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Limited somatosensory functional connectivity differences in youth with ASD, at rest

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Limited somatosensory functional connectivity differences in youth with ASD, at rest

by

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Abstract

Children and adolescents with autism spectrum disorder typically experience sensory sensitivities, involving over- and/or under-reactions to sensory stimuli. Tactile hyper-reactivity, in particular, is implicated in negative outcomes such as aversion to oral hygiene, dietary issues, and self-harm. Presently, there is no established overarching neurological basis for these sensitivities in autism. Understanding the underlying causes of these sensitivities may help guide pharmacological and behavioural interventions. Motivated by suggested linkages between over-connectivity measures and negative outcomes in ASD, this thesis used resting-state functional-MRI to examine somatosensory functional connectivity differences in youth with autism. Connectivity differences, arising in the somatosensory region, may represent a good marker of sensory sensitivities in ASD. Our findings show limited functional connectivity differences in ASD, and scarce changes in age by diagnosis interaction or autism symptom severity. This suggests that functional connectivity of the somatosensory network in youth with autism is not disrupted, at rest, compared to neurotypical controls.

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List of Symbols, Abbreviations, and Nomenclature

SYMBOL	DEFINITION
ABIDE	Autism Brain Imaging Data Exchange
ADHD	Attention Deficit Hyperactivity Disorder
ADOS	Autism Diagnostic Observation Schedule
ADI-R	Autism Diagnostic Interview-revised
ASD	Autism Spectrum Disorder
BOLD	Blood Oxygenation-Level Dependent
CSF	Cerebrospinal Fluid
dACC	dorsal Anterior Cingulate Cortex
DMN	Default Mode Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
EPI	Echo Planar Imaging
fMRI	functional Magnetic Resonance Imaging
FSIQ	Full Scale Intelligence Quotient
FWE	Family-Wise Error (correction)
FWHM	Full-Width Half-Maximum
GLM	General Linear Model
GM	Gray Matter
KKI	Kennedy Krieger Institute
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
NYU	New York University
PCA	Principal Component Analysis
PIQ	Performance Intelligence Quotient
RF	Radio Frequency
ROI	Region(s) of Interest
RRB(s)	Restrictive Repetitive Behaviour(s)
SI/SII	Primary, Secondary Somatosensory Cortex
SRS	Social Responsiveness Scale
SS	Sensory Sensitivities
TD	Typically Developing (controls)
UCLA	University California Los Angeles
UM	University of Michigan
VIQ	Verbal Intelligence Quotient
WM	White Matter

Overview of thesis structure

This thesis contains a preliminary study to identify robust differences of functional connectivity in the brain of youth with autism, compared to controls, which could then be followed up by more specific studies in sensory sensitivities. Chapter One contains the rationale behind the work presented here. It summarizes the collection of conditions classified as autism spectrum disorder (ASD), the sensory sensitivities presented prominently by those with ASD, diagnostic measures of ASD (as well as correlates of SS), functional magnetic resonance imaging (fMRI), and previous literature investigating brain differences in ASD using MRI. These sections suggest the use of fMRI to investigate associations between functional connectivity measures and diagnostic measures of ASD, compared to TD, and encouraged the work presented in this thesis. Following are the study hypotheses and the objectives of this research, wherein we sought to uncover functional connectivity differences in the brains of children and adolescents with ASD which may be related to sensory sensitivities, compared to typically developing (TD) controls, and how those connections change in strength with age. Chapter Two describes the methods used in this thesis. Chapter Three presents the findings of our study, which are then discussed in Chapter Four. Chapter Five closes the thesis with the limitations of this study, future directions, and concluding statements.

1.0 Background

1.1 Autism Spectrum Disorder

Autism Spectrum Disorder is a highly prevalent neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction as well as restricted, repetitive patterns of behaviours (RRBs), interests, or activities (American Psychiatric Association 2013). Persistent deficits in communication and interaction can include, but are not limited to, reduced social-emotional reciprocity, such as failure to engage in normal back-and-forth communication, inability to engage in verbal communications, abnormalities in nonverbal communication such as lack of understanding of gestures or facial expressions, aversions to eye contact, as well as problems in developing and maintaining interpersonal relationships. RRBs include stereotyped or repetitive motor movements, such as lining up toys, abnormal speech (e.g., echolalia), insistence on sameness (e.g., distress at the change of a routine), fixated interests including preoccupation with unusual objects, and the focus of this thesis: hyper- or hypo-reactivity to sensory input (e.g., indifference to painful stimuli, or excessive response to tactile sensations). ASD is a lifelong syndrome, diagnosed as early as two years of age (CDC 2014), though some symptoms may not fully manifest until later in life, or may be masked by learned strategies (American Psychiatric Association 2013). ASD has a global prevalence of around 1% (American Psychiatric Association 2013).

Manifestation of the disorder varies greatly: according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013) ASD now encompasses many previously separately classified disorders: early infantile autism, childhood autism, Kanner's autism, high-functioning autism, atypical autism, pervasive developmental disorder not otherwise specified, childhood disintegrative disorder, and Asperger's disorder. Hence, the use of the term *spectrum*.

While roughly only 15% of cases of ASD can be attributed to known genetic markers/mutations (American Psychiatric Association 2013), it is one of the most familial psychiatric disorders, with a heritability around 80% (Lichtenstein et al. 2010; Geschwind 2011). Other risk factors include parental age, low birth weight, and fetal exposure to valproate (American Psychiatric Association 2013). Co-morbidities of ASD may include attention-deficit/hyperactivity disorder (ADHD), developmental coordination disorder, anxiety, depressive or bipolar disorders, tics or Tourette's disorder, self-injury, intellectual impairment and structural language disorder (American Psychiatric Association 2013). ASD is also highly heterogeneous in both its presentation and genetic linkages, and may be better considered a collection of rare diseases which present similarly (Lenroot & Yeung 2013; Lai et al. 2016). While there appear to be many causes of ASD, it has been argued that what is relevant to ASD is the convergence of these many factors on the development of specific aspects of the social brain networks (Kaiser et al. 2010).

1.2 Sensory Sensitivities/Over-responsivities, Social Responsiveness and Restrictive Repetitive Behaviours

The latest revision of the DSM-5 (2013) reclassified the criteria of restrictive repetitive patterns of behaviours and interests to include sensory sensitivities (SS), due to their hallmark presence in the majority of individuals, particularly youth, with ASD (Ben-Sasson et al. 2014; Stein et al. 2011; Reynolds et al. 2011). Previously, SS may have been classified as 'sensory dysfunction' or 'sensory difference' (Bauman & Kemper 1994). SS are hyper- or hypo-reactivities to sensory input or unusual interest in sensory aspects of the environment (seeking). Hyper-responsivitity is the overreaction to stimuli, such as outbursts after physical contact. Hypo-responsivities present as under-response, or apparent indifference, to stimuli such as pain and extreme temperature. Finally, unusual seeking interests often include, but are not limited to, excessive smelling or touching of objects, and visual fascinations with lights or movement. SS in the tactile modality may contribute most severely to the negative aspects on the daily lives of those with ASD, as compared to visual and auditory (Joosten & Bundy 2010; Shelley O'Donnell, Jean Deitz, Deborah Kartin, Theresa Nalty 2012; Brock et al. 2012). Tactile sensation, specifically, is among the most often reported as aversive for children with autism (Tomchek & Dunn 2007). Varying levels of these SS however, in single or multiple domains, can be present in the same person, adding to the highly heterogeneous presentation of ASD. Indeed, a recent meta-analysis has shown no pattern in the modalities (auditory, tactile, gustatory, visual, et c.) of SS present in persons with ASD (Ben-Sasson et al. 2009), but did show a correlation between the severity of sensitivities and the

severity of ASD. This suggests that although the extent of SS presented in ASD is linked to autism severity, the types of SS are not, underscoring how little is known about their role in ASD pathophysiology.

Though present in adults with ASD, and the typical population to some extent (Kauer et al. 2015), SS appear to be most prominent during late childhood in ASD (Ben-Sasson et al. 2009; Kern et al. 2006), decreasing in severity and prevalence into adulthood. It is unclear whether this is due to neurodevelopmental changes or learned coping mechanisms. The vast neurodevelopmental changes occurring in adolescence, a period of rapid brain development, however, suggests that relationships between brain function and sensory processing in ASD may change with brain development.

Measures of SS, such as the Sensory Profile have been developed to help quantify the impact of SS in ASD and typical populations (Dunn & Westman 1996). Sensory sensitivities have also been correlated to symptom severity more generally. Specifically, RRBs have been positively correlated with sensory sensitivities in autism, and may be particularly correlated with hyper-responsiveness rather than hypo-responsiveness (Chen et al. 2009). Social Responsiveness Scale (SRS) scores, a questionnaire developed to quantitatively measure traits of autism across the spectrum (Constantino et al. 2003), have also been positively correlated with SS (Gotts et al. 2012). Even scores on the standardized Autism Diagnostic Observation Schedule (ADOS), primarily used

for diagnosis of ASD, have been shown to correlate well to sensory measures (Wiggins et al. 2009), further suggesting that SS are positively correlated with autism severity. Thus, when direct SS measures are not present, associations between other ASD diagnostic criteria might and typical connectivity may be linked to SS.

One way of examining the underlying roots of these SS differences is through neuroimaging, where various physiological measures of the brain can be captured. A few hypotheses to help explain SS in ASD have already been tested using neuroimaging techniques. That sensory over-responsivity may be due to heightened (sensory) stimuli responses in the primary sensory or limbic/emotional regions has been recently supported (Green et al. 2013; Green et al. 2015). Relatedly, reduced habituation to sensory responses including auditory (Lawson et al. 2015), tactile (Puts et al. 2014), and audiovisual (Turi et al. 2016) inputs, in ASD, has also been proposed. Other work finding underconnectivity, at rest, in ASD between areas related to speech processing (the posterior superior temporal sulcus) and emotional centers (the amygdala and orbitofrontal cortex) supports the social motivation theory of ASD, predicting impaired function of emotional systems (Abrams et al. 2013), encouraging further investigation towards sensory-limbic functional connections. The level of underconnectivity between these regions also predicted severity of communicative deficits in ASD, which may indicate similar correlations in other sensory modalities (i.e., tactile) as well.

As children with ASD demonstrate excessive reliance on proprioceptive, as opposed to visual or motor tasks, and the extent of this reliance correlates with social impairments in these children (Haswell et al. 2009), in the present study we decided to focus on the resting somatosensory network as it relates to the tactile modality. Due to the negative effects of SS on quality of life, most obvious from tactile over-responsivity, we believe that the investigation of underlying neurological associations between diagnoses and connectivity in ASD is of particular priority.

1.3 The Somatosensory Network

Located along the postcentral gyrus, in the parietal lobe of the brain, (Figure 1.1), the somatosensory network can be subdivided into primary (SI) and secondary (SII) somatosensory regions (Brenner et al. 1978; Hari & Kaukoranta 1985).

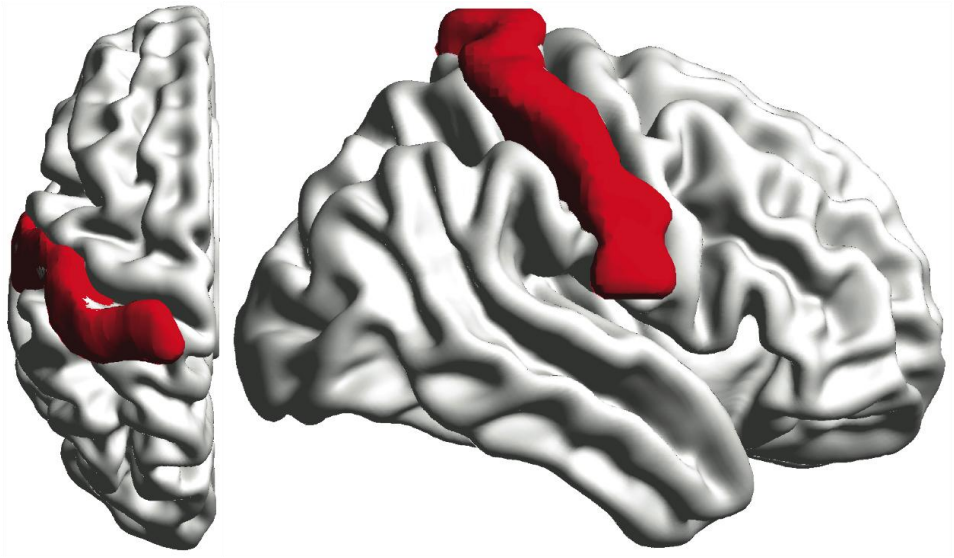

Figure 1. 1: The postcentral gyrus, involved in processing somatosensory input. The somatosensory cortex is the main sensory receptive area for the sense of touch in humans. Tactile representation is arranged from the toe and legs at the most dorso-medial point of the postcentral gyrus to the mouth head and face along the lateral stretch. This mapping is often represented by a cortical homunculus, also showing the relative size of the sensational brain area – the hands mouth and tongue being more heavily represented due to importance of fine sensory inputs.

SI is labeled in the Brodmann's atlas as areas 1, 2, and 3. Brodmann's area 3, in particular, located most anterior, is highly connected to the thalamus via thalamocortical projections - through which almost all sensory and motor information is relayed in the brain - and is heavily associated in proprioceptive functions (Jamali & Ross 2012). SII is located in the parietal operculum on the ceiling of the lateral sulcus, that is, in the Sylvian fissure at the postcentral gyrus (Eickhoff et al. 2006). SII is involved in light touch (from wide areas of the body

surface), visceral sensation, and tactile attention (Disbrow et al. 2000). SII has strong connections to SI, the insular cortex, amygdala, and hippocampus (Benarroch 2006).

1.4 Magnetic Resonance Imaging

Neuroimaging is a powerful, non-invasive, way of investigating neurodevelopmental disorders, by examining brain anatomy and physiology, correlates of brain activity, and connection patterns of the brain.

Nuclear magnetic resonance (NMR), first described by Isidor Rabi in the 1930s (Thomas et al. 2005), became relevant to medicine in 1973 when Paul Lauterbur was the first to create an NMR image (Lauterbur 1973). NMR was later renamed magnetic resonance imaging (MRI), due to the negative connotations behind the word ‘nuclear’. Lauterbur, jointly with Sir Peter Mansfield, later received the Nobel Prize in Physiology or Medicine 2003 “for their discoveries concerning magnetic resonance imaging” (Nobelprize.org. 2014).

The underlying measurement in MR imaging is the signal produced by atoms with unpaired protons in a magnetic field. The most abundant of these in the human body is hydrogen (protons) in water molecules, though, any element with unpaired protons can be imaged, including carbon-13, flourine-19, oxygen-17, and sodium. Without an external magnetic field, these unpaired protons spin about their 3-dimensional axes in random orientation, and the summation of their magnetic dipole vectors results in no net magnetization (Pooley 2005). When

placed in an external magnetic field (denoted B_0), protons align in discrete energy states, depending on their level of alignment within that field, and a net magnetic dipole vector (M_0) is produced. In real-world measurements, M_0 arises from just a small fraction of protons, on the order of handfuls of protons per million hydrogen nuclei (Hendrick 1994), around 10 protons per million at a common field strength of 3T. But, due to the vast amount of water, and therefore protons, in the human body; even a cubic centimeter can have around 10^{19} protons aligned with B_0.

To produce a measurable signal, an object is placed in a static magnetic field, typically produced by a powerful electromagnet, and a radio frequency (RF) pulse is applied to excite the protons in the field and disturb their precession – how they spin in alignment with B_0. This disturbance of precession moves the alignment of the protons away from the z-axis (the direction of B_0), also called the longitudinal plane. This shifts M_0 into the transverse (x-y) plane of 3-dimensional space, where signal can be detected via receiver coils, evaluated, and reconstructed into an MR image (Pooley 2005). Disruption of M_0 to the transverse plane is done most efficiently if the RF pulse is performed at hydrogen's (or the imaging element of interest's) resonance frequency. Resonance frequency is dependent on the strength of B_0, commonly referred to as the Larmor frequency:

$$\omega = \gamma B_0$$

where □ is the gyromagnetic ratio (□$_{Hydrogen}$ = 42.58 MHz/T). The resulting motion of magnetization, M, in the rotational transverse plane, can be described as a function of time via the Bloch equation:

$$\frac{\delta \vec{M}}{\delta t} = \gamma \vec{M} x \vec{B} - (M_x \hat{x} + M_y \hat{y})/T_2 - (M_z - M_0)/T_1 \hat{Z}$$

Where T1 characterizes signal recovery into the longitudinal plane (z-axis), and T2 is the signal decay in the transverse (x-y) plane. T1 is defined as the relaxation time of M_0 to reach 67% of its longitudinal vector. T2 is defined as the time at which M_0 in the transverse plane has decayed to 37% of its maximum transverse value. T1 signal is always greater than or equal to T2. T1 imaging is particularly sensitive to lipids and large proteins and therefore used largely for anatomical imaging. T2 imaging is more sensitive to higher water content compounds such as cerebral spinal fluid (CSF) and blood (Bushberg 2002). Field inhomogeneities resulting mainly from intrinsic defects in B_0 due to mechanical limitations, or local modifiers such as susceptibility-induced field distortions from tissues or other materials in the field (Chavhan et al. 2009), result in another physiologically relevant signal: T2*,which is the root signal acquired in fMRI research.

1.5 Functional MRI (fMRI)

Functional MRI is a unique sub-type of MR imaging. Discovered and pioneered by Ogawa and Kwong, fMRI measures the blood oxygenation level-dependent (BOLD) signal as a correlate of neural activity (Ogawa et al. 1990; Kwong et al. 1992). The BOLD signal arises through the magnetic susceptibility differences between diamagnetic oxyhemoglobin and paramagnetic deoxyhemoglobin. Greater field inhomogeneities are produced by deoxyhemoglobin, lowering its T2*, in comparison to oxyhemoglobin. Thus, oxyhemoglobin causes slower decay in the transverse-plane, resulting in higher signal.

Localized neural activity leads to stimulation of vascular blood supply, and an overcompensation of supply of oxygen-rich blood to the region. This over-response produces an increase in oxygenated hemoglobin relative to deoxygenated, resulting in increased MR signal. These localized changes in blood magnetic susceptibility can be quantified over time, producing a timecourse for discrete volumetric spatial regions in the brain, typically on the order of cubic millimeters.

1.6 Resting State Functional Connectivity

When the BOLD signal is temporally correlated in spatially remote regions of the brain, those regions are considered *functionally connected* (Friston 1994). A commonly employed technique, called seed-to-voxel analysis, is to construct functional connectivity maps, which describe the strength of signal correlation

between a given region and other distance-separated brain regions. This is done by extracting the averaged BOLD signal timecourse from an investigator-chosen region of interest (ROI, the *seed region*) and determining the temporal correlation between the extracted signal and the timecourses from other discrete measurable unit volumes in the brain (voxels; 'volumetric pixels') (Fox & Raichle 2007). This method is useful when (an) *a priori* seed region or regions are implicated for study, but connected locations are unknown or unclear. When discrete regions of the brain correlate strongly together, that is, have similar temporal BOLD signals, a *functional network* can be described.

Though studies of functional connectivity often employ task paradigms to actively modulate the BOLD signal, physiologically relevant measures can also be extracted from intrinsic, resting-state, brain activity. These measures were discovered through the observation of correlated low-frequency (~0.01-0.1Hz) spontaneous BOLD signal fluctuations, during an fMRI scan where no particular task was performed, leading to the discovery of intrinsically functionally connected regions, named *resting state networks* (Biswal et al. 1995). Resting state networks can be reliably identified across the population, and can resemble patterns of co-activation during specific cognitive tasks (Shehzad et al. 2009; Long et al. 2014).

Resting state studies are particularly useful for large-scale analysis, since they allow for the aggregation of datasets from multiple sites and trials, and sidestep

the challenges of task-based fMRI studies, particularly where tasks may be difficult for test populations to complete inside of the MRI (Menon 2011). Pooling of rs-fMRI data has been encouraged as a viable approach to increasing sample sizes, despite acquisition protocol variances (Biswal et al. 2010).

1.7 Functional Connectivity Differences in Autism

MRI has been widely used to investigate brain differences in ASD (Jou et al. 2009; Hardan et al. 2008; Philip et al. 2012; Dichter 2012; Cerliani et al. 2015; Just et al. 2004). The general underconnectivity theory of autism, likely the first theory on altered functional connectivity in ASD was proposed by Just et al. (2004) after finding decreased functional connectivity of language areas (Wernicke's, Broca's) with the rest of the brain during verbal sentence processing compared to TD controls. Since then, multiple groups have supported this idea, showing distributed decreased connectivity in the brain (Cherkassky et al. 2006; Müller et al. 2011; Mostofsky et al. 2009; Anderson et al. 2011; Nair et al. 2013; A. J. Khan et al. 2015). This theory is not without controversy, however. For example, multiple studies have indicated hyperconnectivity in ASD, and even correlated the degree of hyperconnectivity to measures of social deficits in ASD (Supekar et al. 2013; Di Martino et al. 2014; Hernandez et al. 2014; Cerliani et al. 2015; Padmanabhan et al. 2013). Further, some recent studies suggest a mixed scenario of functional connectivity in ASD, with both hyper- and hypo-connectivity, as well as potentially no differences (Barttfeld et al. 2012a; Hahamy et al. 2015), or differences attributable to age (Uddin et al. 2013). To date, across the whole

brain, under-connectivity is more commonly described in ASD (Philip et al. 2012; Di Martino et al. 2014; Lombardo et al. 2010), including in resting-state studies (Weng et al. 2010), rather than hyperconnectivity. Literature reports on functional connectivity of the primary sensorimotor cortices, however, seem to more consistently show hyperconnectivity in ASD (Cerliani et al. 2015; Di Martino et al. 2014; Green et al. 2013; Duerden et al. 2014; A. J. Khan et al. 2015; Nebel, Eloyan, et al. 2014).

1.8 Differences in somatosensory functional connectivity and structure in ASD

A recent multi-site fMRI investigation identified increased functional connection strength between the primary sensorimotor and subcortical regions in individuals with ASD relative to control subjects, suggesting that hyperconnectivity of the sensory cortices may contribute to sensory sensitivities in ASD (Di Martino et al. 2014). This analysis, however, included participants aged 7-64 years old, and didn't provide targeted findings on connectivity differences specifically within children and adolescents with ASD, nor did it separate the somatosensory network from the bundled sensorimotor network (motor and somatosensory networks together). Another set of examinations using resting-state data found abnormal functional connectivity in the precentral gyrus, part of the primary motor control network, to be positively correlated differences with motor impairments (Nebel, Joel, et al. 2014; Nebel, Eloyan, et al. 2014). Positive correlational findings as these suggest that symptoms may be related to differences in connectivity of their associated brain regions. Extending this to somatosensory

function, it is reasonable that sensory sensitivities may correlate with functional differences in primary sensory areas: the somatosensory network. Lacking direct data on sensory sensitivities, we elected to examine associations between diagnostic measures and connectivity, instead. As the post-central and pre-central gyri are often bundled together as the sensorimotor network, it may be reasonable to predict over-connectivity measures in the motor network in ASD to also be similarly observed in the somatosensory division.

Decreased functional connectivity measures have been observed, using magnetoencephelography (MEG), between SI and SII, during vibrotactile finger stimulation in children and adolescents aged 8-18 with ASD (S. Khan et al. 2015). In addition to hyperconnectivity within the precentral and postcentral gyri, Hahamy et al. also found idiosyncratic interhemispheric functional connectivity within adult ASD participants, as compared to age-matched controls (Hahamy et al. 2015).

A few studies have also pointed to subcortical and cerebellar differences in sensorimotor connectivity in ASD (Cerliani et al. 2015; Di Martino et al. 2014; Mostofsky et al. 2009; Padmanabhan et al. 2013). Overconnectivity between primary somatosensory cortices and the thalamus as well as the striatum (Di Martino et al. 2014; Cerliani et al. 2015), further motivates investigation of potential hyperconnectivity measures of the limbic network in ASD. While not widely studied, there is evidence of between the cerebellum and sensorimotor

regions, which may also be important in the etiology of ASD (Mostofsky et al. 2009).

Structural measures may also be sensitive to differences in this region. For example, increased measures of self-injurious behaviour have been linked with alterations in the white matter structure and function of the somatosensory system in children with ASD (Duerden et al. 2014). At least one study has indicated higher grey matter (GM) concentration (density) in the post central gyrus, in males with ASD (mean age 12.4 years), compared to neurotypical controls (Foster et al. 2015). This difference in GM was most pronounced in younger boys (age 8), and steadily decreased with age into late adolescence (18 years), while TD level stayed steady.

1.9 Functional connectivity changes with age in ASD and TD

Rs-fMRI studies have identified reorganization of resting-state networks in normal brain aging from childhood to senescence (Wang et al. 2012). Changes in functional connectivity strengths and directionality (increasing or decreasing with age) varied across the brain and can be described using both linear and quadratic models. Findings suggest that functional connectivity across the whole brain tends to decrease in short-range (within) resting state networks, and increase in long-range (between) networks with age (Supekar et al. 2009). Within the sensorimotor systems, Betzel et al. showed functional connectivity in hand somato-motor, visual, mouth somato-motor, and auditory subdivisions to

decrease linearly with age in the normal brain while increasing linearly in connectivity to the limbic network (Betzel et al. 2014).

Targeted to the somatosensory cortex, Tomasi & Volkow supported this reorganization of resting-state networks with age by showing increasing long-range somatosensory cortex functional measures in a similar age group (20-senescence) in neurotypical subjects (Tomasi & Volkow 2012). Within network measures of functional connectivity of the somatosensory network of TD individuals, both the left and right postcentral gyri exhibit decreasing functional connectivity strength to the left Rolandic operculum, left insula, and left Heschl's gyrus (transverse temporal gyrus), with aging across the lifespan (ages 8-49 years) (Wang et al. 2012). Functional connectivity within association systems (default, frontal-parietal control, salience, dorsal attention, ventral attention, cingulo-opercular control) also decreases with age across the TD lifespan, though at more pronounced rates than other systems (ages 20-90 years) (Chan et al. 2014). Although the connectivity strength of the sensorimotor network was different in ASD, Anderson et al found no age-related decreases in the sensorimotor network, compared to TD, with age, but had few subjects below the age of 15 (Anderson et al. 2011).

In ASD, it has been found that functional connectivity strength of the default mode network (DMN) decreases with age, while increasing in TD individuals (10-19 years) (Wiggins et al. 2011). More specifically, the DMN appears to be

hyperconnected in children with ASD (Nomi & Uddin 2015), and then 'levels-out' with age until no group functional connectivity differences are seen after age 18 or in adulthood.

The salience network, involved in the process of discerning noticeable events from extraneous, particularly within the striatum, in ASD also been shown to change differently with age than in neurotypical controls while at rest (Padmanabhan et al. 2013). While both groups showed cortico-striatal decreases with age (8-36 years), those with ASD showed increased striatal-parietal cortex connectivity measures, and decreasing connectivity between striatal-prefrontal cortex compared to TD. Padmanabhan et al. posited that these differences might underlie differences in cognitive and social reward processing (in ASD). Due to its role in discerning notable events, examination of connectivity measures between the salience and somatosensory networks may also provide useful insight into SS in youth with ASD.

Additionally, resting state networks in adolescents with ASD have also been associated with specific symptoms of ASD (including poorer verbal/non-verbal communication, and increases in RRB) and these networks can change in functional connectivity strength moving into adulthood (Lombardo et al. 2010; Bos et al. 2014).

How the somatosensory network changes with age in ASD is not fully understood, with a paucity of data focusing on the age range of youth most at risk to experience negative effects of SS. The ‘leveling out’ effects in other networks, combined with the apparent decrease in SS in persons with ASD as they grow into adulthood, seems to suggest the presence of ASD functional overconnectivity in the somatosensory network which may then decrease with age.

1.10 Hypothesis

Despite the high prevalence of SS in children and adolescents with ASD, the neurophysiological basis of these SS remains unclear. Functional neuroimaging has been shown to be a useful method of examining brain properties in ASD, which may lead to improved treatments and pharmacological approaches.

We hypothesized that resting-state functional connectivity measures in youth aged 8-15 years with ASD would exhibit bilateral over-connectivity between eight functionally distinct divisions of the somatosensory cortices, and between these somatosensory divisions and the whole brain, relative to TD controls. Given previous connectivity differences described in ASD, we predicted to find targeted changes in the limbic, cerebellar, and salience regions of interest. In line with previous literature indicating decreases of severity of SS with age, we hypothesized that this functional over-connectivity in ASD would decrease with age, compared to age-matched controls. Further, we predicted correlations

between functional connectivity measures and symptom measures of ASD, which have previously been associated with SS and may act as a marker of SS.

1.11 Objectives

While many studies have used rs-fMRI to investigate functional connectivity differences in ASD, along with age effects, further investigation of differences in the somatosensory network in ASD, specifically across childhood and early development, is necessary in describing the differences and development of functional connectivity potentially related to SS in ASD.

The objective of this thesis was to compare functional connectivity from regions of interest in the somatosensory cortex to the whole brain, between ASD and TD groups. Effects of age and age-diagnosis interaction effects were also analyzed. Finally, we examined correlations between connectivity and ASD symptoms, as SS tend to be more pronounced in persons with greater ASD symptoms.

2.0 Methods

2.1 Overview

Functional connectivity analyses were performed to determine if there were group differences (ASD vs. TD), or an interaction between diagnosis and age on functional connectivity between eight postcentral gyrus ROIs and the rest of the brain. Follow-up analyses were used to evaluate the relationship between severity of ASD symptoms and functional connectivity. Measures of sensory sensitivity are not available in the ABIDE dataset (which was used for all analyses), so global symptom measures were used instead, as these have been shown to correlate with sensory difficulties (Ben-Sasson et al. 2009; Robertson & Simmons 2013; Glod et al. 2015; Leekam et al. 2007).

2.2 Seed and Target Regions of Interest

Eight ROIs along the somatosensory strip bilaterally, defined through a connectivity-based parcellation (Shen et al. 2013)(Figure 2.1), were chosen as seed regions for this study. In primary analyses, GM of the whole brain was searched, with no *a priori* target regions. We also chose a set of target regions in which to perform small volume correction, effectively limiting the voxels in a search space, based on previous literature showing distributed brain differences in connectivity in ASD (Cerliani et al. 2015; Di Martino et al. 2014; Mostofsky et al. 2009; Padmanabhan et al. 2013) (Figure 2.2). Targeted regions included the anatomical cerebellum, and limbic system, as well as the functionally defined

salience network. Small volume correction is appropriate when there is an implicated area of interest, as it lowers both the risk of a false positive finding outside hypothesized regions as well as lowering the risk of false negatives within the ROI. Limbic and cerebellar masks were defined anatomically from the Wake Forest University WFU_PickAtlas toolbox (http://www.nitrc.org/projects/wfu_pickatlas/). The salience network mask was generated using a resting-state connectivity-based network parcellation (Shirer et al. 2011).

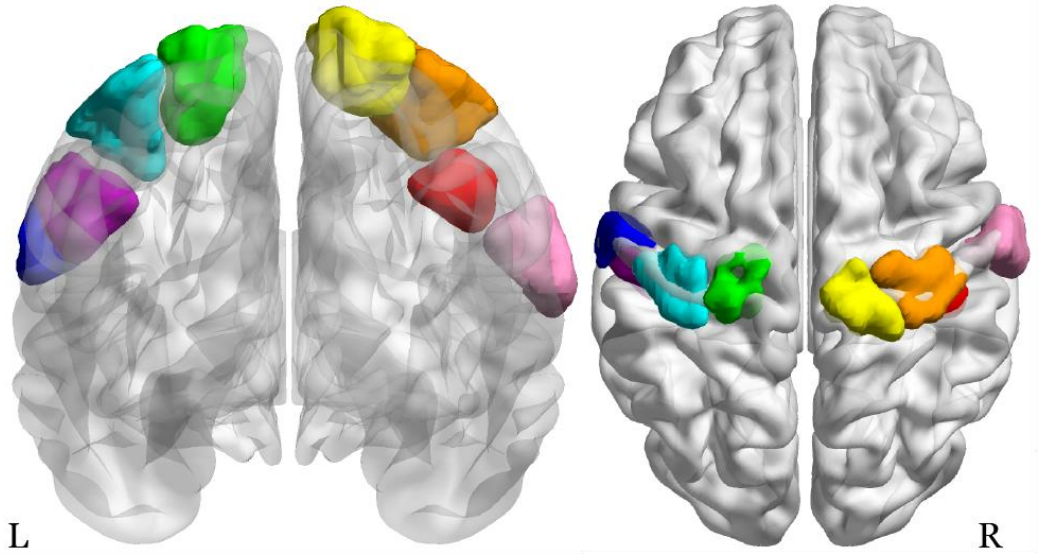

Figure 2. 1: Somatosensory regions of interest in the postcentral gyrus. Regions were parcellated based on functional connectivity patterns (Shen et al. 2013) rather than following anatomical or cytological borders. Left to right: (blue) LBA 4.1, (purple) LBA1.3, (teal) LBA1.2, (green) LBA1.1, (yellow) RBA1.1, (orange) RBA1.2, (red) RBA1.3, and (pink) RBA1.4.

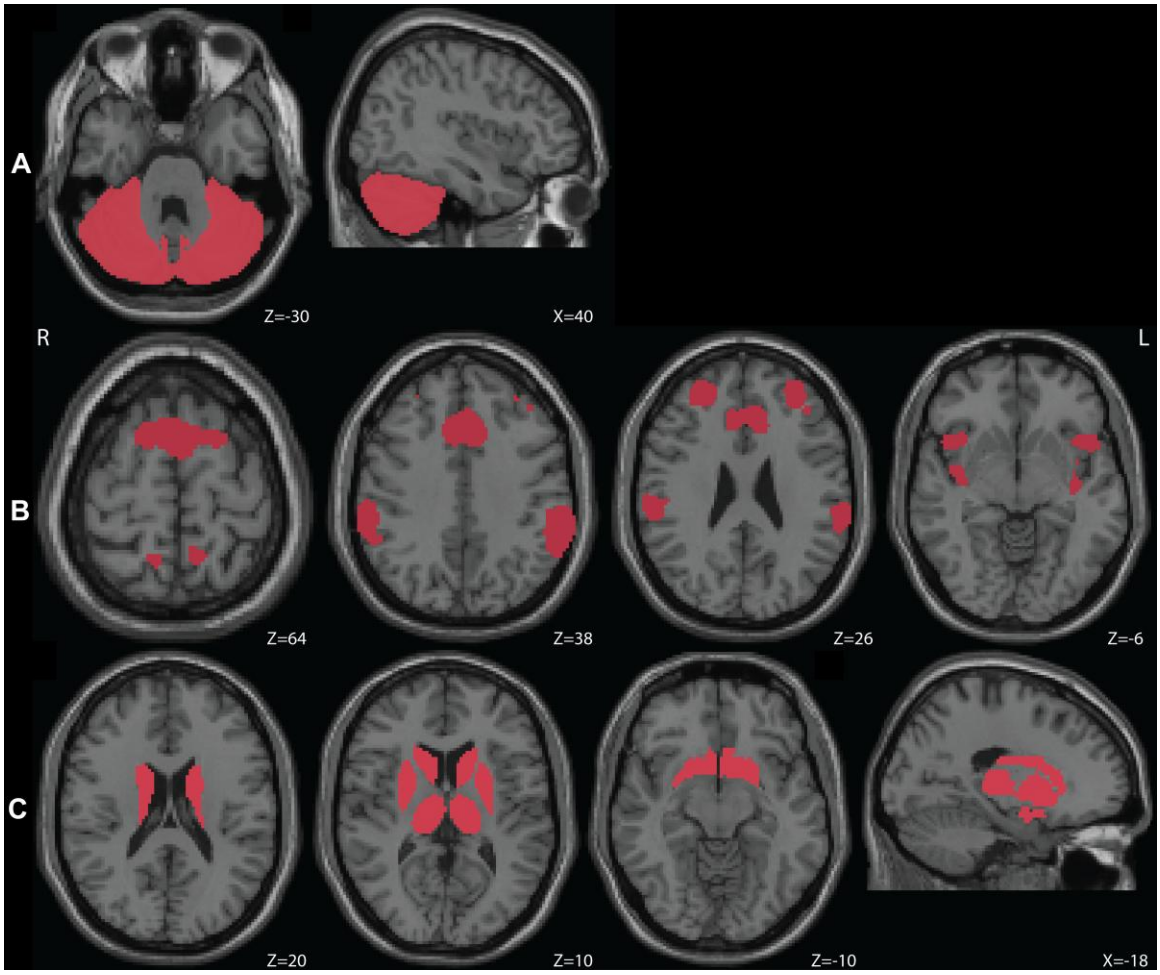

Figure 2. 2: Regions of Interest for small volume correction: A) anatomically defined cerebellum, B) the salience network, and C) the limbic network, both as defined by Shirer et al (2011).

2.3 Data

Participants and Collection Sites

Data were downloaded from the Autism Brain Imaging Data Exchange (ABIDE) database (Di Martino et al. 2014). The ABIDE database was made public in August 2012, and can be accessed at http://fcon_1000.projects.nitrc.org/ini/abide/. The database contains phenotypic and imaging data for (at the time of writing) 539 individuals with ASD and 573 TD

controls. Site-specific recruitment details, scanning parameters, and ethics approval documentation, are available at the ABIDE website listed above. All sites received ethical study approval from their local board. All data were fully anonymized prior to access for this study.

Data from all sites that included more than 40 subjects aged 8-15 years were included in this study. Included imaging sites were: New York University (NYU) (60/52, TD/ASD), the Kennedy Krieger Institute (KKI) (33/22), Yale (24/19), the University of Michigan (UM) (49/58), and the University of California Los Angeles (UCLA) (44/55). Children and adolescents aged 8-15 (inclusive) were selected, for a total of 416 potential participants (ASD=206, TD=210), giving a potential sensitivity to detect a mid-to-small effect size of f=0.177 (α=0.05, Power=0.95).

Neuroimaging Data

Anatomical and resting-state functional scans were available for all subjects. Scanning parameters, including MRI scanner, TE and TR, varied between sites and are detailed in Suppl. Table 1. Anatomical (T1) scan parameters ranged from TR=250-2530 ms, TE=1.73-5.7 ms, FOV=250-256 mm, and resolution of 1.0-1.7mm^3. Functional (T2*) scan parameters ranged from TR=2000-3000 ms, TE = 15-30 ms, 120-300 functional volumes, FOV=192-256mm, resolution of 28.8-46.2mm^3, and scan duration t=6:00-10:00 min. All sites used echo planar imaging (EPI) acquisition sequences, except UM which employed a reverse spiral acquisition sequence for functional scanning.

Phenotypic Data

Phenotypic information available for all sites included: age at time of scan, IQ, sex, diagnosis (including confirmation of ASD via the ADOS and/or the Autism Diagnostic Interview-revised (ADI-R)) (Lord et al. 1989; Lord et al. 1994), ADOS-Gotham scores, handedness, and eye-status (open vs. closed) during the functional scan. Phenotypic data available only at select sites included: medication status at time of scan (NYU, KKI, UM, UCLA), comorbidities (NYU), and SRS scores (NYU, Yale). Phenotypic data of the final dataset used (after fMRI preprocessing and exclusions, below) are shown in Tables 2.1 and 2.2. After other exclusions noted below, 20 (17 ASD) subjects were identified as ingesting one or more of 21 different medications on the day of the scan (Suppl. Table 2). Medication status and comorbidities were not included as covariates due to difficulty in the modeling of multiple pharmaceutical compounds and disorders and their effects on functional connectivity in the GLM

Table 2. 1: ABIDE participant phenotypic data for datasets included in final sample (N=188), after exclusions for excessive motion, from five sites: NYU, KKI, Yale, UM, ULCA.

Measure	NYU	KKI	Yale	UM	UCLA	Total
Mean Age ASD	12.2	13.5	13.5	13.3	13.0	12.7
Mean Age TD	11.4	10.6	12.7	12.9	12.9	12.2
Mean Age	11.7	12.9	12.9	13.1	12.9	12.4
IQ ASD	107.4	91.5	94.5	108.3	105.8	105.8
IQ TD	112.8	113.9	105.6	107.5	107.2	109.5
IQ	111.0	108.3	102.8	107.8	106.7	108.1
Female (n)	14	3	5	11	5	38
Left-Handed (n)	6	1	2	16	2	27
Eyes-open (n)	8	-	-	-	-	8
ASD (n)	19	4	4	28	12	67
TD (n)	36	12	12	38	23	121
Total (n)	55	16	16	66	35	188

Table 2. 2:

Autism diagnostic scores [mean(SD)] where available in the ABIDE data. Analyzed sites were: New York University (NYU), Kennedy Krieger Institute (KKI), Yale, University of Michigan (UM), and University California Los Angeles (UCLA). scores are displayed after exclusions for excessive motion. SRS scores, ranging from 3-150 (max. possible 190) in these data, evaluates social responsiveness for both ASD and TD. ADOS and its derived (Gotham) measures are only available for ASD participants. ADOS-RRB scores ranged from 0-7 (max. possible 10) while Gotham RRB and Severity measures ranged from 0/1 to 8/10, respectively, on a standardized scale from 0-10.

	Site						
Measure	**NYU**	**KKI**	**Yale**	**UM**	**UCLA**	**All Sites**	**Description**
SRS (ASD/TD)	91.3/20.2 (31.6/13.6)	-	77.5/19.3 (18.5/15)	-	-	88.9/20 (29.8/13.8)	Social Responsiveness Scale, scores increase with social deficits. Scores over 59 indicate mild or worse ASD severities.
ADOS-RRB	2.6 (1.2)	3.8 (2.1)	-	-	1.8 (2.5)	2.5 (1.8)	Subset of Autism Diagnostic Interview Schedule, scores increase with RRBs in ASD. Scores range 0-10.
Gotham-RRB	2.9 (1.2)	5.3 (2.8)	2.8 (1.3)	2.5 (1.6)	2.4 (2.2)	2.8 (1.8)	Calibrated ADOS-RRB scale, scores increase with ASD RRB severity (scale: 0-10).
Gotham-Severity	7.3 (1.7)	9.3 (1.5)	7.5 (0.6)	6.1 (2.3)	7.2 (2.2)	6.9 (2.8)	ADOS-Calibrated scores, increase with ASD severity (scale: 0-10).

2.4 fMRI preprocessing

The ArtRepair toolbox (https://www.nitrc.org/projects/artifact_detect/) was used to identify volumes with excessive scan-to-scan motion, which were flagged and censored, in accordance with recent guidelines (Power et al. 2014). Functional volumes with scan motion exceeding 0.2mm were flagged for removal. Subjects with remaining functional data totaling less than five minutes of scan time were excluded from further analysis. 139 subjects with ASD, and 89 TD controls were

excluded, leaving 67 ASD and 121 TD participants for analysis (N=188), each with at least 5 minutes of data with less than 0.2mm of motion, representing ability to detect an effect size of f=0.264 α=0.05, Power=0.95).

Functional connectivity processing steps were performed using the SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) in MATLAB 2014a (Mathworks, Natick, MA, USA), using the ConnToolbox 15d extension (https://www.nitrc.org/projects/conn/) (Whitfield-Gabrieli & Nieto-Castanon 2012). Functional images were preprocessed in a standard fMRI pipeline. Slice-timing correction was performed to correct for temporal differences in sampling. Images were realigned to the first functional image through a rigid body transformation. Images underwent spatial smoothing to a full-width at half-maximum (FWHM) kernel size of 4mm. 3-D rigid body motion correction was performed. All functional images were normalized to the Montreal Neurological Institute (MNI) template (with resampling to $2mm^3$ isotropic voxels), and spatially smoothed with a 7mm FWHM Gaussian kernel. Artifact detection was done in the ART toolbox (https://www.nitrc.org/projects/artifact_detect/) to identify and censor motion-outlier volumes using a threshold of 0.2mm framewise displacement or gray matter signal variation away from the mean by more than 1.3%.

Segmentation and normalization of the T1 structural volume into white matter (WM), GM, and CSF masks was performed. WM, GM, and CSF masks, along with the ROIs of the study, were coregistered to the MNI template. WM and CSF

masks were used to extract confounding factors related to physiological noise. The ConnToolbox implements an anatomical aCompCor correction (Behzadi et al. 2007), using principal component analysis (PCA) to identify principal components from regions which are unlikely to contain any signal modulated by neural activity (in this case, WM and CSF regions). PCA defined 3 WM parameters, and 3 CSF parameters, which were removed through linear regression. The resulting residual time series signals were bandpass filtered using a 0.01-0.1 Hz passband (Van Dijk et al. 2010).

2.5 fMRI analysis

Seed timecourses were derived by spatial averaging voxels within each ROI. These were entered into a set of 8 first-level general linear models (GLMs) for each subject, to estimate functional connectivity with the rest of the brain. Nuisance covariates were motion estimates and censored volumes. Contrasts on the main effect of seed timecourse were entered into second-level GLMs, with group-level covariates: diagnosis (ASD, TD), age, sex, imaging site, full-scale IQ (FSIQ), and eye status during scan (open, closed). Linear covariates were entered as mean-centered values. Contrasts were run to assess group differences in both directions, i.e. ASD over-connectivity (ASD – TD) and under-connectivity (TD – ASD). The effect of age was evaluated, as well as the interaction between age and diagnosis. As comorbidities were only available from one imaging site, and medication status was quite varied, neither were used as covariates for analyses reported here.

Four additional sets of group-level models were run to assess associations between connectivity and symptom severity, specifically: SRS (N=71, ASD=23, TD=48), ADOS Total (N=63), Gotham Severity scores (Gotham et al. 2009) (N=61), and Gotham Restrictive Repetitive Behaviours (RRB) (N=57). Covariates of no interest for all sub-analyses were sex, imaging site, full-scale IQ, handedness, and eye-status (open/closed) during scanning. Both positive and negative relationships (SRS, ADOS total etc.) were evaluated. Finally, all models were repeated using a sub-sample strictly matched 1:1 on age, IQ, and sex (N=134). First, all male ASD participants (N=67) were matched to a same-site TD participant closest in age and IQ. Next pairs of females were chosen to be age and sex matched, with a female from a different site chosen if a same-site counterpart could not be identified.

Inferences were drawn at a peak threshold of $p<0.001$ and $p<0.05$ cluster-level family-wise error (FWE) correction over the whole brain. We report significant clusters surviving Bonferroni correction for 8 multiple comparisons (i.e., accounting for 8 seeds; $p<0.00625$). We also report trend-level clusters (surviving FWE-level correction at $p<0.05$, but not multiple comparison correction at $p<0.00625$). In order to test *a priori* hypotheses about connectivity with specific networks, small volume corrections were performed in cerebellar, limbic, and salience network ROIs, and are reported at $p<0.05$ after FWE cluster-level correction without correction for multiple comparisons. 3.0 Results

3.0 Results

3.1 Participant demographics

Significantly more participant datasets with ASD (67.5%) were removed compared to TD control (42.4%) (Fisher's exact, $p<0.0001$). Motion exclusion rates of participants were not significantly different based on sex in the ASD group (Fisher's exact, $p=0.141$), but were significant based on sex in the TD group ($p=0.035$) with 46.5% of total TD males excluded due to motion and 29.4% of total TD females. IQ was significantly lower in excluded ASD participants (100 ± 16.7) compared to those included (105 ± 17.7) ($t_{(203)}=2.26$, $p=0.02$). IQ in excluded TD participants (110 ±13.8) was not significantly different from included TD participants (109 ± 11.8) ($t_{(208)}=0.29$, $p=0.77$). Severity of autism, based on ADOS-Gotham Severity scores, did not vary between included and excluded ASD participants ($t_{(199)}=0.19$, $p=0.85$).

Residual total scan times between ASD (7.04 min ± 1.55) and TD (7.00 min ± 1.62) groups were not significantly different ($t_{(186)}=0.27$, $p=0.79$). The final sample of 188 datasets had significantly fewer female participants with ASD than TD (Fisher's exact, $p=0.0009$): 6/61(8.96%) female participants with ASD, and 36/121 (29.75%) female TD participants. Groups did not differ in age (ASD=12.7(2.0), TD=12.2(2.3), $t_{(186)}=1.60$, $p=0.11$), or IQ (ASD=105.8(17.7), TD=109.5(11.8), $t_{(186)}=1.72$, $p=0.13$).

3.2 Group Differences in Functional Connectivity

Over-connectivity in ASD compared to TD was observed between a left lateral somatosensory seed (LBA4.1) and Brodmann's Area 7 (-28, -76, 44; N=350; peak Z=4.66; p=0.008) within the left parietal cortex (Figure 3.1). Effect size between groups was 0.322 f.

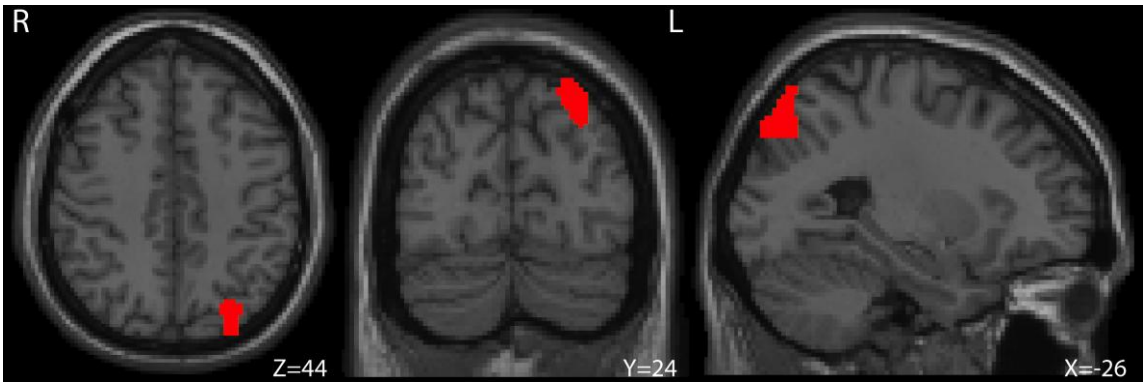

Figure 3. 1: Over-connectivity in ASD relative to TD between LBA4.1 and the left parietal cortex (-28, -76, 44; N=350; peak Z=4.66; p=0.008).

Trend-level over-connectivity in ASD was observed between a right medial somatosensory seed (RBA1.1) and the right anterior lobe of the cerebellum and some of the brainstem (22, -38, -36; N=142; peak Z=4.32; p=0.048 FWE-corrected) (Figure 3.2). This finding did not survive correction for multiple comparisons (p=0.384). Small volume correction within the cerebellum (see Figure 2.2a) did not produce any additional regions of significance.

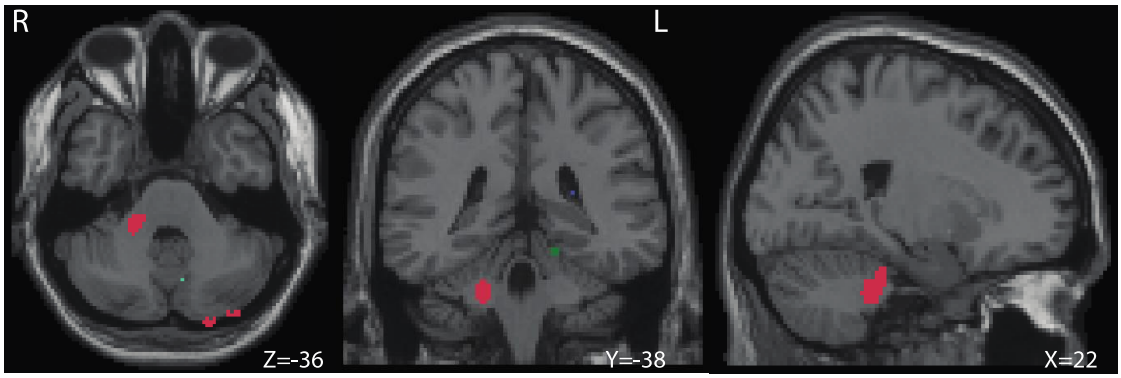

Figure 3. 2: Trend-level over-connectivity in ASD compared to TD between RBA1.1 and the right anterior cerebellar lobe (22, -38, -36; N=142; peak Z=4.32; p=0.048 FWE-corrected). Cluster did not survive correction for multiple comparisons (p=0.384).

Trend-level under-connectivity in ASD was observed between a left medial somatosensory seed (LBA1.2) and the left prefrontal cortex (Brodmann's Area 10) (-10, 54, 0; N=194; peak Z=4.27; p=0.009 uncorrected) (Figure 3.3). This cluster did not survive correction for multiple comparisons (p=0.072), and it did not fall within any of our *a priori* hypothesized regions for small volume correction.

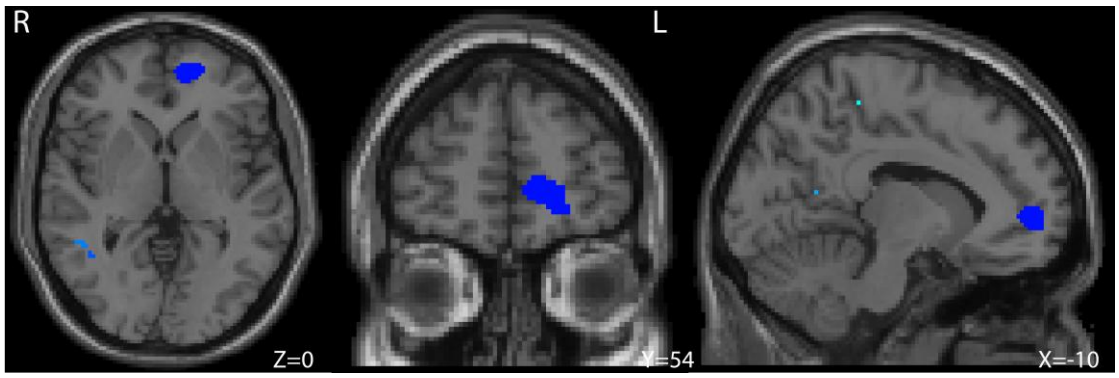

Figure 3. 3: Trend-level under-connectivity in ASD compared to TD between LBA1.2 and the left pre-frontal cortex (-10, 54, 0; N=194; peak Z=4.27; p=0.009 FWE-corrected). Cluster did not survive correction for multiple comparisons (p=0.072).

3.3 Differences with Age

A trend-level age-diagnosis interaction effect was found between a right lateral somatosensory ROI (RBA1.4) and the dorsal anterior cingulate cortex (4, 16, 40; N=196; peak Z=4.31; p=0.011 uncorrected) (Figure 3.4). This result was significant after small volume correction within the *a priori* selected salience network (see Figure 2.2b) (4, 16, 40; N=196; peak Z=4.31; p=0.008): connectivity was significantly positively associated with age in ASD (p=0.0016) with a negative trend-level association in the TD group (p=0.059) (Figure 3.4).

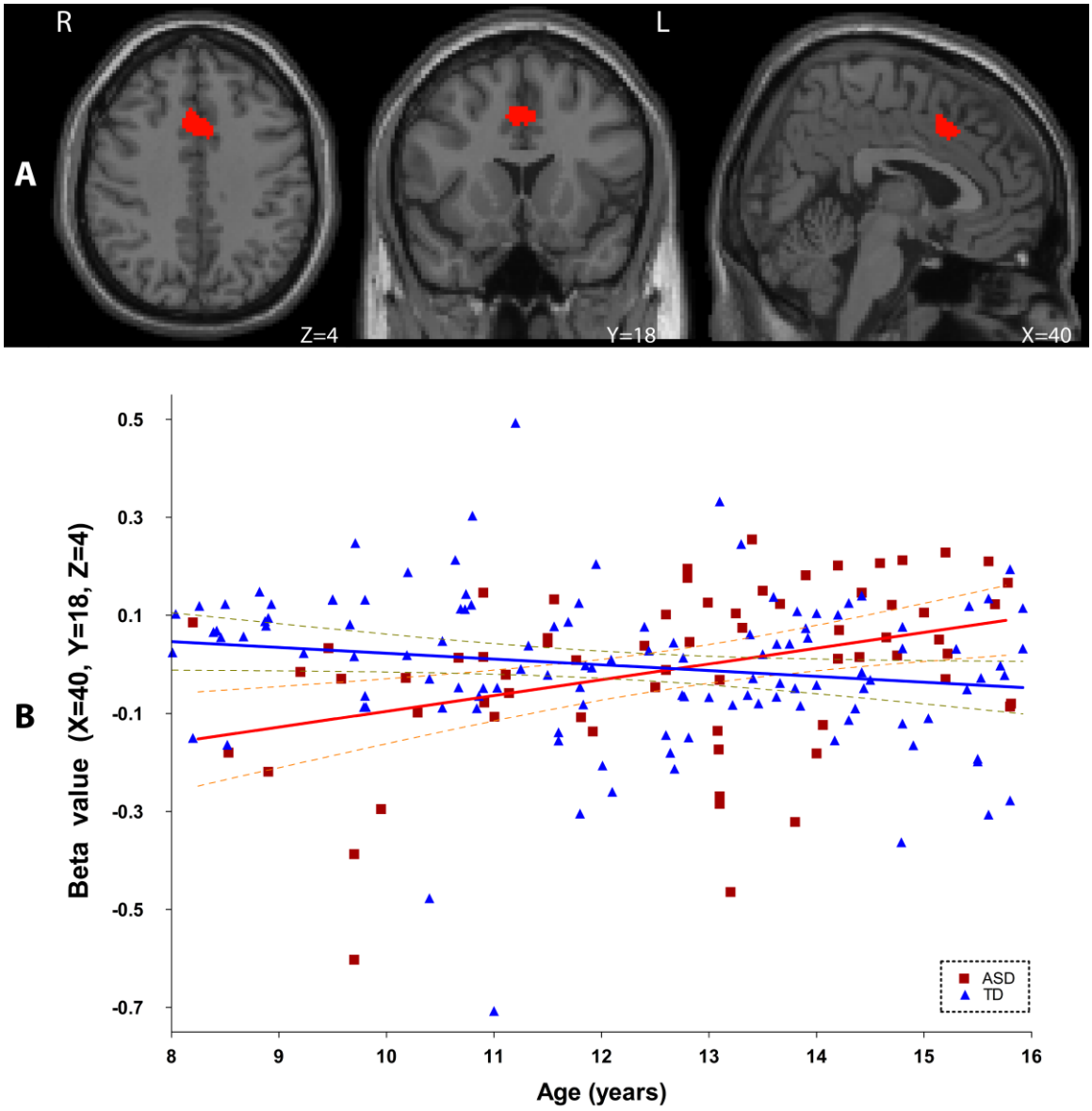

Figure 3. 4: A) Location of trend-level age-diagnosis interaction observed between RBA1.4 and the dorsal anterior cingulate cortex (4, 16, 40; N=196; peak Z=4.31; p=0.011 uncorrected). B) Association between connectivity values (beta value at peak voxel in the dorsal anterior cingulate cortex) and age in both groups; connectivity showed a significant positive association with age in ASD (p=0.0016), but only a trend-level decrease in TD (p=0.059). ASD and TD values had significantly different associations with age (p<0.001). 95% confidence intervals of the mean are shown as hashed lines around each trendline (mean beta value by age). Beta values represent the coefficient of connectivity between seed and voxel for each subject after controlling for other parameters.

3.4 Severity Associations

ADOS measures

Only one trend-level association between connectivity and severity was observed (Figure 3.5). In the Gotham-RRB subtest (n= 57, score =2.81 ± 1.80), the left superior temporal gyrus (Brodmann's Area 22) (-66, -6, 2; N=170; peak Z=4.61; p=0.016 uncorrected) showed higher connectivity with a right lateral somatosensory seed (RBA1.4) associated with higher RRB scores.

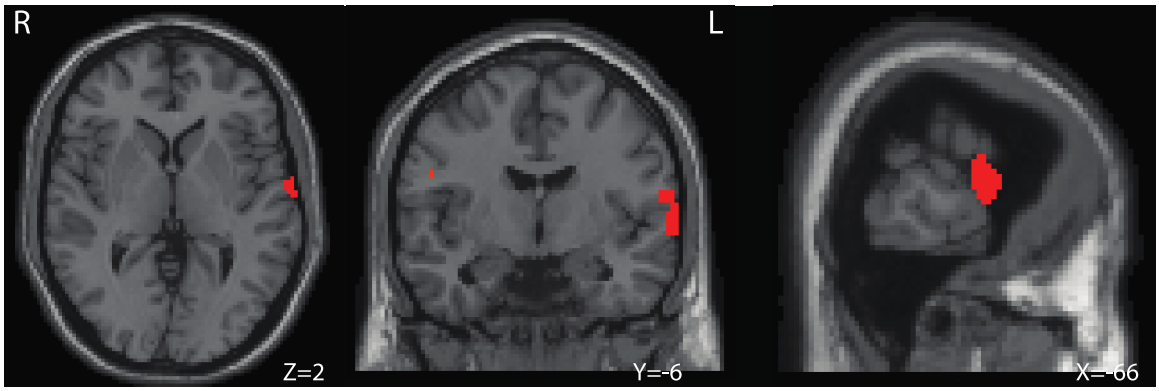

Figure 3. 5: Trend-level positive associations of functional connectivity between RBA1.4 and the left temporal gyrus (-66, -6, 2; N=170; peak Z=4.61; p=0.016 uncorrected) with Gotham-RRB scores in ASD. Cluster did not survive correction for multiple comparisons (p=0.128).

Social Responsiveness Score

SRS was significantly higher in the ASD group (88.9 ± 30.0) than the TD group (20.0 ± 13.8) ($t_{(27)}$=10.55, p<0.0001), as expected. Trend-level connectivity differences were observed between the left medial somatosensory seed (LBA1.2) and Brodmann's Area 39 (36, -74, 22; N=122; peak Z=3.72; p=0.033 uncorrected) in the right parietal cortex (Figure 3.6a); where connectivity was positively associated with SRS scores. Further, connectivity between LBA1.2 and

the right hippocampus (20, -14, -20; N=120; peak Z=4.78; p=0.036 uncorrected) was negatively correlated with SRS scores (Figure 3.6b).

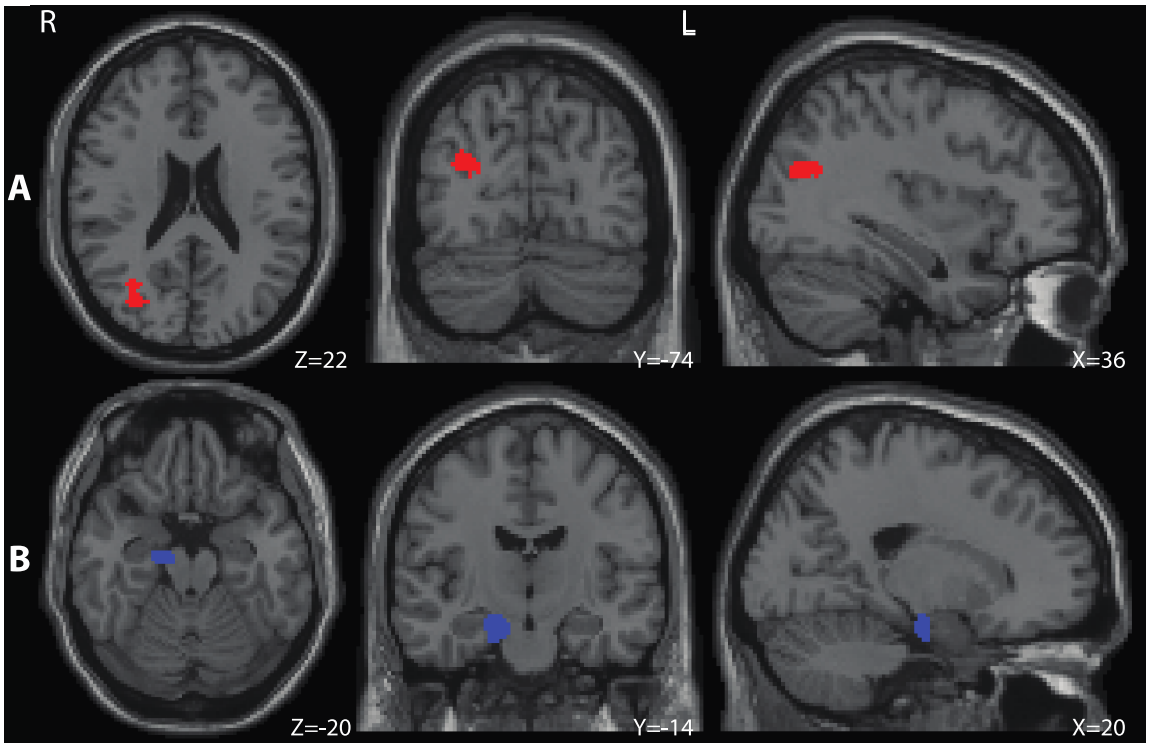

Figure 3. 6: Trend-level connectivity changes with increasing SRS scores, a) the right parietal cortex (36, -74, 22; N=122; peak Z=3.72; p=0.033 uncorrected) increasing between LBA1.2 and b) decreasing connectivity in the right hippocampus (20, -14, -20; N=120; peak Z=4.78; p=0.036 uncorrected). Clusters did not survive correction for multiple comparisons (p_A=0.264, p_B=0.288).

3.5 Age-IQ-Sex Matched subsets

A set of 1:1 matched analyses were performed on a subset of 134 (67/67 ASD/TD) subject datasets which did not differ in age (12.8 years ±2.1, p=0.68) or IQ (106.5 ± 14.2, p=0.550) between groups. Significant over connectivity in ASD was still observed between the left lateral somatosensory seed (LBA4.1) and the left parietal cortex, comparable to the full sample (-28,-84,46; N=437; peak

Z=4.44; p<0.001). The trend-level ASD over-connectivity effect between RBA1.1 and the right temporal pole was no longer observed, neither was the trend-level ASD under-connectivity effect between LBA1.2 and the left prefrontal cortex.

3.6 Nuisance and covariate findings

No significant effects of sex or eye status were observed in the full sample analysis, or 1:1 matched subset. Further, effect of site differences did not appear to significantly contribute to the model as 'leave-one-out' analyses produced statistically and visually (i.e. network images) similar results.

4.0 Discussion

4.1 Summary of Findings

The primary aim of this thesis was to determine if there were robust differences of functional connectivity between the somatosensory network and the whole brain in ASD compared to TD. Only one significant group difference (ASD hyperconnectivity) in functional connectivity was observed; this was located between LBA4.1 and the left temporal gyrus. One trend-level age by diagnosis interaction effect was observed between RBA1.4 and the dorsal anterior cingulate cortex, which was significant after small volume correction for the salience network. No severity association measure displayed significant correlation to functional connectivity. A strict 1:1 sex and age-IQ matched sub-analysis did not show any significant effects. Each analysis was comprised of a total of 16 contrasts, and each contrast was further evaluated within three small volume masks, and using a 1:1 IQ-Sex-Age matched sub-sample (which also repeated small volume corrections). We believe that this comprehensive approach would have detected group differences in this sample, if any existed. Thus, in this group, our findings suggest instead that there are no strong group differences involving functional connectivity of the somatosensory network.

4.2 ASD vs. TD Group Differences

Analysis of connectivity from eight subdivisions of the somatosensory network to the whole brain revealed only one significantly over-connected cluster (Figure 3.1). Here, the seed (LBA4.1 (blue), Figure 2.1) ROI corresponds to a left lateral parcellation of the somatosensory strip. Along the sensory homunculus, this ROI likely corresponds to the physical brain mapping of sensory input for the head and face (Hari & Kaukoranta 1985). The cluster found to be over-connected to this seed, located in the left lateral posterior superior parietal cortex, is contained within the somatosensory association network (Brodmann's Area 7) (Brodmann 1909).

Previous research on the superior parietal lobule shows primarily thalamocortical-somatosensory underconnectivity (Rausch et al. 2016), in addition to thalamo-parietal underconnectivity (Nair et al. 2015) in ASD. Our finding is likely too posterior to be involved in sensorimotor function, and too lateral-superior to be involved in visuo-spatial activities (DeRamus et al. 2014); instead aligning with a region known to be involved in cognitive processing, and likely important in theory of mind activities (Margulies et al. 2009).

To the best of our knowledge, no previous literature has described overconnectivity between the lateral somatosensory cortex and the superior parietal lobule. Indeed, overconnectivity in an area associated with theory of mind is not in agreement with much of the previous literature supporting the

general underconnectivity theory of autism, making this finding difficult to fit within our model. We could speculate that this overconnectivity is related to subtle proprioceptive activity occurring during the scan, relating to the subject's awareness of their head in the headcoil and scanner. Additionally, power (P=0.95), was quite high, suggesting that, in this study, there are not likely to be further functional connectivity differences involving the somatosensory cortices of the brain.

Cheng et al (2015), using the ABIDE database as well, have suggested that altered functional connectivity in the precuneus (medial to our finding) in ASD plays a role in face expression, theory of mind, and the expression of self. Their global connectivity analysis, however, was untargeted for regional connectivity, and comparison of every single voxel pair in the brain – versus a hypothesis-driven targeted ROI approach – is methodologically distinct, and difficult to compare to our study.

Connectivity to select *a priori* ROIs (the anatomical limbic network and cerebellum, and a connectivity-derived salience network) did not reveal connectivity differences, as have been previously described in ASD (Cerliani et al. 2015; A. J. Khan et al. 2015). Cerliani et al, while also using the ABIDE database, selected a much larger age range, included only male participants, included data from all 17 sites, and performed ICA identification of network regions. These methodological differences make comparison of our findings difficult. Khan et al

used a loose motion correction (≥1.5 mm framewise displacement), even in light of the suggestions by Power et al, and fewer than half as many datasets as that presented in this thesis. As well, our choice to examine functionally parcellated ROIs within the somatosensory cortex may have contributed to our lack of confirmation of these differences.

4.3 Differences with Age

Contrary to our predictions, we did not find robust evidence of somatosensory functional connectivity changing with age, in either ASD or TD, from 8-15 years. After small volume correction in the salience network, we did observe a significant interaction effect of age-diagnosis on functional connectivity (Figure. 3.4) between our right lateral seed (RBA1.4) and the dorsal anterior cingulate cortex (dACC). Effect size (f=0.0437) without correction, however, was too small to achieve meaningful power (P=0.02), and thus the likelihood of type II error high. Even a low-to-moderate effect of age-by-diagnosis interaction (f=0.2) in our study would have had adequate likelihood of detection (α=0.05, P=0.78). Further, the 4 outliers (more than two standard deviations from the population mean), 2 in each ASD and TD groups, were unremarkable for phenotype or scan (motion levels, total included scan time) parameters, discouraging their removal from analyses. Therefore, we believe that if any true differences existed between these groups, that our analysis would have detected them. Should we, however, consider this interaction finding to be meaningful, investigation of connectivity differences in the dACC deserves discussion.

The dACC has been attributed primarily to cognitive functions (rather than emotional functions processed by the ventral anterior cingulate), including modulation of attention or sensory response selection, error detection, and working memory (Bush et al. 2000). It is functionally a key portion of the salience network.

Salience refers to the quality of one thing to stand out among others, and salient stimuli principally engage the salience network. In humans, the salience network has been identified to consist of the anatomical dACC, orbitofrontoinsular cortices, bilateral insulae (Seeley et al. 2007), and more recently the inferior parietal lobule and supramarginal gyrus (Shirer et al. 2011). The network responds to behaviourally salient events, such as face recognition, error detection, anxiety, and social rejection (Eisenberger et al. 2003; Seeley et al. 2007; Ham et al. 2013).

In individuals with autism, the fMRI literature presents conflicting measures of over- and under-connectivity in the salience network (von dem Hagen et al. 2013; Uddin et al. 2014). Connectivity measures of the dACC appear to be dependent on the task applied, and are among the strongest fMRI classifiers of ASD (Barttfeld et al. 2012b; Uddin et al. 2014). Bartfield et al indicated hyperconnectivity of the dACC during an interoceptive task (focus on internal task; respiration), and underconnectivity during an exteroceptive task (external

task: auditory stimulus). Decreased functional connectivity of the dACC was shown during an anti-saccadic inhibitory test (Agam et al. 2011), while social face detection resulted in over-connectivity (Dichter et al. 2009). Between Brodmann's area 32 (which includes the dACC) and 8 (part of the frontal cortex), it has also been shown that ASD participants exhibit resting state hypo-connectivity and task hyper-connectivity, while a TD control group showed the opposite (You et al. 2013).

Functional connections between the postcentral gyrus and the left insula, Rolandic operculum, and Heschl's gyrus have been previously shown to decrease linearly from early childhood towards senescence in neurotypical controls (Wang et al. 2012). Overall, however, the somatosensory network has been suggested to decrease in segregation – increasing long range functional connectivity – from early adulthood (20 years) to old age (Chan et al. 2014). But, these changes in connectivity are highly region-pair specific (Betzel et al. 2014); normal aging from childhood (7 years) to adulthood showed increasing connectivity between hand/body somato-motor network and the dorsal attention network, but a distinct pattern of increasing between face/head somato-motor network and the limbic network. Our finding did not replicate connectivity to the limbic network shown by Betzel, and instead suggests differential development of somatosensory to salience network connectivity in ASD. Like most other studies regarding longitudinal functional connectivity measures in ASD, Betzel examined

a much wider age-range (7-85 years) than the present study, and it is unclear if the reported group differences would remain in a smaller age-ranged sample.

Our finding of functional connectivity increasing with age in ASD does not support our hypothesis of SS being driven by functional over-connectivity of the somatosensory network. That is, if increased somatosensory functional connectivity leads to tactile SS, then our results showing that the dACC is increasingly connected to the somatosensory network with age suggest increasing SS in ASD across late childhood and adolescence, rather than declining SS. Instead, it may be that the dACC is increasingly recruited to guide cognitive/behavioral responses, particularly from somatosensory input, which may play a role in the reduction of SS (or their measured behavioural responses) in children and adolescents with autism over time. Though resting-state salience network connectivity measures have recently been shown to predict outcomes of adaptive behaviours (Adaptive Behavior Assessment System-Second Edition) and SRS scores (Plitt et al. 2015), to our knowledge, no study has assessed the effect of salience network functional connectivity changes with age and SS outcomes in youth with ASD.

4.4 Functional Connectivity Relations to Severity Measures

This study did not detect significant correlations of symptom severity (SRS, RRBs, ADOS scores) and functional connectivity between the somatosensory network and the whole brain. One trend-level finding correlating to ADOS-

severity, and two correlating with SRS were detected in this study. Corrected p-values for these findings, however were well beyond even trend levels ($p_{corrected}$= 0.128, 0.264, 0.268, respectively), so these may be false positives resulting from the number of tests run.

In a recent study by Green et al. (Green et al. 2015), over-connectivity between primary sensory regions and the amygdala in autism was shown to correlate with RRBs and SS (Sensory Over Responsivity, and Short Sensory Profile scores). This study, however, differed significantly from ours by performing auditory and tactile stimulation tasks during fMRI. Our comparative lack of findings suggests that the neuroimaging correlates of SS in autism may be more sensitive to task-based examination rather than intrinsic connectivity measures.

4.5 IQ

Mental impairments, particularly lower full scale and verbal IQs (FSIQ, VIQ, respectively), are a common co-morbidity in autism. While performance IQ (PIQ) scales may provide better comparisons of intelligence in persons with neurodevelopmental disorders to controls than FSIQ (Mungkhetklang et al. 2016), too few participants had PIQ available for use in this study. FSIQ data were measured at all included sites. Though not significant, the final sample group (N=188) did trend to lower FSIQ scores in ASD (mean=105.8) compared to TD (109.5). Further, participants with ASD were significantly more likely to be excluded due to motion criteria if they had decreased FSIQ scores. Excluded TD

participants, however, did not have different IQ from included TD participants. IQ, however is heterogeneous in ASD, and its relation to autism severity and cognitive deficits (including lowered cognition, working memory, and visual pattern recognition) varies (Rommelse et al. 2015).

While it is unclear whether bias for less affected ASD participants was introduced into the final sample, participants with ASD were not disposed to increased exclusion due to motion based on ADOS-Gotham Severity scores. Though this suggests that ASD severity was not a factor in participant ability to adequately participate in the full MRI scan, it does not preclude the potential that individuals more strongly presenting the symptoms of ASD self-selected prior to the full scan, or did not tolerate the scan long enough to generate data.

4.6 Motion

It has been suggested that the disparity in findings of over and under-connectivity stems from methodological choices regarding the processing of fMRI data, rather than physiologically relevant differences (Müller et al. 2011). Head motion, in particular, during rs-fMRI scanning has been shown to significantly influence functional connectivity measures (Satterthwaite et al. 2012), and the effects of motion on functional connectivity measures are receiving increased attention following recent critiques of standard fMRI preprocessing practice (Power et al. 2012; Power et al. 2014). In review of functional connectivity studies of autism, Müller et al found only 13/32 studies mentioned motion, and of those,

only 4 mention group differences in head motion (ASD vs. TD) (Müller et al. 2011).

In line with current recommendations on motion control (Power et al. 2012), we excluded volumes along strict criterion (<0.2mm motion) to reduce the likelihood of non-BOLD signal influencing connectivity measurements. After excluding motion-corrupted volumes, it was important to ensure sufficient scan data for each participant, to determine subject-level connectivity estimates. It has been suggested that five minutes of total scan time is adequate for rs-fMRI functional connectivity analyses and that total scan time is more important than closely temporally connected volumes (Birn et al. 2013).

More than half (96/163) of the potential ASD datasets did not meet inclusion criteria, meaningfully reducing the anticipated sample size of this study. Exclusions in the TD group (68/189), were not as numerous, but still meaningfully impacted power of the study. Overall, from an initial ability to detect effect size differences of 0.177 (small) (N=416), was reduced to 0.264 (small-medium) (N=188) after exclusions. Considering the trend-level findings observed, it is possible that additional meaningful results may be detected through a larger dataset. Recent augmentation of the ABIDE dataset with approximately 1000 more subjects may be encouraging for futher work in this approach.

4.7 Other Nuisance Variables and Implications

Group-level confounds of potential impact were IQ, age, sex, handedness, and the imaging site, and were modeled in the group-level regression GLM. Aggregation of multi-center datasets is a particularly important topic in fMRI research (Voelker et al. 2016; Forsyth et al. 2014; Wurnig et al. 2013; Friedman et al. 2006). While we did our best to model confounds, this is a highly heterogeneous sample. Sex differences were expected, given that autism is expressed differently between males and females (males typically expressing higher restrictive repetitive behaviours (Van Wijngaarden-Cremers et al. 2014)), and previous literature on functional connectivity differences between sex and ASD (Jung et al. 2015; Alaerts et al. 2016); however, sex differences were not significant in our study. This study, however, had significantly fewer female datasets, including in the age-IQ-sex matched sub-analysis, which reduced the ability to detect sex differences.

Physical and mental state have also been shown to play important roles in functional connectivity studies. This includes medication status, and even caffeine, during time of scan (Barttfeld et al. 2012a). Medication status and comorbidities were not included as covariates due to difficulty in the modeling of multiple pharmaceutical compounds and disorders and their effects on functional connectivity in the GLM. It is unclear as to the number of, and whether, participants not marked as ingesting medication on the day of the scan would still be under the effect of longer acting medications (ex. Citalopram, half-life=35

hours, risperidone=~20 hours in poor metabolizers. Similarly, 14 (11 ASD) subjects were identified as having one of 10 identified comorbidities, including phobias, ADHD, and mood disorders). These highly heterogenous and categorical sets of factors make for questionable inclusion as covariates in a GLM. Given a more robust reporting of medications and comorbidities, inclusion may be indicated, or potentially analyzed via other methods including clustering approaches.

Eye status, also shown to be relevant to fMRI connectivity studies, was noted and included the model (Zou et al. 2015; Wang et al. 2015). Only eight (2 with ASD) datasets had participants with open eyes during the scan, though impact on resting-state connectivity has been suggested as minimal and mostly contained to within-network effects (Patriat et al. 2013). Regardless, no significant effects of eye-status were observed in the model.

Trend-level results were reported above, as there was the possibility of convergent findings prompting further investigation. If multiple sub-critical results were found implicating a singular structure or brain network, it would have been appropriate to re-evaluate these connections, and why these findings were not significant under our model. One likely explanation would have been the strict statistical corrections employed in our study. However, our results did not indicate a collection of sub-threshold connectivity differences. Further, reporting

of trend-level results may help guide future investigations into these areas, especially given the shared nature of the ABIDE database.

As such, due to our lack of concerted significant or trend-level findings, we cannot conclude that there exist robust functional connectivity differences between the two sampled groups.

5.0 Conclusion

5.1 Limitations

The hallmark sensory symptoms of ASD, including tactile and auditory SS, and hyper-responsiveness to stimuli, make imaging of subjects with more severe tactile and/or auditory SS challenging or impracticable. Therefore, in practice, participants who are more receptive to MRI scanning procedures are disproportionately included in studies, presenting a bias in the research. This limits the use of neuroimaging in ASD, as physiological differences in less severely affected participants with ASD may not be detectable with respect to TD controls, whereas individuals with higher ASD symptom severities may exhibit more pronounced functional connectivity alterations.

Use of resting-state fMRI data may limit detection of brain correlates of sensory sensitivities more prominently seen in evoked responses to sensory stimuli. Additionally, most imaging studies of ASD, including this thesis, have employed a binary categorical diagnosis of ASD, examining whether there are one or more corresponding brain differences that can be recognized, despite the heterogeneity of the condition (Lenroot & Yeung 2013).

Functional connectivity measures do not guarantee structural linkage, direct communication between functionally connected sites, nor do they specify directionality. That is, it is possible that common inputs from a third region can

cause two or more regions to be concurrently active – rather than those two regions being relevantly co-active, making this measure challenging to interpret.

The use of FWE correction may be overly conservative for this analysis, however examination using false discovery rate correction did not detect additional significant clusters.

5.2 Future Directions

Given that sensory over-responsivities were recently associated with functional connectivity differences in the brains of youth with ASD during task (Green et al. 2015), combined with our lack of robust results, resting-state paradigms alone may not be indicated for continuation into sensory over-responsivity research in ASD. Alternatively, associations between diagnostic measures and connectivity in ASD (including ADOS, RRBs, and SRS) may not closely enough represent the tactile modality of SS. Elucidation of the neural basis of SS in autism remains an important area, to potentially guide the development of behavioural interventions as well as pharmacological treatments. Combining task-based fMRI studies with resting-state approaches may prove highly valuable in improving our understanding of SS in youth with autism, and how they change with age.

Describing the heterogeneity seen in ASD as a collection of conditions (Lenroot & Yeung 2013; Lai et al. 2016), resting-state studies may remain a useful method of research in ASD. Due to the relative practicality of collecting rs-fMRI data in

ASD, compared to task-based paradigms, analyses exploring sub-groupings (particularly genetic) of ASD may be more feasible in rs-fMRI. This sub-grouping of ASD participants could prove important in both separating out functional connectivity differences, with respect to controls, as well as potentially suggesting patient-level interventions – as it is possible that one particular sub-group of autism responds well to behavioural therapies, but is non-responsive to pharmacological treatments.

5.3 Closing Remarks

This thesis adds to the literature of functional connectivity of the somatosensory network in autism spectrum disorders. But given the amount of tests run, and background supporting our hypotheses, it is important to note the lack of robust findings. Few significant differences, as well as limited trend-level findings, instead suggest that at rest in youth with ASD, the brain may not express functional connectivity aberrations with regards to the somatosensory network. Our lack of robust findings of functional connectivity differences in ASD with respect to TD, combined with multiple task-based fMRI studies indicating primary somatosensory differences, may suggest that the neural mechanisms behind SS in autism are not tied to intrinsic functional connectivity changes, but rather task-active effects.

APPENDIX: SUPPLEMENTARY DATA

Suppl. Table 1: Scanning Parameters for included ABIDE sites. Anatomical (T1) scan parameters ranged from TR=250-2530 ms, TE=1.73-5.7 ms, FOV=250-256 mm, and resolution of 1.0-1.7mm^3. Functional (T2*) scan parameters ranged from TR=2000-3000 ms, TE = 15-30 ms, 120-300 functional volumes, FOV=192-256mm, resolution of 28.8-46.2mm^3, and scan duration t=6:00-10:00 min.

		NYU	KKI	Yale	UM	UCLA
Structural	TR (ms)	2530	8000	1230	250	2300
	TE (ms)	3.25	3.7	1.73	5.7	2.84
	FOV (mm)	256	256	250	256	256
	Resolution (mm^3)	1.3x1.0x1.3	1.0x1.0x1.0	1.0x1.0x1.0	1.0x1.0x1.2	1.2x1.0x1.0
Functional	TR (ms)	2000	2500	2000	2000	3000
	TE (ms)	15	30	25	30	28
	FOV (mm)	240	256	220	220	192
	Resolution (mm^3)	3.0x3.0x4.0	2.67x2.67x3.0	3.4x3.4x4.0	3.44x3.44x3.0	3.0x3.0x4.0
	Scan Time	6:00	6:40	6:40	10:00	6:06
	Volumes	180	128	156	300	120
	Sequence	EPI	EPI	EPI	GE Reverse Spiral	EPI
	Acquisition	Interleaved	Sequential	Interleaved	Interleaved	Interleaved
	Manufacturer	Siemens	Philips	Siemens	GE	Siemens
	B0	3.0	3.0	3.0	3.0	3.0

Suppl. Table 2: Medication and comorbidity details for included subjects (N=188), where noted in the ABIDE phenotypic data. Overall, 31 subjects (17 ASD) were identified as taking one or more of 21 different medications on the day of the scan. 13 (10 ASD) subjects were indicated as presenting one of 8 comorbidities.

Medication	ASD	TD	Comorbidity	ASD	TD
Guanfacine (incl. Extended release)	4		Mood Disorder NOS	3	
Citalopram	1		ADHD Inattentive	3	
Risperidone	6		Generalized Anxiety Disorder	1	
Escitalopram	3		Phobia(s)	1	2
Dexmethylphenidate	1		Disruptive disorder NOS	1	
Peroxatine	1		ODD	1	
Methylphenidate (incl. Extended release)	4		Dysthymic disorder	1	
Clonidine	1				
Atomoxetine	1				
Dextroamphetamine	3				
Amphetamine	3				
Fluoxetine	1				
Quetiapine	1				
Melatonin	2				
Trazodone	1				
Aripiprazole	3				
Sertraline	2				
Bupropion	1				
Zinc	1				
Valproic Acid	1				
Levothyroxine		2			

References

Abrams, D. a et al., 2013. Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *Proceedings of the National Academy of Sciences of the United States of America*, 110(29), pp.12060–5. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3718181&tool=pmcentrez&rendertype=abstract.

Agam, Y. et al., 2011. Reduced cognitive control of response inhibition by the anterior cingulate cortex in autism spectrum disorders. *NeuroImage*, 52(1), pp.336–347.

Alaerts, K., Swinnen, S. & Wenderoth, N., 2016. Sex Differences in Autism: A resting-state fMRI investigation of functional brain connectivity in males and females. *Soc Cogn Affect Neurosci*, Epub Ahead.

American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders* 5th ed., Arlington, VA: American Psychiatric Publishing.

Anderson, J.S. et al., 2011. Decreased interhemispheric functional connectivity in autism. *Cerebral Cortex*, 21(5), pp.1134–1146.

Barttfeld, P. et al., 2012a. State-dependent changes of connectivity patterns and functional brain network topology in autism spectrum disorder. *Neuropsychologia*, 50(14), pp.3653–3662.

Barttfeld, P. et al., 2012b. State-dependent changes of connectivity patterns and functional brain network topology in autism spectrum disorder. *Neuropsychologia*, 50(14), pp.3653–3662.

Bauman, M.L. & Kemper, T.L.., 1994. *The Neurobiology of Autism.*, Baltimore, MD: Johns Hopkins University Press.

Behzadi, Y. et al., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, 37(1), pp.90–101. Available at: http://dx.doi.org/10.1016/j.neuroimage.2007.04.042.

Ben-Sasson, a. et al., 2014. Early and Concurrent Features of ADHD and Sensory Over-Responsivity Symptom Clusters. *Journal of Attention Disorders*. Available at: http://jad.sagepub.com/cgi/doi/10.1177/1087054714543495.

Ben-Sasson, A. et al., 2009. A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39(1), pp.1–11.

Benarroch, E.E., 2006. *Basic neurosciences with clinical applications.*, Edinburgh: Butterworth Heinemann/Elsevier.

Betzel, R.F. et al., 2014. Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage*, 102, pp.345–357. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1053811914006508.

Birn, R.M. et al., 2013. The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *NeuroImage*, 83, pp.550–558. Available at: http://dx.doi.org/10.1016/j.neuroimage.2013.05.099.

Biswal, B. et al., 1995. Functional connectivity in the motor cortex of resting

human brain using echo-planar MRI. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 34(4), pp.537–541.
Biswal, B.B. et al., 2010. Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences*, 107(10), pp.4734–4739. Available at: http://www.pnas.org/cgi/doi/10.1073/pnas.0911855107.
Bos, D.J. et al., 2014. Developmental differences in higher-order resting-state networks in Autism Spectrum Disorder. *NeuroImage: Clinical*, 4, pp.820–827. Available at: http://dx.doi.org/10.1016/j.nicl.2014.05.007.
Brenner, A.D. et al., 1978. Somatically Evoked Magnetic Fields of the Human Brain Author (s): D . Brenner , J . Lipton , L . Kaufman and S . J . Williamson Reviewed work (s): Source : Science , New Series , Vol . 199 , No . 4324 (Jan . 6 , 1978), pp . 81-83 Published by : Amer. , 199(4324), pp.81–83.
Brock, M.E. et al., 2012. Temperament and Sensory Features of Children with Autism. *J Autism Dev Disord.*, 42(11), pp.2271–2284.
Brodmann, K., 1909. *Localisation in the Cerebral Cortex*, Springer Berlin Heidelberg.
Bush, G., Luu, P. & Posner, M., 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Science*, 4(6), pp.214–222.
Bushberg, J., 2002. *The essential physics of medical imaging*, Philadelphia: Lippincott Williams & Wilkins.
CDC, U., 2014. Autism Spectrum Disorder. Available at: http://www.cdc.gov/ncbddd/autism/data.html [Accessed March 24, 2015].
Cerliani, L. et al., 2015. Increased Functional Connectivity Between Subcortical and Cortical Resting-State Networks in Autism Spectrum Disorder. *JAMA Psychiatry*. Available at: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2015.0101.
Chan, M.Y. et al., 2014. Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences*, 111(46), pp.E4997–E5006. Available at: http://www.pnas.org/lookup/doi/10.1073/pnas.1415122111.
Chavhan, G. et al., 2009. Principles, techniques, and applications of T2*-based MR imaging and its special applications. *Radiographics*, 29, pp.1433–1449.
Chen, Y.H., Rodgers, J. & McConachie, H., 2009. Restricted and repetitive behaviours, sensory processing and cognitive style in children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39(4), pp.635–642.
Cherkassky, V.L. et al., 2006. Functional connectivity in a baseline resting-state network in autism. *Neuroreport*, 17(16), pp.1687–1690.
Constantino, J. et al., 2003. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *J Autism Dev Disord*, 33(4), pp.427–433.
DeRamus, T.P. et al., 2014. Enhanced parietal cortex activation during location detection in children with autism. *Journal of neurodevelopmental disorders*,

6(1), p.37. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4190580&tool=pmcentrez&rendertype=abstract.
Dichter, G.S., 2012. Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues in Clinical Neuroscience*, 14(3), pp.319–352.
Dichter, G.S., Felder, J.N. & Bodfish, J.W., 2009. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. *Social Cognitive and Affective Neuroscience*, 4(3), pp.215–226.
Van Dijk, K.R. a et al., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *Journal of neurophysiology*, 103(1), pp.297–321.
Disbrow, E., Roberts, T. & Krubitzer, L., 2000. Somatotopic organization of cortical fields in the lateral sulcus of Homo sapiens: Evidence for SII and PV. *Journal of Comparative Neurology*, 418(1), pp.1–21.
Duerden, E.G. et al., 2014. Self-injurious behaviours are associated with alterations in the somatosensory system in children with autism spectrum disorder. *Brain Structure and Function*, 219(4), pp.1251–1261.
Dunn, W. & Westman, K., 1996. The Sensory Profile : National Sample of Children without disabilities. *American Journal of Occupational Therapy*, pp.25–34.
Eickhoff, S.B. et al., 2006. The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cerebral Cortex*, 16(2), pp.254–267.
Eisenberger, N.I., Lieberman, M.D. & Williams, K.D., 2003. Does rejection hurt? An FMRI study of social exclusion. *Science (New York, N.Y.)*, 302(5643), pp.290–292. Available at: http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=Related Articles&IdsFromResult=14551436&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.
Forsyth, J.K. et al., 2014. NeuroImage Reliability of functional magnetic resonance imaging activation during working memory in a multi-site study : Analysis from the North American Prodrome Longitudinal Study. *NeuroImage*, 97, pp.41–52. Available at: http://dx.doi.org/10.1016/j.neuroimage.2014.04.027.
Foster, N.E. V et al., 2015. Structural Gray Matter Differences during Childhood Development in Autism Spectrum Disorder: A Multimetric Approach. *Pediatric Neurology*, 53(4), pp.350–359.
Fox, M.D. & Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature reviews. Neuroscience*, 8(9), pp.700–711.
Friedman, L., Glover, G.H. & The FBIRN Consortium, 2006. Reducing interscanner variability of activation in a multicenter fMRI study: Controlling for signal-to-fluctuation-noise-ratio (SFNR) differences. *NeuroImage*, 33(2), pp.471–481.
Friston, K.J., 1994. Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, 2(1-2), pp.56–78. Available at:

http://doi.wiley.com/10.1002/hbm.460020107.
Geschwind, D.H., 2011. Genetics of Autism Spectrum Disorders. , 15(9), pp.409–416.
Glod, M. et al., 2015. Psychological Correlates of Sensory Processing Patterns in Individuals with Autism Spectrum Disorder: A Systematic Review. *Review Journal of Autism and Developmental Disorders*, pp.199–221. Available at: http://link.springer.com/10.1007/s40489-015-0047-8.
Gotham, K., Pickles, A. & Lord, C., 2009. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 39(5), pp.693–705.
Gotts, S.J. et al., 2012. Fractionation of social brain circuits in autism spectrum disorders. *Brain*, 135(9), pp.2711–2725. Available at: http://www.brain.oxfordjournals.org/cgi/doi/10.1093/brain/aws160.
Green, S. a. et al., 2015. Neurobiology of Sensory Overresponsivity in Youth With Autism Spectrum Disorders. *JAMA Psychiatry*, 72(8), p.778. Available at: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2015.0737.
Green, S. a. et al., 2013. Overreactive brain responses to sensory stimuli in youth with autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*, 52(11), pp.1158–1172.
von dem Hagen, E.A.H. et al., 2013. Reduced functional connectivity within and between “social” resting state networks in autism spectrum conditions. *Social Cognitive and Affective Neuroscience*, 8(6), pp.694–701.
Hahamy, A., Behrmann, M. & Malach, R., 2015. The idiosyncratic brain : distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nature Neuroscience*, 18(2).
Ham, T. et al., 2013. Cognitive control and the salience network: an investigation of error processing and effective connectivity. *The Journal of Neuroscience*, 33(16), pp.7091–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23595766.
Hardan, A.Y. et al., 2008. An MRI and proton spectroscopy study of the thalamus in children with autism. *Psychiatry Research - Neuroimaging*, 163(2), pp.97–105.
Hari, R. & Kaukoranta, E., 1985. Neuromagnetic studies of somatosensory system: Principles and examples. *Progress in Neurobiology*, 24(3), pp.233–256.
Haswell, C.C. et al., 2009. Representation of internal models of action in the autistic brain. *Nature neuroscience*, 12(8), pp.970–972.
Hendrick, R., 1994. The AAPM/RSNA physics tutorial for residents. Basic physics of MR imaging: and introduction. *Radiographics*, 14(4), pp.829–846.
Hernandez, L.M. et al., 2014. Neural Signatures of Autism Spectrum Disorders: Insights into Brain Network Dynamics. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, 40(July), pp.171–189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25011468.
Jamali, S. & Ross, B., 2012. Precise mapping of the somatotopic hand area

using neuromagnetic steady-state responses. *Brain Research*, 1455, pp.28–39. Available at: http://dx.doi.org/10.1016/j.brainres.2012.02.038.
Joosten, A. V. & Bundy, A.C., 2010. Sensory processing and stereotypical and repetitive behaviour in children with autism and intellectual disability. *Australian Occupational Therapy Journal*, 57(6), pp.366–372.
Jou, R. et al., 2009. Brainstem Volumetric Alterations in Children with Autism. *Psychol Med*, 39(8), pp.1347–1354.
Jung, M. et al., 2015. Sex Differences in the Default Mode Network with Regard to Autism Spectrum Traits : A Resting State fMRI Study. , pp.1–17.
Just, M.A. et al., 2004. Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain*, 127(8), pp.1811–1821.
Kaiser, M.D. et al., 2010. Neural signatures of autism. *Proceedings of the National Academy of Sciences of the United States of America*, 107(49), pp.21223–8. Available at: http://www.pnas.org/content/107/49/21223.full.
Kauer, J. et al., 2015. Adult picky eating. Phenomenology, taste sensitivity, and psychological correlates. *Appetite*, pp.1–10. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0195666315000938.
Kern, J.K. et al., 2006. The pattern of sensory processing abnormalities in autism. *Autism : the international journal of research and practice*, 10(5), pp.480–494.
Khan, A.J. et al., 2015. Cerebro-cerebellar Resting-State Functional Connectivity in Children and Adolescents with Autism Spectrum Disorder. *Biological Psychiatry*, 78(9), pp.625–634. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0006322315002735.
Khan, S. et al., 2015. Somatosensory cortex functional connectivity abnormalities in autism show opposite trends, depending on direction and spatial scale. *Brain*. Available at: http://www.brain.oxfordjournals.org/cgi/doi/10.1093/brain/awv043.
Kwong, K. et al., 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A*, 89(12), pp.5675–5679. Available at: http://www.pnas.org/content/89/12/5675.abstract\nhttp://www.pnas.org/content/89/12/5675.full.pdf\nhttp://www.pnas.org/cgi/content/abstract/89/12/5675.
Lai, J.K.Y. et al., 2016. Regional brain volumes changes in adult male FMR1-KO mouse on the FVB strain. *Neuroscience*, 318, pp.12–21. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0306452216000403.
Lauterbur, P., 1973. Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature*, 242(5394), pp.190–191.
Lawson, R.P. et al., 2015. A striking reduction of simple loudness adaptation in autism. *Scientific reports*, 5, p.16157. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4633623&tool=pmcentrez&rendertype=abstract.
Leekam, S.R. et al., 2007. Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders*, 37(5), pp.894–910.
Lenroot, R.K. & Yeung, P.K., 2013. Heterogeneity within Autism Spectrum

Disorders: What have We Learned from Neuroimaging Studies? *Frontiers in human neuroscience*, 7(October), p.733. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3812662&tool=pmcentrez&rendertype=abstract.

Lichtenstein, P. et al., 2010. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *American Journal of Psychiatry*, 167(11), pp.1357–1363.

Lombardo, M. V. et al., 2010. Atypical neural self-representation in autism. *Brain*, 133(2), pp.611–624.

Long, X. et al., 2014. Functional connectivity-based parcellation of the human sensorimotor cortex. *The European journal of neuroscience*, 39(8), pp.1332–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24417550.

Lord, C. et al., 1989. Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, 19(2), pp.185–212.

Lord, C., Rutter, M. & Couteur, A. Le, 1994. Rutter1994_ADI-R.pdf. *Journal of Autism and Developmental Disorders*, 24(5), pp.659–685.

Margulies, D.S. et al., 2009. Precuneus shares intrinsic functional architecture in humans and monkeys. *Proceedings of the national academy of sciences of the United States of America*, 106(47), pp.20069–20074.

Di Martino, A.M.D.. et al., 2014. The Autism Brain Imaging Data Exchange: Towards Large-Scale Evaluation of the Intrinsic Brain Architecture in Autism. *Mol Psychiatry*, 19(6), pp.659–667.

Menon, V., 2011. Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, 15(10), pp.483–506. Available at: http://dx.doi.org/10.1016/j.tics.2011.08.003.

Mostofsky, S.H. et al., 2009. Decreased connectivity and cerebellar activity in autism during motor task performance. *Brain*, 132(9), pp.2413–2425.

Müller, R.A. et al., 2011. Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. *Cerebral Cortex*, 21(10), pp.2233–2243.

Mungkhetklang, C. et al., 2016. Comparison of Measures of Ability in Adolescents with Intellectual Disability. *Frontiers in Psychology*, 7(May), pp.1–11. Available at: http://journal.frontiersin.org/article/10.3389/fpsyg.2016.00683.

Nair, A. et al., 2013. Impaired thalamocortical connectivity in autism spectrum disorder: a study of functional and anatomical connectivity. *Brain*, 136(6), pp.1942–1955. Available at: http://www.brain.oxfordjournals.org/cgi/doi/10.1093/brain/awt079.

Nair, A. et al., 2015. Regional specificity of aberrant thalamocortical connectivity in autism. *Human Brain Mapping*, 4511(August), pp.4497–4511.

Nebel, M.B., Joel, S.E., et al., 2014. Disruption of Functional Organization Within the Primary Motor Cortex in Children With Autism. *Human Brain Mapping*, 35(2), pp.567–580.

Nebel, M.B., Eloyan, A., et al., 2014. Precentral gyrus functional connectivity signatures of autism. *Frontiers in systems neuroscience*, 8(May), p.80.

Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4030180&tool=pmcentrez&rendertype=abstract.
Nobelprize.org., 2014. The Nobel Prize in Physiology or Medicine 2003. *Nobel Media AB*. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/2003 [Accessed May 27, 2016].
Nomi, J.S. & Uddin, L.Q., 2015. NeuroImage : Clinical Developmental changes in large-scale network connectivity in autism. *YNICL*, 7, pp.732–741. Available at: http://dx.doi.org/10.1016/j.nicl.2015.02.024.
Ogawa, S. et al., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Science USA*, 87(December), pp.9868–9872.
Padmanabhan, A. et al., 2013. Age related changes in striatal resting state functional connectivity in autism. *Frontiers in human neuroscience*, 7(November), p.814. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3842522&tool=pmcentrez&rendertype=abstract.
Patriat, R. et al., 2013. The effect of resting condition on resting-state fMRI reliability and consistency: A comparison between resting with eyes open, closed, and fixated. *NeuroImage*, 78(01), pp.463–473.
Philip, R.C.M. et al., 2012. A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. *Neuroscience and Biobehavioral Reviews*, 36(2), pp.901–942. Available at: http://dx.doi.org/10.1016/j.neubiorev.2011.10.008.
Plitt, M. et al., 2015. Resting-state functional connectivity predicts longitudinal change in autistic traits and adaptive functioning in autism. *Proceedings of the National Academy of Sciences*, 112(48), pp.E6699–6706. Available at: http://www.pnas.org/content/112/48/E6699.full.
Pooley, R., 2005. Fundamental Physics of MR Imaging 1. *Radiographics*, 25(4), pp.1087–1099.
Power, J.D. et al., 2014. NeuroImage Methods to detect , characterize , and remove motion artifact in resting state fMRI. *NeuroImage*, 84, pp.320–341. Available at: http://dx.doi.org/10.1016/j.neuroimage.2013.08.048.
Power, J.D. et al., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, 59(3), pp.2142–2154. Available at: http://dx.doi.org/10.1016/j.neuroimage.2011.10.018.
Puts, N. a J. et al., 2014. Impaired tactile processing in children with autism spectrum disorder. *Journal of neurophysiology*, 111(9), pp.1803–11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24523518.
Rausch, A. et al., 2016. Altered functional connectivity of the amygdaloid input nuclei in adolescents and young adults with autism spectrum disorder: a resting state fMRI study. *Molecular Autism*, 7(1), p.13. Available at: http://www.molecularautism.com/content/7/1/13.
Reynolds, S. et al., 2011. A pilot study examining activity participation, sensory

responsiveness, and competence in children with high functioning autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 41(11), pp.1496–1506.
Robertson, A.E. & Simmons, D.R., 2013. The relationship between sensory sensitivity and autistic traits in the general population. *Journal of Autism and Developmental Disorders*, 43(4), pp.775–784.
Rommelse, N. et al., 2015. Intelligence may moderate the cognitive profile of patients with ASD. *PLoS ONE*, 10(10), pp.1–17.
Satterthwaite, T.D. et al., 2012. Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. *NeuroImage*, 60(1), pp.623–632. Available at: http://dx.doi.org/10.1016/j.neuroimage.2011.12.063.
Seeley, W.W. et al., 2007. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neurosciences*, 27(9), pp.2349–2356.
Shehzad, Z. et al., 2009. The resting brain: Unconstrained yet reliable. *Cerebral Cortex*, 19(10), pp.2209–2229.
Shelley O'Donnell, Jean Deitz, Deborah Kartin, Theresa Nalty, G.D., 2012. Sensory Processing, Problem Behavior, Adaptive Behavior, and Cognition in Preschool Children With Autism Spectrum Disorders. *The American Journal of Occupational Therapy*, 66, pp.586–594.
Shen, X. et al., 2013. Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *NeuroImage*, 82, pp.403–415. Available at: http://dx.doi.org/10.1016/j.neuroimage.2013.05.081.
Shirer, W.R. et al., 2011. Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns W. *Cerebral Cortex*, 22(January), pp.1460–2199.
Stein, L.I. et al., 2011. Oral care and sensory sensitivities in children with autism spectrum disorders. *Special Care in Dentistry*, 31(3), pp.102–110.
Supekar, K. et al., 2013. Brain Hyperconnectivity in Children with Autism and its Links to Social Deficits. *Cell Reports*, 5(3), pp.738–747. Available at: http://dx.doi.org/10.1016/j.celrep.2013.10.001.
Supekar, K., Musen, M. & Menon, V., 2009. Development of large-scale functional brain networks in children. *PLoS Biology*, 7(7).
Thomas, A., Banerjee, A. & Busch, U., 2005. *Classic Papers in Modern Diagnostic Radiology*,
Tomasi, D. & Volkow, N.D., 2012. Aging and Functional Brain Networks. *Molecular Psychiatry*, 17(5), pp.471–558.
Tomchek, S.D. & Dunn, W., 2007. Sensory Processing in Children With and Without Autism: A Comparative Study Using the Short Sensory Profile. *American Journal of Occupational Therapy*, 61(2), pp.190–200. Available at: http://ajot.aota.org/article.aspx?articleid=1866937.
Turi, M. et al., 2016. No rapid audiovisual recalibration in adults on the autism spectrum. *Scientific reports*, 6(February), p.21756. Available at: http://www.nature.com/srep/2016/160222/srep21756/full/srep21756.html.
Uddin, L.Q. et al., 2014. Salience Network–Based Classification and Prediction of Symptom Severity in Children With Autism. *JAMA Psychiatry*, 70(8), pp.869–

879.
Uddin, L.Q., Supekar, K. & Menon, V., 2013. Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Frontiers in human neuroscience*, 7(August), p.458. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3735986&tool=pmcentrez&rendertype=abstract.
Voelker, M.N. et al., 2016. The traveling heads : multicenter brain imaging at 7 Tesla. *Magnetic Resonance Materials in Physics, Biology and Medicine*. Available at: "http://dx.doi.org/10.1007/s10334-016-0541-8.
Wang, L. et al., 2012. Decoding Lifespan Changes of the Human Brain Using Resting-State Functional Connectivity MRI. *PLoS ONE*, 7(8).
Wang, X.H. et al., 2015. Investigating the temporal patterns within and between intrinsic connectivity networks under eyes-open and eyes-closed resting states: A dynamical functional connectivity study based on phase synchronization. *PLoS ONE*, 10(10), pp.1–20.
Weng, S.-J. et al., 2010. Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain research*, 1313(May), pp.202–214. Available at: http://dx.doi.org/10.1016/j.brainres.2009.11.057.
Whitfield-Gabrieli, S. & Nieto-Castanon, A., 2012. Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity*, 2(3), pp.125–141.
Wiggins, J.L. et al., 2011. Using a self-organizing map algorithm to detect age-related changes in functional connectivity during rest in autism spectrum disorders. *Brain research*, 1380, pp.187–197. Available at: http://dx.doi.org/10.1016/j.brainres.2010.10.102.
Wiggins, L.D. et al., 2009. Breif report: Sensory abnormalities as distinguishing symptoms of autism spectrum disorders in young children. *Journal of Autism and Developmental Disorders*, 39, pp.1087–1091.
Van Wijngaarden-Cremers, P.J.M. et al., 2014. Gender and age differences in the core triad of impairments in autism spectrum disorders: A systematic review and meta-analysis. *Journal of Autism and Developmental Disorders*, 44(3), pp.627–635.
Wurnig, M.C. et al., 2013. Variability of clinical functional MR imaging results: a multicenter study. *Radiology*, 268(2), pp.521–31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23525207.
You, X. et al., 2013. Atypical modulation of distant functional connectivity by cognitive state in children with Autism Spectrum Disorders. *Frontiers in human neuroscience*, 7(August), p.482. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3753572&tool=pmcentrez&rendertype=abstract.
Zou, Q. et al., 2015. Reliability comparison of spontaneous brain activities between BOLD and CBF contrasts in eyes-open and eyes-closed resting states. *NeuroImage*, 121, pp.91–105. Available at: http://dx.doi.org/10.1016/j.neuroimage.2015.07.044.