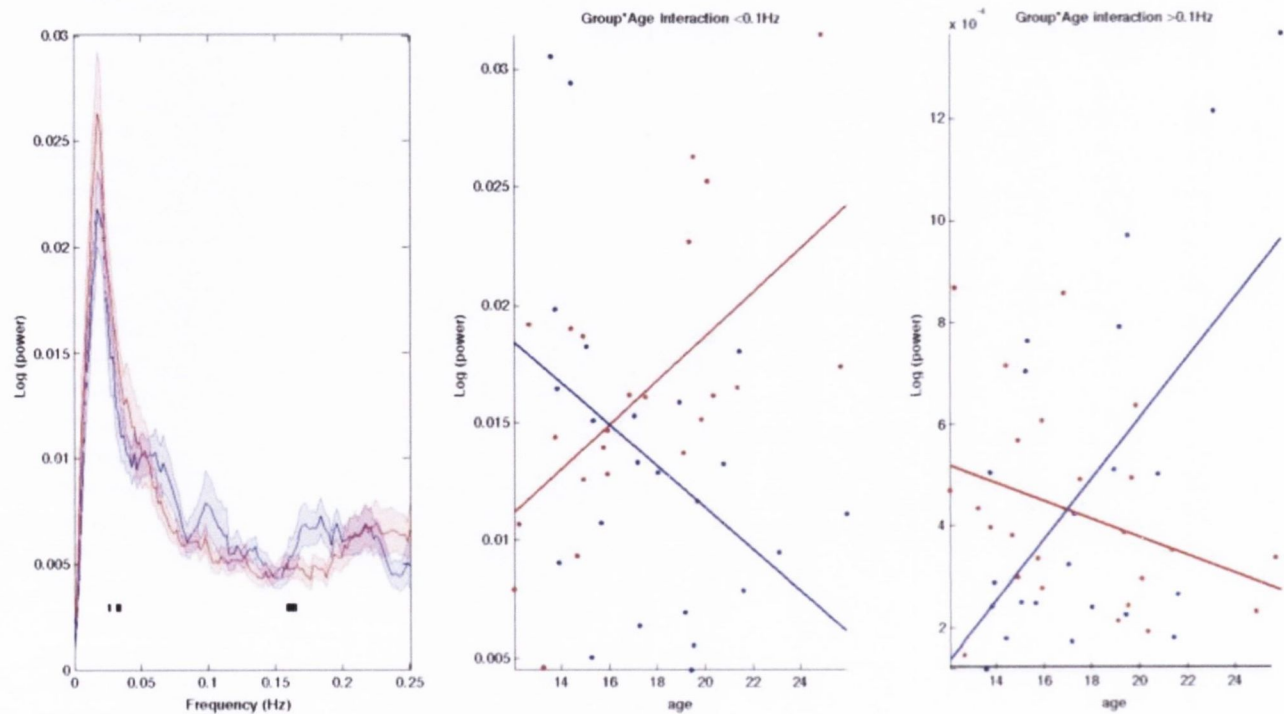


Figure 5.5 Group Spectral Power Profiles and Group-by-age Interactions.

The left column shows group spectral power distributions for controls (red) and ASD (blue) with shaded error bars showing the standard error. Black markers underneath highlight the frequency bands that showed a significant group-by-age interaction. The middle column shows spectral power changes with age for significant low frequency effects (<0.1 Hz). The right column shows spectral power changes with age for significant high frequency effects (>0.1 Hz).

5.4 Discussion

The results of the present study indicated that the ASD group showed diffuse grey and white matter structural abnormalities. VBM results indicated that the ASD group showed increased grey matter volume in the temporal lobes as well as the supramarginal gyrus, and decreased grey matter volume in the frontal lobes, with grey matter differences primarily lateralised to the right hemisphere. Abnormalities in terms of white matter structural integrity were found in frontal, temporal, occipital, cerebellar and subcortical regions with the ASD group showing both increased and decreased FA as well as increased MD. There was evidence of abnormal developmental trajectories in ASD in terms of MD values in the right ILF/fusiform gyrus. Unlike controls the ASD group did not show a decrease in MD with age. In addition, FA differences in frontal and occipital regions were associated with social and communicative impairments as measured by the ADI-R and the SRS. There were no significant group differences in functional connectivity; however, there were significant group-by-age interactions in spectral power in the default mode network. Results between modalities somewhat converged in the right temporal lobe, with both increased grey matter volume and increased white matter MD evident in ASD group. However, the overall results indicated that structural and functional differences were dispersed across cortical and subcortical regions (see figure 5.6).

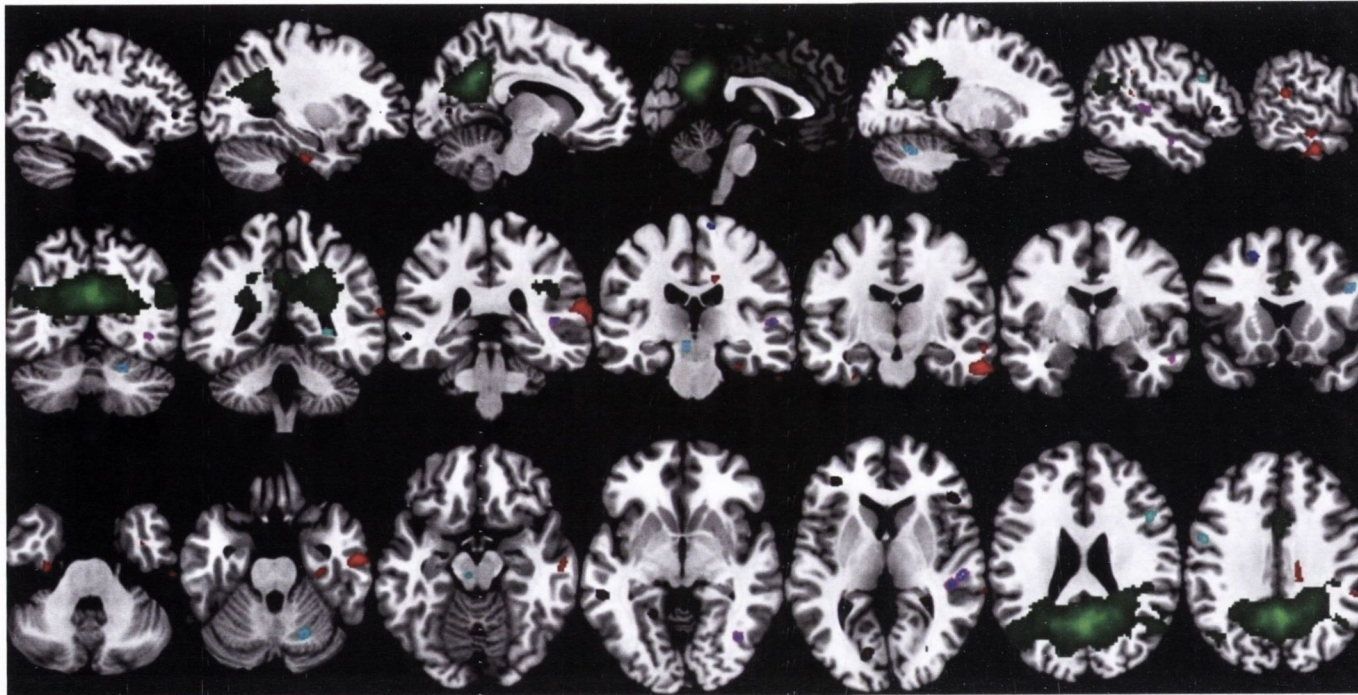


Figure 5.6 Composite Figure of Results from VBM, TBSS and ICA Analysis.

The default mode network component is shown in green. The VBM results are shown in red (ASD increased grey matter volume compared to controls) and blue (ASD decreased grey matter volume compared to controls). TBSS results are shown in blue/purple (ASD increased MD compared to controls), turquoise (ASD increased FA compared to controls) and red-hot (ASD decreased FA compared to controls). Data are displayed in neurological convention.

5.4.1 VBM Study of Grey Matter Volume

The results of the present study indicated increased grey matter volume in the temporal lobes in ASD, in particular in the right hemisphere. These results replicate previous reports of increased grey matter volume and/or density in the right inferior temporal gyrus (Abell et al., 1999; Ecker et al., 2012), middle temporal gyrus (Abell et al., 1999; Cauda et al., 2011; Ecker et al., 2012; Rojas et al., 2006), parahippocampal gyrus, temporal pole (Ecker et al., 2012) and in the left fusiform gyrus (Cauda et al., 2011; Herbert et al., 2002; Neeley et al., 2007) in ASD. The temporal lobes have previously been associated with deficits in social perception (Ashwin, Baron-Cohen, Wheelwright, O’Riordan, & Bullmore, 2007; Schultz, 2005; Schultz, 2000) and cognition in ASD (Castelli et al., 2002; Silani et al., 2008; Wang, Lee, Sigman, & Dapretto, 2006). Increased grey matter volume was also found in the right inferior parietal lobe in the supramarginal gyrus, which has previously been reported (Ke et al., 2008), and is thought to play a role in language processing deficits in ASD (Stefanatos & Baron, 2011). Decreased grey matter volume was observed in the left middle frontal gyrus, as has previously been found (Hyde et al., 2010), and in the right SMA, thought to be involved in executive function (Christakou et al., 2012) and motor deficits in ASD respectively (Rinehart, Bradshaw, Brereton, & Tonge, 2001). These results are uncorrected and therefore should be interpreted with caution. However, they replicate previous findings and suggest that high functioning ASD in older subjects, i.e. adolescents/young adults, is characterised by subtle differences in grey matter structure.

5.4.2 TBSS Study of White Matter Integrity

The superior longitudinal fasciculus (SLF) is a major association fibre that connects frontal, parietal, occipital and temporal lobes (Mori et al., 2008). Non-human primate and diffusion tensor imaging studies have indicated that the SLF is made up of four sub-divisions (Makris et al., 2005; Petrides & Pandya, 1984). SLF I extends to dorsal premotor and dorsolateral prefrontal regions from the superior parietal lobe and is thought to be involved in regulating higher aspects of motor behaviour (Makris et al., 2005). SLF II extends from the angular gyrus to caudal-lateral prefrontal regions and is thought to be involved in spatial functions (Makris et al., 2005). SLF III connects the rostral part of the inferior parietal lobe and the lateral inferior frontal lobe. It is thought to be involved in somatosensory processes including the articulation and monitoring of orofacial and hand actions (Makris et al., 2005). The fourth sub-division of the SLF comprises the arcuate fasciculi connecting the superior temporal gyrus to the lateral PFC and is thought to be involved in visuospatial processing and some aspects of language (Catani & Thiebaut de Schotten, 2008).

The ASD group showed reduced FA bilaterally in the SLF, in the left IFG pars opercularis, right IFG pars triangularis and the left middle temporal gyrus, corresponding to SLF II-III and the AF, as well as increased FA in the left SLF in the precentral gyrus of the frontal lobe. Previous studies using TBSS among children and adolescents have shown bilateral increases (Cheng et al., 2010; Cheung et al., 2009; Weinstein et al., 2011) and decreases (Barnea-Goraly et al., 2010; Jou et al., 2011; Kumar et al., 2009; Shukla et al., 2011) in the SLF in ASD. In the present study, increased FA in the left SLF was associated with greater social impairment in ASD as

measured by the SRS. This is in line with a previous report indicating that FA values in the left frontal SLF is associated with social impairment as measured by the ADI-R (Cheung et al., 2009).

The inferior longitudinal fasciculus (ILF) is a ventral associative fibre pathway which connects the occipital regions to the amygdala and hippocampus in the temporal lobes (Catani, Jones, Donato, & Ffytche, 2003). It is involved in face-processing (Fox, Iaria, & Barton, 2008) and visual perception (Ffytche, 2008). In the present study, the ASD group showed decreased FA in the right ILF at the precuneus and increased FA in the right ILF in the occipital lobe (lingual gyrus). Decreased FA in both the left and right ILF has been reported in ASD (Bloemen et al., 2010; Cheon et al., 2011; Groen, 2011; Jou et al., 2011; Shukla et al., 2011), with one study also reporting increased FA in the left ILF (Wolff et al., 2012). In addition, as previously reported (Shukla et al., 2011), the ASD group showed increased MD in the right temporal part of the ILF.

There was a significant group-by-age interaction on MD values in right inferior longitudinal fasciculus in the fusiform gyrus. The fusiform gyrus has been consistently implicated in ASD pathology and is thought to be involved in face processing abnormalities that characterise ASD (Schultz, 2005). The controls showed a decrease in MD with age whereas the ASD group showed no change with age. MD values typically decrease with age until the mid-twenties (Snook et al., 2005). Previous studies indicate white matter does not undergo the typical developmental trajectory in ASD (Alexander, Lee, Lazar, Boudos, et al., 2007; Ben Bashat et al., 2007; Lee et al., 2007). Together with the results of Shukla et al. (2011), the present findings suggest that ASD subjects fail to show the typical decrease in MD during adolescence in circumscribed

brain regions. Altered developmental trajectories in FA have previously reported in the right STG in ASD (Lee et al., 2007), therefore the results of the present study provide further evidence of abnormal white matter development in the right temporal lobe in ASD.

The anterior thalamic radiation (ATR) is a projection fibre which extends from the thalamus, penetrating the anterior limb of the internal capsule and carrying reciprocal connections from the hypothalamus and limbic structures to the frontal cortex (Mori, Wakana, Zijl, & Nage-Poetscher, 2005). In the present study the ASD group showed increased FA in the left ATR. One previous study reported increased FA in the right ATR in ASD (Cheng et al., 2010), although the majority of studies have found decreased FA in the ATR in ASD (Bloemen et al., 2010; Cheon et al., 2011; Jou et al., 2011; Shukla et al., 2011). Decreased FA in the ATR has been associated with social impairment in ASD (Cheon et al., 2011), though in the present study there were no significant correlations between FA in the ATR and behavioural symptoms.

The inferior fronto-occipital fasciculus (IFOF) is a ventral associative bundle that connects the ventral occipital lobe to the orbitofrontal cortex (Catani & Thiebaut de Schotten, 2008). The IFOF is thought to be involved in reading, attention and visual processing (Catani & Thiebaut de Schotten, 2008). The ASD group showed reduced FA bilaterally in frontal (right IFG opercularis, left frontal pole) and occipital regions (right precuneus, left lingual gyrus) of the IFO. This is in line with previous studies that have shown decreased FA in the IFOF in ASD (Bloemen et al., 2010; Cheng et al., 2010; Jou et al., 2011; Shukla et al., 2011) though increased FA in the right IFOF has also been reported (Bode et al., 2011). In the present study reduced FA in the left IFOF (lingual

gyrus) was associated with greater social impairment as measured by the ADI-R.

Previous studies have not reported correlations with behavioural measures; therefore further study is needed to delineate the role of the IFOF in ASD symptoms.

The ASD group showed increased FA in the right IFG, pars opercularis. Decreased FA has previously been reported in the left IFG in children with ASD (Ke et al., 2009), which is associated with language processing (Just, Carpenter, Keller, Eddy, & Thulborn, 1996). The pars opercularis of the IFG, in particular in the right hemisphere, is associated with mirror neuron properties (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Dapretto et al., 2006; Iacoboni et al., 2005). Mirror neuron dysfunction is postulated to play a role in imitation, theory of mind and social communication deficits in ASD (Williams, Whiten, Suddendorf, & Perrett, 2001). In the present study increased FA in the right IFG pars opercularis was associated with fewer communication deficits as measured by the ADI-R, perhaps reflecting a compensatory mechanism in ASD.

There is a large body of evidence indicating abnormal cerebellar anatomy, neurotransmitter function and cerebellar motor and cognitive deficits in ASD (Fatemi et al., 2012). In the present study, the ASD group showed increased FA in right lobule VI of the cerebellum. Lobule VI is involved in a number of cognitive functions with right lobule VI particularly involved in language processing (Stoodley & Schmahmann, 2009). Reduced FA in intra-cerebellar fibres and in the cerebellar peduncle (Catani et al., 2008; Shukla et al., 2011) and increased FA in the right middle cerebellar peduncle have been reported in DTI studies of cerebellar white matter in ASD (Sivaswamy et al., 2010). In the present study, increased FA in Lobule VI was not associated with

behavioural impairments in ASD, therefore further examination of the functional role of FA changes in the cerebellum in ASD is merited.

FA is thought to reflect fibre bundle density and corresponding axonal membranes, modulated by the degree of myelination, with increased FA suggesting increased white matter integrity (Beaulieu, 2002). Increased MD is thought to reflect demyelination or axonal damage (Basser, 1995; Basser & Pierpaoli, 1996). AD and RD are thought to be more specific measures than FA and MD and index axonal and myelin integrity respectively (Song et al., 2003). In the current study, the ASD group showed increased FA in the right lobule VI of the cerebellum and a corresponding increase in AD in the same region. Similarly, the ASD group showed increased MD in the ILF (in the middle temporal gyrus), with a corresponding increase in AD. This suggests that changes in AD, thought to reflect axonal integrity (Song et al., 2003), may underlie group differences in FA and MD, for these specific tracts. For a number of other regions in which there were group differences in FA and MD, there was no corresponding change in AD or RD (see Appendix E) suggesting that the change in FA and MD was due to the proportional relationship between AD and RD. In addition, the results of the AD and RD analysis highlighted a number of regions that did not differ between groups in terms of FA and MD, suggesting that the specificity of AD and RD make these measures more sensitive to changes in white matter integrity in ASD. These results suggest that FA, MD, AD and RD metrics may be sensitive to different aspects of white matter microstructural changes in ASD. However, further study is necessary in order to elucidate potential neuropathological mechanisms underlying changes in these measures in ASD, as the interpretation of DTI metrics may be less accurate in disorders such as ASD (Jones, 2010; Kleinhans et al., 2012), in which white matter is thought to

be formed abnormally and is likely to be subjected to atypical developmental processes (Kleinmans et al., 2012).

5.4.3 ICA of Resting-state Functional Connectivity

In the present study there were no significant group differences in functional connectivity or spectral power that survived correction for multiple comparisons. However, there was a significant group-by-age interaction in spectral power in the posterior default mode network (DMN). The DMN comprises a set of midline structures including the precuneus/posterior cingulate cortex, ventral anterior cingulate cortex, the medial prefrontal cortex (mPFC) and the inferior parietal lobes (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001; Raichle & Snyder, 2007), with the lateral temporal cortex and hippocampal formation also considered part of this network in some studies (Buckner et al., 2008). It is composed of several interacting, yet distinct sub-networks or hubs, each with its own time-course (Allen et al., 2011; Buckner et al., 2008; Kim et al., 2009; Uddin, Kelly, Biswal, Xavier Castellanos, & Milham, 2009). The DMN deactivates during the performance of cognitively demanding tasks, but is active during rest (Raichle et al., 2001; Raichle & Snyder, 2007; Singh & Fawcett, 2008). It is also active during mentalising and internally directed thoughts such as thinking about one's past or future (Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Ochsner et al., 2004; Schilbach et al., 2008; Spreng, Mar, & Kim, 2008). Numerous studies have implicated the DMN in autism pathology (Assaf et al., 2010; Cherkassky et al., 2006; Rudie et al., 2011; Weng et al., 2010), including unpublished results from the ABIDE consortium, which showed decreased long-range functional connectivity in the DMN in a sample of 539 individuals with ASD and 573

controls. Previous studies have shown that ASD is characterised by a failure to deactivate the DMN during cognitive tasks (Kennedy, Redcay, & Courchesne, 2006; Murdaugh et al., 2012; Spencer et al., 2012) and abnormal DMN resting-state functional connectivity (Assaf et al., 2010; Lynch et al., 2013; Monk et al., 2009; Murdaugh et al., 2012; Von dem Hagen et al., 2012). Both increased and decreased connectivity has been reported in the DMN, with the posterior cingulate showing increased connectivity with temporal regions and the precuneus showing decreased connectivity with the basal ganglia and visual cortex (Lynch et al., 2013). In line with the present findings, a recent study reported increased connectivity within the DMN in ASD (Washington et al., 2013). This was accompanied by reduced connectivity between DMN nodes. Additionally, the ASD group showed a lack of appropriate age-related changes in connectivity between DMN nodes. Whereas the control group showed an increase in inter-node connectivity in the DMN between childhood and adolescence, the ASD group did not show significant age-related changes in connectivity.

The DMN is characterised by low frequency BOLD oscillations, with the greatest power between 0.01 and 0.05 Hz, though oscillations at higher frequencies are also present, albeit at lower amplitudes (Baria et al., 2011). The mean power distribution for each frequency band shows a specific spatial location within the DMN. The posterior part of DMN - the precuneus/posterior cingulate - is dominated by low frequency oscillations between 0.01 and 0.05 Hz, while orbital frontal and temporal cortex parts of DMN show BOLD oscillations mainly at 0.10-0.20 Hz (Baria et al., 2011). In the present study, there was a significant group-by-age interaction in spectral power in the posterior DMN, in the precuneus/posterior cingulate. Controls showed an increase in low

frequency power with age, whereas the ASD group showed a decrease in low frequency power with age. In addition the ASD group showed an increase in high frequency power with age. These findings suggest that where typical development is associated with increased spectral power at low frequency, ASD is characterised by increased high frequency power. This reflects findings from previous studies which have shown that patient groups - including schizophrenia, bipolar disorder and chronic pain sufferers - also show reduced low frequency BOLD fluctuations below 0.05 Hz and stronger fluctuations above 0.1 Hz (Calhoun et al., 2012; Garrity et al., 2007; Malinen et al., 2010). Low frequency oscillations (<0.1 Hz) are thought to reflect cyclical modulation of gross cortical excitability and long distance synchronisation (Balduzzi, Riedner, & Tononi, 2008; Vanhatalo et al., 2004). High frequency oscillations are thought to reflect reduced connectivity within the network (Garrity et al., 2007; Malinen et al., 2010). This is in line with previous studies indicating reduced functional and structural connectivity of the DMN in ASD (Assaf et al., 2010; Monk et al., 2009; Shukla, Keehn, & Mueller, 2010). The present findings, which suggest that ASD is characterised by a lack of increase in low-frequency power with age, reflect those of a recent study showing that ASD subjects do not show typical age related increases in connectivity between nodes in the DMN (Washington et al., 2013).

It has been proposed that ASD may be a general disorder of neural processing, characterised by neural noise, which may be the result of a proliferation of neural connections and/or glutamatergic and GABAergic synaptic dysregulation (Belmonte et al., 2004; Simmons et al., 2009). Previous studies have recorded increased within-subject trial-by-trial variability in ASD, with corresponding reductions in signal-to-noise ratios, in sensory and motor regions of cortex (Dinstein et al., 2012). Increased fractal

scaling - or randomness - of the BOLD signal has also been recorded in ASD in cortical midline structures, the medial temporal lobes, lateral temporal-parietal and inferior frontal areas, and subcortical structures (Lai et al., 2010). These findings provide support for the hypothesis that ASD is characterised by increased neural noise. The results of the present study suggest that there may be changes in temporal dynamics of the BOLD signal, perhaps reflecting reduced synchronisation with age in ASD, that cannot be detected in General Linear Model (GLM) analyses. Interestingly, there were no significant group differences in SM functional connectivity in the DMN in the present study. Therefore, spectral power may be more sensitive to changes in the DMN in ASD, which may be characterised by temporal rather than spatial re-organisation of functional connectivity.

In terms of the potential functional significance of these findings in ASD, an exploratory analysis, examining correlations with behavioural measures, indicated that high frequency spectral power was associated with communication difficulties in childhood in the ASD group as measured by the ADI. This is in line with the results of a previous study indicating that greater connectivity in the DMN in ASD was associated with increased communication impairment (Weng et al., 2010). High frequency spectral power was also associated with fewer current social difficulties as measured by the ADOS. The DMN plays an important roles in social cognition (Schilbach et al., 2008), therefore high frequency power in the DMN in older subjects with high functioning ASD could possibly reflect compensatory mechanisms.

5.4.4 Convergence between Modalities

The majority of the findings from this chapter indicated that group differences in grey and white matter were dispersed throughout cortical and subcortical brain regions. However, both increased grey matter volume and increased white matter MD were observed in the right temporal lobe in the ASD group. The temporal lobes play an important role in social perception and cognition (Adolphs, 2001) and previous studies have indicated that the temporal poles play a role in higher-level social cognitive deficits in ASD (Castelli et al., 2002; Silani et al., 2008; Wang et al., 2006). The right fusiform gyrus, right inferior temporal gyrus and bilateral superior temporal gyri show abnormal activation during face processing in ASD (Ashwin et al., 2007; Schultz, 2005; Schultz, 2000). Additionally, evidence suggests the relationship between volumetric measures of grey and white matter in different temporal lobe structures (left fusiform gyrus grey and white matter, right temporal stem and right inferior temporal gyrus grey matter), can be used to distinguish ASD from control subjects (Neeley et al., 2007). Finally, group differences were primarily lateralised to the right hemisphere, which is in line with evidence indicating right hemisphere grey matter structural asymmetries in ASD (Herbert et al., 2002, 2005). The present findings therefore add to a growing body of literature implicating temporal lobe dysfunction and structural abnormalities in the right hemisphere in ASD pathology.

5.4.5 Limitations and Future Directions

Though the results of the VBM analysis were in line with previous findings, results were reported uncorrected, given the relatively small sample size, therefore the results should be interpreted with caution. VBM studies of high-functioning subjects

with ASD are likely to require larger samples as seen in recent studies (Ecker et al., 2012; Greimel et al., 2012). Several factors should be considered when interpreting TBSS findings from the present study. The results should be interpreted in the light of age, IQ and TIV effects, as it was not possible to covary for these factors in the NPM toolbox. There were no significant group differences on FA, MD, RD or AD using the TCFE correction in FSL. This is in line with previous research indicating that TBSS with TCFE correction, may be less sensitive to differences in measures of white matter integrity in older, high functioning subjects with ASD, than other methods (Alexander et al., 2009). Results from both the VBM and TBSS studies presented here suggest that differences in brain structure among high-functioning older subjects with ASD are subtle and that future studies in this population will need to recruit larger samples to ensure the reliability of results.

DTI is associated with a number of important confounds. In particular, DTI cannot model crossing-fibres, which can lead to paradoxical findings, such as increased FA where white matter is compromised in a disease-group (Jones, 2010). (The limitations of DTI are further discussed in section 6.5). There are also known limitations inherent in the TBSS approach, though it is frequently used for performing whole-brain DTI analysis. TBSS uses a skeleton-projection based approach to minimise differences due to spatial misalignment. This results in spatial heterogeneity in the statistical power to detect group differences, with more central regions exhibiting less variance within a population (Edden & Jones, 2011). In addition, Edden and Jones (2011) demonstrated that the width of the skeleton depends on the relative orientation to the imaging matrix, such that there are more likely to be significant group differences in regions that are orientated obliquely to the imaging matrix. The reliability of microstructural measures

derived from TBSS have been further called into question by a recent study showing that significant effects of behavioural measures on DTI metrics varied between 100 bootstrapped permutations among the same 24 participants (Bells, McGonigle, Evans, & Jones, 2012). These methodological issues suggest that the results of TBSS studies should be interpreted with caution.

An important factor to consider when performing ICA analyses is that the number of components selected for analyses can affect the results. Overestimating the number of components can lead to splitting of the components, whereas underestimation can lead to the loss of relevant information (Beckmann & Smith, 2004; Li et al., 2006). For the current analyses we sought to overcome this limitation by using the MDL method (Li et al., 2006), which estimates the number of appropriate components using an entropy matching principle in order to estimate the number of components in samples that violate assumptions of independence. In addition, subject movement has been shown to produce significant changes on the time-course of resting-state data (Power et al., 2012; Van Dijk et al., 2012). Though ICA successfully identifies motion-related signals (Koshino et al., 2005; McKeown, Hansen, & Sejnowski, 2003), which were removed from the analysis in the present study, residual motion related variance can be present in RSNs. We sought to mitigate these effects by covarying for head motion, and ensuring that significant effects were not associated with head motion, thus minimising the potential confounding effect of motion on the present results.

The high spatial resolution of the BOLD signal comes at the cost of its temporal resolution, with compression in the range of oscillatory frequencies that can be observed. However, recent studies suggest that examining the spectral content of the

BOLD signal can provide insights into the temporal coherence intrinsic RSN activity (Baria et al., 2011). The interpretation of BOLD spectral power $>0.1\text{Hz}$ is controversial, due to the potential effect of non-neural, physiological noise from sources such as cardiac or respiratory signals (Birn, Diamond, Smith, & Bandettini, 2006; Wise, Ide, Poulin, & Tracey, 2004; Zuo et al., 2010). However, Baria et al.(2011) recently demonstrated that neocortical and subcortical BOLD oscillations, between .01 and .20 Hz, are minimally contaminated with physiological noise (heart rate and respiration), while brainstem and cerebellar BOLD signals contain more noise (Baria et al., 2011). This suggests that the results of the present study are unlikely to be due to physiological factors. Previous studies have shown that ICA can isolate physiological noise from functional networks (Allen et al., 2011; Birn, Murphy, & Bandettini, 2008) and in the present study these artifactual components were carefully excluded from the second level analysis. Additionally, a previous study, which also used group-ICA to examine resting state data, reported that physiological factors did not influence group-wise comparisons (Malinen et al., 2010).

The precise electrophysiological correlates of BOLD spectral power are still unknown; therefore the present study was exploratory in nature. Combined electroencephalography (EEG)-fMRI studies are beginning to uncover the relationships between fMRI spatial maps and EEG frequency bands. The DMN has been consistently associated with beta band activity, which is associated with active concentration (Balsters et al., 2011; Jann, Kottlow, Dierks, Boesch, & Koenig, 2010; Laufs et al., 2003; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007). The evidence suggests that the DMN is also associated with activity in the alpha band (associated with relaxed wakefulness), though greatest power is in the beta band (Mantini et al., 2007). Increased beta power

has previously been reported in ASD (Coben, Clarke, Hudspeth, & Barry, 2008; Murias, Webb, Greenson, & Dawson, 2007), in particular in midline regions (Coben et al., 2008). Together with the present findings, the results of these previous studies suggest that electrophysiological methods combined with fMRI, provide a potentially promising avenue for uncovering the temporal and spatial dynamics of neuropathology in ASD.

Combining modalities, for example functional and structural data or EEG with fMRI, could reveal relationships which could unify inconsistent findings (Guye, Bartolomei, & Ranjeva, 2008; Skudlarski et al., 2010; Sui et al., 2011) in the ASD brain imaging literature. By examining shared information between modalities multimodal techniques can reveal unique information that cannot be seen when each modality is taken separately (Sui, Adali, Pearlson, Clark, & Calhoun, 2009). Joint ICA (JICA) extracts maximally spatially or temporally independent maps for each modality that are coupled together by a shared loading parameter (Calhoun, Adali, Pearlson, & Kiehl, 2006). An exploratory analysis using JICA was performed, to examine functional changes, as revealed by group ICA of resting-state data, in relation to grey matter volume and white matter integrity as indexed by FA maps. Unfortunately, neither the functional (spectral power) nor structural decompositions were readily interpretable (see Appendix G). However, other studies have shown that combined methods may improve biomarker generation (Sui et al., 2009). A combined fMRI-white matter FA study in schizophrenia and bipolar disorder showed disease-specific function-structure relationships (Sui et al., 2011). Therefore multimodal techniques provide a promising avenue for future ASD research.

5.5 Conclusions

The results of these whole brain analyses were largely in line with previous studies, indicating that high functioning ASD is characterised by subtle and diffuse differences in grey and white matter structure. There was convergence between modalities in the right temporal lobe, with the ASD group showing increased grey matter volume and white matter MD in this region. In addition, these findings indicate that different developmental trajectories may underlie certain structural changes. There were no significant group differences, surviving correction for multiple comparisons, in functional connectivity. However, there was a significant group-by-age interaction in spectral power in the DMN. This adds to the previous literature implicating the DMN in ASD pathology and suggests that examining the temporal properties of the BOLD signal is a promising avenue for future studies of ASD.

6 General Discussion

6.1 Introduction

This chapter provides an overview of the results from the experimental chapters of this thesis, considers the findings in terms of their contribution to improving understanding the neuropathology of ASD and discusses potential implications for informing interventions. The strengths and limitations of the studies presented, and possible avenues for future research, are then discussed.

6.2 Review of Thesis Aims and Results

The aims of this thesis were 1) to examine social and non-social reward processing in ASD; 2) to examine the structure and connectivity of the frontostriatal system in ASD; 3) to use whole-brain analyses to evaluate group differences in the function and structure of frontostriatal circuitry in the context of other potentially important brain anomalies in ASD and to explore potential convergence between neuroimaging modalities; 4) to investigate group differences in brain structure and function in terms of behavioural measures of ASD symptoms and 5) to examine potential differences in developmental trajectories underlying group differences in brain function and structure in ASD.

The results of the first experimental chapter (chapter 3) showed that, during the receipt of rewards, the ASD group showed reduced activity in the dorsal striatum (DS) compared to controls for social rewards but not monetary rewards. The ASD group also showed decreased activation for social rewards compared to monetary rewards whereas controls showed no significant difference between the two reward types. The

results suggested that group differences were not due to different developmental processes as there was not a significant group-by-age interaction underlying group differences in the DS. In both groups, increased activation in the DS during social reward processing was associated with faster response times (RT) for rewarded trials, compared to un-rewarded trials. This was in line with behavioural results indicating that the ASD group showed less of a reduction in RT for rewarded compared to un-rewarded trials. Additionally, reduced activation to social rewards was associated with increased repetitive behaviour in ASD. These results can be understood in the light of the role of the DS in executive function and in linking reward representations to action control (Balleine & O'Doherty, 2009; Grahn et al., 2008) and indicate that ASD is characterised by abnormal activation in this region during social reward processing.

The results of the second experimental chapter (chapter 4) demonstrated that the ASD group showed increased connectivity between the striatum (accumbens and caudate - primarily in the right hemisphere) and the right anterior cingulate (ACC), the right middle frontal gyrus (MFG) and the bilateral paracingulate gyrus (Pcg). There was a significant group-by-age interaction on connectivity values between the right MFG and the right caudate, suggesting that group differences in connectivity may be due to between group differences in the development of connectivity between these structures. In an exploratory analysis it was found that increased connectivity between the left caudate and the anterior cingulate was associated with deactivation to social rewards in the left caudate in the ASD group during social reward processing. In terms of correlations with behavioural symptoms in the ASD group, greater connectivity between the right MFG and the right caudate was associated with higher scores on the ADI-R restricted and stereotyped behaviour scale, greater connectivity between the

right ACC and right accumbens was associated with less impairment in terms of communication as measured by the ADI-R. These results suggest that increased frontostriatal connectivity in ASD could reflect compensatory mechanisms as well as behavioural impairments. There were no significant group differences in the structure of the striatum in terms of shape or volume and there were no group differences in white matter integrity, as indexed by fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) or axial diffusivity (AD) values.

In the third experimental chapter (chapter 5), there were subtle group differences in grey matter volume between groups, with the ASD group showing increased grey matter volume in temporal and parietal lobes and reductions in the frontal lobe and thalamus. In terms of white matter integrity, there were significant group differences in a number of major white matter fibre bundles including the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), the anterior thalamic radiation (ATR) and the inferior fronto-occipital fasciculus (IFOF), as well as in right inferior frontal gyrus and in the right cerebellum. There was a significant group-by-age interaction on MD values in the right ILF in a region approximating the fusiform gyrus, suggesting that abnormal developmental trajectories could underlie group difference in this region. In terms of behavioural correlations increased FA in the ASD group in the right IFG was associated with less impairment in terms of communication as measured by the ADI-R. Reduced FA in the right IFOF in the ASD group was associated with greater social impairment as measured by the ADI-R. The ASD group showed greater FA in the left SLF in the frontal lobe and this was associated with greater social impairment as measured by the SRS. There were no significant group differences in intra- or inter- network connectivity, or spectral power, as measured by independent

components analysis (ICA). However, there was evidence of abnormal developmental changes in spectral power properties in the ASD group, evidenced by a significant group-by-age interaction on spectral power values in the default mode network (DMN). Whereas controls showed an increase in low frequency power with age, the ASD group showed a decrease with age. Additionally the ASD group showed an increase in high frequency power with age. High frequency spectral power in the ASD group was positively associated with communication difficulties during early childhood as measured by the ADI and negatively correlated with current social deficits as measured by the ADOS.

6.3 Contributions of the Current Findings

The results of the first study (chapter 3) provided support for the ‘Social Motivation Theory’ of ASD, as the ASD group showed reduced activation to social but not monetary rewards, when compared to controls. Dawson et al. (2005a) suggested that an alternative to the social motivation hypothesis is that differences in the perceptual system could account for abnormalities in face-processing, and by implication social impairments more generally, in ASD. The results of the first chapter speak against potential perceptual differences in face processing as there were no group differences or group-by-age interactions in regions involved in basic visual perception or face processing. Differences were observed in the striatum, complementing previous findings of abnormal activation to social rewards in the striatum (Scott-Van Zeeland et al., 2010), and supporting the social motivation theory.

In the second study (chapter 4) there were differences in functional connectivity between groups, with the ASD group showing hyperconnectivity between regions of

frontal cortex and the striatum. The direction of increased connectivity between frontostriatal regions cannot be inferred based on the methods used in this study and could reflect increased top-down processing (perhaps reflecting increased inhibitory processes in the ASD group) or increased bottom-up processing. There were no group differences in the structure of the striatum or of frontostriatal tracts, which contrasts with the fMRI results and suggests that differences in functional connectivity may not be due to differences in striatal structure or frontostriatal white matter. Differences in frontostriatal functional connectivity could be due to abnormalities within the frontal lobes, as previous research has documented frontal lobe pathology in ASD (as discussed in 4.1.1), or other regions implicated in frontostriatal circuitry such as the thalamus or midbrain (as discussed in 4.4.3).

The final study (chapter 5) showed that there were a number of structural alterations in cortical and subcortical regions that are not directly implicated in reward processing. This suggests that a reward processing deficit, originating in the striatum, may not be primary to ASD neuropathology. Similarly, genetic studies have implicated genes involved in neuronal growth and cell migration, inhibitory and excitatory neurotransmission and serotonin regulation, rather than genes involved in dopamine regulation in ASD pathology (Abrahams & Geschwind, 2008), suggesting that reward dysfunction could be a secondary effect of other pathological processes. Genes associated with oxytocin and vasopressin (involved in affiliative behaviours) have been associated with ASD (Jacob et al., 2007; Lerer et al., 2007; Modahl et al., 1992; Yirmiya et al., 2006), which could specifically affect social reward processing in ASD via interaction with dopamine (Skuse & Gallagher, 2009). However, associations between oxytocin/vasopressin and ASD have not been consistently replicated by independent

research groups, and mutations on these genes do not consistently result in ASD, suggesting that they may be a modulating risk factor (or that the effect size of the risk is small), with other risk factors also involved (Abrahams & Geschwind, 2008).

The final experimental chapter (chapter 5) added to a growing body of literature implicating the DMN in ASD pathology. Reduced functional and structural connectivity in the DMN have been reported in ASD (Assaf et al., 2010; Monk et al., 2009; Murdaugh et al., 2012; Shukla et al., 2010), and the present findings, together with a recently published study (Washington et al., 2013) suggest that abnormal developmental processes occur in ASD, characterised by a lack of age-appropriate synchronisation between distal regions of the DMN. These findings can be understood in the light of a large body of evidence that has shown that the DMN is involved in mentalising and internally directed thoughts (Andrews-Hanna et al., 2010; Ochsner et al., 2004; Schilbach et al., 2008; Spreng et al., 2008) both of which are impaired in ASD (Baron-Cohen, 2001; Lombardo et al., 2007).

The studies presented in this thesis were carried out on a relatively homogeneous sample of high-functioning medication-free males all of whom met gold standard diagnostic assessments for ASD, as well as age and IQ matched controls. As such these studies make an important contribution to our understanding of the neuropathology of ASD, compared with samples used in the extant literature pertaining to social reward. It is important to match groups on age, IQ and gender, given that these factors affect neuroanatomy (Blakemore & Choudhury, 2006; van den Bos, Crone, & Güroğlu, 2012), however, this has not always been systemically carried out in MRI studies of ASD. An important methodological issue in the field is that numerous studies have

included subjects who were taking psychoactive medication, or have failed to report the medication status of participants. Psychoactive medication affects brain function and structure (Iannetti & Wise, 2007; Navari & Dazzan, 2009; Vernon et al., 2012) and therefore some of the previously reported neuroimaging studies of ASD are likely to have been subject to this important confound. Of particular relevance to this thesis, a review of the effects of antipsychotic drugs on brain structure suggests that antipsychotics increase basal ganglia volumes (Navari & Dazzan, 2009). Previous studies have reported increased caudate volumes in ASD (Estes et al., 2011; Hollander et al., 2005; Langen et al., 2007; Sears et al., 1999; Stanfield et al., 2008), which was not replicated in other studies (Langen, et al., 2011; McAlonan et al., 2005), or in the present study, perhaps owing to the difference in medication status between studies.

One of the strengths of the studies presented in this thesis is that several MRI modalities, including task based and resting-state fMRI as well as DTI data, were collected within the same sample. This made it possible to examine group differences in functional activation in the context of structural changes within the same participants. Also, by performing functional connectivity analysis in independent resting-state fMRI data, rather than task based fMRI data, the issue of double-dipping was avoided. Many studies of functional connectivity in ASD have used activation-driven correlations which may reflect differences in the task-related response rather than connectivity per se (Jones et al., 2010; Müller et al., 2011). Additionally, using different MRI methods within the same population provided the opportunity to gain insight into those that may be more sensitive to neuroanatomical changes in older subjects with high-functioning ASD. For the *a priori* hypothesis-driven studies fMRI

measures appeared to be more sensitive than structural MRI, but for whole brain approaches this was not the case.

The use of several neuroimaging modalities within the sample population revealed some similarities in results between modalities. For example, group differences in activation to social rewards was in a region of striatum that is connected to caudal-motor regions (primary motor and premotor cortex) and regions implicated in executive function (MFG and anterior prefrontal cortex) (Tziortzi et al., 2013). Similarly, a separate analysis of resting-state functional connectivity indicated increased connectivity between the striatum and executive function regions, as well as limbic regions of the frontal cortex, complementing the results from the first study.

Deactivation to social rewards in the left caudate in the ASD group was associated with increased functional connectivity between the left caudate and the anterior cingulate during resting-state, further indicating convergence in findings between different modalities. In the whole brain analyses there was convergence between the VBM and TBSS results with increased grey matter volume and increased MD in the right temporal lobe in the ASD group. There was also divergence between modalities, as illustrated in figure 5.6.

6.4 Treatment Implications

The results of the first study in this thesis suggest that ASD may be characterised by abnormal neural responses to social rewards in the presence of normal responses to other forms of reward such as monetary rewards. This suggests that behavioural interventions that seek to improve certain skills and reduce maladaptive behaviours that are based on operant conditioning may be more beneficial when tangible

rewards, such as monetary rewards, are used rather than positive social feedback (Kohls, Chevallier, Troiani, & Schultz, 2012). In terms of improving social abilities in ASD, behavioural modification programmes have typically employed reinforcers such as food to improve social skills in ASD (Margolies, 1977). However, improved social skills often fail to generalise to improvements in daily social functioning (Koegel, Koegel, & McNerney, 2001). The 'Social Motivation Theory' predicts that interventions aimed at promoting social motivation could improve social learning abilities in ASD (Chevallier, Kohls, et al., 2012), which could have a positive effect on the development of social cognition and language skills (Dawson et al., 2012). Pivotal response treatment (PRT) is a behavioural intervention aimed at improving motivation to initiate and respond to social stimuli in ASD (Koegel et al., 2001). PRT and other interventions aimed at improving social motivation can lead to generalisation of social seeking behaviours (Kasari, Freeman, & Paparella, 2006; Koegel, Koegel, Shoshan, & McNerney, 1999; Mahoney & Perales, 2003) and preliminary evidence suggests that PRT may enhance BOLD activation to social stimuli (Voos et al., 2012). As mentioned in the introduction, interventions that seek to improve synchronisation between parents and their children, such as the 'Early Start Denver Model,' may confer improvements in adaptive behaviour and communication in ASD (Dawson et al., 2010; Siller & Sigman, 2002) via their influence on social motivation. However, further research is needed to examine how these interventions compare to other behavioural intervention programmes, to enhance social functioning and well-being, as well as promote the normalisation of brain function, in ASD.

Given the possible involvement of oxytocin-dopaminergic circuitry in social motivation deficits in ASD, there has been growing interest in the potential for oxytocin as a

pharmacological intervention for ASD (Kohls, et al., 2012). Oxytocin administration has been shown to improve social learning, social cognition and co-operation, reduce repetitive behaviour and improve quality of life measures in ASD (Anagnostou et al., 2012; Andari et al., 2010; Guastella et al., 2010; Hollander et al., 2003, 2007). However, the evidence suggests that there may be no effect on core symptoms (Anagnostou et al., 2012) and further research will be needed to examine efficacy and potential side-effects. It has been suggested that oxytocin administration alone may only have limited beneficial effects and that combining pharmacological treatment with behavioural intervention programmes may be more effective in the long-term (Kohls, Chevallier, et al., 2012). The results from chapter three of this thesis support a potential role for interventions that target social motivation and/or oxytocinergic circuitry in improving social impairments in ASD. However, converging evidence from further studies will be required and future studies using fMRI as well as behavioural measures and clinical observations will be necessary to evaluate whether such interventions translate to normalisation of neural activation to social stimuli, as well as improvements in social functioning, in ASD.

6.5 Limitations of the Current Studies and Future Directions for MRI Studies of ASD

An important question for future research will be to examine how deficits in social reward processing can be understood in the light of other known disturbances in ASD. The evidence suggests that abnormal reward responses to items of special interest to people with ASD could account for restricted interests and repetitive behaviour symptoms in ASD (Dichter & Adolphs, 2012; Dichter et al., 2010). An interesting

question for future research will be to examine if abnormalities in social reward processing and neural responses to items of interest in ASD have the same or different aetiologies. Additionally, it will be important to consider other known deficits in ASD – language impairments and sensory difficulties for instance – in relation to theoretical accounts of abnormal reward responses in ASD. The results of the final chapter of this thesis implicated regions outside reward circuitry, such as the default mode network (DMN), in ASD pathology. Therefore it will be important to consolidate findings from the neuroimaging literature of ASD, which have not focused on reward processing, with reward processing accounts of ASD.

Social motivation theory provides a model for understanding the social impairments that characterise ASD. However, like the ‘Theory of Mind’ hypothesis (see section 1.5) it does not seek to address the other core deficit in ASD; restricted interests and repetitive behaviours. This is a potential limitation of the social motivation hypothesis. However, it has been suggested that ASD should be regarded from a multiple-deficits perspective, whereby different theoretical accounts could best explain different sets of symptoms (Chevallier, et al., 2012; Happé, Ronald, & Plomin, 2006; Rajendran & Mitchell, 2007). The results of the studies in this thesis support the social motivation theory but also suggest that deficits in executive function could account for some of the findings. For example, in chapter 3 the ASD group showed abnormal activation to social rewards in the dorsal striatum, a region implicated in linking rewards with executive functions (Balleine & O’Doherty, 2009; Grahn et al., 2008). Similarly, in chapter 4 the ASD group showed abnormal functional connectivity between the striatum and the MFG/dIPFC (which is implicated in executive functions). These findings suggest a potential link between deficits in social motivation and executive

dysfunction in ASD. Therefore future studies, seeking to improve understanding of the core deficits in ASD may need to take several theoretical accounts into consideration.

Reward circuitry dysfunction has been implicated in a number of psychiatric and neurodevelopmental disorders including addiction, eating disorders, depression, schizophrenia, ADHD and OCD (Dichter, Damiano, & Allen, 2012). A recent study indicated that both social anxiety disorder and ASD are characterised by reduced striatal activation during social reward anticipation, and that participants with social anxiety disorder showed greater activation to social rewards in the amygdala than the ASD group (Richey et al., 2012). This suggests that there may be important commonalities and distinctions in reward processing deficits between ASD and other disorders. As disorders such as schizophrenia and ADHD show similar social deficits to ASD (Sprong, Schothorst, Vos, Hox, & van Engeland, 2007; Uekermann et al., 2010), future studies could examine the degree to which social reward processing deficits in these disorders converge with the abnormalities reported in ASD. Similarly abnormal frontostriatal circuitry has been associated with Tourette syndrome, OCD and ADHD (Durstun, van Belle, & de Zeeuw, 2011; Langen, Durston, et al., 2011). Therefore examining the degree to which neuroanatomical abnormalities within this circuitry converge across disorders could improve understanding of the overlap in clinical profiles in these disorders.

Given constraints on sample size for the studies presented in this thesis, only right-handed medication-free high-functioning males with ASD were recruited in order to minimise heterogeneity that would have been introduced if females and those with intellectual disabilities had also been included. This however, this presents an

important limitation as the results of these studies, like many other MRI studies of ASD, are only applicable to high-functioning males with ASD. Recent research suggests that there may be important similarities and differences in the functional and structural neuroanatomy of males and females with ASD (Beacher et al., 2012; Beacher et al., 2012). Similarly, very little is known about the neuroanatomical basis of ASD with co-morbid intellectual disability (ID), though structural MRI studies have begun to examine the role of ID in ASD (Pardini et al., 2009) and of ASD in ID (Spencer et al., 2006). As mentioned in the introduction, ASD is associated with a number of psychiatric and neurological conditions (Leyfer et al., 2006; Maski et al., 2011; Mazefsky et al., 2008) and future MRI studies may help to delineate the affect of these co-morbidities on brain function and structure in ASD. Addressing the heterogeneity in ASD symptom presentation is an important challenge for future research. The recruitment of larger samples with well-defined homogenous subgroups (for example those with and without ID or other co-morbidities, males and females) will potentially help to overcome some of the discrepancies in the field and improve understanding of the neuroanatomical basis of ASD across the entire spectrum.

The results of the studies presented in this thesis suggest that developmental differences underlie some, but not all, group differences in brain function and structure in ASD. These results add to a growing body of literature showing abnormal functional and neuroanatomical developmental trajectories in ASD (Di Martino et al., 2010; Greimel et al., 2012; Hua et al., 2011; Langen et al., 2009). For example, for the functional connectivity analyses in chapter 4, there was a significant group-by-age interaction on connectivity values between the right MFG and the right caudate, but not for other frontostriatal regions showing group differences in functional

connectivity. For the TBSS results there was a significant group-by-age interaction on MD values in the right ILF near the fusiform gyrus, but not in other regions where there were group differences in FA or MD. Interestingly, the ICA results indicated that group-by-age interactions on default mode spectral power were stronger than group differences, surviving correction for multiple comparisons, whereas group differences did not withstand correction. These abnormal developmental trajectories suggest that differences in default mode spectral power could be secondary to other neuropathological processes in ASD. Examining group-by-age interactions in future studies could provide important insight into primary and secondary neuropathological changes in ASD.

Participants in the studies presented here were aged between 12 and 25. This presents a relatively large age range and given that important developmental processes occur during adolescence (Blakemore & Choudhury, 2006), and that ASD is characterised by atypical maturational processes (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012), this is an important factor to consider. Age was therefore included as a covariate in the analyses and group-by-age interactions were examined where there were significant group differences. However, negative findings should be treated with caution as age-related heterogeneity in the data could have reduced power to detect group differences. Longitudinal and cross-sectional studies have begun to delineate the atypical maturational processes that characterise ASD (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012; Hua et al., 2011), and results suggests that this presents a promising avenue for future research.

Exploratory analyses between neuroimaging findings and behavioural symptoms yielded a number of interesting results. For example, group differences in activation to social rewards were associated with repetitive behaviours and not social impairments. This finding may be understood in the light of evidence suggesting that social impairments and restricted interests and repetitive behaviours are related in ASD and that symptoms are best represented by a unitary construct (Constantino et al., 2004). Previous studies have not found associations between abnormal activation to social rewards and social impairments or repetitive behaviours in ASD (Kohls, Schulte-Rüther, et al., 2012; Scott-Van Zeeland et al., 2010). This has potential implications for the social motivation theory of ASD as it implies that deficits in social reward processing may not be associated with behavioural impairments. However, these results could reflect difficulties in relating behavioural measures with neuroimaging data.

An important limitation of the studies presented here, and of other neuroimaging studies of ASD, is that there is a lack of appropriate quantitative scales for relating neuroimaging data with clinical variables. The ADOS-G – which provides information about current functioning – and ADI-R – which provides information about current functioning and childhood behaviour – (Lord, Risi, et al., 2000; Lord, Rutter, & Couteur, 1994) are typically used for this purpose. However, the use of these scales present several limitations. Firstly, these are diagnostic scales which are designed to establish a categorical diagnosis of ASD rather than measuring symptom severity and therefore are not normally distributed. Secondly, the ADI-R sub-scale scores reflect childhood behaviour and therefore may not be the most appropriate measure for correlating current brain function and structure with autistic behaviour. Thirdly, these

measures are not used among controls; therefore findings are specific to the autism samples.

The SRS was used in the current study as it is a quantitative scale of social impairments associated with ASD, which is continuously distributed in the general population (Constantino, 2011; Constantino & Todd, 2003). A potential limitation of the SRS is that it focuses on social impairment, without a separate scale for repetitive behaviour. Additionally, the SRS is a parent report measure and therefore may reflect parental biases in the reporting of symptom severity. The development of appropriate scales of current functioning, that reflect both social and communication deficits and restricted interests and repetitive behaviours, and that are continuously distributed in the general population, could yield more consistent correlations between neuroimaging findings and clinical symptoms across studies.

Factor analytic studies suggest that the sub-scales of the ADI-R, which currently reflect the three factor structure of the DSM-IV, may be better represented by two factor structures as in the DSM-5 model of ASD (Frazier et al., 2008; Georgiades et al., 2012). I sought to address this potential issue by using the two-factor solution of the ADI-R – which classifies ASD behaviours into social and communication deficits (SCD) and restricted interests and repetitive behaviours (RRB) – as reported in (Georgiades et al., 2012), to correlate ADI-R measures with neuroimaging findings (see Appendix H). There was both convergence and divergence of results using the two and three-factor solutions. Future studies with larger samples and greater distribution of factor loadings may clarify this issue. As mentioned above, there is also evidence that ASD symptoms can be represented by a single dimension (Constantino et al., 2004). Further research

into the construct of the ASD phenotype will potentially clarify some of the inconsistencies that have been reported in the literature in terms of relating neuroimaging findings to behavioural symptoms.

A final issue pertaining to the issue of relating neuroimaging data to behavioural measures is that of correction for multiple comparisons. There does not appear to be a consensus in the literature as to how this should be performed – some studies do not correct for multiple comparisons, others correct for the number of scales with which the neuroimaging data are correlated and others correct for the number of regions with which behavioural measures are correlated. It may be best to correct for the overall number of correlations (i.e. behavioural measures and number of regions) but this would result in very stringent thresholds. Additionally, neither the behavioural measures nor the neuroimaging metrics are likely to be truly independent therefore calling into question the appropriateness of a Bonferroni correction. In the studies presented here we corrected for the number of measures (i.e. ADOS, ADI and SRS) as this would maintain a consistent threshold across studies. Given the importance of relating neuroimaging findings to behavioural measures and the associated challenges that have been discussed, the analyses presented in this thesis should be regarded as exploratory.

There are several limitations specific to the MRI methods employed in the current study that should be taken into account. Firstly, I did not examine the function, structure or connectivity of the midbrain due to the fact that the midbrain is particularly susceptible to artefacts from cardiac (Dagli, Ingelholm, & Haxby, 1999; Greitz et al., 1992) and respiratory (Raj, Anderson, & Gore, 2001) signals. This is an

important limitation, given that midbrain dopaminergic activity plays an important role in reward processing (Haber & Knutson, 2009; Schultz, Dayan, & Montague, 1997). Future studies could examine midbrain function in ASD using optimised fMRI methods (Limbrick-Oldfield et al., 2012). As discussed in chapter 4, the functional connectivity analyses that were used did not provide information about the direction of effects between anatomical areas, therefore increased frontostriatal functional connectivity could be due to greater top-down or bottom-up processes. Future studies using effective connectivity techniques and including the thalamus and midbrain, which are implicated in reward processing together with frontostriatal and amygdala regions (Haber & Knutson, 2009), could shed further light on abnormal functional connectivity in reward circuitry in ASD. Similarly, effective connectivity analysis of fronto-basal ganglia circuitry (Jahfari et al., 2011, 2012) could improve understanding of response inhibition deficits (Rajendran & Mitchell, 2007), and potentially repetitive behaviours, in ASD.

Diffusion tensor imaging is associated with a number of important confounds (Jones, 2010). One of the most important confounds is the inability of the tensor model to characterise diffusion in regions of complex fibre architecture, or 'crossing fibres,' where fibres 'kiss,' twist, splay kink or bend (Basser et al., 2000; Frank, 2001; Jones, 2010; Tuch, 2004). FA, in particular, has been shown to be strongly affected by crossing fibres, showing a decrease in these regions (Alexander, Hasan, Lazar, Tsuruda, & Parker, 2001; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). This can result in paradoxical findings whereby white matter degeneration can lead to increased FA in regions where there are crossing fibres (Jones, 2010). Recent findings indicate that MD values are also influenced by the architectural configuration of white matter, with MD

values lower in crossing fibre regions, in comparison to single fibre regions (Vos et al., 2012). Furthermore, MD values are not only influenced by the diffusivity of the fibre but also the acquisition parameters, such as the b-value (Vos et al., 2012). Similarly, simulations have shown that AD and RD can cause fictitious changes in each other's values, in voxels characterised by crossing fibres (Wheeler-Kingshott & Cercignani, 2009). Until recently, crossing fibres were thought to make up approximately 33% of white matter (Behrens et al., 2007), however recent estimates suggest the prevalence is as high as 90% (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2012). This suggests that tensor derived metrics are significantly confounded and therefore may not provide a reliable measure of white matter integrity. Improved understanding of brain structural connectivity in ASD will therefore require the use of high angular resolution diffusion-weighted imaging (HARDI) methods such as constrained spherical deconvolution (CSD). The results of chapter 5 of this thesis highlighted a further important issue in this and other MRI studies of ASD. Group comparisons for the whole brain analyses either did not survive correction for multiple comparisons (as in the case of the VBM and resting-state ICA) or were very subtle (as in the case of TBSS results) demonstrating the necessity for larger sample sizes, in particular when conducting whole brain analyses.

In chapter 5, the ASD group showed abnormal changes in spectral power with age in the posterior default mode network. This suggests that ASD may be characterised by changes in the temporal dynamics of the BOLD signal, supporting the hypothesis that ASD is a disorder of neural processing characterised by neural noise (Belmonte et al., 2004; Simmons et al., 2009). The appeal of this hypothesis is two-fold; firstly there is a plausible genetic mechanism that could underlies such differences – with both

glutamatergic and GABAergic genes implicated in ASD pathology which likely results in synaptic dysregulation (Simmons et al., 2009) and secondly, it has the potential to account for a wide variety of anatomical and functional abnormalities in ASD (Belmonte et al., 2004). The results of the present study should be interpreted with caution, given that the precise electrophysiological correlates of BOLD spectral power are still unknown. However the results suggest that the neural noise hypothesis could provide a useful model for linking aetiological factors to neuroanatomical findings in ASD. Future studies examining this hypothesis could use combined fMRI-EEG methods and/or imaging genetic approaches, both of which have the potential to improve understanding of neural information processing in ASD.

An important avenue for future research into the neural basis of ASD will be to corroborate findings from the neuroimaging literature with results of studies using other methodologies. As illustrated in the introduction, fMRI is not direct measure of neural activity (Huettel et al., 2009). Though MRI is particularly useful because it allows in-vivo examination of brain function and structure, it has a major limitation in that causation cannot be inferred from MRI findings. Corroborative evidence from other methods such as transcranial magnetic stimulation (TMS) or lesion studies are needed to infer causation, though it is not always possible to implement these methods. Evidence from post-mortem studies could be used to substantiate structural MRI findings in the ASD literature. MRI in conjunction with other methods including positron emission tomography (PET) and magnetic resonance spectroscopy, as well as neuroimaging genetic studies, could help to uncover the aetiology of changes in brain maturation observed in ASD. As of yet, the findings that have been reported cannot be attributed to genetic or environmental risk factors, or secondary effects of having ASD,

which may result in the under- (or over-) use of certain brain regions (Greimel, Nehrkorn, Schulte-Rüther, et al., 2012). The degree to which abnormal functional and structural neuroimaging findings reflect compensatory mechanisms in ASD remains unknown and presents an important challenge for future research.

Neuroimaging studies have improved understanding of ASD and have the potential to be of use in evaluating treatment studies (Lange, 2012). Steps have already been made in this direction, with a recent study indicating that behavioural interventions can result in normalisation of brain function in ASD (Voos et al., 2012) and can improve measures of white matter integrity in the uncinate fasciculus (Matteo Pardini et al., 2012). Further progress in the field will require large, long-term, multicentre studies to identify neuroanatomical features unique to ASD (Lange, 2012), with comprehensive data collection – including demographic, genetic, MRI and behavioural data – and will need to include patients across the entire spectrum. Several data sharing initiatives have already been established for genetic studies of ASD (Fischbach & Lord, 2010; Geschwind et al., 2001; Szatmari et al., 2007). However, the neuroimaging community has been slower to adopt this approach. Recently, the Autism Brain Imaging Data Exchange (ABIDE), was established in order to aggregate previously collected resting-state fMRI data from international sites. The resulting database includes 539 individuals with ASD and 573 age-matched typical controls. The data collected for this thesis were contributed to the consortium and the data have been openly released, which will allow for replication studies, as well as novel analyses. This presents an important milestone for neuroimaging studies of ASD and paves the way for further studies which, with the inclusion of additional phenotypic, demographic and genetic data, has the potential to substantially improve understanding of ASD neuropathology.

6.6 Final Conclusions

The results of the studies presented in this thesis suggest that ASD may be characterised by abnormal neural responses to social rewards in the presence of normal responses to non-social, monetary rewards. These findings have implications for informing interventions and suggest that using positive social feedback may not be the optimal reinforcer when using interventions based on operant conditioning. On the other hand, the social motivation theory suggests that interventions aimed at improving social motivation could have positive secondary effects on the development of social, communication and language skills. The results of the second and third experimental chapters showed that there were no group differences in the structure of regions implicated in reward processing but that there were diffuse structural differences in other cortical and subcortical regions. This suggests that the primary neuropathology in ASD may not be localised to reward circuitry. The results of these studies also demonstrated that both hypothesis and data driven approaches can improve understanding of ASD neuropathology, and that using hypothesis-driven, region-of-interest methods in isolation may overlook important differences in brain structure and function in ASD. The next step for neuroimaging studies of ASD will be to perform large, long-term, multicentre studies, aggregating demographic, behavioural, genetic and neuroimaging data. This will potentially improve understanding of how genetic and environmental risk factors translate to abnormalities in neuroanatomy and brain function in ASD. Improved understanding of the disorder could lead to novel treatments and more precise methods for evaluating interventions.

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Appendix A: Selection of Face for Social Reward Task

20 Caucasian males (mean age = 29.3; SD = 4.71) were asked to rate the 8 female Caucasian faces in the NimStim set in terms of how pleasant they found the faces on a scale of 1-10 where 1 represented 'very unpleasant' and 10 represented 'very pleasant'. When evaluating how pleasant the faces were, they were asked to consider both how attractive and how pleasant they found the picture based on their facial expression. Participants were shown all three 'Happy' faces (Happy-Closed; Happy-Open; Happy-Exuberant) for each face and were asked to rate each one individually. They were then asked to choose the actor with the most pleasant overall.

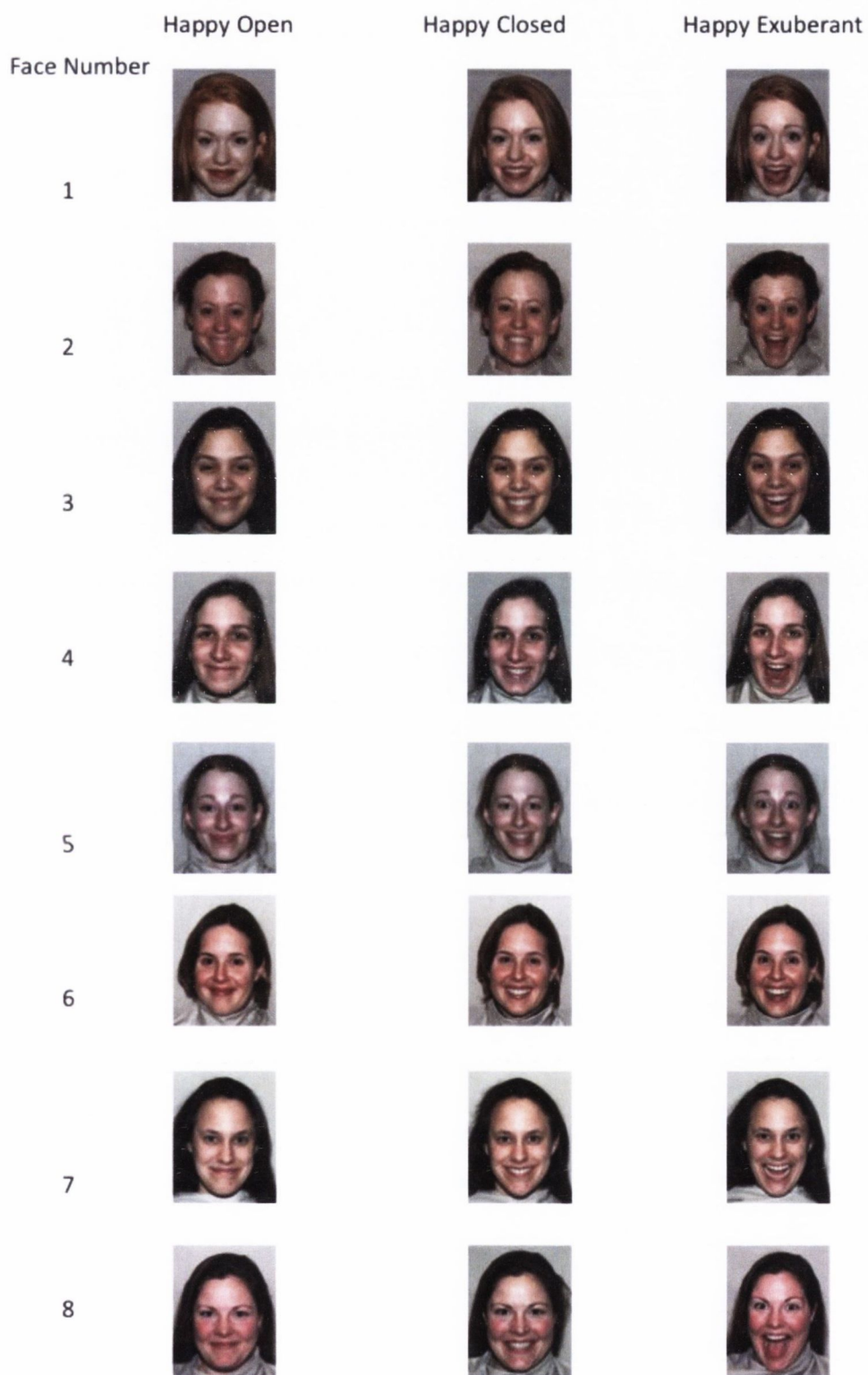


Figure A.1. Female Caucasian faces from the Nimstim set of stimuli.

Face number one was chosen as being most pleasant by 55% of raters, this was followed by face numbered 2 (15%), 3(10%), 6(10%), 7(5%), 8(5%), 4 (0%) and 5 (0%). Total 'pleasantness' scores for each face were also calculated from the individual pleasantness ratings of each of the three happy faces for each actor (one to eight). Using Friedman's ANOVA, there was a significant difference in the 'pleasantness' ratings for the different faces ($\chi^2 (7) = 36.08$; $p < .05$). Face number one was rated as being most pleasant overall, with a mean ranking of 6.52. Using a Wilcoxon signed rank test, a significant difference was observed between ratings of face number 1 and the next most pleasant face, face number 6 (rank = 5.68) ($T = 38.5$; $p < .05$; $r = -0.325$). Based on these results, Face number one was chosen as the most pleasant face.

Friedman's one way ANOVA was used to examine differences in pleasantness ratings for all of the Caucasian faces at each of the three levels of Happiness. A significant difference was found between the pleasantness ratings for three levels of Happy faces ($\chi^2 (2) = 15.688$; $p < .05$). Wilcoxon signed ranks test showed that Happy-Open faces were rated as more pleasant than Happy-Closed and Happy Exuberant faces ($T = 8.5$; $r = -.45$; $p < .0167$; $T = 9.5$; $r = -.44$; $p < .0167$ respectively) and that there was no significant difference in ratings of Happy-closed and Happy-Exuberant faces ($T = 57$; $r = -.197$; $p < .0167$; $T =$; $r =$; $p < .0167$).

Friedman's one way ANOVA was then used to investigate whether there were significant differences in pleasantness ratings for Face number one at each of the three levels of Happy. A significant difference was found between the pleasantness ratings for three levels of Happy faces ($\chi^2 (2) = 13.368$; $p < .05$). Wilcoxon signed ranks test showed that the Happy-Open face was rated as more pleasant than Happy-Closed and

Happy Exuberant face ($T = 4.5$; $r = -.46$; $p < .0167$; $T = 25$; $r = -.39$; $p < .0167$ respectively) and that there was no significant difference in ratings of Happy-closed and Happy-Exuberant faces ($T = 61$; $r = -.14$; $p < .0167$).

In summary, face number one was rated as the most pleasant of the eight female Caucasian faces. Happy-open faces were rated as significantly more pleasant than Happy-closed and Happy-exuberant faces for the eight faces when analysed together and also for face number one when ratings for this face were analysed separately. Therefore, face number one was selected to present FB in the SID task with the Happy-Closed face used as a small reward and the Happy-Open face used as a larger social reward.

Appendix B: Supplementary Tables for Self-reported Ratings of Social and Monetary Rewards.

Table B. 1. Wilcoxon signed–ranks tests to examine the effect of reward magnitude on valence and arousal ratings (Asterisks indicate differences surviving correction for multiple comparisons with bonferroni correction for 12 tests $p<.004$).

Level	Task	Valence/Arousal	Z score	P value
Small Reward – No Reward	MID	Valence	$z=-5.255$	$P <.0001^*$
		Arousal	$= -2.828$	$P=.005$
	SID	Valence	$z=-5.234$	$P <.0001^*$
		Arousal	$z=-2.656$	$P=.008$
Large Reward – Small Reward	MID	Valence	$z= -5.313$	$P <.0001^*$
		Arousal	$z= -4.824$	$P=.005$
	SID	Valence	$z=-2.397$	$P=.017$
		Arousal	$z=-3.118$	$P=.002^*$
Large Reward – No Reward	MID	Valence	$z=-5.468$	$P <.0001^*$
		Arousal	$z=-4.386$	$P <.0001^*$
	SID	Valence	$z= -5.486$	$P <.0001^*$
		Arousal	$z= -3.599$	$P <.0001^*$

Table B.2. Mann-Whitney tests to examine group differences on valence and arousal ratings

Level	Task	Valence/ Arousal	Mean		U	P value
			ASD	Control		
No Reward	MID	Valence	4.33	4.15	U= 184.00	p=.477
		Arousal	3.76	2.75	U= 162.00	p=.199
	SID	Valence	3.85	3.71	U= 216.00	p=.906
		Arousal	3.57	3.24	U= 187.50	p=.396
Small Reward	MID	Valence	6.47	6.35	U= 197.00	p=.718
		Arousal	4.28	4.90	U= 172.00	p=.315)

	SID	Valence	6.00	5.86	U= 207.50	p=.733
		Arousal	4.28	4.05	U= 200.00	p=.602
Large Reward	MID	Valence	7.48	8.05	U= 156.00	p=.136
		Arousal	5.86	6.85	U= 160.50	p=.188
	SID	Valence	6.38	6.24	U= 220.50	p=1.00
		Arousal	4.90	4.95	U= 216.50	p=.919

Appendix C: Within-group results for Social and Monetary Reward Processing.

Table C. 1. One sample t-tests for Controls for the MID for the contrast correct cue>baseline. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE $p<.05$) at cluster or peak level, cross (†) indicates a small volume correction.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Frontal				
Left Inferior Frontal Gyrus p. Orbitalis †	37	4.83	38 22 -14	38
Left Precentral Gyrus	12	4.61	-34 -12 66	6

Left Precentral Gyrus	20	4.25	-40 -4 50	6 (40%)
Left Middle Cingulate †	39	4.49	-8 14 36	24
Left Inferior Frontal Gyrus p. Orbitalis	17	4.07	-42 18 -10	38
Occipital				
Left Calcarine Gyrus*	2222	8.96	-6 -92 -2	17 (50%); 18(50%)
Right Cuneus	68	5.59	8 -78 22	18 (50%)
Left Calcarine Gyrus	47	4.83	-18 -68 8	17 (70%)
Right Calcarine Gyrus	111	4.67	18 -72 10	17 (80%)
Right Fusiform Gyrus	52	4.61	28 -70 -12	19; hOC4v (70%)

Right Fusiform Gyrus	21	4.16	28 -56 -18	37
Parietal				
Left Postcentral Gyrus*	146	5.29	-44 -22 46	3b (70%)
Right Superior Parietal Lobule	44	5.14	30 -48 48	SPL (7PC) (50%)
Subcortical				
Left Nucleus Accumbens†	20	4.95	-10 10 0	NA
Right Nucleus Accumbens	21	4.51	12 4 -2	NA

Cerebellum				
Left Lobule VIIa Crus 1	84	6.1	-12 -80 -30	66%
Right Lobule VIIa Crus 1	15	5.6	14 -74 -34	25%
Right Lobule VIIa Crus 1	95	5.37	40 -54 -32	84%

Table C.2. One sample t-tests for Controls for the SID for the contrast correct Cue>baseline. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE $p<.05$) at cluster or peak level.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Occipital				
Left Calcarine Gyrus *	142	6.71	-6 -88 6	18 (70%)

Table C.3. One sample t-tests for ASD for the MID for the contrast correct cue>baseline. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE p<.05) at cluster or peak level.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Frontal				
Left Inferior Frontal Gyrus p. Orbitalis	67	5.13	-28 22 -14	47
Right Precentral Gyrus	24	4.95	42 -6 60	6 (20%)
Right SMA	59	5.32	12 4 66	6 (60%)
Occipital				

Right Calcarine Gyrus*	1496	9.06	8 -88 -2	17 (80%)
Subcortical				
Left Amygdala	18	4.49	-36 -2 -26	NA
Left Pallidum	10	4.15	-10 2 0	NA
Right Caudate Nucleus	10	4.33	14 10 4	NA
Right Hippocampus	14	4.63	40 -10 -26	CA (40%)
Right Hippocampus/Insula	10	5.19	40 -8 -18	NA
Cerebellum				
Left Lobule VIIa	17	4.67	-32 -54 -50	77%
Right Lobule VI*	166	5.74	30 -40 -26	64%

Right Lobule VIIa Crus I	10	4.37	48 -54 -36	98%
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Table C.4. One sample t-tests for ASD for the SID for the contrast correct cue>baseline

	Cluster Size	T	MNI	BA and/or
	Voxels	(Peak)	Co-ordinates	Probability (if
			(x,y,z)	available)
Occipital				
Left Calcarine Gyrus	75	7.33	-6 -90 -8	18 (80%)
Right Lingual Gyrus	25	4.78	6 -84 -4	17 (70%)
Left Middle Occipital Gyrus	21	4.46	-24 -100 -6	18 (70%)

Table C.5. One sample t-tests for controls for the MID for the contrast correct feedback>baseline. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE p<.05) at cluster or peak level, cross (†) indicates a small volume correction.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Frontal				
Left Anterior Cingulate Cortex *	145	6.75	-4 40 6	32
Right Middle Orbital Gyrus †	66	5.49	14 46 -8	11
Right Inferior Frontal Gyrus p. Opercularis	40	5.11	42 24 -18	38

Occipital				
Left Calcarine Gyrus *	1382	12.06	-12 -104 6	17 (70%)
Right Middle Occipital Gyrus *	1885	9.48	34 -94 0	18; hOC3v (V3v)
Right Fusiform Gyrus				(40%)
Left Fusiform Gyrus*	72	5.51	26 -48 -18	
	157	4.68	-36 -52 -20	37
				37
Subcortical				
Right Olfactory Cortex	12	4.29	30 10 -20	NA

Cerebellum				
Left Lobule VIIA Crus 1	18	5.38	-30 -82 -24	100%
Right Lobule VIIa (Vermis)	37	4.55	2 -62 -32	61%

Table C.6. One sample t-tests for Controls for the SID for the contrast correct feedback>baseline. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE $p<.05$) at cluster or peak level.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Occipital				
Left Middle Occipital Gyrus*	3002	13.88	-24 -102 0	18 (80%)
Left Inferior Occipital Gyrus				
Right Inferior Occipital Gyrus				
Right Fusiform Gyrus				
Left Calcarine Gyrus	20	5.16	30 -26 -12	20

Right Cuneus				
Subcortical				
Right Hippocampus	20	5.16	30-26 -12	FD 100%

Table C.7. One sample t-tests for ASD for the MID for the contrast correct FB>baseline. † Corrected for multiple comparisons with the OFC masks. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE p<.05) at cluster or peak level, cross (†) indicates a small volume correction.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Frontal				
Right Anterior Cingulate *	173	6.97	4 32 20	24
Left Inferior Frontal Gyrus p. Orbitalis †	12	3.99	-38 24 -8	47
Occipital				
Right Occipital Gyrus *	2710	15.16	30 -96 -4	18 (30%); 17 (20%0

Left Lingual Gyrus *	2205	12.25	-26 -96 -14	18 (50%); hOC3v (v3v) (50%)
Temporal				
Right Insula Lobe	43	5.14	30 16 -16	48
Subcortical				
Left Amygdala†	18	4.66	-12 -6 -12	NA
Cerebellum				
Left Lobule VI	10	4.11	-32 -54 -34	84%
Left Lobule VI	14	4.76	-16 -68 -18	100%
Left Lobule VI	47	4.85	-34 -42 -30	90%

Left Lobule X	41	4.65	-20 -38 -44	78%
Left Lobule VIIa Crus II	23	4.34	-32 -52 -44	14%
Left Lobule VIIb (Vermis)	11	4.31	-4 -72 -32	66%

Table C.8. One sample t-tests for ASD for the SID for the contrast correct FB>baseline. Asterisks (*) indicates regions surviving correction for multiple comparisons (FWE p<.05) at cluster or peak level.

	Cluster Size Voxels	T (Peak)	MNI Co-ordinates (x,y,z)	BA and/or Probability (if available)
Occipital				
Left Inferior Occipital Gyrus/ Left Calcarine Gyrus *	838	12.19	-14 -98 -10	18 (50%); 17 (50%)
 Right Cuneus *	813	8.29	40 -46 -22	17 (60%); 18 (30%)

Right Fusiform Gyrus	79	5.41	40 -46 -22	37
Cerebellum				
Left Lobule VIIa	25	4.48	-20 -62 -44	NA

Deactivation to social rewards in the ASD group.

The ASD group showed significant deactivation for social rewards compared to no reward in the left DS ($F= 3.42$; extent threshold: >10 voxels; $p<.001$ uncorrected). Controls did not show a significant difference between the social reward baseline (see figure C.1 below).

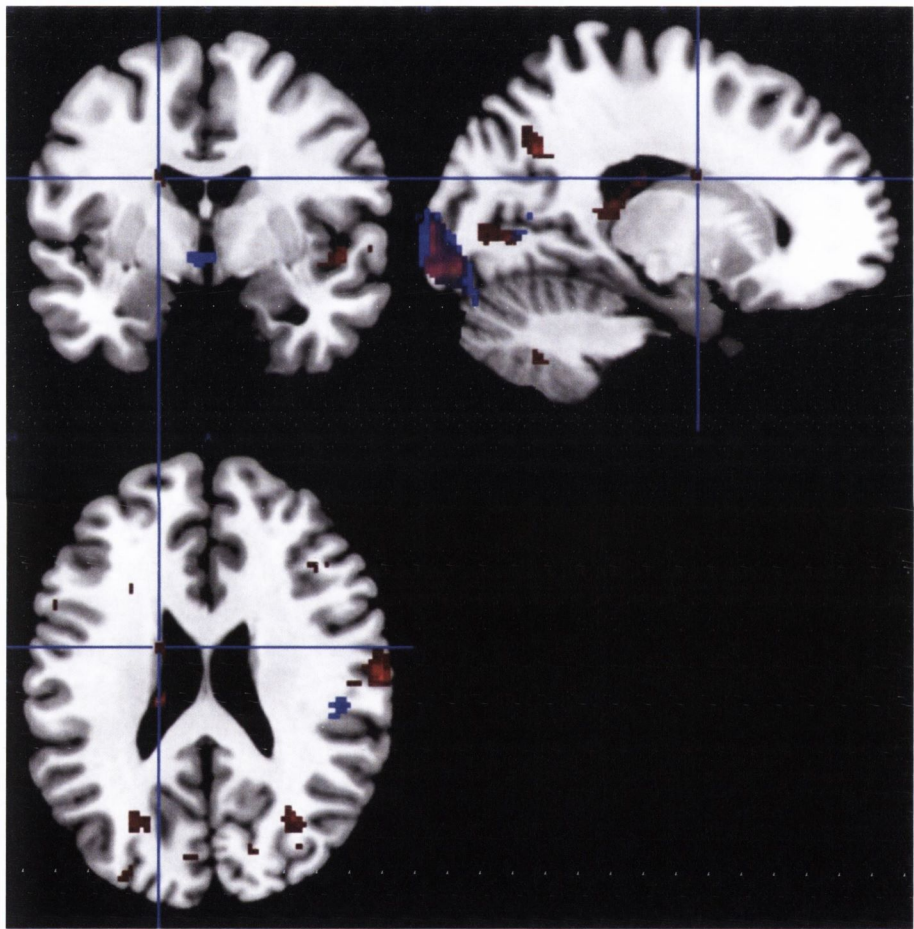


Figure C.1. BOLD response to social rewards at peak co-ordinates for the group by reward type interaction (MNI =18 -2 24) as indicated by the cross hairs. The ASD group is shown in red and controls are shown in blue. The ASD group showed significant deactivation compared to baseline for social rewards whereas controls did not show a significant difference from the baseline.

Age effects in the left DS

Age was not associated with percent signal change in the left DS for either the ASD (MID: $p=.090$; SID $p=.132$) or control groups (MID: $p=.653$; SID $p=.527$). Using a 3-way ANOVA (factors: age, group, reward type) there were no significant main effects of age ($p=.671$) or interaction effects between age and group ($p=.952$) or age and reward type ($p=.084$) on percent signal change in the left DS

Appendix D: Supplementary information for Frontostriatal Connectivity.

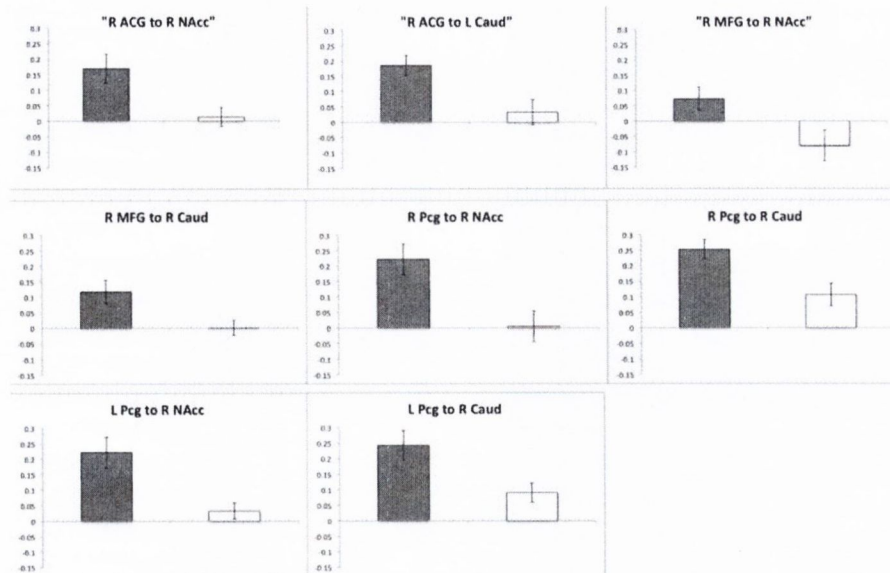


Figure D.1. Group differences in functional connectivity between the frontal cortex and the striatum, without age and IQ adjustments. Bar charts show Z-transformed R-Values for connectivity between each of the regions for which there was a significant group difference. The ASD group is shown in grey and the controls in white with standard error of the mean displayed. R=Right; L=Left; ACC =Anterior Cingulate Cortex; MFG= Middle Frontal Gyrus; Pcg= Paracingulate Gyrus; NAcc = Nucleus Accumbens; Caud=Caudate.

Table D.1. T-scores and p-values for regions showing significantly increased connectivity in the ASD group without age and IQ adjustment.

Source	Target	T – Value	P -Unc	P- FDR
Right Cingulate Gyrus, anterior division	Right Accumbens	2.60	0.013	0.039
	Left Caudate	2.88	0.006	0.038
Right Middle Frontal Gyrus	Right Accumbens	2.55	0.015	0.043
	Right Caudate	2.69	0.010	0.043
Right Paracingulate Gyrus	Right Accumbens	3.48	0.001	0.007
	Right Caudate	3.06	0.004	0.012
Left Paracingulate Gyrus	Right Accumbens	3.37	0.002	0.010
	Right Caudate	2.83	0.007	0.022

Table D.2. Group-wise comparisons using non-parametric Mann-Whitney tests and multivariate tests including age, IQ and total intracranial volume as covariates for FA, MD, AD and RD in the Right and Left Caudate and Accumbens to Prefrontal tracts.

Tract		Mean (SD)	Mann-Whitney P-Value	Multivariate Tests P-Value
Right Caudate	FA	ASD = .3971 (.0100) Control= .3943 (.01402)	.541	.758
	MD	ASD = .0008 (.00002) Control= .0008 (.00002)	.285	.458
	AD	ASD = .0011 (.00003) Control=.0011 (.00002)	.330	.378
	RD	ASD = .0006 (.00002) Control=.0006 (.00002)	.308	.786
Left Caudate	FA	ASD = .3959 (.00948) Control=.3991 (.01476)	.961	.895
	MD	ASD = .0008 (.00002) Control= .0008 (.00002)	.383	.640
	AD	ASD = .0012 (.00002) Control=.0011 (.00002)	.453	.409
	RD	ASD = .0006 (.00002) Control= .0006 (.00002)	.525	1.00
Right	FA	ASD = .3917 (.03047)	.662	.869

Accumbens		Control=.3936 (.01663)		
	MD	ASD =.0011 (.00003) Control=.0012 (.00003)	.900	1.00
	AD	ASD =.0006 (.00003) Control=.0006 (.00002)	.961	.750
	RD	ASD =.0007 (.00002) Control=.3983 (.02035)	.865	.685
Left Accumbens	FA	ASD =.4025 (.01678) Control=.0008 (.00002)	.307	.525
	MD	ASD =.0008 (.00001) Control=.0008 (.00002)	.187	.766
	AD	ASD =.0012 (.00003) Control=.0012 (.00003)	.439	.400
	RD	ASD =.006 (.00002) Control=.0006 (.00002)	.897	1.00

Appendix E: Group-wise Comparisons of AD and RD using TBSS

Table E. 1. AD differences between groups.

White Matter Tract and/or Corresponding Cortical Area	Cluster Size Voxels	Z (Max)	Voxel Co-ordinates (x,y,z)
ASD>CON			
Temporal			
Left Superior Longitudinal Fasciculus	12	4.38	-52 -39 -11
Right Middle Temporal Gyrus	11	3.7	49 -5 -24

Parietal			
Right Angular Gyrus/Precuneus	12	3.67	25 8 41
Right Angular Gyrus/Precuneus	11	4.1	30 -53 33
Cerebellum			
Right Lobule VI	42	4.59	21 -60 -28
CON>ASD			
Frontal			

Left Inferior fronto-occipital fasciculus	13	4.61	-36 40 3
Left Insular Cortex	14	4.32	-37 -7 -5
Left Superior Longitudinal Fasciculus	10	3.76	-49 7 14
Temporal			
Left Middle Temporal Gyrus	20	3.9	-57 -37 -3
Left Middle Temporal Gyrus	11	4.91	-56 -43 4
Occipital			
Right Lateral Occipital Cortex	13	4.08	15 -69 49

Subcortical			
Left Thalamus	21	2.38	-14 -29 2

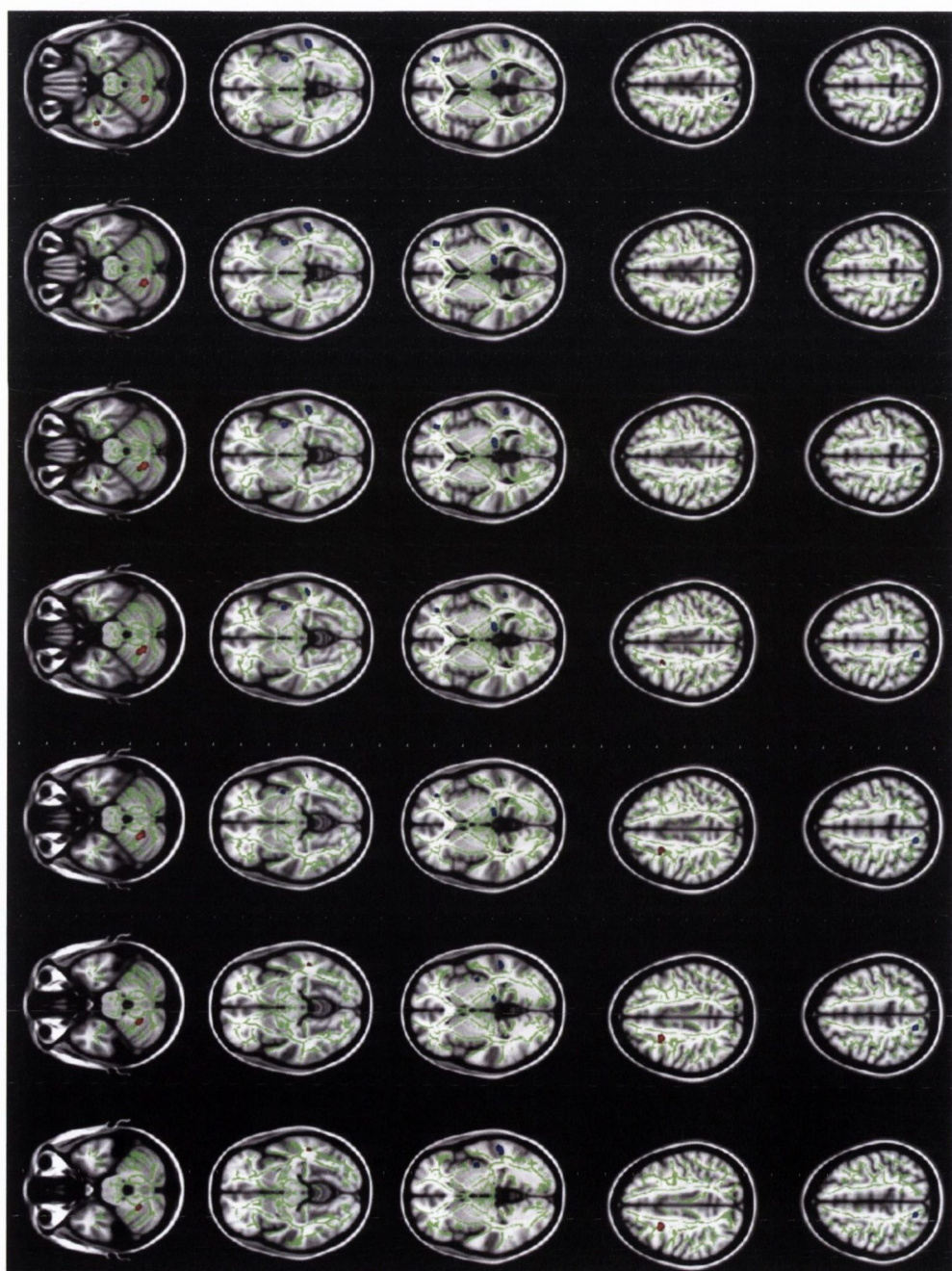


Figure E.1. Axial slices showing increased AD in the ASD group (red) and decreased AD in the ASD group (blue). Images are displayed in radiological convention (left is right) and areas of significant difference have been highlighted using TBSSfill.

Table E 2. RD differences between groups

White Matter Tract and/or Corresponding Cortical Area	Cluster Size	Z	Voxel Co-ordinates
	Voxels	(Max)	(x,y,z)
ASD>CON			
Frontal			
Right Inferior Frontal Gyrus, Pars Triangularis	22	4.45	47 30 3
Left Frontal pole	14	3.7	-35 42 5

Right Frontal pole	12	3.97	44 37 -8
Left Uncinate Fasciculus	12	3.93	-15 51 -12
Occipital			
Right Lateral Occipital Cortex	11	4.47	18 -69 49
Right Lateral Occipital Cortex	11	3.8	22 -80 42
Right Occipital Pole	10	4.069	11 -89 22
Temporal			

Right Inferior Fronto-occipital Fasciculus	16	3.27	41 -18 -12
CON>ASD			
Frontal			
Right Middle Frontal Gyrus	26	4.49	49 18 29
Subcortical	12	3.17	-23 -24 2
Left Internal Capsule			

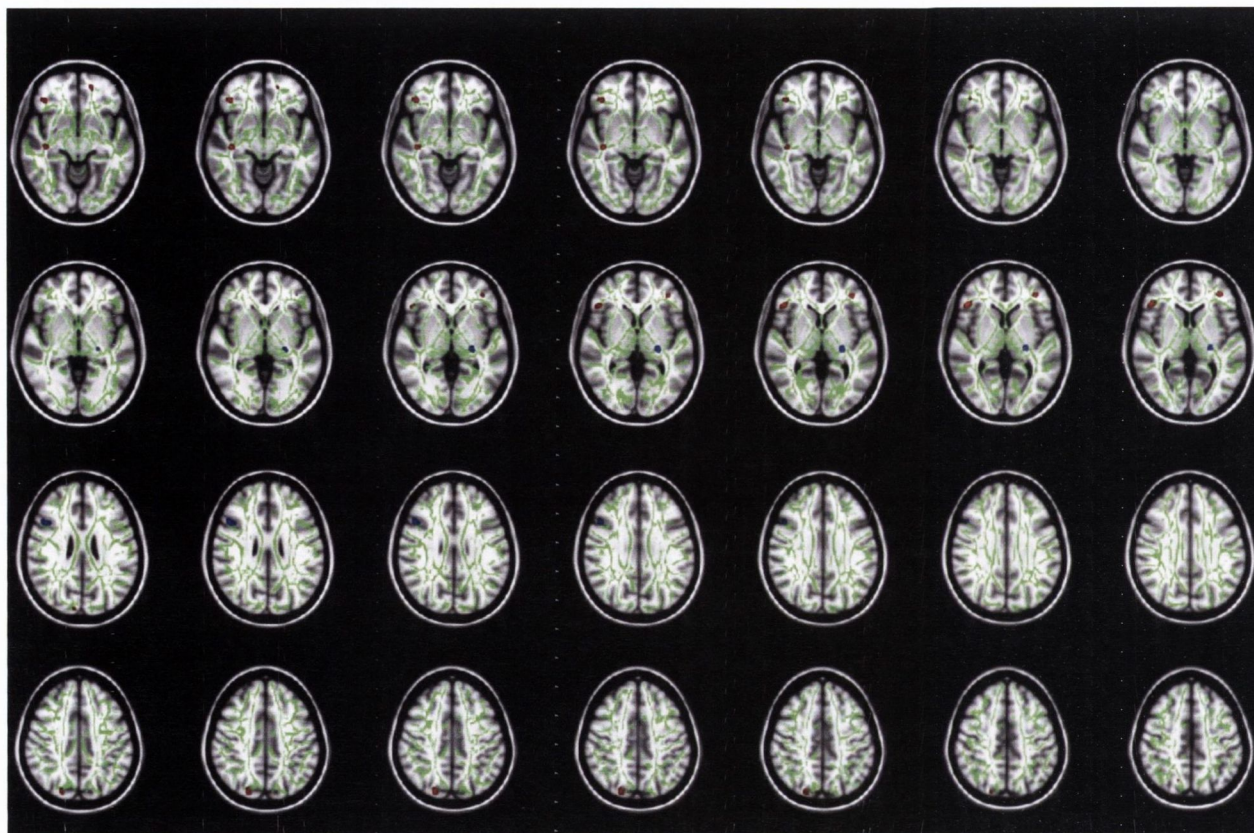


Figure E.2. Axial slices showing increased RD in the ASD group (red) and decreased RD in the ASD group (blue). Images are displayed in radiological convention (left is right) and areas of significant difference have been highlighted using TBSSfill.

Appendix F: Correlations between MRI data and Behavioural Measures.

Table F. 1. Tests of Normality for ADOS and ADI subscale scores.

	Kolmogorov-Smirnov Statistic	Kolmogorov-Smirnov P-value	Skew	Kurtosis
ADOS Communication	.227	.004	.204	-.343
ADOS Social	.251	.001	.804	-.761
ADOS Behavioural	.167	.111	.186	3.463
ADI Social	.153	.200	-.023	-.671
ADI Communication	.120	.200	-.082	-.884
ADI Behaviour	.208	.014	1.059	.399
SRS ASD	.143	.200	.452	-.226
SRS Controls	.141	.179	1.563	3.333

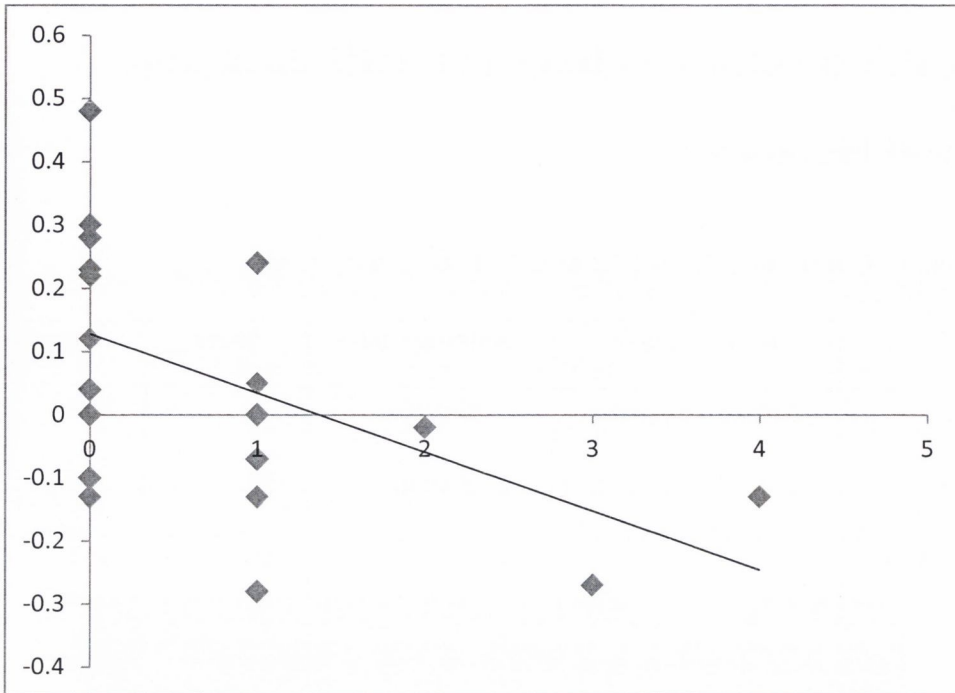


Figure F.1. Correlation between ADOS-G repetitive behaviour score (x-axis) and BOLD signal to social rewards in the dorsal striatum (y-axis) in the ASD group.

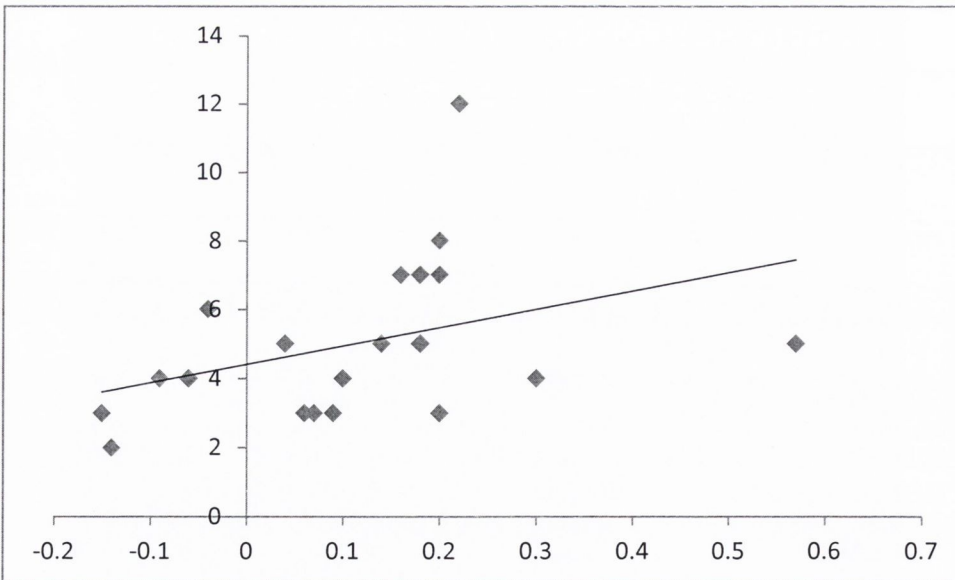


Figure F 2. Correlation between right MFG and right caudate functional connectivity (x-axis) and scores on the ADI-R restricted and stereotyped behaviour scale (y-axis) in the ASD group.

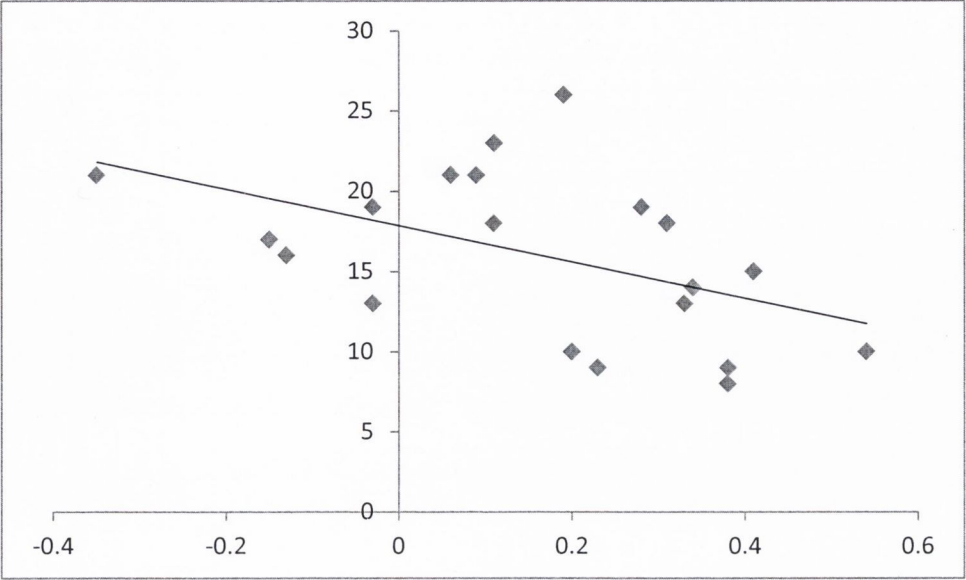


Figure F 3. Correlation between the right ACC and right accumbens functional connectivity (x-axis) and ADI-R communication scores (y-axis) in the ASD group.

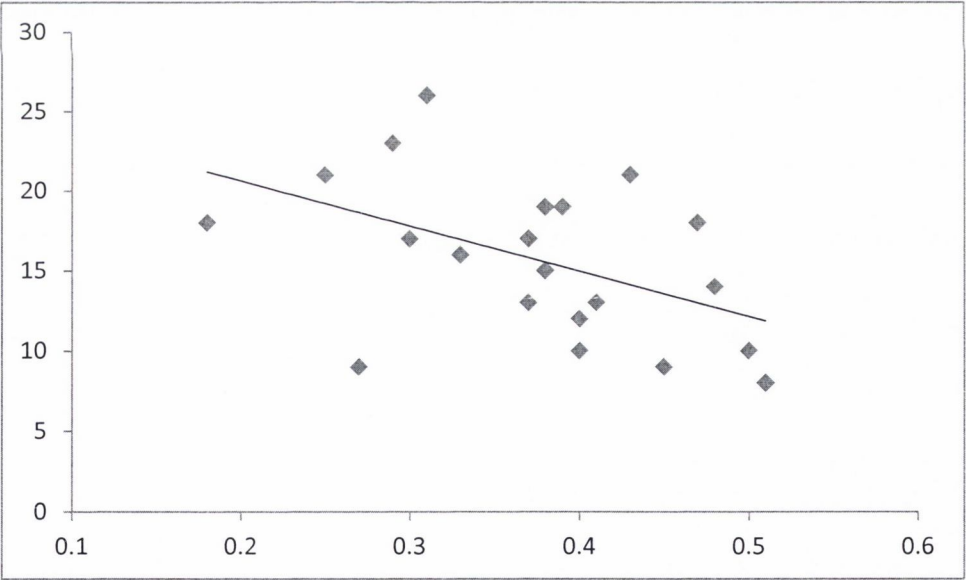


Figure F.4. Correlation between and FA in the right IFG (x-axis) and ADI-R communication score (y-axis) in the ASD group.

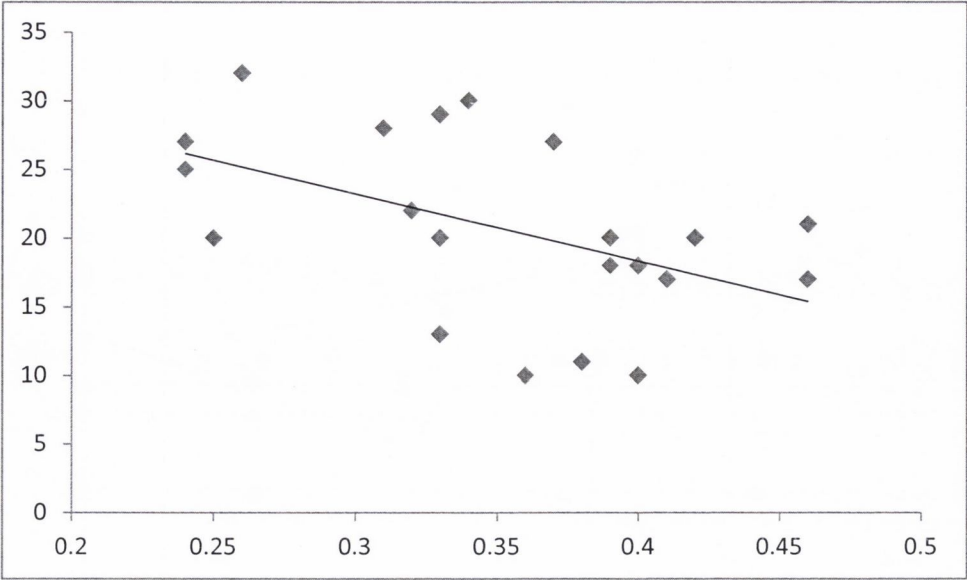


Figure F.5. Correlation between FA in the right inferior fronto-occipital fasciculus (x-axis) and ADI-R social interaction score (y-axis) in the ASD group.

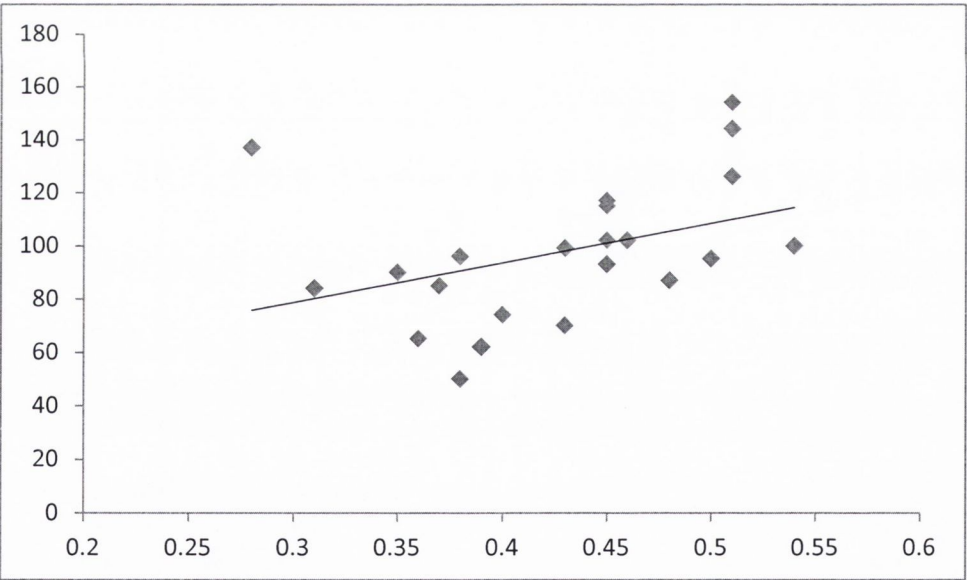


Figure F. 6. Correlation between FA in the left superior longitudinal fasciculus (precentral gyrus) and SRS in the ASD group.

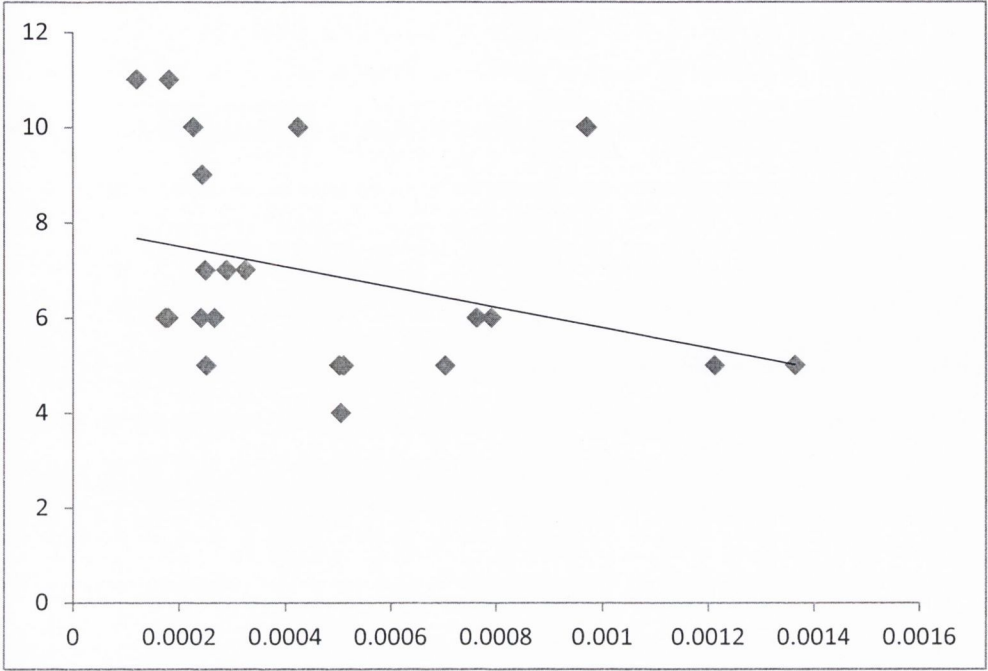


Figure F7. Correlation between spectral power (>.01; x-axis) and ADOS-G social score (y-axis) in the ASD group.

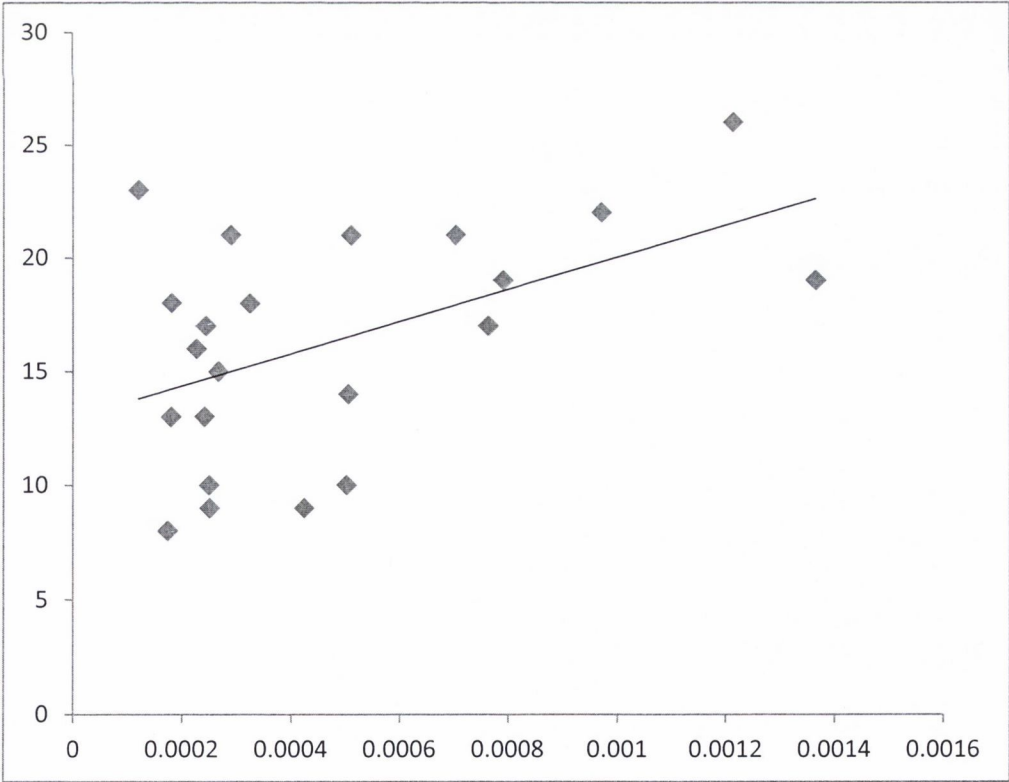


Figure F8. Correlation between spectral power (>.01; x-axis) and ADI-R communication score (y-axis) in the ASD group.

Appendix G: Joint ICA of Resting-state Data with Grey Matter Volume and White Matter Integrity.

The Spectral Power time-course for the default mode component in the group ICA analysis for which there was a significant group difference was combined with 1) grey matter volume (GM) and 2) white matter (WM) integrity (FA maps). For GM volume, smoothed modulated images from the VBM analysis were input along with the spectral power time course. For WM integrity, motion distortion corrected normalised FA maps were used. Multimodal canonical correlation analysis (mCCA) and Joint ICA (JICA) was performed using the Fusion ICA (FIT) toolbox (<http://mialab.mrn.org/software/fit/index.html>). Twenty-two components were selected for component estimation for grey matter and 21 components for white matter. This was the maximum number of components that could be selected given the number of subjects in the ASD group (N=22 and 21 respectively). ICASSO was run 100 times and components were excluded from further analysis if the Iq index was less than 0.9. FIT first performs dimension reduction on each dataset separately using singular value decomposition (SVD). MCCA is then used to relate the two datasets via correlation between mixing matrices which contain subject-specific loading parameters for each modality. Finally, JICA is performed on the concatenated maps from mCCA to maximise the joint independence for each component. Unfortunately the results of the WM, GM and spectral power decompositions were unreliable therefore the results of the analysis could not be interpreted. Examples of the WM-spectral power JICA analyses are shown in figure 1. In figure 2 an example has been taken from (Calhoun & Adalı, 2009).

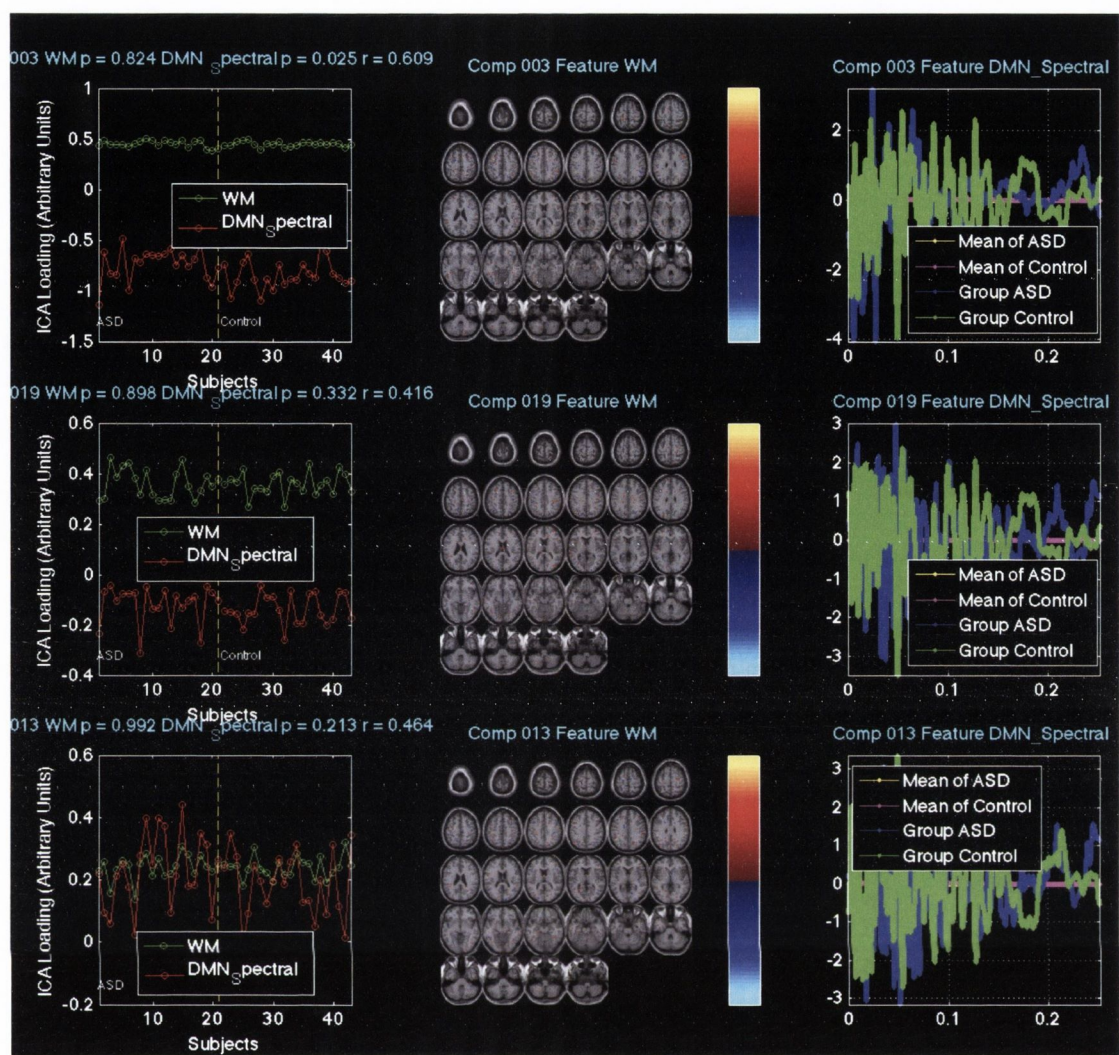


Figure G 1: Joint ICA analysis for white matter (WM) and spectral power in the posterior default mode network (DMN). The image shows the first three components, sorted in terms of group differences (e.g. for component 3 spectral power differences were significant between groups). The panel on the left hand side shows the magnitude of group differences for WM and the DMN. The centre panel shows the WM decomposition and the panel on the right hand side shows the spectral power decomposition for each group. As can be seen from the figure above the decomposition of WM and spectral power were not interpretable.

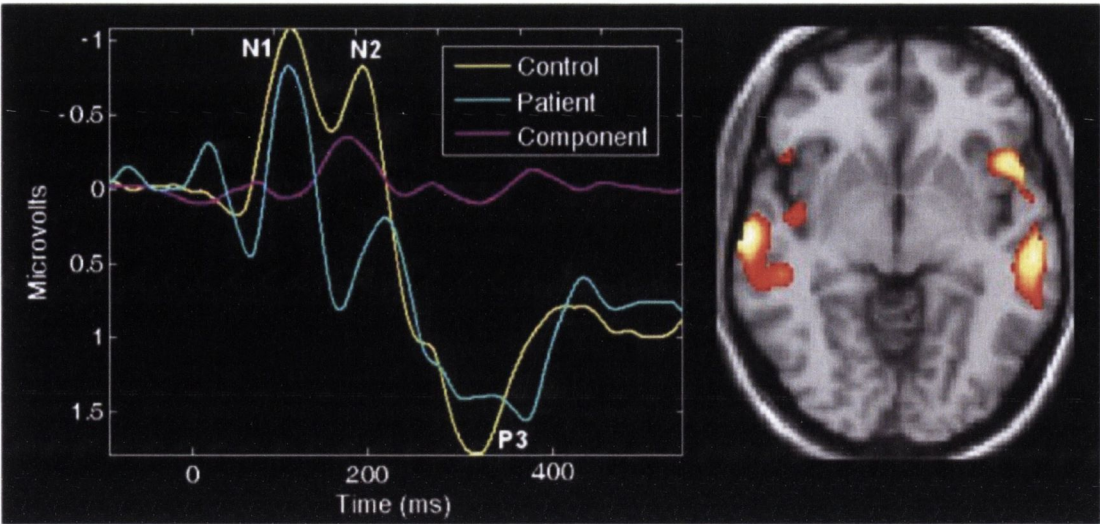


Figure G.2. Example image to illustrate utility of JICA from a combined EEG/fMRI study. This example shows how group differences in event related potentials (ERPs) can be related to fMRI data to localise ERP differences between patients and controls (Calhoun & Adalı, 2009).

Appendix H: Correlations between the ADI-R Social Interaction and Communication (SCD) and Restricted Interests and Repetitive Behaviours (RRB) and Neuroimaging Findings.

The ADI-R adopts the three-factor structure of the DSM-IV, i.e. deficits in social interaction, communication and restricted interests and repetitive behaviours.

However, the DSM-5 will use two dimensions – social and communicative deficits (SCD) and restricted interests and repetitive behaviours (RRB) - for ASD diagnostic criteria. A number of factor analytic studies have provided support for the two factor model (Boomsma et al., 2008; Frazier et al., 2008; Georgiades et al., 2012; Mandy et al., 2012). The aim of the current analysis was to use the two factor model of the ADI-R (Georgiades et al., 2012), to correlate symptoms with neuroimaging findings.

Total SCD and RRB scores were calculated for ASD participants using the 20 SCD and the six RRB items described by (Georgiades et al., 2012). Non-parametric correlations were carried out between ADI-R scores and functional or structural metrics (BOLD signal, connectivity values, TBSS results) in regions where there were significant group differences (as well as spectral power, where there was a significant group-by-age interaction). Table H.1 provides summary statistics for tests of normality of the distributions.

There were no significant correlations between BOLD response to social rewards and either SCD or RRB. Increased connectivity between the right middle frontal gyrus (MFG) and the right caudate was positively associated with RRB ($r=.573$; $p=.008$, figure

1), increased connectivity between the right paracingulate (Pcg) and the right accumbens was negatively associated with SCD ($r=-.511;p=.012$; figure 2) and increased connectivity between the left Pcg and the right accumbens was also negatively associated with SCD ($r=-.572$; $p=.008$; figure 3). Mean diffusivity in the right inferior longitudinal fasciculus (ILF) in the occipital cortex (MNI co-ordinates = 40 -65 - 40) was positively correlated with RRB in the ASD group ($r=.543$; $p=.009$; figure 4). There were no significant correlations between spectral power and RRB or SCD.

Table H.1 Normality tests for ADI SCD and RRB.

	Kolmogorov- Smirnov Statistic	Kolmogorov- Smirnov P-value	Skew	Kurtosis
ADI SCD	.117	.200	-.269	-.972
ADI RRB	.193	.032*	1.654	3.156

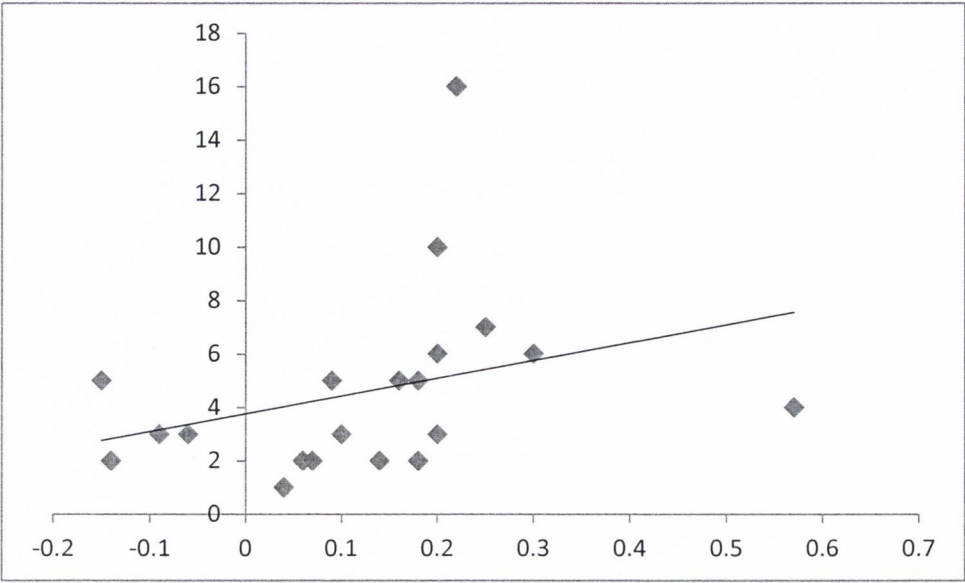


Figure H.1. Graph showing increased connectivity between the right MFG and right caudate (x-axis) is associated with increased RRB (y-axis) in the ASD group.

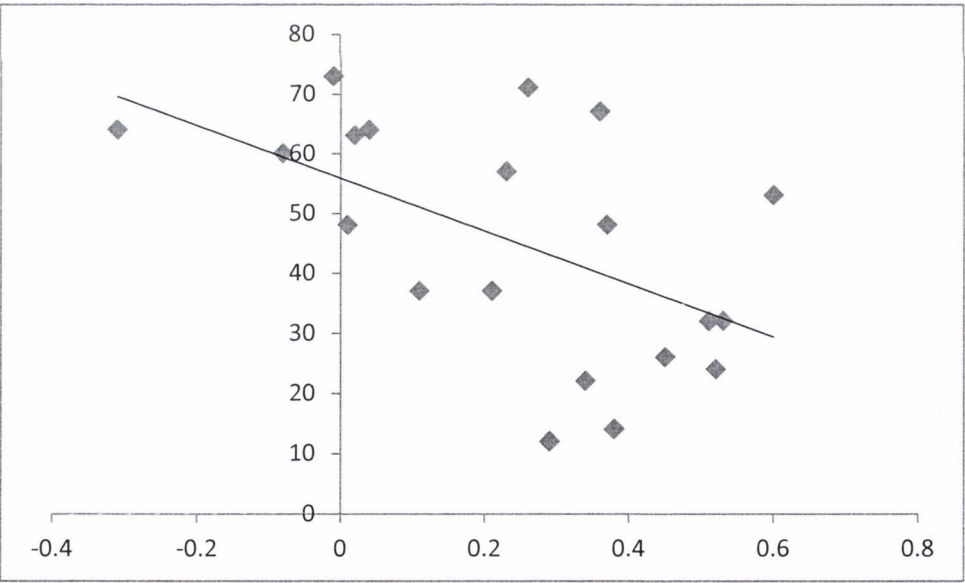


Figure H.2. Graph showing that increased connectivity between the right paracingulate and the right accumbens (x-axis) is associated with decreased SCD (y-axis) in the ASD group.

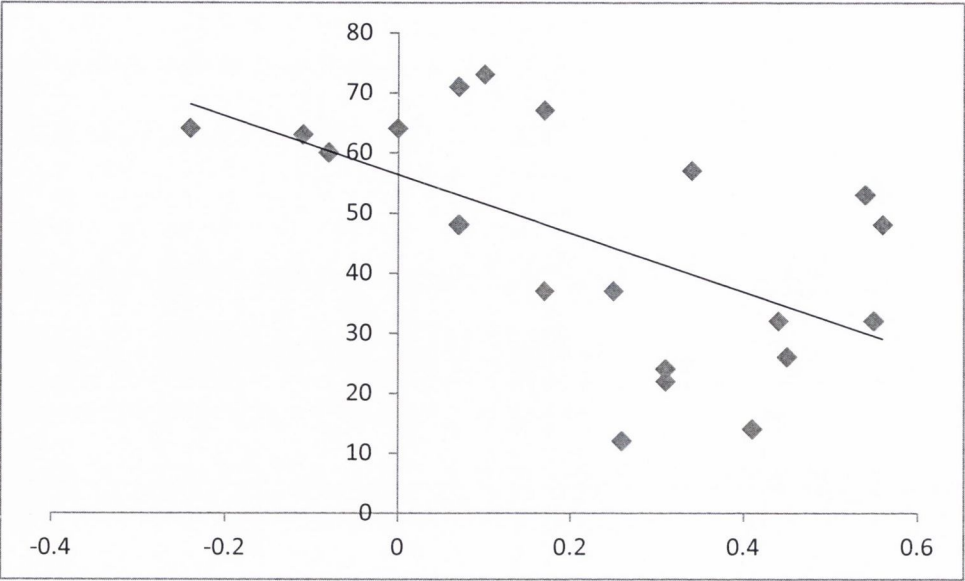


Figure H. 3. Graph showing that increased connectivity between the left paracingulate and the right accumbens (x-axis) is associated with decreased SCD (y-axis) in the ASD group.

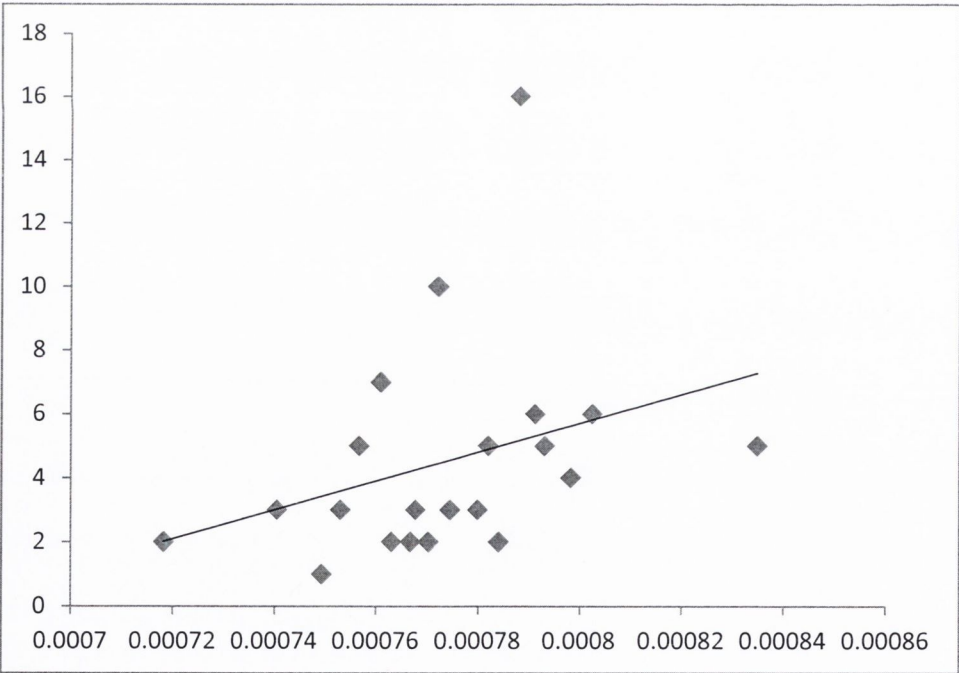


Figure H. 4. Graph showing that higher MD values in the right ILF (x-axis) are associated with increased RRB (y-axis) in the ASD group.

In summary, connectivity between the right middle frontal gyrus and the right caudate was associated with more impairment in terms of RRB; similar to previous results (see section 4.3.2.4). Increased connectivity between the left and right paracingulate was associated with less impairment in terms of SCD. This is similar to previous results but the previous findings indicated a significant correlation between the anterior cingulate, rather than the paracingulate, and communication. Unlike previous analyses there were no significant associations between FA and social or communicative impairments (see section 5.3.2.3), but MD in the right ILF was associated with RRB. Finally for spectral power there were no significant correlations with SCD or RRB; whereas previous findings suggested an association with social and communication behaviours (see section 5.3.3.3). This suggests that the factor structure of the behavioural measurement used for correlation analyses influences the results and hence the interpretation of neuroimaging findings.