Summer 8-31-2019

Developmental and sex modulated neurological alterations in autism spectrum disorder

Azeezat Azeez
New Jersey Institute of Technology

Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research." If a, user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use" that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select "Pages from: first page # to: last page #" on the print dialog screen

ABSTRACT

DEVELOPMENTAL AND SEX MODULATED NEUROLOGICAL ALTERATIONS IN AUTISM SPECTRUM DISORDER

by
Azeezat Azeez

Autism Spectrum Disorder (ASD) was first described in 1943 by Dr. Leo Kranner in a case study published in *The Nervous Child*. It is a neurodevelopment disorder, with a range of clinical symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), used by clinicians to diagnose mental disorders, a child needs to have persistent social deficits, language impairments, and repetitive behaviors, that cannot be explained by neurological damage or intellectual disability. It is known that children diagnosed with ASD are often are developmentally delayed therefore alterations in the typical developmental trajectory should be a major factor in consideration when studying ASD. As of 2016, 1 in 68 children in the USA is diagnosed with ASD, of those diagnosed young males are four times more likely to be diagnosed than their female peers. Although genetic and behavioral theories exist to explain these differences, the cause for the disparity is still unknown.

This Dissertation presents a unique opportunity to understand the intersection of altered neurodevelopment and the alarming sex disparities in patients with ASD from a neuroimaging perspective. The hypothesis is that there exist differences due to development and sex in with ASD. Access to ABIDE (Autism Brain Imaging Data Exchange), a open source large scale data sharing consortium of functional and anatomical MR data. Analyzing MR data for alterations due to ASD, developmental trajectory, and sex as well as the intersection of these factors. Theses modulations are

observed in three Project Aims that employ various analytical approaches: (1) Structural Morphology, (2) Resting-state Functional Connectivity, and (3) Graph Theory.

The major findings lie at the interaction of these three factors; developmental stage-by-diagnosis-by-sex. Structural Morphological Analyses of anatomical data show differences in cortical thickness, on the left rostral middle frontal gyrus and surface area in along the sensory motor strip, of the left paracentral gyrus and right precentral gyrus. Resting-state Functional Connectivity analyzed in multiple data driven approaches, and altered resting state connectivity patterns between the left frontal parietal network and the left parahippcampal gyrus are reported. The regions found in the Morphological Analyses are used as seeds for *a priori* connectivity analysis, connectivity between the left rostral middle frontal cortex and bilateral superior temporal gyrus as well as the right precentral gyrus and right middle frontal gyrus and left inferior frontal gyrus are described. Finally using Graph Theory analysis, which quantifies a whole brain connectivity matrix to calculate metrics such as path length, cluster coefficient, local efficiency, and betweeness centrality all of which are altered by the interaction of all three factors. The last investigation is an attempt to correlate the behavioral assessments, conducted by clinicians with theses neuroimaging findings to determine if there exist a relationship between them.

Significant interaction effects of sex and development on ASD diagnosis are observed. The goal of the Study is to provide more information on the disorder that is by nature highly heterogeneous in symptomatology. Studying these interactions, may be key to better understand a disorder that was introduced into the medical literature 75 years ago.

DEVELOPMENTAL AND SEX MODULATED NEUROLOGICAL ALTERATIONS IN AUTISM SPECTRUM DISORDER

by
Azeezat Azeez

A Dissertation
Submitted to the Faculty of
New Jersey Institute of Technology
and Rutgers University Biomedical and Health Sciences – Newark
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Biomedical Engineering

Department of Biomedical Engineering

August 2019

.

APPROVAL PAGE

DEVELOPMENTAL AND SEX MODULATED NEUROLOGICAL ALTERATIONS IN AUTISM SPECTRUM DISORDER

Azeezat Azeez

Dr. Bharat B. Biswal, Dissertation Advisor — Date
Distinguished Professor of Biomedical Engineering, NJIT

Dr. Sergei Adamovich, Committee Member — Date
Professor of Biomedical Engineering, NJIT

Dr. Tara L. Alvarez, Committee Member — Date
Professor of Biomedical Engineering, NJIT

Dr. Michael Cole, Committee Member — Date
Assistant Professor, Center for Molecular and Behavioral Neuroscience,
Rutgers University-Newark

Dr. Xin Di, Committee Member — Date
Assistant Research Professor, NJIT

Dr. Xiaobo Li, Committee Member — Date
Associative Professor of Biomedical Engineering, NJIT

Dr. Yiyan Liu MD,PhD, Committee Member — Date
Professor, Radiology Rutgers New Jersey Medical School

BIOGRAPHICAL SKETCH

Author: Azeezat Kikelomo Azeez

Degree: Doctor of Philosophy

Date: August 2019

Undergraduate and Graduate Education:

- Doctor of Philosophy in Biomedical Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2019

- Bachelor of Science in Biomedical Engineering,
  The City College of New York, Grove School of Engineering,
  New York, NY, 2015

Major: Biomedical Engineering

Presentations and Publications:

Azeez, A. K., & Biswal, B. B. (2017). A Review of Resting-State Analysis Methods. *Neuroimaging Clinics of North America, 27*(4), 581-592. doi: https://doi.org/10.1016/j.nic.2017.06.001

Di, X., Azeez, A., Li, X., Haque, E., & Biswal, B. B. (2017). Disrupted focal white matter integrity in autism spectrum disorder: A voxel-based meta-analysis of diffusion tensor imaging studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. doi: https://doi.org/10.1016/j.pnpbp.2017.11.007

Azeez, A. K., X. Di and B. B. Biswal (2017). Biological Sex Modulations on Cortical Thickness in Autism Spectrum Disorder: An Analysis of Autism Brain Imaging Data Exchange II. International Meeting for Autism Research. San Francisco, CA.

I believe, small though we are, insignificant though we may be, we can reach a full understanding of the universe. You were right when you said you felt small, looking up at all that up there. We are very, very small, but we are profoundly capable of very, very big things.

— Stephen Hawking

To Every Teacher, I have encountered in my academic journey, who saw in me a potential, I did not see in myself.

Education is the most powerful weapon
which you can use to change the world.

— Nelson Mandela

To My Grandmother, who planted the value of education into my family tree and sowed seeds of compassion.

We delight in the beauty of the butterfly, but rarely admit
the changes it has gone through to achieve that beauty.

— Maya Angelou

To My Mother, my first teacher, who set an example of hard-work, self discipline, and above all self reliance.

I am the captain of my ship
I am the mistress of my fate
I am the maker of my density

— Adapted from Invictus

To Myself, you are worthy, capable,
and your potential knows no bounds.
Never forget this.

ACKNOWLEDGMENT

I would like to sincerely thank my advisor, Dr. Bharat Biswal, who has helped guide, support, and encourage me in the completion of my PhD. You saw potential in a young scientific mind four years ago. I Thank You.

To my Committee Members; Dr. Sergei Adamovich, Dr. Tara Alvarez, Dr. Michael Cole, Dr. Xin Di, Dr. Xiaobo Li, Dr. Yiyan Liu, I extend my genuine appreciation for taking the time to advise, guide, and provide constructive insights throughout this scientific endeavor.

To all of lab mates in the Brain Connectivity Lab who have aided in research and provided friendship throughout the program; Dr. Keerthana Karunakaran, Hafiz Rakibul, Dr. Marie Wölfer, Dr. Rui Yuan, Dr. Suril Gohel, Dr. Xin Di I thank you immensely.

Many thanks to the Department of Biomedical Engineering, front desk staff, Candida Rocha, Selenny Fabre many thanks for your kindness and professionalism.

And finally I want to extend a huge thanks all of my family and friends who helped me throughout the program with encouraging words, continual prayers, and endless positive energy.

TABLE OF CONTENTS

TABLE OF CONTENTS
(Continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES
(Continued)

Figure **Page**

CHAPTER 1

STUDY INTRODUCTION

In 1943 Dr. Leo Kranner, the leading child psychiatrist of his generation, published the seminal paper *Autistic Disturbance of Affective Contact*. Published in a special edition of *The Nervous Child,* it was the first systematic description of a unique developmental disorder. He profiled 11 cases of children with "fascinating Peculiarities". These features would later become the bases for our current diagnoses of Autism Spectrum Disorders (ASD). Dr. Kranner reported "extreme autistic aloneness;" children showing no desire to communicate with others including their parents, family, caretakers or peers. Inability to use language for commutation; the children had "excellent rote memory" but often spoke with "parrot-like repetitions" it is unclear if they are capable of communication or have a desire to be understand. Children were seen to prefer the sameness of specific sensory stimuli; food, noises, touch, motion; "monotonously repetitious". The lack of communication, pervasive sameness in interest and stereotypical repetitive behaviors were all carefully annotated. These observations would eventually result in the term "infantile autism" to be entered 37 years later, in the 1980 DMSIII (Diagnostic and Statistical Manual of Mental Disorders). Our understanding of Autism has grown since Dr. Kranner's groundbreaking work. It is now defined as a neurodevelopmental disorder whose official name is Autism Spectrum Disorder (ASD), current DSM-5 criteria requires that a:

> *"child has persistent impairments in social communications and interactions across multiple contexts as well as restricted or repetitive patterns of behavior, interests, or activities. These symptoms are present in early childhood and cause significant functional impairments and that these impairments are not better explained by intellectual disability"(Association 2013)*

Symptoms can be detected as early as 18 months after birth, but a reliable diagnosis can be made by age 2 by clinicians who use a variety of clinical measures (Lord, Risi et al. 2006, CDC 2018). Diagnostic tools include, cognitive and observational test; IQ, Autism Diagnostic Observation Schedule (ADOS), and Autism Diagnostic Interview (ADI).

It has been 75 years since the original publication and much has been learned in the psychiatric diagnosis and treatment of the patients as well as our understanding of the basic sciences that govern the disorder; and much research has been conducted on the pathogenesis of ASD; genetic and epigenetic etiology, developmental models (cognitive, emotional, hormonal), and neuropathology (Hobson 1993, Baron-Cohen 2000, Amaral, Schumann et al. 2008, Miller, Bales et al. 2013, Stavropoulos and Carver 2013, Waye and Cheng 2018). Notable advancement have been made in the clinical characterization, treatment options, understanding etiological origins, and heterogeneous pathogenesis of ASD. The emergence of MR technology has expanded our understanding of ASD in the neuroimaging arena.

Magnetic Resonance Imaging (MRI) is allows us to noninvasively image the brain, it uses a series of magnetic fields, radio waves, and field gradients to generate images of inside the body (Azeez and Biswal 2017). This MRI data can be analyzed and morphological measures can be made; gray matter (GM) and white matter (WM) volumes, surface areas, cortical thickness, and gyrification, of the whole brain or specific regions. Like MRI its functional counterpart, fMRI (functional Magnetic Resonance Image) can be used to investigate the state of the brain over time. Metabolic markers can be obtained from fMRI data, most prominent; blood-oxygenation level-dependent (BOLD) signal. BOLD is a metabolic signal that measures changes in the ratio of oxy-

hemoglobin to deoxy-hemoglobin that are attributed to changes in neural activity, this is the most commonly used measure of neurologic change. An examination of these neurological changes that occur without external stimulation, is resting-state. Functional Resting-state connectivity is the synchronization of brain regions that are temporally correlated with one another, yet are spatially remote. Since its inception a number of distinct resting state connectivity networks have been defined and attributed to various neurological/psychological functions (Biswal, Zerrin Yetkin et al. 1995). Various analytical methods are used to calculated connectivity in the temporal domain; independent component analysis (ICA), regional homogeneity (ReHo) and frequency domain; fractional Amplitude of Low Frequency Fluctuation (fALFF), and data driven approaches such as seed-based connectivity. Alterations in these connectivity measures can be suggestive of neurological/psychological disorders.

Since its introduction in the 1995, 24 years ago, technological advancements have generated more connectivity data sets and thus more publications. As a result, the emergence of new multidisciplinary approaches to studying brain connectivity have lent to Complex Network Analysis (Bullmore and Sporns 2009). Borrowed from mathematicians, Graph Theory is a large-world level analysis that attempts to characterize the architecture of a network (van den Heuvel and Hulshoff Pol 2010). It lays down the theoretic framework for these complex topographic networks to be examined. The human brain is one of the most complex biological systems, and graph theory analysis attempts to link the many brain networks into one complex system. The neural networks are constructed from of nodes and edges; nodes representing brain regions, and edges the links between them. This creates a connectivity matrix, illustrative

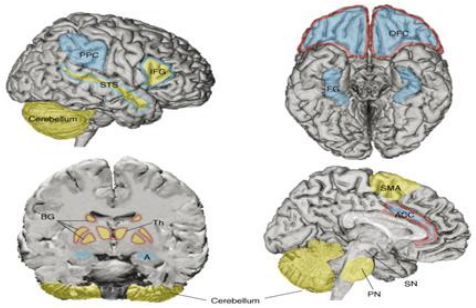
of whole brain network. Nodes can be derived from anatomical data, which correlate to white mater (WM) tracts, myelination axonal fibers that connect different regions of the cortex (Gerrish, Thomas et al. 2014). Node can also originate from functional data, which corresponds to temporal correlation in brain activity. These nodes are created from extracted time-series and cross-correlation of BOLD signal serve as network edges. The location of nodes is determined by brain parcellation atlas. Many of these atlases are derived from anatomical or functional maps; Powers, Dosenaceh, AAL, Craddock (Tzourio-Mazoyer, Landeau et al. 2002, Desikan 2006, Dosenbach, Nardos et al. 2010, Power, Cohen et al. 2011, Craddock, James et al. 2012). Graph Theory Measures fall into various categories of interpretation, basic measures of network architecture, local and global organization, network segregation, integration, and efficiency (Rubinov and Sporns 2010, Wang, Zuo et al. 2010).

These imaging approaches allow us to better characterized neuropsychiatric diseases/disorders. ASD is spectrum of highly heterogeneous clinical traits, quantitative measures of morphology, connectivity and network organization provide biomarkers that we hope can potentially be used in conjunction with behavioral observations from clinicians, to ultimately aid in better patient diagnose and care.

1.1 Study Background

The neuroanatomical representation of ASD, is heterogeneous however areas associated with the pathology are widespread, and overlapping, thus making ASD a difficult condition to characterize globally (Martinez-Murcia, Lai et al. 2016). The three major symptoms of ASD have been associated with specific brain regions. Social impairments:

frontal, superior temporal, parietal lobes and amygdala; Communication deficits: Broca and Wernicke's Area; Repetitive Behaviors: similar to regions found in OCD, orbital frontal cortex and caudate (Ha, Sohn et al. 2015). Structural differences that have been reported show that there are differences in gray and white matter cortical thickness, as well as overall total brain volume (Amaral, Schumann et al. 2008).



Social impairment	Communication deficits	Repetitive behaviors
OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala mirror neuron regions IFG – Inferior frontal gyrus PPC – Posterior parietal cortex	IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei cerebellum	OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus

TRENDS in Neurosciences

Figure 1.1 Regions Associated with Autism Spectrum Disorder Symptomology: Brain areas that have been implicated in the mediation of the three core behaviors that are impaired in ASD: social behavior, language and communication, and repetitive and stereotyped behaviors.

Sources: Amaral, D., Schumann, C., & Nordah, l. C. (2008). Neuroanatomy of autism. Trends in Neruoscience, 137-145.

Prevalent in about 1-2% of the population the disorder has a distinct effect on neurodevelopment (Kim, Leventhal et al. 2011). The absence of key social, communication and cognitive milestones; lack of eye contact, social smiles, aversion to intimacy and unusual sensory behavior, may point towards a diagnoses of ASD (Dereu, Warreyn et al. 2010). It is been established that human neurodevelopment doesn't follow a linear trajectory, cognitive, structural and functional changes occur following an inverted U shape. This non-linear trajectory follows a pattern of gradual increases in childhood, then peaks in adolescence, then sustained loss continuing into adulthood (Giedd, Blumenthal et al. 1999, Gogtay and Thompson 2010). A child's failure to meet

developmental milestones in time or at all, can be indicative of a pervasive developmental disorder. Table 1.1 is a brief summation of some relevant developmental milestones of children aged two months- five years. This inherent disruption of development make developmental trajectory an outstanding co-factor to consider when studying ASD.

Biological sex is a major variable in typical neurodevelopment, as young women, reach developmental peaks 1-2 year before their male peers (Giedd, Blumenthal et al. 1999). Males also have greater total brain volumes and cerebral spinal fluid (CSF) volumes in ventricle, and (Cosgrove, Mazure et al. 2007, Ruigrok, Salimi-Khorshidi et al. 2014). The role of sex has modulating effects on performance on verbal and spatial cognitive task (Cosgrove, Mazure et al. 2007). Male perform better on motor and spatial cognitive task, while females are faster in emotion identification and nonverbal reasoning task (Satterthwaite, Wolf et al. 2015). More importantly, of those diagnosed with ASD, a sex disparity persist, males are approximately four times more likely to be diagnosed than females (Werling and Geschwind 2013). Popular theories suggest a genetic, hormonal, or psychosocial mechanism for the inequality in diagnoses. "Female Protective Effect," proposes that females with ASD are protected from the symptoms of ASD, as they require more genetic abnormalities to be diagnosed (Jacquemont, Coe et al. 2014). The "Extreme Male Brain Theory", implies that ASD is the extreme of a typical male brain profile, built to systemize rather than empathize (Baron-Cohen 2002). Female "cloaking", a psychosocial mechanism, suggests that females are naturally better at social mimicry, as a result they seem to evade diagnosis (Attwood and Grandin 2006). Finally the hypo-connectivity theory of ASD attributes the disorder to reduced anatomical and functional

connectivity between frontal and posterior cortical regions (Just, Keller et al. 2012). There is still no agreed upon theory; thus, this presents the prospect of using imaging techniques to define quantifiable neurological measures. ASD is neurodevelopmental disorder with a disproportional prevalence in one sex, this presents a compelling opportunity to study the interplay of two factors that may have a great influence on the presentation of the disorder.

Table 1.1 Childhood Developmental Milestones

Age	Social/ Emotional	Communication/ Language	Cognitive
2 Months	Voluntarily eye contact	Turns head towards sound	Cries when board
4 Months	Social smiles	Copies sounds	Follows moving thing with eyes
6 Months	Responds to others emotions	Babbled speech	Curiosity about things
9 Months	Has favorite toy	Understand "no"	Responds to own name
12 Months	Has affinity for people and objects	Says mama/dada	Copies gestures
18 Months	May have temper tantrums	Says and shakes head "no"	Can follow 1-step verbal commands
2 Years	Parallel play with other children	Used 2-4word sentences	Recognizing familiar people and objects
3 Years	Shows affection for friends	Speaks in sentences	Can sort objects by shape/color
4 Years	Plays with other children	Constantly asking questions	Understands counting and time
5 Years	Wants to be liked by friends	Can tell simply stories	Can dress self

Source**:** CDC. (2017). Milestone Checklist. https://www.cdc.gov/ncbddd/actearly/pdf/checklists/all_checklists.pdf
Dereu, M., Warreyn, P., Raymaekers, R., Meirsschaut, M., Pattyn, G., Schietecatte, I., & Roeyers, H. (2010). Screening for Autism Spectrum Disorders in Flemish Day-Care Centers with the Checklist for Early Signs of Developmental Disorders. Journal of autism and developmental disorders, 40(10), 1247-1258. doi:10.1007/s10803-010-0984-0
Speaks, A. (2018b). Developmental Milestones by Age. https://www.autismspeaks.org/what-autism/learn-signs/developmental-milestones-age

1.2 Neurodevelopment in Typically Developing Populations

There are differences in developmental stages of Typically Developing (TD) populations, the cognitive ability of children, compared to adolescents and adults is evident. These differences can be seen in morphological studies of gray and white matter, in differences in functional connectivity, as well as changes in graph theory measures. The cognitive

trajectory of humans is one that becomes more fine-tuned with age; early milestones are centered about mastering primary; motor, sensory, and language functions. As humans begin to mature, higher order skills will manifest; sensor motor integration, spatial awareness, language comprehension and sustained attention (Casey, Tottenham et al. 2005). Anatomical differences report non-linear changes in gray matter volume in childhood and adolescents (Gogtay and Thompson 2010). GM volume follows an inverted U shape, with peaks at different lobes at different times (Lenroot and Giedd 2006). The GM trajectory follows that of the cognitive one, lower order to higher order. Most GM volume increases are seen prior to puberty and are followed by volume loss post-puberty (Giedd, Blumenthal et al. 1999). The signs of cortical maturation are seen as GM loss first in dorsal parietal cortices those involved in the primary sensor motor activities, then to frontal cortex, associated higher order cognitive function. Lastly the temporal cortex; important for integrating audio-visual inputs, object recognition and the integration of memory, is the last lobe to reach adult levels of maturation (Calvert 2001, Martin and Chao 2001). Although frontal lobes begin to mature early they do not stop until well into late adolescent, particularly in the dorsal lateral prefrontal cortex, know to play a major role in decision making abilities, executive function, and inhibitions (Gogtay, Giedd et al. 2004).This observed socially as the risky and immature behavior often seen in adolescences. Sex plays a major role in GM volume rates, as females reaching peak volume 1-2 year earlier then male counterparts (Giedd, Blumenthal et al. 1999). Parietal lobe peaks occur at 10.2 years for girls, 11.8 for boys, frontal lobe peaks occur at 11 years for girls and 12 for boys, and finally peaks at 16.7 for girls and 16.2 for boys in the temporal lobe (Giedd, Blumenthal et al. 1999). Typical WM volume

trajectories unlike GM, is increases linearly with age, decreases don't begin to manifest until age 40 (Giedd, Blumenthal et al. 1999).

Functional connectivity, follows a similar pattern, networks with higher order function show significant differences between children and adults, with children having weaker with-in network integration in the DMN, and attention networks (de Bie, Boersma et al. 2012, Hoff, Van Den Heuvel et al. 2013). While networks associated with primary functions that mature early in childhood, show little difference between adults and children (de Bie, Boersma et al. 2012). In early childhood during the first two years of life, the sensory motor network has the most significant increase in growth, this is followed by visual networks. This increase in network size is seen in the DMN and dorsal attention, but the network is also the most fragmented at this time, which is a possible sign of immaturity (Lin, Zhu et al. 2008, Gao, Zhu et al. 2009). A characteristic of immaturity is weak-within-network connectivity and is seen in the default mode, cingulo-opercular, ventral, and dorsal frontoparietal networks, all higher-order cognitive networks (de Bie, Boersma et al. 2012). As children approach adolescents the configuration of these higher-order networks become comparable to those of an adult (Jolles, van Buchem et al. 2011, Hoff, Van Den Heuvel et al. 2013). This further demonstrates that more complex functions may require more fine-tuning as adolescents reach adulthood.

"A healthy mature human brain is optimally organized into a collection of specialized functional networks that flexibly interact in rapid response to various cognitive demands" (Wang, Zuo et al. 2010). This is a small world organization, one that is simultaneously highly segregated and integrated(Rubinov and Sporns 2010). Mathematically speaking, a network with high local clustering coefficients, and low

characteristic path lengths. In prenatal development, the neural communications consist of mostly short range links between regions, as humans begin to age theses small local networks become increasing integrated and longer connections form between occipital, parietal, temporal, and frontal lobes (Fair, Dosenbach et al. 2007, Fair, Cohen et al. 2009, Hoff, Van Den Heuvel et al. 2013). In children, the frontoparietal and cingulo-opercular is a singular connected network that gradually becomes two distinct networks in adulthood. The DMN also becomes more densely connected in adulthood suggesting an increases in functional integration (Fair, Dosenbach et al. 2007). Dosenbach showed in TD participants aged 7-30 a weakening of short rages connections and strengthening of long rage ones correlated with age (Dosenbach, Nardos et al. 2010). While on a global scale, the human brain becomes more integrated with age. Specific networks reach a mature local efficient at different stages. The primary sensory motor networks reach a maturity between 5-9 years old, early in childhood while these efficiency levels are seen in high-order associative networks (Khundrakpam, Reid et al. 2013). The centrality of a node changes also with age (Sridharan, Levitin et al. 2008, Menon and Uddin 2010). The right fronto-insular cortex (rFIC) a hub which lies in the Salient network, mediates attentional control between external (central executive network) and internal (DMN) stimuli. Uddin and colleges reported that the nodes influence on the salient and executive control networks is weaker children (Uddin, Supekar et al. 2011). Taken together these studies support that childhood is spent developing sensory motor functional, while adulthood sees the maturation of higher order cognitive control. The use of graph theory metrics have shown that with normal aging come a brain network that is more globally integrated (Wang, Zuo et al. 2010). Reports have also shown reduced efficiency, both

globally and locally (Achard and Bullmore 2007). Shifting hubs of centrality have also been seen as subjects mature (Meunier, Achard et al. 2009)

Developmental changes exist in TD populations, and have been quantified using various analytical methods; morphological, resting state connectivity, and graph theory metrics (Ernst, Torrisi et al. 2015). These finds help to establish a comparison when we explore alteration caused by neurodevelopmental disorders- Autism Spectrum Disorder.

1.3 Sex Differences in Typically Developing Populations

In TD populations, there exist differences between the female and male brain, as noted by rates of cognitive maturity. On a structural level, males on average have larger total brain volumes then women. Difference in structure are highly influenced by age and neurological stages of development (Ruigrok, Salimi-Khorshidi et al. 2014). In 2014, Ruigrok and colleagues used meta-analysis to demonstrate that the amygdala, hippocampus, insula, and temporal poles are areas where gray matter volume is greater in males. Frontal gyrus and orbital cortex are corresponding areas with greater gray matter volume in females. Gray matter volume in the frontal and parietal lobes are larger in girls during puberty (Lenroot, Gogtay et al. 2007). White Matter (WM) alterations also exist, men and adolescent boys had higher WM volumes than their female counterparts (De Bellis and Keshavan 2001, Lenroot, Gogtay et al. 2007, Perrin, Leonard et al. 2009). WM integrity also varies between the sexes; specifically, the results have showed higher fractional anisotropy, as measured by DTI in the left occipito-parietal, frontal, and left parietal regions (Biswal, Mennes et al. 2010).

Resting state and task-active studies have also confirmed that significant sex modulated connectivity differences do exist. ICA and seed based analysis revealed significantly greater resting state connectivity between the posterior cingulate cortex, medial prefrontal cortex and the inferior parietal lobe (DMN) in women (Biswal, Mennes et al. 2010). These studies support the assumption that structural and functional differences exist, between the sexes.

In healthy adults, men have reported higher path lengths in the right hemisphere, but lower clustering coefficients in the left hemisphere, suggesting a hemispheric interaction (Gong, He et al. 2011, Tian, Wang et al. 2011). Asymmetry due to sex has been reported cognitive as well as functionally, suggesting these hemispheric asymmetries can be seen in topological analysis. Greater local and global efficiencies were reported in women. In the left Heschl's gyrus, superior temporal gyrus, superior parietal gyrus, inferior parietal gyrus, insula, and right fusiform gyrus, women have higher regional efficiencies, while only right rolandic operculum and triangular inferior frontal gyrus where greater in men (Gong, Rosa-Neto et al. 2009). Very few publications exist on the use of graph theory methodology to study natural sex differences.

Longitudinal studies have provided valuable insight as to the typical changes expected in a healthy persons aging. Anatomical and functional maturity on the cortex parallel with those of cognition; with primary functions evolving early in life, followed by complex systems later in life. There are underlying neurological differences that exist due to typical development and sex. The presences of ASD alters the brain noticeably and its effects can be seen in morphological in changes in primary visual cortex, superior temporal gyrus, frontal cortical areas. In resting state functional connectivity alterations

in DMN, Salience and Attention networks have been reported. The hypo-connectivity theory of ASD is quite popular and has also been reported (Just, Keller et al. 2012). But recent studies report an overall hypo-connectivity in males with ASD and hyper-connectivity in females (Alaerts, Swinnen et al. 2016). Graph Theory network analysis suggest that atypical distribution changes the underpinning connectivity pattern. Currently, there is not a clear understanding as to how sex and development contribute to the neurological and clinical representation of ASD. The timing and a ability to reach maturation in males and females is what classifies subjects as typically developing. Comparing these TD populations with a disease population is imperative to explore the neuropathology of ASD and the intersection of development and sex.

1.4 Study Rational

In recent years, awareness as grown in the pop-cultural sphere of ASD, television and films have portrayed fictional and non-fictional characters with ASD and their families authentically; *Rain Man (1988), Temple Grandin (2010), The Good Doctor (2017), Atypical (2017),* and most recently the debut of autistic Muppet Julia on *Sesame Street (2017).* The Centers for Diseases Control (CDC) has reported as of 2018 1 in 59 children in the United States is diagnosed with ASD (CDC 2018). The prevalence has steadily been increasing. In 2012, the occurrence was 1 in 68, a 15% increase (Speaks 2018). Of those diagnosed with ASD young males are four times more likely to be diagnosed than their female peers (CDC 2018). Interestingly, the State of New Jersey has the highest prevalence in the US, 1 in 46 (Baio 2012). The combination of alarming statistics and

increased culturally awareness have coincided with many research initiatives to further our scientific understanding.

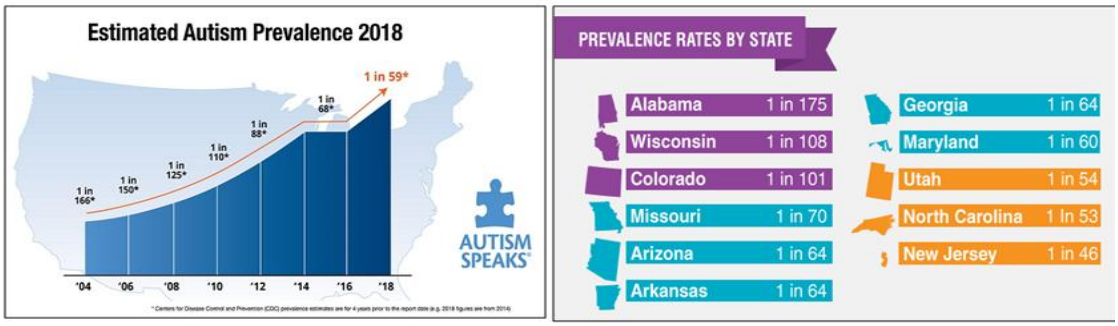


Figure 1.2 Prevalence of Autism Spectrum Disorder: In the US the rates have been steadily increasing in the past 10 years, as of 2018 1 in 59 children are diagnosed. Currently the state of NJ has the highest rate(1/46), higher than the national average.

Source: CDC. (2018a). Data & Statistics on Autism Spectrum Disorder. http://www.cdc.gov/ncbddd/autism/data.html
Speaks, A. (2018a). CDC increases estimate of autism's prevalence by 15 percent, to 1 in 59 children: Autism Speaks calls on nation's leaders to adequately fund critically needed research and support services. https://www.autismspeaks.org/science-news/cdc-increases-estimate-autisms-prevalence-15-percent-1-59-children
Healthline. (2010). Autism Rates by State. https://www.healthline.com/health/autism/autism-rates-by-state#1

This Dissertation presents the unique opportunity to explore the intersection of altered neurodevelopment and the alarming sex disparities in patients with ASD from a neuroimaging perspective, using multiple analytical approaches. ASD is a complex heterogeneous lifelong neurodevelopmental disorder. It requires a multifaceted approach as the underling disorder alters the brain. We studied if there exist neurobiological interactions due to development and/or sex in children with ASD. We analyze MR data and hypothesize that these quantifiable interactions exist in three **Projects: (1) Structural morphology, (2) Resting-state functional connectivity, and (3) Graph Theory**.

PROJECT 1: Structurally Morphology

Specific Aim 1:To determine if there exist structurally difference due to the interactions of developmental trajectory and biological sex in ASD diagnoses. We will investigate what differences exist between subjects with ASD and their typically developing (TD) counterparts. Using structural measures we will compute differences in cortical thickness and surface area, on the cortical surface.

PROJECT 2: Resting-State Functional Connectivity

Specific Aim 2:To determine if there exist functional difference in the interactions of developmental trajectory and biological sex in ASD diagnoses. Using resting state analytical methods we will identify connectivity differences between the ASD and TD groups as they interact with development and sex. Focus on networks associated with sensory processing, visual, auditory, salience, and default mode networks, all whom have been reported in ASD studies. We will observe with-in network connections, using Regional Homogeneity (ReHo), fractional Amplitude Low Frequency Fluctuations (fALFF), and Independent Component Analysis (ICA).

PROJECT 3: Graph Theory

Specific Aim 3: To determine if there exist changes in global and local Brain Network Organization ASD. Using a Graphical Theory approach we will explore difference in network properties as a result of these clinical factors We will determine if and how much of a contribution each of these factors play in the neuroimaging and clinical presentation of the ASD. Finding altered connectivity and/or morphological trajectories in male and females with ASD at different developmental time points would be pivotal to

the research of understanding the sex disparity as well as the variation in clinical presentation of the disorder. And ultimately providing insight to the long debated theories of connectivity (over or under).

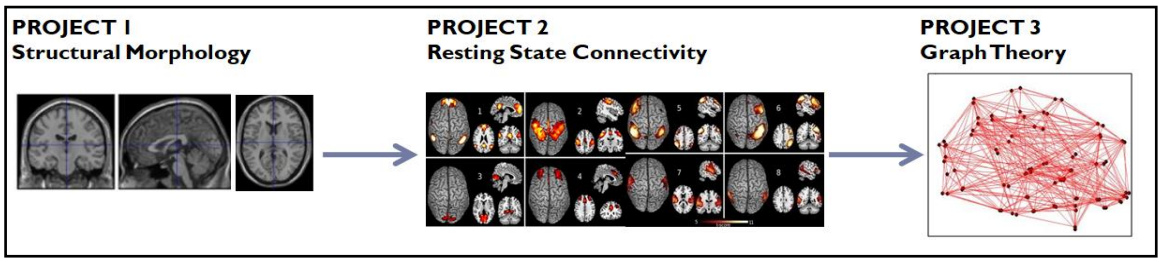


Figure 1.3 Study Flow: The overall approach to the investigation of the interactions of development stage and sex in ASD. Our study is pursued from three methodologies in Projects: (1) Structural Morphology, (2) Resting-state Functional Connectivity, and (3) Graph Theory.

1.5 Subject Pool

For all three Projects of this Dissertation , we source our imaging data from Autism Bank Imaging Data Exchange (ABIDE) (http://fcon_1000.projects.nitrc.org/indi/abide). ABIDE is a large scale data sharing consortium, "where functional and anatomical imaging data have been aggregated from various sites and has helped researchers accelerate our understanding of the neural bases of autism"(Di Martino, Yan et al. 2013). The global collaboration is funded by the National Institute of Health was founded by Dr. Adriana Di Martino. All contributing investigators and institutes who were willing to share previously collected awake resting-state fMRI data and associative MR Images as well as phenotypic information; diagnostic information, age at scan, sex, IQ, and ASD behavioral assessment. All data was approved by local Institutional Review Boards and participants protected information identifiers were removed in accordance to HIPPA guidelines. All data in the consortium was visually inspected and corresponding

phenotypic data where inspected for quality assurance. Its first release, ABIDE I was made publically available in August 2012, a total of 1112 (539 ASD, 573 TD) datasets, ages 7-64 were sourced from 17 different sites (Di Martino, Yan et al. 2014). While the establishment of ABIDE "demonstrated the feasibly and utility of aggregated MRI data across sites" (Di Martino, O'Connor et al. 2017). It did reveal some caveats of large data banks; site collection variability, differences in demographics and imaging parameters and unbalanced male to female ratios. Although the data sets are incredibly heterogeneous, significant result have been published on varying hypothesis on ASD populations (Martinez-Murcia, Lai et al. 2016). Its second iteration, ABIDE II attempts to address these pitfalls, increased sample size, better phenotypic characterized, increased number of available datasets from females with ASD, and a subset of dataset with Diffusion Tensor Images (DTI). ABIDE II was released in June of 2016 and has a total of 1114 (521 ASD, 593 TD) datasets, aged 5-64 years sourced from 19 sites. Two sites include longitudinal samples collected over a 1-4 year interval, more samples with phenotypic characterization, and an additional 73 datasets from females with ASD form the 65 in ABIDE I.

The open and free exchange of data promotes neuroimaging discovery in ASD. It has thus far yielded many collaborations, findings, and publications since its release to the scientific community in 2012. The largeness of the data bank allows us to study a heterogeneous cohort, intersection of alarming ASD incidence, and gender statistics our access to this immense MRI data; is the unique junction that the current dissertation resides.

All of the subjects for our research are sourced from the two releases of the banks, ABIDE I and II a total of 428 subjects. Each bank is sources from multiple sites all which have their own scanning protocols and image resolutions each subject anatomical and functional image was visually inspected for quality assurance. ABIDE I sources images from five sites uses California Institute of Technology, NYU, University of Pittsburg, UCLA, and Yale and ABIDE II from six sites; Institut Pasteur and Robert Debré Hospital, Indiana University, Olin Neuropsychiatry Research Center Institute of Living at Hartford Hospital, Kennedy Krieger Institute, Georgetown University, and Oregon Health and Science University. Table 1.3 describe data acquisition parameters for each site. To explore the interaction of developmental stage and sex we divided the ASD and TD data by developmental stages; adult, 18 years and older and child, under 11 years of age. We choose from sites where there were at least two female subjects with ASD, to circumvent the limitations of this specific cohort. Subjects with Full IQ below 70 are excluded, for subjects without this information, the site criteria excluded subjects FIQ below 80 (Institut Pasteur and Robert Debré Hospital). All individuals with ASD have been clinical diagnosed using the DSM-IV criteria and no other existing co-morbidities. TD participants have no history of neurological or psychiatric disorders. Table1.2 describe Participants Demographics for our research. For each individual Project subjects may have been removed due to specific Project criteria.

Table 1.2 Participant Demographics

Participant Demographics	**ASD**	**TD**	**p-val**
Children(<11) n=229	105	124	
SEX			
Male	76	70	
Mean age(std)	9.47(1.15)	9.49(1.07)	0.93
Age range	7-10.96	6.47-10.99	
Mean Full IQ(std)	107.96(18.56)	114.13(13.87)	0.02
ADOS Social	8.01		
ADOS Communication	3.58		
ADOS Behavior	2.63		
ADOS Total	11.85		
Female	29	54	
Mean age	9.15(1.22)	9.41(0.90)	0.27
Age range	6.05-10.97	8.04-10.96	
Mean Full IQ	104.93(16.57)	117.32(14.63)	0.001
ADOS Social	8.10		
ADOS Communication	3.73		
ADOS Behavior	2.36		
ADOS Total	13		
Adult(>18) n=199	73	126	
SEX			
Male	57	85	
Mean age(std)	25.21(7.27)	25.51(6.80)	0.80
Age range	18-55.4	18.59-56.2	
Mean Full IQ(std)	111.41(13.40)	115.92(10.0)	0.02
ADOS Social	7.41		
ADOS Communication	3.67		
ADOS Behavior	1.57		
ADOS Total	11.08		
Female	16	41	
Mean age(std)	26.26(9.59)	25.68(7.21)	0.81
Age range	18.06-54	19-46.6	
Mean Full IQ(std)	112.47(19.57)	112.41(12.44)	0.99
ADOS Social	8.5		
ADOS Communication	3.93		
ADOS Behavior	1.93		
ADOS Total	12.43		

Table 1.3 Imaging Parameters

Site	n	Scanner	T1 Voxel Size(mm)	TR (ms)	TE (ms)	Time Points	fMRI Voxel Size (mm)	No. Slices
ABIDE I	**196**							
California Institute of Technology (Caltech)	36	Siemens Trio 3T	1.0x1.0x1.0	2000	30	150	3.5x3.5x3.5	34
New York University (NYU)	106	Siemens Allegra 3T	1.3x1.0x1.3	2000	15	180	3.0x3.0x4.0	33
University of Pittsburg School of Medicine (Pitt)	22	Siemens Allegra	1.1x1.1x1.1	1500	25	200	3.1x3.1x4.0	29
University of California Los Angeles (UCLA)	16	Siemens Trio 3T	1.0x1.0x1.2	3000	28	120	3.0x3.0x4.0	34
Yale School of Medicine	16	Siemens Trio 3T	1.0x1.0x1.0	2000	25	200	3.4x3.4x4.0	34
ABIDE II	**231**							
Institut Pasteur and Robert Debré Hospital (IP)	37	Philips Achieva 1.5T	1.0x1.0x1.0	2700	45	85	3.59x3.65x4.00	32
Indiana University (IU)	39	Siemens Trio 3T	0.7x0.7x0.7	813	28	433	3.4x3.4x3.4	42
Olin Neuropsychiatry Research Center Institute of Living at Hartford Hospital (ONRC)	31	Siemens Skyra	0.8x0.8x0.8	475	30	947	3.0x3.0x3.0	48
Kennedy Krieger Institute (KKI)	58	Philips Achieva 3T	1.0x1.0x1.0	2500	30	128/156	3.0x3.0x3.0	47
Georgetown University (GU)	52	Siemens Trio 3T	1.0x1.0x1.0	2000	30	152	3.0x3.0x2.5	43
Oregon Health and Science University (OHSU)	14	Siemens Trio 3T	1.0x1.0x1.1	2500	30	120	3.8x3.8x3.8	36
TOTAL	**427**							

ABIDE I from 5 sites: Caltech, NYU, Pitt, UCLA, Yale

ABIDE II from 6 sites: IP, IU, ONRC, KKI, GU, OHSU

CHAPTER 2

MORPHOLOGY ALTERATIONS IN AUTISM SPECTRUM DISORDER DUE TO DEVELOPMENTAL AND SEX INTERACTIONS

Young males are four times more likely to be diagnosed than their female peers. Although, genetic and behavioral theories exist to explain these differences, the cause for the disparity is still largely unknown. Children diagnosed with ASD often are developmentally delayed, and therefore it is of the most importance that they are diagnosed, early, correctly and receive intervention as soon as possible as to mitigate the social, behavioral and communication abnormalities that are classically associated with the disorder. Alterations in the developmental trajectory should be a major factor for consideration when studying ASD.

We sourced our data from the Autism Bank Imaging Data Exchange (ABIDE), and open source consortium of anatomical and resting state MRI data compiled from various imaging institutes. Approximately 500 subjects anatomical MR scans are visually inspected for quality assurance before inputted into FreeSurfer for an automated morphological analysis of Cortical Thickness and Surface Area. We report morphological changes at the intersection of developmental stage-by-diagnosis-by-sex. We find clusters of significance in our inquires of cortical thickness, in the left rostral middle frontal cortex and surface area, over the left paracentral and right precentral gyrus. We also report associative interactions and main effects of each factor. Ultimately our results demonstrate the use of quantitative measures to further our understanding of a disorder that has eluded the neuroscientific community, in the hopes that these stride will improve the quality of life of all patients, of every sex and developmental stage.

2.1 Background

Structural differences that have been reported, with a diagnosis of ASD. Differences in GM, WM, and cortical thickness, as well as overall total brain volume have been shown (Amaral, Schumann et al. 2008). Vertex based studies suggest that ASD subjects have thinner cortices and reduced surface are (Ecker, Shahidiani et al. 2014). In ASD reductions in white matter integrity are reported, partially in regions associated with emotional processing, language, and executive functions, splenium of the corpus callosum, and the anterior thalamic nuclei (Noriuchi and Kikuchi 2010). DTI studies have made strong correlations with reduced FA in ASD subjects in the cerebral peduncle and reduced scores in motor task (Hanaie, Mohri et al. 2013). White matter reductions are reflective of decreases in fiber density and lack of fiber coherence, these differences are only seen in children with ASD, suggesting structural changes coincide with adolescent developmental growth.

It has been established that typical human neurodevelopment does not follow a linear trajectory, cognitive, structural, and functional changes occur with age. The signs of cortical maturation are seen as GM volume loss (Lenroot and Giedd 2006). GM volume follows an inverted U shape, with peaks at different lobes at different times. Volume increase are seen up until adolescences, at which point they begin to plateau and decline into adulthood (Thompson, Sowell et al. 2005). Although frontal lobes begin to mature early, they do not stop until late into end adolescent, particularly in the dorsal lateral prefrontal cortex, know to play a major role in decision making abilities, executive function, and inhibitions (Gogtay, Giedd et al. 2004). This is seen culturally as the risky and immature behavior often see in adolescences. Much of childhood is spent mastering

primary motor and language skills and this is reflected in the brain regions that mature at these developmental milestones (Casey, Tottenham et al. 2005). In infancy areas that support vision, hearing and sensorimotor functions; occipital, temporal, and sensorimotor cortexes mature rapidly. While areas of speech, language comprehension, and executive function, seem to follow the human evolutionary sequences (Dennis and Thompson 2013).

The decreases in GM have also been associated with cortical pruning, as WM connections are systematically eliminated with age (Sowell, Peterson et al. 2003). In childhood major lobes, showed cortical thinning with age, while Brocas and Wernicke's areas thickened (Sowell, Thompson et al. 2004). The active changes in GM make developmental trajectory an outstanding co-factor to consider when studying morphology in ASD. In the clinical setting the absence of key social, communication and cognitive milestones; lack of eye contact, social smiles, aversion to intimacy and unusual sensory behavior, early in life may point towards a diagnosis of ASD (Dereu, Warreyn et al. 2010).It should also be noted that biological sex is a major variable in typical neurodevelopment, young women, reach developmental peaks 1-2 year before their male peers (Giedd, Blumenthal et al. 1999).

When observing differences in neurotypical populations, we must also consider the effects of sex. Studies have shown that men outperform women in motor and spatial cognitive task while women perform better emotional identification and nonverbal reasoning task (Satterthwaite, Wolf et al. 2015). GM differences also exist due to sex, overall men have larger GM volumes, and specifically greater volumes in the amydgala, hippocampus, and temporal poles while women have greater GM volumes in middle

frontal gyrus, thalamus, and frontal pole (Ruigrok, Salimi-Khorshidi et al. 2014). Sex difference in the human brain structure are normal but the alarming sex gap seen in ASD diagnoses is one of great scientific interest (Cosgrove, Mazure et al. 2007, Werling and Geschwind 2013).

In this Project, we aim to explore the individual role of development and sex and subsequent interactions on the neuroanatomical presentation on ASD. We hypothesize that there exist structural difference due to the interactions of developmental stage and biological sex in ASD diagnoses. We report differences that exist between adult and children, both male and female with ASD and their typically developing (TD) counterparts. We compute morphological measures, cortical thickness and surface area and explore alteration in these measures as a result of sex, developmental stage in ASD.

2.2 Methods

Participants: High resolution T1-weighted anatomical MR images were downloaded from Autism Bank Imaging Data Exchange (ABIDE). Typical spatial resolution of these images are $1mm^3$, specify site resolution can be seen in Table 1.2

Table 2.1 Projects 1 Subject Pool

AGE	ASD Female	ASD Male	TD Female	TD Male	Total
Child(<11) n	29	67	51	65	**212**
Mean age	9.15	9.39	9.44	9.49	
Age range	6.05-10.97	7-10.96	8.04-10.96	6.47-10.99	
Mean FIQ	104.92	108.77	116.90	114.68	
Adult(>18)n	14	57	41	85	**197**
Mean age	25.82	25.21	25.68	25.51	
Age range	18.06-54	18-55.4	19-46.6	18.59-56.2	
Mean FIQ	108	110.41	112.40	115.92	
Total	**43**	**124**	**92**	**150**	**409**

Data Processing: MR images were processed using FreeSurfer, v5.3 (https://surfer.nmr.mgh.harvard.edu), an open-source software package, to derive models of the cortical surface. The well-validated pipeline allows for calculations of the anatomical brain, including sub-cortical volumes and cortical morphology equivalent to manual methods (Fischl and Dale 2000). The pre-processing steps include; intensity normalization, registration to MNI native space, skull stripping, tissue segmentation, surface tessellation of the white matter boundary is generated using a deformable template (Fischl and Dale 2000). After visual inspection, 17 subjects where rejected due to poor registration to the MNI template. Thus a total of 409 subjects (212 children and 197 adults) are used for morphological calculations Table2.1. Vertex-wise measures of cortical thickness and surface area are computed from the 3D cortical mesh model of approximately 150,000 vertices over each hemisphere. This was followed by a 10mm full width at half maximum (FWHM) Gaussian kernel spatial smoothing. neuroanatomical labels are automatically assigned to each location on the cortical surface. All scans were processed on the same hardware and software to avoid confounding covariates.

Statistical Analysis: We wanted to localize regions on the cortical surface where development, sex and diagnosis of ASD interact to alter cortical thickness and surface area. We used a general linear model (GLM) to estimate the interaction of diagnosis (ASD, TD)-by-developmental stage(Adult, Child)-by-sex(Male, Female) for both cortical thickness and surface area. Using this 2 (Developmental stage)x 2 (Diagnosis) x 2 (Sex) ANOVA to test significance. The test was then followed by a Monte Carlo cluster-wise multiple comparison simulation for cortical thickness and surface area. The simulation was run with 10,000 iterations, with cluster-wise threshold set to voxel p=0.01, clusters

are considered significant if α=0.05. FreeSurfer annotation labels give us the location of maximum clusters and voxel size, we report the most significant clusters for each test and group means at this location.

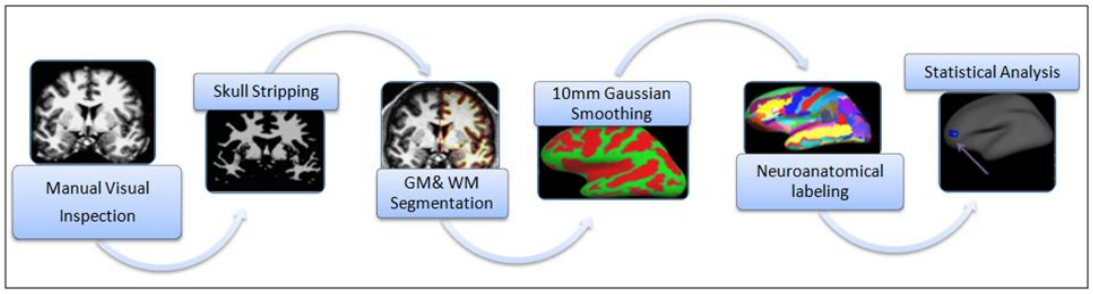


Figure 2.1 Morphological Methods: Using FreeSurfer vertex-wise measures of cortical thickness and surface area are calculated

2.3 Results

We report difference in the main effects of each experimental factors (developmental stage, diagnosis, sex). Along with this we also report interaction effects in cortical thickness and surface area all summarized in Table 2.2. Our corresponding figures include, cluster size, and annotation label, as well as group mean plots with standard error of mean error bars for each factor, we only report the most significant cluster in each hemisphere.

Table 2.2 Project 1 Results

EFFECTS	Cortical Thickness	Surface Area
developmental stage-by-diagnosis-by-sex Interaction	LH Rostral Middle Frontal Cortex	LH Paracentral Gyrus RH Precentral Gyrus
diagnosis-by-sex Interaction	-	-
developmental stage-by-diagnosis Interaction	RH Supramarginal Gyrus	-
developmental stage-by-sex Interaction	LH Posterior Cingulate RH Posterior Cingulate	LH Entorhinal Cortex RH Medial Orbitofrontal Cortex
Main effect of Development	Globally	LH Insula RH Insula
Main effect of Sex	LH Transverse Temporal RH Superior Frontal Gyrus	Globally
Main effect of Diagnosis	LH Lingual	LH Middletemporal Gyrus

Interaction Effects of Cortical Thickness: When observing the interactions of development-by-sex-by-diagnosis we find a significant cluster in the left hemisphere rostral middle frontal cortex (rMFC) ($p=0.03$, size=$452.30mm^3$).The cluster-wise subject average is calculated for each group at the most significant cluster. We see in our TD populations in childhood females have an additional 0.021mm of thickness, while in adulthood the inverse occurs, males have an additional 0.047mm of thickness in the rMFC. In the case of ASD groups we find that group averages show that female children have thinner cortexes compared to males the 0.298mm reduction is the largest between sexes in all groups. while in adulthood on average females have 0.173mm more cortical thickness than males. Of all 8 distinct groups (three factors with two levels each), male children with ASD have the greatest cortical thickness (CTh) of all groups, (CTh=2.634mm) while TD female adults had the thinnest (CTh=2.291mm)[Figure 2.2].

Interactions of developmental stage-by-diagnosis are localized to the right supramarginal gyrus (p=0.0012, size=738.67mm^3), of the 4 groups (Child/Adult, ASD/TD) the general trend is that ASD subjects both old and young in this cluster have 0.1mm less thickness compared to TD subjects. Among all groups TD children have the greatest thickness (CTh=2.713mm), followed by TD adults (CTh=2.703mm), adults with ASD (CTh=2.699mm), and finally children with ASD have the thinnest in the group (CTh=2.670mm). [Figure 2.2].

Effects of development-by-sex are seen symmetrically across the medial area with most significant clusters found in both left and right posterior cingulate (p=0.01, size=544.58mm^3; p=0.023, size=485.66mm^3)[Figure 2.2]. The same trend is seen in both hemispheres, within sex adults have thinner cortices in the posterior cingulate compared to children. In both left and right hemisphere the greatest thickness are in the female children (CTh=2.692mm, 3.042mm). No significant interaction effects of diagnosis-by-sex were found at our threshold.

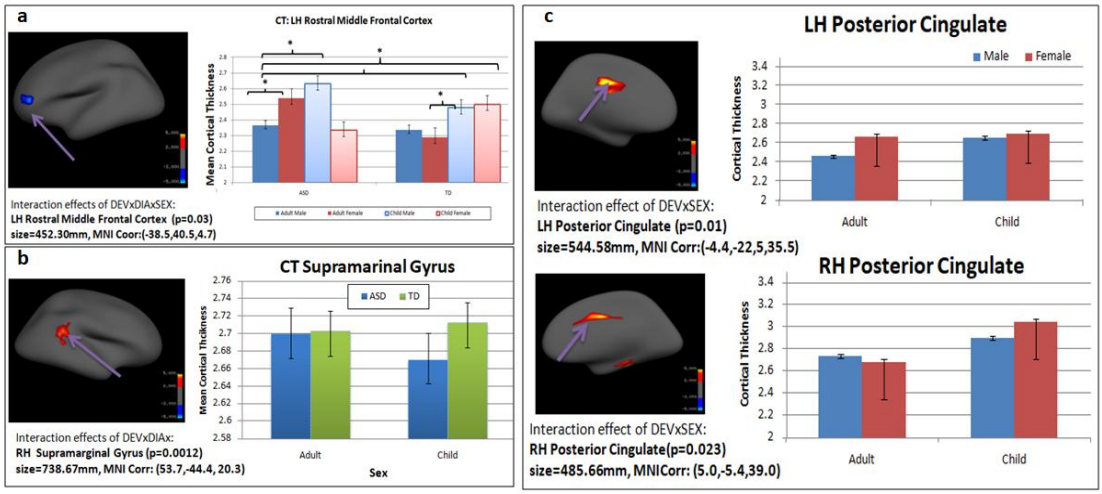


Figure 2.2 Interaction Effects of Cortical Thickness Results: (a)Three way interactions in the rostral middle frontal cortex (b), Interactions of developmental stage-by-diagnosis in supramaginal gyrus (c), and Interactions of developmental stage-by-sex along the bilateral posterior cingulate .

Main Effects of Cortical Thickness: We report individual main effects of each factor to observe general trends development effects are seen globally, there is an overall decrease in thickness seen in children over the entire cortex, with focus on the left insula and right isthmuscingulate (p=0.0001) [Figure 2.3]. Group effects of sex, show reduced thickness in females in the left hemisphere temporal area, the transverse temporal gyrus (p=0.011,size=537.51mm^3) and in the superior frontal gyrus (p=0.018, size=510.71mm^3) of the right hemisphere. Females of all ages and diagnoses showed slightly greater mean cortical thickness in both regions [Figure 2.3]. In the case of main effect of diagnosis it is only in the left hemisphere are there significant increases in thickness in ASD groups compared to TD counterparts localized to the lingual (p=0.0109, size=490.57mm^3) [Figure2.3].Each factor individually has significant clusters where cortical thickness has been altered.

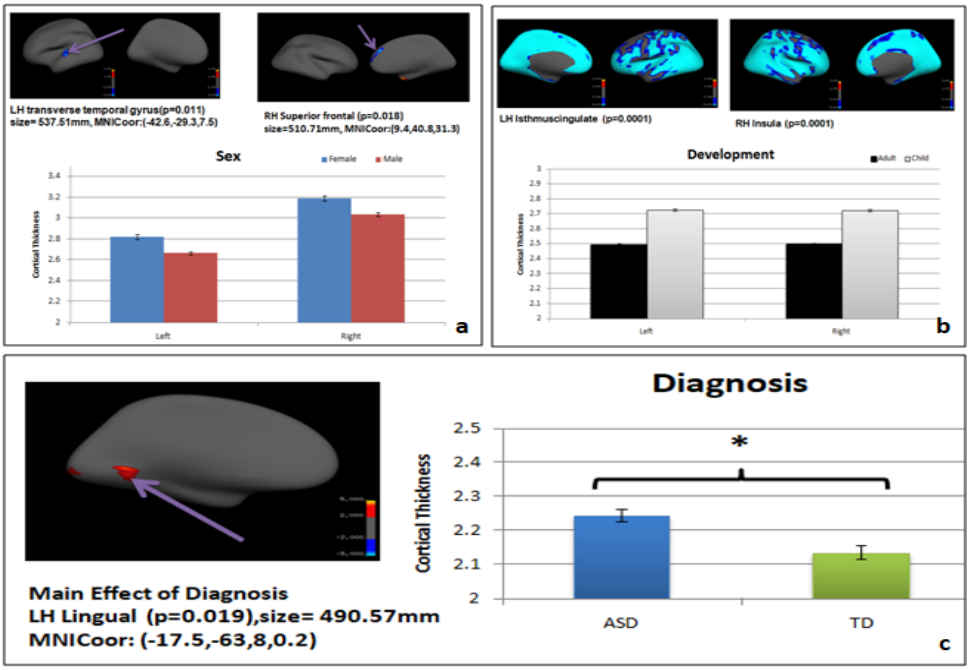


Figure 2.3 Main Effects of Cortical Thickness Results: Main effect of sex localized to transverse temporal and superior frontal gyrus (a), developmental effects are seen globally (b), Main effects of diagnosis are seen in the Lingual.

Interaction Effects of Surface Area: The interaction of development-by-sex-by-diagnosis, in which we report significant clusters that are seen in both hemispheres over the cortical strip associated with the sensorimotor region [Figure 2.4]. In the left hemisphere, we see a significant clusters in the paracentral gyrus (p=0.044, size=595.42mm^3), and the right hemisphere a cluster in the precentral gyrus (p=0.011, size=803.22mm^3). In the left paracentral gyrus, the greatest difference between sex is seen between adult males and females with ASD an additional 0.091 mm^2 area is seen in males. In TD children when comparing males and females, males have 0.048mm^2 more surface area. Of all 8 groups on average in the PCC, male adults have the largest surface area (SA=0.452mm^2). In the right hemisphere precentral gyrus, adult females with ASD have the greatest cortical surface area.

Most significant clusters for interactions of development-by-sex are seen in both hemispheres, in the Entorhinal cortex (p=0.001, size=2059.63mm^3) located on the left lateral side, and the right medial orbitofrontal cortex (p=0.001, size=2059.63mm^3) [Figure 2.4]. In the entorhinal, it is males who have greater area then female in both developmental stages. Male children reported the greatest area (SA=0.732mm^2) followed, by adult males (SA=0.711mm^2), female children (SA=0.699mm^2) and female adults (SA=0.628mm^2). Mean surface areas for the right medial orbitofrontal cortex, report a similar trend, with adult females having the smallest surface area (SA=0.558mm^2). There are no significant interaction effects of development-by-diagnosis or diagnoses-by-sex.

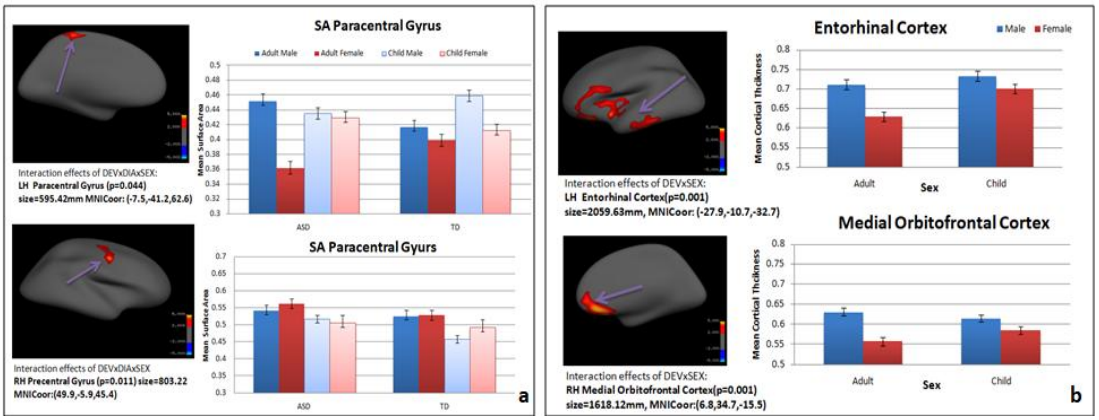


Figure 2.4 Interaction Effects of Surface Area Results:(a) Interactions of development-by-sex-by-diagnosis are seen along the motor strip (b), while those of development-by-sex are seen entorhinal cortex and medial orbitofrontal cortex.

Main Effects of Surface Area: The mean surface area is reported for the most significant clusters. Individual effects of development are centralized in temporal and frontal areas of the cortex. The most significant clusters are located in the insula of both hemispheres (p=0.0001,size=1321.13mm^3 p=0.0002,size= 1285.50mm^3), in both the average surface areas in adults are greater than that of children[Figure 2.5]. Effects of sex are visualized over the entire cortex, with large clusters centered at the insula, and superior frontal gyrus (p=0.0001) [Figure 2.5], both of which show greater surface areas in males compared to females. Main effects of diagnose, like those of cortical thickness, only seen in the lateral side of left hemisphere (p=0.0001, size=3188.34mm^3), at the middle temporal gyrus, reduced area in subjects with ASD subjects [Figure 2.5].

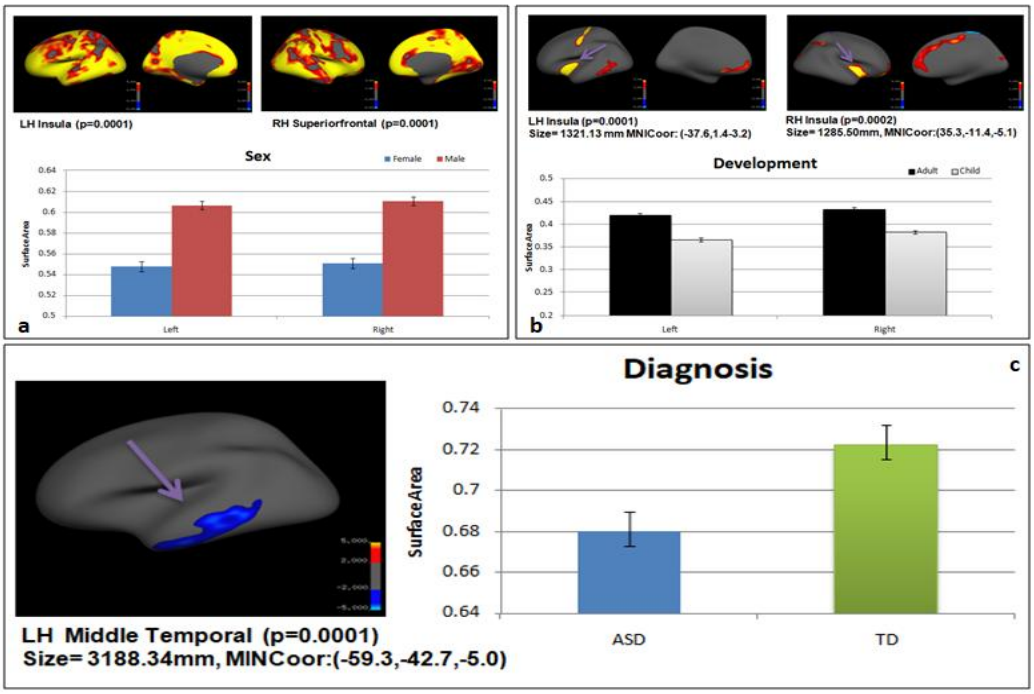


Figure 2.5 Main Effects of Surface Area Results: (a)Main effects of sex are reported globally,(b) Developmental effects are seen in bilateral insula (c), Main effects of Diagnosis are centered at the middle temporal gyrus .

2.4 Discussion

The Aim of this Project was to investigate the alterations to cortical thickness and surface area in ASD, we report with confidently that development, sex individually and interactions with a diagnoses of ASD, all modulate morphological measures. The only interaction effect was that did not produce significant clusters in either cortical thickness or surface area was that of diagnoses-by-sex, this infers that sex alone cannot be the only determining factor in the sex disparity prevalent in the ASD. The interaction of other contributing factors all play a role in our understanding of this incredibly heterogeneous disorder.

Cortical Thickness: Refers to the density of cell matter over the cortex, in humans the thickness varies with age, sex as well as disease states. Changes in thickness

has been implicated in cognitive development, executive function, memory, visual recognition, general intelligence, and cognitive ability (Engvig, Fjell et al. 2010, Menary, Collins et al. 2013, McGugin, Van Gulick et al. 2016, Schmidt, Burge et al. 2016, Righart, Schmidt et al. 2017) .Longitudinal studies have shown abnormalities in cortical thickness due to ASD at different developmental stages in males, with thinning in childhood, and increases in thickness in adulthood compared to TD in frontal, parietal and occipital lobes (Zielinski, Prigge et al. 2014)

Interaction effects of all three factors are localized in the left hemisphere Rostral Middle Frontal Cortex (rMFC) [Figure 2.2] this region has been implicated in humans ability to interpret emotional stimuli (Roy, Shohamy et al. 2012).One of the classical symptoms of ASD is social defect, specifically difficulty understanding emotions. Many emotional face processing task, have shown patients with ASD having difficulty in recognizing emotional faces (Ha, Sohn et al. 2015). In general females have a tendency to outperform males in emotional identification task also greater GM volume in middle frontal gyrus have been reported (Ruigrok, Salimi-Khorshidi et al. 2014, Satterthwaite, Wolf et al. 2015). In neurotypical cognitive development it is been established that adults exhibit more emotional maturity than children. These interactive factors, result in eight distinctive subject groups. We further investigate mean cortical thickness plots for these groups to show that although all groups have similar averages the most interesting take away is that adult females with ASD have greater thickness in the rMFC than adult males with ASD. This suggest to us that adult females with ASD maybe better at distinguishing emotional stimuli, then their male counter parts.

When we further explore the results of diagnoses-by-development interacting, we find changes in cortical thickness in the right supramarginal gyrus. This gyrus has been shown to play a role in recognizing empathy towards others, and egocentrisms (Silani, Lamm et al. 2013).Which again fall under the social impairments seen in ASD (Kanner 1943, Amaral, Schumann et al. 2008, Park, Lee et al. 2016). Intuitively, it is expected for adults to be more emotionally mature, than children. This brings us to conclude from our four group mean barplot, that overall children with ASD have the thinnest cortex compared to other groups, overall adults show minimal differences between ASD and TD groups. A major findings is that TD children have greater thickness then ASD children. Suggesting to us that children with ASD may have impairments in emotional intelligence, that can be easily perceived in childhood, further cementing the importance of early diagnoses and intervention.

The medial area of posterior cingulatecortex (PCC) in both hemispheres are significant in the interactions of developmental stage-by-biological sex. The PCC is a hub of many intrinsic networks, it is involved in sustained attention and spatial memory (Bonnelle, Leech et al. 2011, Leech and Sharp 2014). Males have been shown to outperform females in visual-spatial cognitive task and with maturity comes greater sustained attention abilities, an indicator of maturity (Satterthwaite, Wolf et al. 2015). Individual group means support these previous publications; female children have greater thickness then there male peers, but in adulthood these differences in cortical thickness due to sex are minimal. Again supporting the general idea that deficiencies in attention will likely arise and can be perceived in childhood, regardless of disease.

We expected to see significant main effects, however we choose to explore how studying these specific factors effects the neuroimaging presentation of ASD. Effects of developmental stage are wide spread over the entire cortex, as cortical thickness change are largely tied to changes in development, changes which effect the whole brain. Main effects of sex, show reduced thickness in females in the left hemisphere temporal area, the transverse temporal gyrus and in the superior frontal gyrus of the right hemisphere these differences are not surprising as males have a tendency to reach frontal cognitive maturated later then female peers (Giedd, Blumenthal et al. 1999). While main effect of diagnose are localized to the lingual gyrus and lateral occipital region, both of which have been associated with visual processing, visual memory encoding, and word recognition and identification (Mechelli, Gorno-Tempini et al. 2003, Vinckier, Dehaene et al. 2007).

Surface Area: Cortical surface area, is a measure of the exposed cortical surface and the areas hidden in sulci (Raznahan, Shaw et al. 2011). Overgrowth in child results in significant differences in brain geometry (Ha, Sohn et al. 2015). The calculations of area involve sulci folding, and therefore abnormalities in area may be caused by mechanical tension from axonal white matter (Van Essen 1997).

The major finding of this morphological calculation is that there exist significant regions with altered surface area at the interactions of development, sex and an ASD diagnosis. Centered over the motor/sensiormotor strip right paracentral and left precental gyrus correspond to somatosensory and motor functions (Chouinard and Paus 2006). Human neurodevelopmental trajectory is such that majority of childhood is focused on mastering primary motor and sensory functions (Casey, Tottenham et al. 2005). Patients

with ASD have been reported to have hypersensitivity and aversions to specific stimuli (Kern, Trivedi et al. 2006, Cascio, McGlone et al. 2008). Our mean surface area group bar plots show that adult males with ASD have greater surface areas then adult female with ASD. This suggest that Males with ASD may show differences in oversensitivity to somatosensory stimuli, as significant surface areas differences exist in somatosensory regions.

In the case of development and sex interactions, the left Entorhinal Cortex is an integration site of object and spatial memory in the hippocampus, this is important in object recognition (Schultz, Sommer et al. 2015).The right Medial Orbital Frontal Cortex (mOFC) has been implicated in reward-system development. Lesions of the mOFC have been associated with and failures to retrieve memory out comes, and OCD type repetitive behavior (Gourley, Zimmermann et al. 2016). A review of group plots shows that the overall tread is one of reduced area in adults and female, specifically adult females have the smallest areas in these clusters. This brings us to a logical inference that reward-systems as well as object recognition skills are developed in childhood. Much like results of cortical thickness each individual main effects all have clusters of significance. Development effects are centralized over temporal, medial frontal and motor areas all of which show greater areas in adults compared to children, a measure if developmental maturity. Most significant clusters are in the insula cortex located deep in the lateral sulcus of the cortex. The Insular cortex hold a number of roles, somatosensory, emotion, attention, and speech processing (Uddin, Nomi et al. 2017). All of which are highly correlated to age and cognitive development. The main effects of sex are seen over the entire cortex, this suggest that sex play a significant globally effects of surface area.

Overwhelming the results shows a greater surface areas in males compared to females all over the cortex. Main effect of diagnose much like, cortical thickness are localized to the left hemisphere. Reduced surface area in subjects with ASD are reported in left middle temporal gyrus, a gyri involved in many cognitive processes (Davey, Thompson et al. 2016).

Significant regions of both left and right hemisphere in the analysis of surface area are centered over the motor/sensiormotor strip. The left paracental gyrus corresponds to somatosensory functions the over-sensitivity of in these functions is common in ASD that manifest in "strange" communication and behavior we see from our behavioral correlations adult females with ASD have higher correlated communication and behavior scores. It may be possible that females may present this discomfort clinically different then morphometric analysis.

The geometric product of cortical volume is that of cortical thickness and surface area. Both of these morphological measures have been found to be genetically and phenotypically independent (Winkler, Kochunov et al. 2010). It is this genetic independence that encouraged us to study these cortical measures in ASD. The addition of behavioral correlation also provides insight to potential clinical biases that exist females diagnoses with ASD. Many studies have suggested that ASD has a genetic etiology; twin and sibling studies, along with chromosomal evaluations have shown high levels of heritability (Smalley, Asarnow et al. 1988, Ritvo, Jorde et al. 1989, Monaco and Bailey 2001). While no specific genomes have been identified, ASD behavioral phenotypes have been associated with known genetic disorders. It is the phonotypical presentation that seems to be altered by biological sex as noted by the rate of the

diagnosed (Halladay, Bishop et al. 2015, Baio, Wiggins et al. 2018, Christensen, Braun et al. 2018). To circumvent possible influences of genes we choose to study alterations in cortical thickness and surface area.

2.5 Conclusion

Our primary finding of this project is that alterations in cortical thickness and surface area can be seen in the interaction of developmental stage-by-diagnoses-by-sex. These three factors and their interplay provide insight into to morphological presentations of ASD. We also report associative interaction effects as well (development-by-sex, development-by-diagnose). Interestingly we see no interaction effects of diagnose-by-sex. This further empowers our rational to investigate the interactions of these co-founding factors in the anatomical presentation of ASD. In the case of the gender disparity that persist, sex alone cannot be the only contributing factors in the diagnose of ASD. Our large diverse sample size provide us with great power and we dismiss possibilities of false-positives with our strict statistical analysis. We hope to pair our anatomical results with those of behavioral observations, in hopes that some correlation can be made between severity of symptom and alteration in morphology. In conclusion our results reveal that changes in morphology exist, we hope that quantitative measures such as these can help aid the team of healthcare professional in the diagnose, treatment, and overall wellness of patients with ASD.

CHAPTER 3

RESTING-STATE FUNCTIONAL CONNECTIVITY ALTERATIONS DUE TO DEVELOPMENTAL AND SEX INTERACTIONS IN AUTISM SPECTRUM DISORDER

Resting-state functional connectivity is defined as the synchronization of brain regions with each another (Azeez and Biswal 2017). BOLD signals are used. It refers to a temporal dependence of neuronal activity of regions that do not necessarily have to be physically connected. Although anatomical alterations in the brain do not necessarily denote functional alterations. We make the assumption that in the case of a disorder as complex as ASD. The very wiring of the brain has to be altered by the presences of the disorder. We find altered connectivity pattern using a multi-analytical data driven approach, Dual regression, ReHo, fALLF and model-driven seed-based correlation. Most interestingly changes in the connectivity between the frontal parietal network and the left parahippocampal gyrus seen using the Dual Regression approach. *A priori* ROI-based correlation analysis using, ROI's from Project 1; an analysis of morphological differences at the intersection of developmental stage-diagnose-by sex revealed regions on the cortex, rostral middle frontal gyrus (CTh) and right precentral gyrus (SA). Bilateral superior frontal gyrus and middle frontal gyrus are the accompanying regions that report strong correlations. In this Project we implore various methodical approaches to quantify alterations in resting state connectivity. Currently there is not a clear understanding as to how sex and development contribute to the neurological and clinical representation of ASD.

3.1 Background

Functional alterations also exist as a result of ASD. Networks are associated with the clinical pathology of ASD; social, commutation and repetition behavioral abnormalities, include but are not limited to; DMN, visual, auditory, motor and salience networks, all that include regions that have been investigated on a structurally level to have differences in ASD. The DMN, which includes regions of the social brain; medial prefrontal cortex, amygdala and insula; have reduced functional connectivity in subjects with ASD (Von dem Hagen 2013). Salience network, involved in modulating attention to sensory inputs, ASD subjects often have difficulty down regulating responses to sensory stimuli. A common impairment is sensory over responsivity (Biswal, Mennes et al. 2010). Severity of SOR is correlated with increased inter-network connectivity. Differences across networks also persist especially between primary sensory processing regions (motor, vision, audition) in ASD groups sensory motor (superior temporal gyrus) showed increased connectivity, but visual (primary visual cortex) and auditory showed decreases. Possibly manifesting on the observable clinical level as an aversion to specific visual and auditory stimuli and preferences to particular stimuli (Green and Hernandez 2016).

Alaerts and colleagues, 2016 hypothesis driven study reported sex related functional differences in ASD. Using ICA seed-voxel connectivity analysis, with seeds in the Superior Temporal Sulcus (STS) a center of the social brain (emotional-social processing)and Posterior Cingulate Cortex (PCC) a major hub of the DMN. They report main effects of diagnosis, sex and the interaction of the two. An overall hypoconnectivity (ASD<TD) in males with ASD compared to males with TD is seen between and hyper-connectivity (ASD>TD) in females. Within diagnosed groups, they also show hyper-

connectivity in females with ASD compared to males; likewise greater connectivity in TD males verse TD females. Interaction effects further cemented the hypo-connectivity in females and under connectivity in males, these findings bring insight to the nature of biological sex in ASD (Alaerts, Swinnen et al. 2016).

The developmental disconnectivity model of ASD postulates that "higher-order association areas of the brain that normally connect to the frontal lobe are partially disconnected during development. This concept states that developmental disconnection can accommodate the specific neurobehavioral features that are observed in autism, their emergence during development, and the heterogeneity of autism etiology, behaviors and cognition (Geschwind and Levitt 2007)." Similarly Nonmi et al 2015, reports a large scale network connectivity analysis. Looks into within and between network connectivity children (<11), adolescent (11-18), and adults (>20) using ICA and dual regression. Results showed that children showed both with and between network difference, adolescent only showed between and adults showed neither. For children, with-in network difference in the "DMN and central-executive network showed hyper-connectivity in the right frontal pole, the insula and subcortical areas showed hyper-connectivity in bilateral areas that include insula thalamus, hippocampus, and amygdala." Children with ASD showed a significantly smaller correlation between these two components of DMN network compared with TD for between network differences. Lastly, adolescents with ASD had a significantly smaller between network correlations between the two components of DMN and a subcortical/insula networks (Nomi and Uddin 2015).

There are underlying neurological differences between the sexes and between ASD and TD populations, as well as alteration in typical developments. There is a overlap in the areas reported to change in development, differ by sex and differ with a diagnose of ASD. These regional coincidence can be seen morphological in changes in primary visual cortex, superior temporal gyrus, frontal cortical areas. On a functional resting state level alterations in DMN, Salience and Attention Networks have been reported. The hypo-connectivity theory of ASD is quite popular and has also been reported (Just, Keller et al. 2012). But recent studies report an overall hypo-connectivity in males with ASD and hyper-connectivity in females (Alaerts, Swinnen et al. 2016). Currently, there is not a clear understanding as to how sex and development contribute to the neurological and clinical representation of ASD.

3.2 Methods

Pre-Processing: All raw MR data was pre-processed using our in house pipeline performed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Steps include manually AC Alignment, realignment, anatomical segmentation, functional image co-registration, smoothing (8mm FWHM Gaussian), motion correction, regressing out of 24 motion parameters; six motion parameters, derivatives of each motion parameter, forward derivatives of each motion parameter as well as squared forward derivatives of each motion parameter. An additional five principal components from both CSF and WM were also regressed out, for a grand total of 34 regressors for each subjects time series WM, and CSF. Finally a bandpass temporal filter in the range of 0.01-0.1HZ was applied on all time series, to remove any physiological noise and artifacts. We initially ran the simple

data driven temporal and frequency domain analysis, followed the more complex independent component analysis dual regression, on all 428 subjects, described in Table 3.1.

Table 3.1 Projects 2 Subject Pool

SITE	SUBJECTS	ASD Female	ASD Male	TD Female	TD Male	Total
ABIDE I	**Child(<11)**	6	47	8	32	**93**
	Adult (>18)	6	38	12	47	**103**
ABIDE II	**Child(<11)**	23	28	46	38	**135**
	Adult (>18)	10	19	29	38	**96**
Total		**45**	**132**	**95**	**155**	**42**

DATA DRIVEN APPOCH

Regional Homogeneity (ReHo): We implore this temporal data driven analysis of mapping underlying connectivity activations. ReHo works under the assumption that in a time series neighboring voxels are temporally homogenous (Azeez and Biswal 2017). We set a spatial extent of 27-voxels, on filtered, motion corrected, and spatially smoothed functional images. Each subject returns a whole brain map of Kendall's coefficient of concordance (KCC), which we then normalize by diving each subject ReHo map by its average.

fractional Amplitude of Low Frequency Fluctuation (fALFF): We also perform a frequency domain analysis of low-frequency fluctuations. ALFF has been shown to be correlated with functional related regions (Biswal, Zerrin Yetkin et al. 1995). To circumvent the effects of background noise we report results of fractional ALFF, which is the ratio of the sum of frequencies in ALFF. We input smoothed, normalized functional

images, when then band-pass filter the images at 0.01-0.1Hz, to remove biological artifacts, this is performed in AFNI.

Dual Regression (DR): We perform a global intensity normalization first to circumvent the wide variety in image protocols from the different sites. Dual Regression Analysis, which is a combination of seed-based regression and multi-subject Independent Component Analysis (ICA) that can be used when comparing group-level spatial maps. Both group-averaged ICA maps and subject level ICA maps are computed. The group-averaged spatial maps are spatially regressed into each individual subject spatial-temporal dataset, resulting in subject specific time series. These time series are then regressed, temporally into the same dataset which results in an subject specific spatial map one per group-level map. We then follow the Dual Regression with randomized permutation of 500 iterations to determine differences between groups (Beckmann, Johansen-Berg et al. 2009, Nickerson, Smith et al. 2017). This procedure was performed in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL), a total of 20 independent components (IC's) are used resulting in different resting state group-averaged network maps.

A PRIORI ANALYSIS

Region of Interest (ROI) Connectivity: Seed based correlation is one of the oldest and simplest functional connectivity analytical methods. (Azeez and Biswal 2017). It operates under the assumption that if a seed-voxel or Region of Interest (ROI), is temporally correlated with another it must also be functionally connected. We select our a priori ROI from Project 1, a morphological analysis of cortical thickness and surface area. Where we have reported three regions that are significant in the interaction of developmental stage-

by-diagnosis-by-sex Interaction; left rostral middle frontal cortex (MNI:-38,38,6), left paracentral gryus (MNI:-6,-42,62), and right precentral gyurs (MNI:52,-6,44). From these ROI's a 5mm sphere is created at the MNI and the subjects-wise time-series is extracted at the location and a whole brain connectivity analysis is preformed, this is followed by statistical test. The entire process in completed using (https://afni.nimh.nih.gov/)(Cox 1996).

Statistical Analysis: We perform an series of statistical test to discern significant clusters in resting state networks for all analytical methods used. Each subsequent test more stricter than the last. The first test to deduce statistical significance is a 2 (Developmental stage) x 2 (Diagnosis) x 2 (Sex) ANOVA, to investigate statistical significance of three independent factors; and accompanying interactions effects for all functional analysis. Results of this ANOVA uncover interesting questions pertaining to the interactions of developmental stage, biological sex, and neurodevelopmental disorders. This is then followed by a Monte Carlo Cluster-wise Simulation, we set the uncorrected images to a p-value voxel threshold of 0.005 and the corrected whole brain volume cluster-level is set to α=0.05, the simulation is then run over 1,000 iterations, the outcome is each map will have a critical cluster size (k). Clusters smaller than this are not statistically significant to the cluster-wise multiple comparison simulation. These values insure that reported clusters are have a 5% or less likelihood of false-positives. Using the AFNI Talairach-Tournoux Atlas, we locate peaks of significance. Group mean plots along with standard error of mean bars. A post-hoc paired t-test is performed to identify significant group differences.

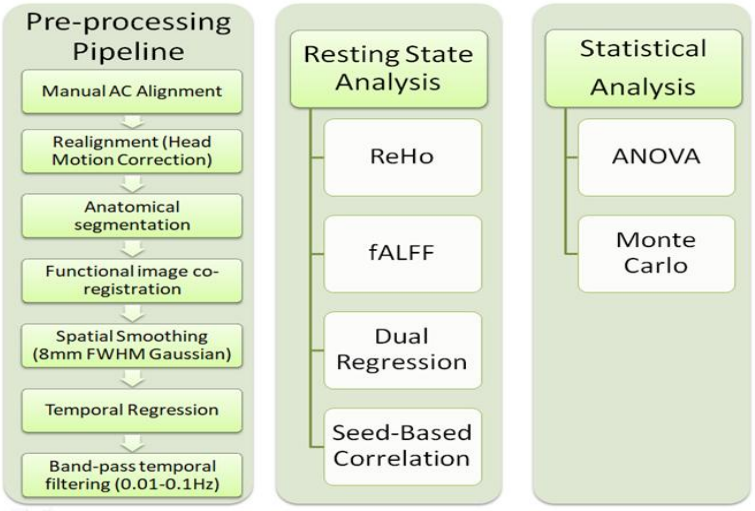


Figure 3.1 Resting-State Methods: Standardized pre-processing pipeline is used. This is followed by three data-driven approaches and one model -driven. Finally Statistics are applied.

3.3 Results

Table 3.2 Project 2 Results

EFFECTS	Dual Regression	ReHo	fALFF	ROI
developmental stage-by-diagnosis-by-sex	FP→ LH Parahippocampal Gyrus	-	-	LH rMF(CTh) → LH&RH STG RH Precentral Gyrus(SA) → LH& RH MFG
diagnosis-by-sex	-	Right Superior Frontal Gyrus	-	-
developmental stage-by-diagnosis	Visual Medial → RH Postcentral Gyrus	-	-	-
developmental stage-by-sex	TP→ RH Cingulate Gyrus Visual Medial → RH Angular Gyrus Primary Visual→ LH Posterior Cingulate FP→ LH Insula	-	Right inferior parietal Lobe	-
Main effect of Development	-	-	-	-
Main effect of Sex	-	Right inferior frontal gyrus	-	-
Main effect of Diagnosis	-	-	-	-

ReHo: We report interaction effects of diagnose-by-sex and main effect of sex. Significant clusters in the Right Superior Frontal Gyrus (p=0.01), k=315. Plots of groups mean KCC for in this cluster show Males with ASD show a stronger connectivity in the regions then females with ASD. TD populations show now sex difference in connectivity in the region. Upon further inspection, our post-hoc t-test show us that differences exist between ASD female, the weakest connection, and all other groups (p<0.001). For main effects of sex, we see males have greater connectivity in the inferior frontal temporal gyrus and cerebellum. Main effect of sex, male greater than female show cluster centered in the frontal temporal gyri as well as the cerebellum [Figure 3.2], we have also reported greater ReHo maps in males in the inferior frontal gyrus and cerebellum.

fALFF: The only effect that we report as significant is the that of developmental stage-by-sex, show region frequencies fluctuations of all subjects centered in the Right Inferior Parietal Lobe (p=0.002),k=242 [Figure 3.2]. The greatest mean is in seen in female children. Post-hoc ttest show that major significant differences are seen between adult male and female children (p<0.001) and between male and female children (p<0.001).

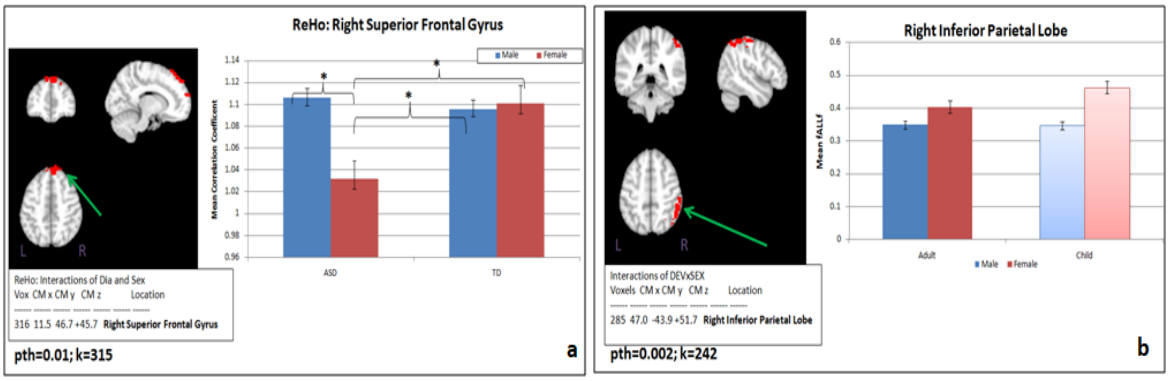


Figure 3.2 ReHo and fALFF Results: (a) Interactions of diagnose-by-sex using ReHo are seen in the superior frontal gyrus (b), fALFF results of developmental stage-by-sex interactions are seen in the inferior parietal lobe.

Dual Regression: We perform this analysis in FSL. Inputting our pre-processed fMRI data and choosing 20 IC for the analysis. Upon visual inspection only 16 IC's are relevant neurological networks[Figure3.3]. After conducting our 2 (developmental stage) x 2 (diagnosis) x 2 (sex) ANOVA we report only interaction effects that survived the Monte Carlo. Four Networks survive to statistical significance, Left-Frontal Parietal, Temporal-Parietal, Primary and Medial Visual Networks: Primary visual network and sub-networks; medial visual (van den Heuvel and Hulshoff Pol 2010, Rosazza and Minati 2011) Associated with higher order visual processing. Left frontal Parietal is one half of a lateralized network, associated with language comprehension, high level executive functions, memory retrieval, and visual-spatial processing (Talati and Hirsch 2005, Smith, Fox et al. 2009, Zevin 2009, Rosazza and Minati 2011, Borsook, Maleki et al. 2015, Sturm, Haase et al. 2016). Finally, the temporal-parietal is a characterized by the intrinsic functional connectivity between cognitive and language processing, and areas linked with language processing and comprehension (Rosazza and Minati 2011).

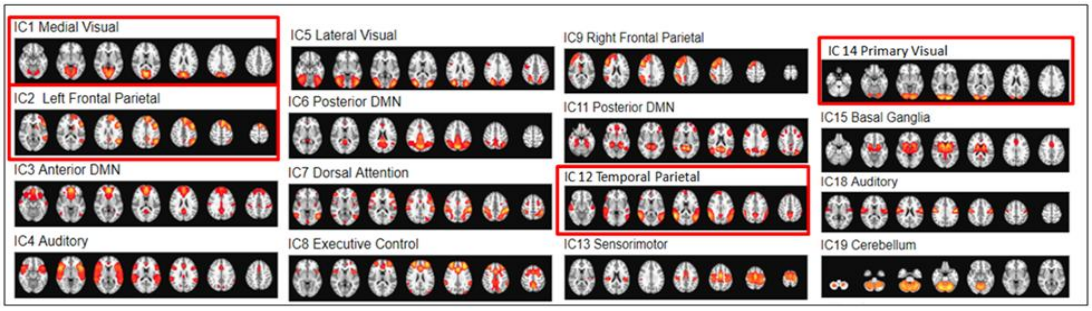


Figure 3.3 Dual Regression ICA Maps: 20 IC Maps where selected for the investigation, 16 where neurologically relevant, 4 survived statically test (ANOVA, Monte Carlo)

Interactions of development stage-by-diagnose-by-sex can be seen between the left parahippocapmpal gyrus (p=0.005) size=, k=41and the Visual medial network. Mean beta estimates, an indirect measure of connectivity , show that in adulthood females with

ASD have the strongest anti-correction with the Visual Medial Network. For interactions of development stage-by-diagnose, we report three major clusters of the Visual medial Network, the largest being in the right postcentral gyrus (p=0.005). While exploring interactions of developmental stage-by-sex we report four Networks with significant clusters; medial visual, primary visual, temporal parietal, and left frontal-parietal, and there corresponding clusters of significance [Figure 3.4].In the Primary Visual the largest cluster lies in the Left Posterior Cingulate (p=0.005). The connectivity pattern is similar to that seen between the right angular gyurs and the medial visual network. The strongest anti-correlation being in Adult Females, Child Females show the strongest connection to the network. Connections between the left insula and the frontal-parietal network show once again Adult Females having the strongest anti-correlation. Finally, in the temporal-parietal network the right cingulate gyrus is revealed the to be positively correlated with all groups. No interaction effects of development-by-sex or main effects of the factors are reported.

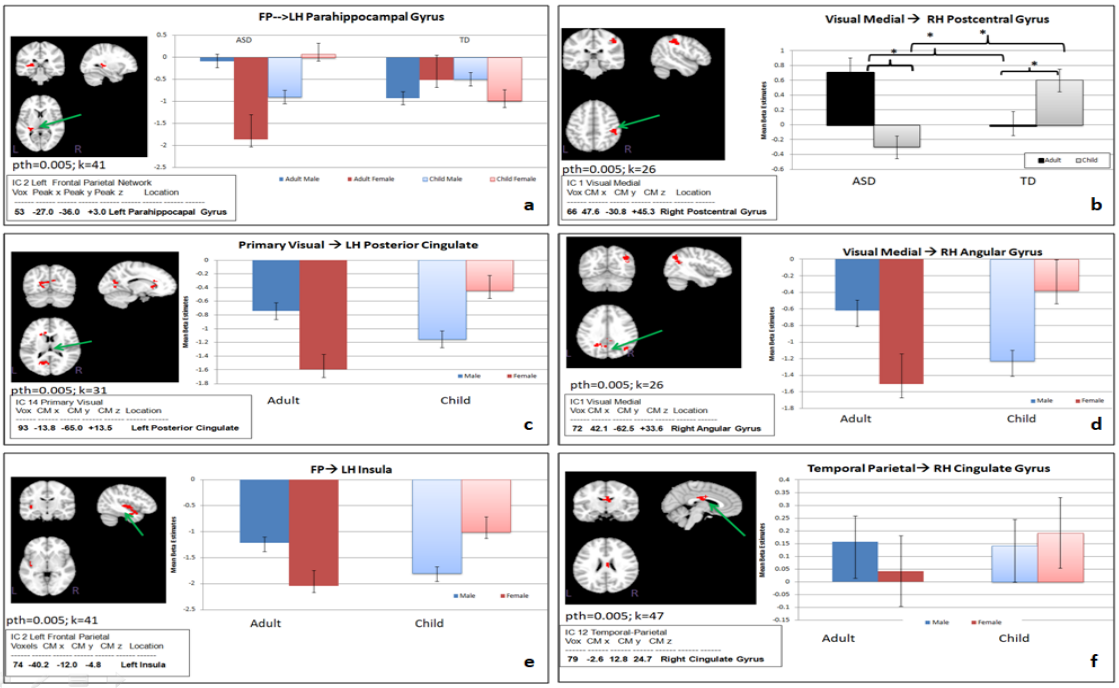


Figure 3.4 Dual Regression Results: (a)Three way interactions seen between frontal-parietal network and parahippocapmpal gyrus (),b interaction effects of developmental stage-by-diagnosis are seen between visual medial network and postcentral gyrus (c-f), developmental stage-by-sex Interactions are seen in medial visual, primary visual, temporal parietal, and frontal-parietal.

ROI Analysis: We find significant connectivity between left rostral middle frontal cortex (rMFC) and both left and right superior temporal gyrus (STG). In mean beta estimates, female children with ASD have the strongest connectivity, although no significant differences between pairs exist. We also see strong temporal correlation between right precentral gyrus and right middle frontal gyrus (MFG) and left inferior frontal gyrus (IFG). Once again the strongest positive connection is seen in female children with ASD, with t-test revealing group differences, with '*, $p<0.05$ 'most significant difference is between child ASD female and TD adult females. No significant clusters came from the ROI in the left paracentral gyrus.

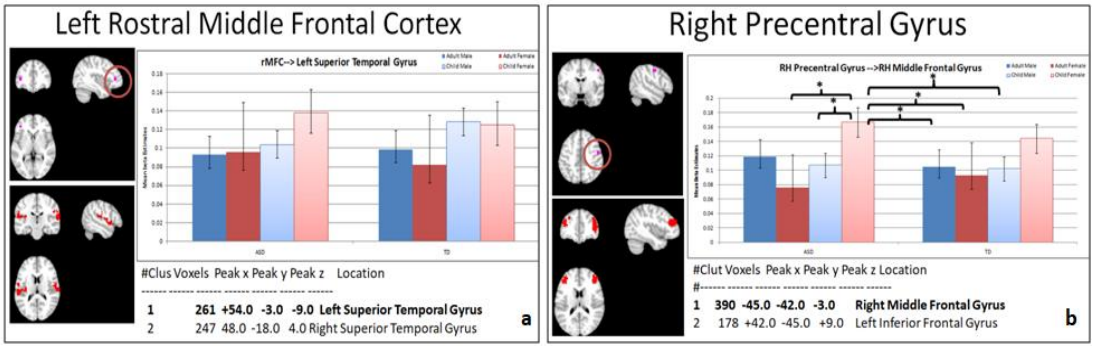


Figure 3.5 Region of Interest Results: (a)Connectivity is seen between the left rostral middle frontal cortex and left temporal gyrus (b), and right precentral gyrus and right middle frontal gyrus.

3.4 Discussion

Interactions of development-by-diagnoses-by-sex are seen only in the dual regression analysis and that of ROI. This was the major interest of this Project. We hypothesized that the interaction of all three factors actively alters the functional connectivity of the brain. We also review the implications of supplementary interaction effects associated with a diagnosis of ASD. We see that in both data driven and *a priori* approaches connectivity is altered. In the Dual Regression the left frontoparietal network connects the dorsal region of the frontal and parietal lobes the network, it has been implicated as a source of attention and cognitive control (Ptak 2011, Marek and Dosenbach 2018). The left parahippocampal gyrus, the only significant cluster, is associated with the memory encoding region of visual-spatial processing and episodic memory (Aminoff, Kveraga et al. 2013). Adult females with ASD have the strongest anti-correlation between left parahippocampus and Frontal Parietal Network. This may possibly reflect differences in the ability to integrate episodic memory. Similarly the strongest and only positive correlation, albeit very small exist in female children with ASD, thismay reflection of

age, suggesting that somewhere along neurodevelopmental process females with ASD begin to develop impairments in visual-spatial processing and episodic memory. Since the defects may appear in adulthood, it is possible that clinical assessment may miss this feature.

Of all our functional connectivity analysis the strongest positive correlations exist between the *a priori* significant anatomical regions in our morphological assessment of the interaction of development-by-diagnoses-by-sex. The left rostral medial frontal cortex (CTh) and right precentral gyrus (SA) are regions assorted with processing emotional stimuli and primary motor area, respectively. These seed ROI's all show connections to pairs of regions on the cortex the, superior temporal gyrus (STG) and middle frontal gyrus (MFG).

The STG is a multisensory integration site, located on both lateral sides of the brain in the temporal cortex, and is associated to many neural processes. Lying in the auditory cortex it plays a role in the processing of sound, particularly important in speech recognition. Wernike's area is located in the posterior of the left STG, In 1871 Dr. Karl Wernicke described lesion in this area to result in loss of ability to comprehend spoken language, this was later termed "Wernicke's aphasia (Zevin 2009)." The infamous "cocktail party effect', in which the brain networks that coordinate attention to speech and vision over lap, allowing the listeners to selectively attend to one talker despite the competing background speech (Miller 2016). The STG has been shown to be coupled to the attend speech in the 'cocktail party' situation (Vander Ghinst, Bourguignon et al. 2016). The site is also instrument in visual perception in case where there is damage to the region it can result in "neglect", a visual impairment where a patient completely

ignores objects in the contra lateral heimfeild (Gage and Baars 2018). The site is also been implicated in processing eye movements and interpreting social information from gaze and body movement (Allison, Puce et al. 2000, Pelphrey, Morris et al. 2005). Sensory and attention processing develops in early childhood (Casey, Tottenham et al. 2005). Lesion studies have postulated that language is lateralized to the left hemisphere in males (Levy 1972, Hampson 1992, Kimura 2000). In auditory task male and female subjects show bilateral activation when speech is heard in the forward direction but lateral differences are seen in males, left STG, when instructed to listen to speech played in reverse (Yamaura, Kansaku et al. 2000). This result coincides with the many cognitive task-based studies that have reported that females regardless of age outperform males in language; speaking early, acquiring vocabulary faster, using more spontaneous language, and superior verbal and written ability (Murray, Johnson et al. 1990, Bauer, Goldfield et al. 2002, Roulstone, Loader et al. 2002, Parsons, Rizzo et al. 2005, Burman, Bitan et al. 2008). This enhanced comprehension ability may result from the recruitment of more cortical area, particularly the bilateral employment of a highly active integration site. A sensory integration, hub, it is of no surprise that the STG has also been implicated in ASD clinical presentation, as ASD patients often have sensory abnormalities and language deficits. Decrease in gray matter volume has been reported in the STG of children with ASD (Boddaert, Chabane et al. 2004, Stigler and McDougle 2013). In emotional face processing task ASD children consistently underperform (Ha, Sohn et al. 2015, Kim, Lee et al. 2016, Aldunate and González-Ibáñez 2017). This interaction of development-by-diagnoses-by-sex show a strong connection between the left rMFC and bilateral STG, regions associated with interpreting emotional stimuli. Although our mean

plots of our eight unique groups we find no between group differences but greatest connectivity exist in female children with ASD in the STG. This may possibly suggest that emotional impairments seen in ASD may not present as severely in clinical observations, due to the recruitment of the bilateral integration site seen in females, perhaps this "Female Protective Effect" is the grounds for the sex disparity seen in ASD (Jacquemont, Coe et al. 2014).

The left paracentral and right precentral gyri are the two regions that are significant in the morphological assessment of surface area for the interaction of development-by-diagnoses-by-sex. As a seed ROI only the right precentral gyrus result in significant bilateral connectivity centered at the bilateral middle frontal gyrus (MFG). The MFG lies in the prefrontal cortex, in humans it is the last to mature (late 20's) (Giedd, Blumenthal et al. 1999). Neuroimaging studies have concluded that the prefrontal cortex is responsible for temporal organization of behavior, speech, reasoning, and working memory (Fuster 2009, Petrides 2016). Japee and associates, 2015 case studies of orientation discrimination task in patients with lesions in the right MFG. The finding of the study suggest that right MFG plays an important role in reorienting internal and external attention control (Japee, Holiday et al. 2015). The strong connectivity seen in female children with ASD, between the primary motor area and the prefrontal cortex, this may suggest that this cohort has better control over complex motor sequences, such as saccades, which may contribute to the visual spatial superiority that females have over males, coupled with the sustained deficiency see in children. The same pattern of connectivity is seen in TD populations it is simply exaggerated in ASD populations.

Of all our analytical approaches, ReHo, reports local homogenous clusters are found for the interaction of diagnose-by-sex in the right superior frontal gyrus(SFG). The right SFG is the most medial gyrus of the frontal lobe, it has been implicated in higher order cognitive control and impulsivity (Hu, Ide et al. 2016). Males have reported higher connectivity suggesting they are more venerable to impulse control disorders (Li, Zhang et al. 2009). Reduced connectivity between the PCC and right superior frontal gyrus was reported in adults in ASD, which was correlated with social impairments (Monk, Peltier et al. 2009). In ASD populations report reduced performance in impulse cotrol task (Hill 2004). In many domains men have higher incidences of risky and problematic behavior linked to impulse control; reckless driving, accident related deaths, verbal and physical aggression, criminal activity, drug use, and higher rates of ADHD (Cross, Copping et al. 2011). The mean connectivity plots show that ASD-Male have significantly greater local connectivity then ASD-Female ($p<0.0001$), suggesting that males with ASD have higher connectivity possible indicative of poorer impulse control, this may result from a compounding of factors that are observably disruptive and can clearly be characterized by clinical test. This result tells that a superior frontal gyurs plays a role in altered behavior in both sex as well as ASD, this cluster lies directly at the intersection of the two. It is possible that the region its self is only observable when imploring a method designed to extract local connectivity measures

Development and diagnosis of ASD obviously contribute to the presentation of the disorder as it is a neurodevelopment disorder. We see the effect of this in significant connection between the Visual Medial and right postcentral gyrus. The postcentral gyrus is located in the primary somatosensory cortex (Chouinard and Paus 2006, Haines and

Mihailoff 2018). Atypical sensory based behavior is ubiquitous to ASD, tactile aversions are commonly reported in patients (Wiggins, Robins et al. 2009, Marco, Hinkley et al. 2011). Adults with ASD have reported hypersensitivity to vibrotactile and thermal stimuli (Cascio, McGlone et al. 2008). Our mean plots show that adults with ASD have strongest connection, between right postcentral gyrus and Visual Medial Network, while children with ASD, show anti-correlation. This may reflect differences in somatosensory and visual stimuli integration in Adults with ASD.

None of the methods we used showed main effects of diagnose or development. Main effects of sex are seen with ReHo with greater correlations in males in the right inferior frontal gyrus (IFG). The region has been implicated in inhibitory control (Aron, Fletcher et al. 2003, Hampshire, Chamberlain et al. 2010). Male typically have more difficulty inhibitory control task (Mansouri, Fehring et al. 2016). A review of gender difference in personality and social behaviors have shown that males display higher incidences of impulsivity, risk taking and sensation seeking (Mather and Lighthall 2012, Del Giudice 2015).

Local frequency fluctuation connectivity is localized to the right inferior parietal lobe. In the interaction effects of diagnose-by-sex Inferior parietal lobe is at the junction of visual, auditory, and somatosenory stimuli (Johns 2014). In visual-spatial processing high functioning children with ASD reported greater activation, suggesting an increasing reliance on visual-spatial processing for information (DeRamus, Black et al. 2014). Male have reported activations in this regions, males recruit visual-spatial areas to in motor inhibition; reinforcing the patter of sexual-dimorphism that exist in functional networks

(Rubia, Lim et al. 2013). This again paves a clear localized region of interactions of diagnoses-by-sex in ASD, particularly in cognitive visual-spatial processing.

Adjacent effects of development-by-sex are seen in 4 functional networks; frontal-parietal, temporal-parietal, primary and medial visual. Two primary sensory networks and two of language comprehension and cognition. All of which are important in developmental milestones are often delayed in ASD, and areas also achieved at different developmental stages due to sex (Giedd, Blumenthal et al. 1999, Lenroot and Giedd 2006). In the Visual Medial Network we seen maxim clusters in parietal areas that have been associated with visual spatial attention of salient features (Singh-Curry and Husain 2009) (Seghier 2013). The primary visual network we there are peaks in the posterior cingulate (PCC) and the caudate associated, both of which are sites of cognitive and motor integration. The PCC is a major integration site of the emotion, learning and intrinsic activity as it is a central node of the DMN (Smith, Fox et al. 2009, Platt and Plassmann 2014). The PCC is also the only significant cluster in the temporal-parietal network, with this interaction. Lastly the Left Frontal Parietal network reports clusters in the insula, which sit at the junction of the frontal, parietal and temporal lobes, who exact function is still largely unknown. And thusly so the insula has been implicated in a wide variety of functions; consciousness, emotional intelligence, and maintaining bodily homeostasis (Uddin, Nomi et al. 2017). We also report cluster in the inferior parietal lobes, a integration site of visual, auditory and somatosensory inputs, while the middle frontal gyrus plays a role in higher order cognitive functions, such as attention(Talati and Hirsch 2005, Sturm, Haase et al. 2016).

3.5 Conclusion

We attempted to use a multi-analytical approach in this Project, to explore resting state functional connectivity and it how it may be altered when the incorporation of other governing factors are considered; developmental stage, diagnose and sex. We find that the strongest effects of these interactions are seen primary in regions emotional processing, sensory integration and modulating attention, despite the data driven or *a priori* approach used we find that these regions report the greatest connectivity in female children with ASD. These finding solidify that this group is greatly over looked in clinical observations of the disorder the postulation we make is that neuroimaging techniques need to be implored in conjunction with classical clinical observation to aiding the early diagnosis, and treatment option for females with ASD.

CHAPTER 4

GRAPH THEORY ALTERATIONS DUE TO DEVELOPMENTAL AND SEX INTERACTIONS IN AUTISM SPECTRUM DISORDER

Graph Theory (GT) is a mathematical approach used to analyze complex networks. We attempt to characterize alterations in ASD populations by observing difference in intrinsic organization of functional brain network as well as changes in Graph Theory metrics. The last of our three Projects, we attempt to capture differences in the network architecture as seen in GT metrics. Still rather new in its implementation many of the metrics don't have obvious neuropsychiatric analogies, thus the crux of this Project lies in the limited literature of GT metrics in neurodevelopment sex and neuropsychiatric diseases/ disorders. We find that the consideration of sex and development in the network architecture of ASD, is most significant in female children with ASD particularly in the metrics of path length, clustering coefficient, local efficiency and between centrality.

4.1 Technical Background

Graph Theory (GT) is a mathematical approach to analyze complex networks. It lays down the theoretical framework for complex topographical networks to be examined. This network analysis allows us to quantify every conceivable iteration of connections that exist between brain regions. Graph Theory can provide an better understanding of local and global organization of resting state networks (van den Heuvel and Hulshoff Pol 2010). A complex network can be constructed from a series of node and edges, and defined as:

$$G= (V, E) \tag{4.1}$$

Where G is a functional brain network; V, nodes for each brain region; and E, functional connections between those regions (van den Heuvel and Hulshoff Pol 2010, Azeez and Biswal 2017). Nodes represent individual brain regions and a series of nodes can be chosen using a brain atlas this is model-driven much like seed-based analysis. The time-series of each subject-wise node is extracted, and a subject-wise correlation matrix for each node in the parcelleation can be made, this is used to calculated various network metrics that can be used to study different pathologies.

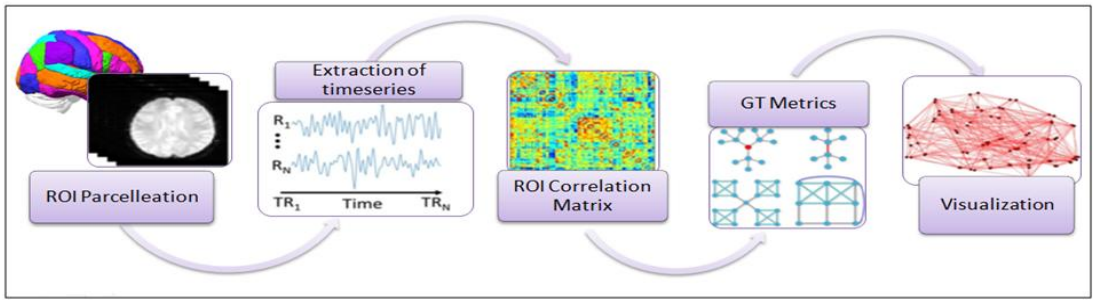


Figure 4.1 Graph Theory Methods: Dosenbach atlas is used to define ROI's, timeseries are extracted from these ROI's and whole correlation matrix is created. This input is used to calculated Graph Theory Metrics, results are then visualized.

4.2 Graph Theory Metrics and Neuropsychiatry

While countless measures exist to characterize a complex network the most common and neurologically relevant ones, fall into a few general categories; basic measures, measures of functional segregation, functional integration, centrality and small world-ness. While these measures are typically used to describe non-biological, its application in a complex, not fully understood biological network is not so intuitive and requires more though in our interpretation. Degree, a basic measure is the connectivity of a node with the rest of the nodes in the network, the degree distribution is a marker of a networks development and resilience (Rubinov and Sporns 2010). Measures of functional segregation describe the ability of the brain to specialize processing, into clusters or modules. Clustering

coefficient is the fraction of triangles around a node this is indicative of segregated neural processing. Modularity measures if a set of nodes with denser links among them but sparser with the rest of the network. The degree at which a network is organized in a modular structure. The ability to transfer information in the local level is measured by Local Efficiency (Rubinov and Sporns 2010, Wang, Zuo et al. 2010).

Functional integration describes the ease at which brain regions communicate (Rubinov and Sporns 2010). GT metrics such as characteristic path length and global efficiency are the most commonly used metrics for describing functional integration. Characteristic path length refers to the average shortest path length between all pairs of node in network. The average inverse shortest path length is related to global efficiency, which measures the ability to transfer information on a global level. Nodal centrality quantifies the importance of a node to a network (Wang, Zuo et al. 2010). Between centrality measures the importance of a node to the network. It is the fraction of all shortest path length that pass through a given node. High centrality denotes a hub, Hubs are important brain regions that facilitate functional integration and communication (van den Heuvel and Sporns 2013). Finally, Small-worldness reflects an optimal balance of functional integration and segregation. It represents the networks penchant with high local clustering and low min path length between node pairs (Wang, Zuo et al. 2010, Medaglia 2017). This model of organization is maximized for efficiency of information transfer at relatively low wiring cost (Sporns, Chialvo et al. 2004, Bassett and Bullmore 2006). We describe a variety of the measures of global connectivity properties, we hope that these metrics when applied to research of development and sex interactions in ASD.

In our literature search, we attempted to summarizes the known resting state information pertaining to GT metrics in studies of neurodevelopment and sex differences as well as altered measures in diseased populations. We know from studies of aging in resting state connectivity that normal aging effects connectivity patterns within and between networks (Geerligs, Renken et al. 2014). Sex differences in TD populations in resting state have also reported differences in network; DMN, auditory, sensorimotor, and attentional networks (Zhang, Cahill et al. 2016). However, the effects of sex and normal aging on resting state functional connectivity are not very well characterized, this compounded with the newness of the GT analytical methods, limits our literature search, to the few studies that have described changes in GT metrics due to sex and normal neurodevelopment (Zhang, Cahill et al. 2016).

The mature human brain is optimized to be highly efficient, this organization allows for the specialization of networks that are flexibly and can rapidly respond to cognitive demands (Wang, Zuo et al. 2010). Based on the theory of economic demand, the brain in resting state should be optimized to be in metabolic energy saving mode (Bullmore and Sporns 2012, Di, Gohel et al. 2013). This is supported by publications by Fair and colleagues that have reported changes in metrics due to normal human aging; in general, there is a simultaneous decrease in functional segregation and increase in integration. While there are no studies that specially investigate the changing metrics from childhood to adulthood, we find studies on the normal aging subjects capped from middle to late adulthood. Reductions in both local and global efficiency follow age, localized to the frontal, temporal, and sub-cortical regions (Achard and Bullmore 2007).

Studies of normal aging showed that changes in segregation occur, specifically that older subjects having greater modularity (Meunier, Achard et al. 2009).

Difference in sex have been previously reported; Zang et al. explore the effects of sex and age in TD adults (22-36years). Using the AAL atlas that encompasses 116 regions and 7 networks, they report that Females have higher whole brain clustering coefficient, while Males have higher local clustering in all nodes expect the cerebellum (Zhang, Cahill et al. 2016). The group report no effects of age or the interaction of age-by-sex (Gong, Rosa-Neto et al. 2009). Hemispheric lateralization has been reported between sexes. Higher with in hemispheric modularity is also reported in males (Ingalhalikar, Smith et al. 2014). Females in the right hemisphere have higher clustering coefficient but lower in the left, suggesting an hemispheric-by-sex interaction (Tian, Wang et al. 2011)

Much like, analysis of structure and functional connectivity, the diagnose of ASD results in atypical network distribution, functionally specialized networks have usual regional distribution (Keown, Datko et al. 2017). Keown et al, 2017 publication calculated many graph theory measures and reported difference between ASD and TD groups. Network Cohesion, a measure of community structure, was reduced in the auditory, memory retrieval, somatosensory, and subcritical networks in ASD, while the ventral attention network had higher cohesion in ASD groups. In high functioning ASD patients, Rudie et al. found that those with ASD had lower clustering, particularly in nodes of the DMN, and secondary visual network. ASD individuals also where less organized a into modular structure. However those nodes in the DMN and sensorimotor had a high degree of centrality. In addition ASD patients also had shorter path lengths

and higher global efficiency (Rudie, Brown et al. 2013). Similarly there are reports of lower characteristic path length and clustering coefficient. They also report loss of Hubs: bilateral superior temporal sulcus, right dorsolateral prefrontal cortex, and precuneus, all which are critical for social and non-social cognitive functions (Itahashi, Yamada et al. 2014). These metrics suggest that ASD results in atypical distribution of networks (Keown, Datko et al. 2017). Changes in functional networks have been reported in sex related differences in ASD. Floris and colleges have show in males with ASD a shift toward maleness in the precuneus and PCC of DMN, associated with higher-order cognitive functions while there is a shift towards femaleness in the sensorimotor network; lower-order sensory motor functions (Floris, Lai et al. 2018). This reinforces the Extreme Male Theory of ASD (Baron-Cohen 2002), but this research does not taking into account developmental, a major factor in ASD clinical presentation is the developmental stage of the child. An developmental changes have shown only in childhood are their differences in with-in and between network differs in ASD children and their TD peers (Nomi and Uddin 2015). While these findings support functional connectivity alterations. We still have questions pertaining to the overall Network Organization in ASD when other co-founding factors are taken into account. The neurodevelopment of children is in flux up until the late twenties. At that point the structural, functional, and cognitive neurodevelopment of men and women of the same age is more or less the same.

In this final Project of our research, we expand upon the methodical analysis from Projects 1 and 2. Our choice to use new innovative method to characterize ASD affords us the opportunity to report on unique finds which pertain to our hypothesis; describing interactions of developmental stage-by-diagnosis-by-sex observable in GT metrics.

Structural and functional network changes all contribute to what we expect to be alteration in whole brain network organization. We hope that our findings can further our understanding of this incredibly complex neurodevelopment disorder.

4.3 Methods

Participants: All functional resting-state data used from Project 2 is used in the GT analysis. We quantified head motion as frame-wise displacement (FD), instantaneous subject-wise FD is calculated as a scalar from the Euclidean distance between consecutive time points of rigid body parameters; x, y, z, roll, pitch, and, yaw, as shown by equations 4.2 and 4.3 (Power, Barnes et al. 2012, Keown, Datko et al. 2017). All subjects with a FD >0.5mm are removed from the GT analysis (16 subjects removed).

$$\Delta d_{ix} = d_{(i-1)x} - d_{ix} \tag{4.2}$$

$$FD_i = |\Delta d_{ix}| + |\Delta d_{iy}| + |\Delta d_{iz}| + |\Delta \alpha_i| + |\Delta \beta_i| + |\Delta_{\gamma i}| \tag{4.3}$$

Pre-Processing: All raw MR data was pre-processed using our in-house pipeline preformed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Steps include manually AC Alignment, realignment, anatomical segmentation, functional image co-registration, smoothing (8mm FWHM Gaussian), motion correction, regressing out of 24 motion parameters; six motion parameters, derivatives of each motion parameter, forward derivatives of each motion parameter as well as squared forward derivatives of each motion parameter. An additional five principle components from both CSF and WM were also regressed out, for a grand total of 34 regressors for each subjects time series WM,

and CSF. Finally a bandpass temporal filter in the range of 0.01-0.1HZ was applied on all time series, to remove any physiological noise and artifacts.

ROI Analysis: 160 ROI's where selected using the Dosenbach Atlas, a whole brain parcellation (Dosenbach, Nardos et al. 2010). The atlas provides accurate predictions about individuals' functional brain maturity across development which is well suited for our investigation of a neurodevelopmental disorder, while providing appropriate resting-state network coverage. The parcellation consist of 160 ROIs that fall into six functional networks; cingulo-opercular, frontoparietal, default mode, sensorimotor, occipital, and cerebellum. Subject-wise time series is extracted from each ROI drawn as 5mm-radius spheres at MNI coordinates. 14 ROI's were removed due to lack of coverage in some subjects, ultimately we are left with a 146*146. Each ROI represents a node and edges are the corresponding connectivity between nodes, which is represented as Pearson's Correlation. A Pearson's Correlation Matrix for each subject is constructed; this matrix is binarized and used to calculated our various GT metrics over sparsity levels ranging from 1-100. The Brian Connectivity Tool Box is used to calculate al GT metrics (brain-connectivity-toolbox.net)

Statistical Analysis: The impact of the research is to characterized interactions of developmental stage-by-diagnose-sex in the GT metric of ASD populations. For all metrics, we regress out effects of; data bank (ABIDE I &II), imaging site (11sites), age and motion. A 2 (Developmental stage) x 2 (Diagnose) x 2 (Sex) ANOVA is preformed, followed by FDR correction $p<0.05$ over sparsity levels 1-50. For significant metrics that survive FDR correction, we plot mean bar plots and standard error of mean error bars for all groups corresponding for the lowest significant sparsity level. Only sparsity levels

between 5-50% are considered, as normal human neuron networks are between this range (Achard and Bullmore 2007, He, Chen et al. 2008, Di, Gohel et al. 2013).

4.4 Results

Table 4.1 Project 3 Results

EFFECTS	Functional Connectivity	Path Length	Cluster Coefficient	Local Efficiency	Between Centrality
Developmental stage-by-diagnosis-by-sex Interaction	p< 0.001	p=0.0414	p< 0.001	p< 0.001	p< 0.001
Diagnosis-by-sex Interaction	-	-	p< 0.001	-	p< 0.001
Developmental stage-by-diagnosis Interaction	-	p=0.0265	p< 0.001	p< 0.001	-
Developmental stage-by-sex Interaction	-	p=0.0187	-	-	-
Main effect of Development	-	-	-	-	-
Main effect of Sex	-	-	p< 0.001	-	-
Main effect of Diagnosis	-	-	p< 0.001	p< 0.001	p< 0.001

Network Architecture: Functional connectivity is measured using Pearson's Correlation Matrix are input into the ANOVA as we are interested in significant connections for each contrast. The only significant effects is that of interaction of developmental stage-by-diagnose-sex (p=1.0243e-06). To visualize the connections, we plot the resulting matrix of p-vals from the ANOVA. Although the main effects of development, diagnosis, or sex are not significant, we display 2-D and 3-D graphical representation of these connections, thresholded p<0.01 for the sake of visual comparison.

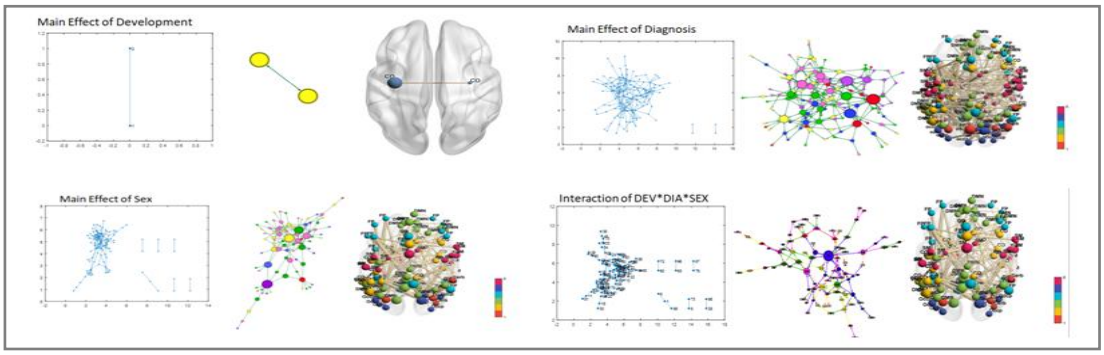


Figure 4.2 Changing Network Architecture Results: Network Architecture evolved as individual main effects and interactions of all factors.

GT Metrics: We describe the results of all interactions associated with a diagnose of ASD. All mean group plots are shown at the lowest sparsity levels for all interactions of development-by-diagnoses-by-sex and associated effects of diagnoses.

Characteristic Path Lengths at 5% sparisity are significant for interactions of developmental stage-by-diagnosis-by-sex ($p=0.0052$) and of developmental stage-by-diagnosis ($p=0.04$). Mean plots of the eight unique groups show the longest path length is see in female children with ASD, 3.46. Following these plots with a paired post-hoc group ttest we see that the most significant group differences exist between female children with ASD and adult females with ASD ($p=0.04$), male children with ASD ($p<0.001$), TD female children ($p=0.01$). Similar characteristic path lengths are reported among TD populations. In interactions of developmental stage-by-diagnosis, we see that path length is longer in adulthood in both, however t-test reveal that no significant differences exist between groups.

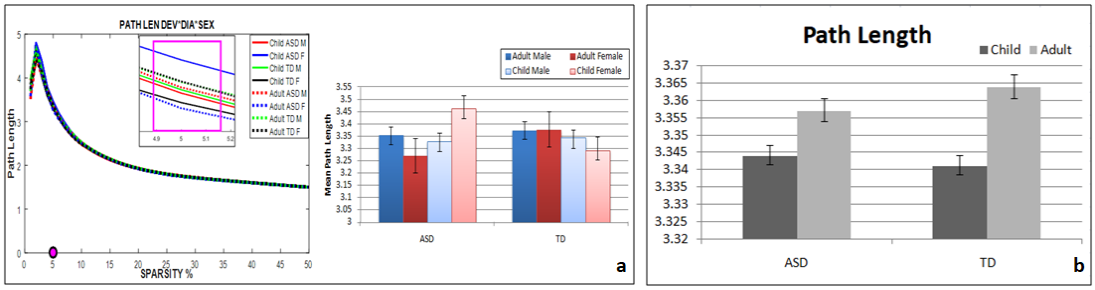


Figure 4.3 Characteristic Path Length Results: (a) Interaction effects of all three factor are present in calculations of Path Length (b), also effects of developmental stage-by-diagnosis.

Clustering Coefficient: at 6% sparisty, we calculate global clustering coefficients and we report effects of developmental stage-by-diagnosis-by-sex ($p<0.0001$) and main effects of diagnosis ($p<0.0001$). The in mean plots of global averages, we see that that female-children with ASD have the greatest number of clusters. We then look into Network level means for the groups, which reveal that the Occipital Network contains the most functionally separated clusters of all groups. Upon further investigation, we find eight nodes that survive FDR correction at $p<0.05$. These nodes are considered the most significant. The most significant node lies in is in the temporal parietal junction ($p=9.79E-5$) of the cingular-opular Network. We look at the significant differences that exist in diagnoses ($p<0.0001$) exist with ASD groups having larger clustering coefficients on average. By network the we see greater coefficients in ASD of the cingulo-opular, fronto-paretial, sensorimotor and default mode networks. We report 7 individual nodes that pass FDR correction. The the most significant node ($p=2.43E-5$) is located at the inferior cerebellum of the cerebellar network, we seee ASD patients have significantly lower clustering coefficients ($p<0.0001$).

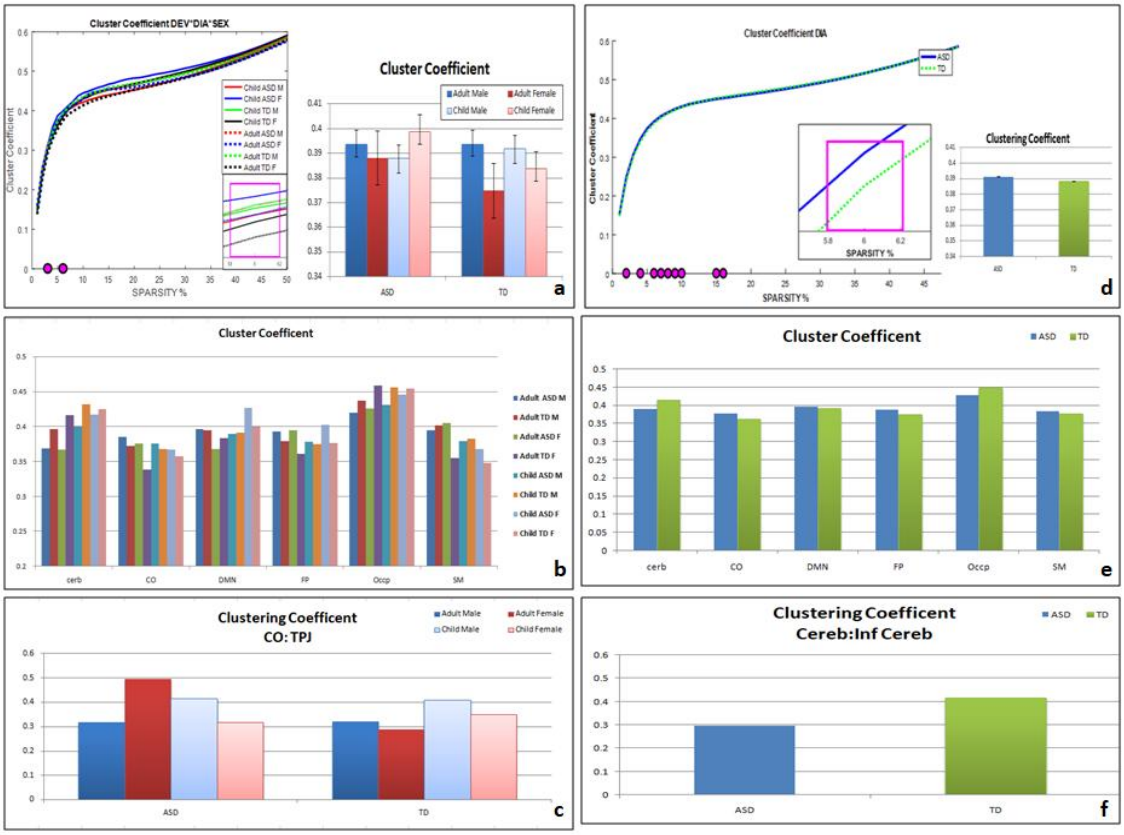


Figure 4.4 Clustering Coefficient Results: (a) We find interactions effects of developmental stage-by-diagnosis-by-sex averaged across the brain (b), networks (c), and subject averaged at the temporal parietal junction. (d-f) Like-wise similar plots are made for main effects of diagnoses,(f) with a focus on group differences at the Inferior cerebellum.

Local Efficiency: averaged across nodes at 9%, greater in efficiency's in general are seen in childhood. Only in females are there differences between adult and children. Female children with ASD have the highest local efficiencies. Network observations again show that female children with ASD have the most networks with the highest local efficiency (cerebellum, DMN, Occipital). Developmental stage-by-diagnosis mean plots show that a consistent trend of local efficiency being higher in childhood regardless of diagnosis. Network effects show that in the greatest efficiencies in are in the occipital cerebellum of TD children, closely followed by ASD children. In observations of main effects of

diagnoses we once again see that significant reductions in the ASD populations are seen in the cerebellum and occipital networks

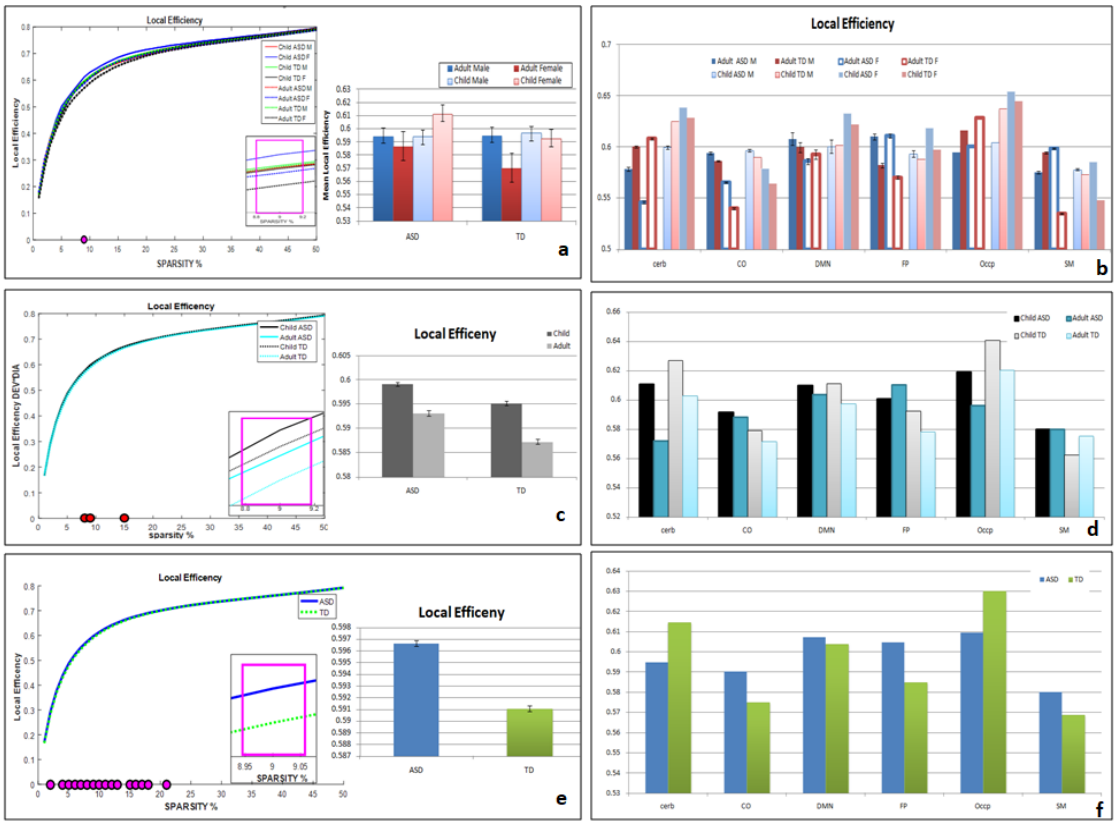


Figure 4.5 Local Efficiency Results: (a-b) Global and network plots for interaction effects of developmental stage-by-diagnosis-by-sex, (c-d) developmental stage-by-diagnosis (e-f), and main effects of diagnosis.

Centrality: In female children with ASD centrality is the highest at 5%**.** Little difference exists in Males regardless of development or diagnoses. The most significant nodes ($p<0.05$), 11Hubs are reported the Mean Centrality calculated for each group. Hub SM11 (SMA) has the greatest influence over all other nodes in the brain, followed by the DMN3 (precuneus). An unusually high peak in SM1 (middle insula) is reported in Adult ASD Females.

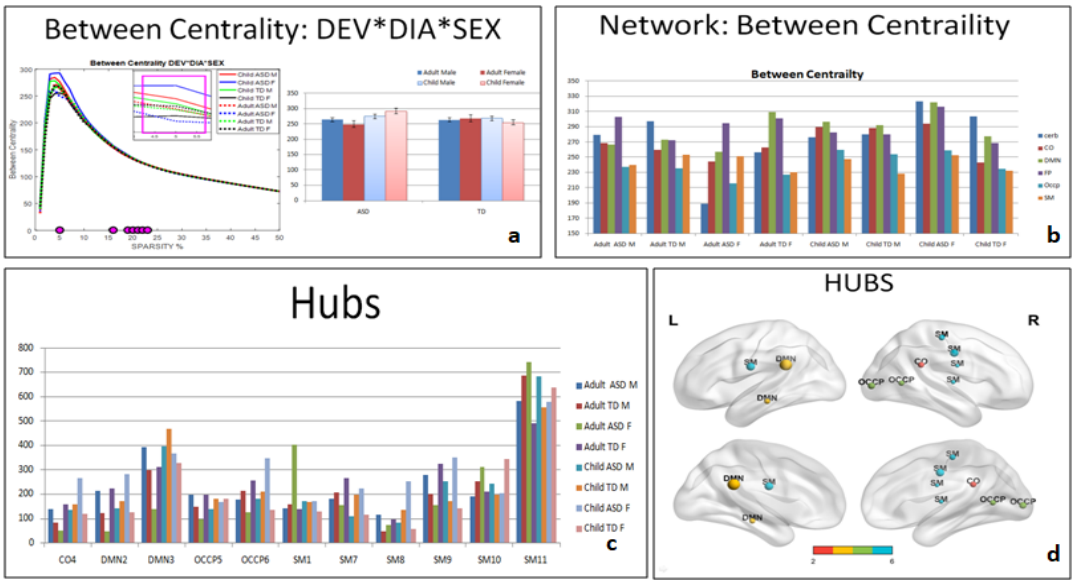


Figure 4.6 Centrality Results: (a-b) Interactions of developmental stage-by-diagnosis-by-sex plotted globally and averaged across networks.(c-d) Most significant nodes (Hubs) are plotted and visualized on a 2-D inflated map.

4.5 Discussion

Functional connectivity is altered by age, sex and disease state seen in our data set. Across all GT metrics what we consistently find is that female children with ASD have the greatest mean group differences. Characteristic path length estimates functional integration between brain regions, shorter path lengths imply stronger integration. In our analysis, female children report the longest path lengths, and shortest path lengths are seen in Adult females with ASD, who have similar means to of TD female children which implies weakest functional integration of the group. In TD populations with age comes more integration, shorter path length, whereas shorter path lengths are reported in females (Tian, Wang et al. 2011, Hoff, Van Den Heuvel et al. 2013). Lower path lengths have been reported in ASD groups (Rudie, Brown et al. 2013, Itahashi, Yamada et al. 2014). Although we report no main effects, we do report all associative effects of developmental stage. In our analysis, we find suggest that development plays a large role

in the presentation of ASD in females in childhood and adulthood. Far more variability by sex and developmental stage exist in ASD groups then in TD groups. Overall what we observe is a strong effect of sex, differences in path length in male fluctuate very little due to diagnose, or developmental stage. While in TD group Adults>Children in ASD groups this trend is reversed and exaggerated, Adults<Children ($p<0.05$). The second measure of functional integration is global efficiency, in our observations we report no significant effects of developmental stage-by-diagnosis-by-sex. However effects of developmental stage-by-diagnosis are report that children with ASD are the least globally efficient. Overall, the interaction of all three factors results in reduced integration particularly in female children with ASD.

A measure of functional segregation, clustering coefficient is the highest in female children with ASD which implies that this group has the most functional segregated networks, On a network level, we see that the occipital network is the most functionally segregated as has been reported in children who achieve mature level of efficiency in primary sensory network. Local information transfer is the highest in female children with ASD. Measures of segregation is higher in females compared to males. We see there are significant main effects of diagnose and sex, those of which seem to govern the interaction the most. Between centrality changes with age, as the importance a node (region) plays in the network changes as the brain develops. This is seen as loss of Hubs in ASD populations. The most powerful hub are seen in sensory motor area of the sensory motor network and the precunes of the DMN. There are major network centers.

4.6 Conclusion

The complex mathematical analysis method allows us to explore the networks architecture of this disorder. A relatively new methodical approach, provides quantitative measures for the brain. We find in our analysis across all GT metrics female children with ASD have the greatest means. This suggest that this group, that is disproportionally diagnoses requires more research. Further detail are also needed to understand the biological implications of the GT metrics. The use of GT in future may provide insight to machine learning applications to help aid in metrics for diagnose of ASD. The use of complex network measures have major advantages over a mass-univariate approaches. All the classical resting state methodological approaches, similarly to those used in Project 2 (Seed-based, fALLF, ReHo, ICA), test independently all connections between all areas of the brain. While these time and frequency domain approaches have been heavily used for the past 25 years in the resting state publications, they all have their limitations. Graph Theory avoids the multiple comparison issues that accompany the established approaches its also allows us to examine complex network measures and specific features that are important for the functioning of the network (Geerligs, Renken et al. 2014). We hope that this Project and the research that encompasses it will provide more insight into the use of Graph Theory metrics to better characterize neuropsychiatric diseases/ disorders.

CHAPTER 5
NEUROIMAGING MEASUREMENTS AND BEHAVIORAL CORRELATIONS

The last analysis that we perform is a behavioral correlations between quantitative measures that have been calculated in each of the three Projects; cortical thickness, surface areas, measures of connectivity, and GT metrics. We have the unique opportunity to have in our disposal ADOS behavioral scores for the majority of the subjects in our pool. The DSM-IV handbooks characterizes the symptoms of ASD as defects in communication, reciprocal social interactions and restricted/ repetitive behaviors (RRB). These difficulties can be observed as early as three years of age (Akshoomoff, Corsello et al. 2006).

A number of behavioral assessments exist to characterized these symptoms; the Gilliam Autism Rating Scale (GARS) rely on parent and teachers to report, while requires limited training by administrators have reported a misdiagnose rate of 58% (Gilliam 1995, South, Williams et al. 2002, Lecavalier 2005). Based on the DSM-III-R, experienced professionals rate children's behavior after direct observations in the Childhood Autism Rating Scale (CARS). The CARS does have a tendency to miss children with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) and over-identifying children with mental retardation (Pilowsky, Yirmiya et al. 1998, Perry, Condillac et al. 2005). Unlike the GARS and CARS the Autism Diagnostic Interview-Revised (ADI-R) is conducted by trained professionals it is a semi-structured interview that is conducted with the parents or primary caregiver (Tadevosyan-leyfer, Dowd et al. 2003). Much like the ADI-R the Autism Diagnostic Observation Schedule (ADOS) it requires trained professionals to administer it. The test involves semi-

structured assessment scoring direct observations of the child's interactions; communication, social interaction, and play (or imaginative use of materials).

The most recent edition in the ADOS-2, Consisting of Modules 1-4 and an additional toddler module. The appropriate module is chosen based on the chronological age of the subject and there language level ranging from nonverbal to verbally-fluent. The assessment takes about 30-60 minutes, the examiner presents the subject with many opportunities to exhibit behaviors of interest through standard 'presses' for communication and social interactions. 'Presses' consist of planned social occasions in which it has been determined in advance that a behavior of a particular type is likely to appear (Murray 1938). Modules 1 and 2 are designed for children, while 3 and 4 are for older children, adolescents and adults all of who are capable of using complex sentences, asking questions about emotions relationships, and ability to retell stories and demonstrate activities (Akshoomoff, Corsello et al. 2006). A standardized set of materials, activities and, scoring are used for the test. To avoid subjective bias, tests are typically video recorded so a team can review it for diagnosis. A 0-3 point system is used 0, normal behavior and 3 indicating that the behavior is abnormal and interferes with the child's functioning in some way. The test, like many, aims to best characterize the classical symptoms of ASD; defects in communication, social interactions, and restricted/ repetitive behavior (RRB). Communication and social difficulties are often detected as a lack of "typical behaviors"; reduced social gestures or responses-eye contact which are observable during a brief interaction. RRB's however are not so obvious during an assessment, often RRBs such as hand flapping only occur in a particular conditions therefore these behavior is limited by both time and context. Modules 1-3 are typically

use for children which contains three sub scores, while adolescents and adults of fluent speech use Module 4. In order to compare severities of ASD symptomology scores between subject demographics a comparison score conversions. This conversion is included in the updated ADOS-2 for Modules 1-3 (Gotham, Risi et al. 2007). But not for Module 4 Hus and Lord 2014 paper provides a severity conversion which we used (Hus and Lord 2014). Nevertheless the ADOS is still a very good predicator of ASD diagnosis and has been wildly used for the almost 15 years by clinicians, scientist and researchers to evaluate the severity of Autistic symptoms its is one of the few diagnostic evaluations where direct observations of a child's interactions are scored while also accounting for the developmental age of the child (Akshoomoff, Corsello et al. 2006, Lord, Risi et al. 2006, Hus, Gotham et al. 2014).

One of the many positives to our subject pool is that most of the ABIDE subjects have phenotypical behavioral scores. ADOS sub scores for communication, social interactions and stereo- typically behavior and sum total scores are available. One of the main goals of this research was to prove that the interactions of developmental stage and sex can be seen on the neurological presentation of ASD. The majority of our analysis are data driven and free from experimental biases. From each Project, we have reported areas in the brains where we report significant interactions of developmental stage-by-diagnosis-by-sex. Due to the nature of our subject pool, high functioning children and adults; all of the behavioral assessments are conducted used Modules 3 or 4.

With the behavioral data available to us, we have the unique opportunity to tie quantitative neuroimaging results with that of observable behavioral assessments. We correlate neuroimaging measures with behavioral scores in hopes to connect the

quantitative measures that we have calculated and the phenotypical assessment that is provided to us by the ABIDE data pool. We are able to plot behavioral correlations which includes a calculation of linear trend-line for each group along with correlation coefficient, r and goodness of fit, r^2, a measure of the fraction of the variation in one variable that may be explained by the other variable. Total ADOS scores are converted depending of module into a severity score. Before we conducted our correlation analysis, we perform a 2x2 ANOVA to determine if there exist differences in the distribution of severity scores in sex and development stage. What we find is that significant differences exist between developmental stage ($p=0.029$) but not in sex ($p=0.206$). Which implies that severity scores are heavily influenced by age. Therefore, the correlations that we report should be understood within this context. The ADOS assessment is preformed in a clinical setting and was specially designed for the evaluation of children's behavior, across the three regions. We find that children with ASD have the highest correlations to their ADOS commutation scores suggesting that in childhood the failures in understanding emotional cues, and particular stereotypical repetitive behaviors are clinically obvious.

5.1 Behavioral Correlations in Morphology

For our development-by-sex-by-diagnosis, interactions that are significant in cortical thickness and surface area, we plot subject-wise means verse available ADOS behavioral scores. Of all the 167 ASD subjects in this Project, only 147 subjects have total, communication, social, and restricted/repetitive behavior (RRB) ADOS scores as well as severity conversion scores. For correlations between rostral middle frontal cortex, we

find that severity scores are all negatively correlated with cortical thickness for all ASD groups, the greatest magnitude is seen in adult females (r=-0.239, r^2=0.011) and female child (r=-0.1, r^2=0.031). From Project 1, we recognized that the rostral middle frontal cortex is associated with emotional processing, a skill essential to effective human communication. females outperform males in emotional identification task and with age comes the matured ability to communicate and distinguish complex emotions (Saul 1947, Ruigrok, Salimi-Khorshidi et al. 2014, Satterthwaite, Wolf et al. 2015, Rajan and Joseph 2019). Our analysis of cortical thickness suggest to us that adult females with ASD maybe better at distinguishing emotional stimuli, then adult male counter parts.

Both the left paracentral and right precentral gyri, there exist differences in surface areas. When ADOS scores are plotted against subject-wise mean surface areas, we find that in the left paracentral gyrus, localized over the motor/sensiormotor strip, correlations of severity scores are the strongest correlation is seen adult females(r=0.519, r^2=0.161) and male children (r=0.170, r^2=0.021). These behavioral correlations cement that our conclusion made in Project 1 is observable in a clinical assessment; males with ASD, specifically children who are in the mist of mastering motor/sensiormotor function show differences in oversensitivity to somatosensory stimuli.

In the right hemisphere of the precentral gyrus, which corresponds to primary motor area. We observe that all correlations are positive in all groups with the largest in adult females(r=0.423, r^2=0.107) and female children (r=0.325, r^2=0.096). This apparent divergence from the trend seen in the left hemisphere hints that our previous assumption may hold true; male adults and children's with ASD may show differences in motor planning and control.

While the behavioral correlations in morphology are weak in magnitude (r<0.5), they do yield promising associations between behavioral scores and mean morphological properties and the conclusions that we have made in Project 1.

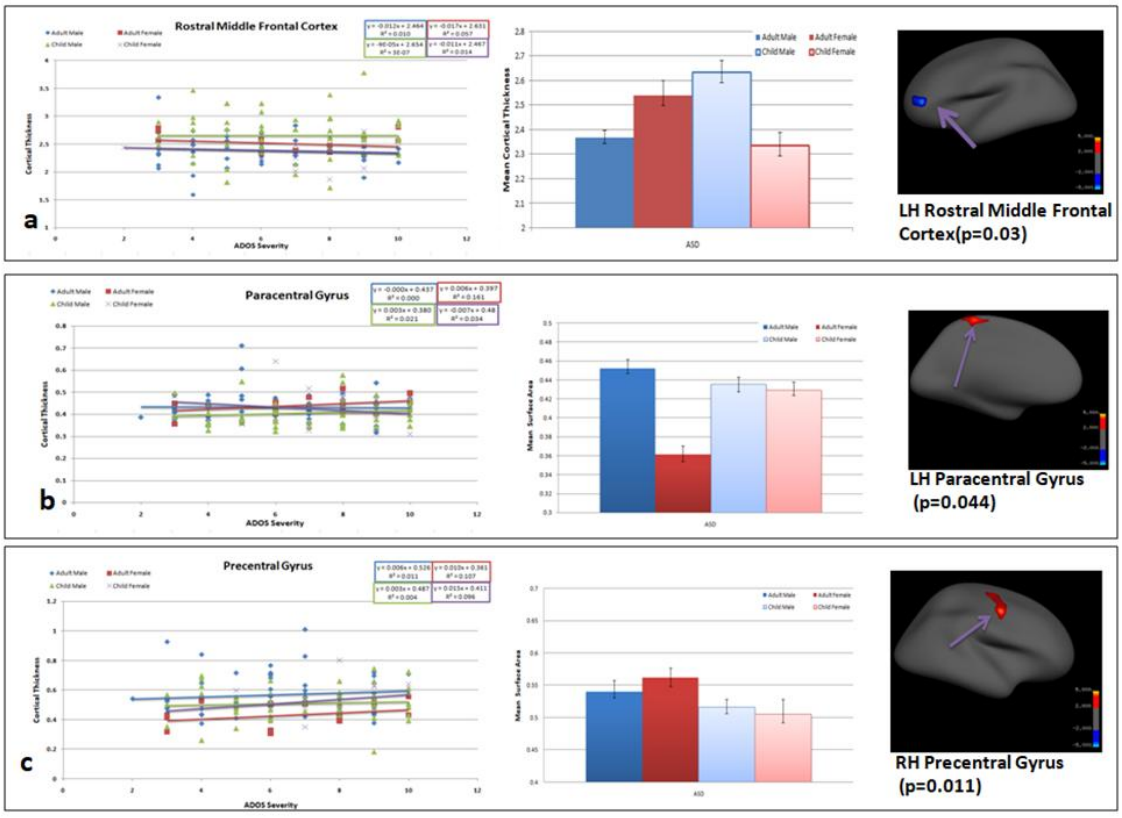


Figure 5.1 Behavioral Correlations Morphology Results: (a)Rostral middle frontal cortex is associated with emotional processing, and severity is strongest in adult females. (b-c)Parcentral and Precentral gyus are linked to sensory and motor function. There mean average surface areas are correlated to ADOS severity scores, with higher rate in adult females.

5.2 Behavioral Correlations in Resting-State Functional Connectivity

As reported in Chapter 3, significant three-way interaction are seen in our dual regression and ROI approach. Of our 177 ASD subjects, 151 have complete ADOS scores. Altered connection is seen between the frontoparietal network and left parahippocampal gyrus in plot. Severity scores are the most correlated in adult males (r=0.131, r^2=0.017), this is the

same group that has the weakest anti-correlation between the network and the region devoted to memory encoding and visual-spatial processing.

We also in our *a priori* analysis in which we set regions from our morphology analysis as seed ROI's for connectivity analysis, what we find is that rostral middle frontal cortex has strong connectivity with the bilateral superior temporal gyrus (STG) with the strongest correlations, in female (r^2=0.004, r=0.065) and male children (r^2=1.69E-4, r=0.013). We reported and similar patterns are seen in the right STG. The STG is a multisensory integration site, that is heavily associated with communication functions; speech recognition and visual perception (Zevin 2009, Gage and Baars 2018). Therefore, it is possible that the complexity of the cite in question, makes it such that the an ADOS assessment many be difficult to characterized into three sub scores.

The second region that yields significant connectivity from our ROI analysis is seen between the right precentral gyri and the right middle frontal gyri (MFG). A region that also multifaceted in function; speech, working memory (Fuster 2009, Petrides 2016). When correlating the beta estimates with the ADOS severity scores, we see that male children (r^2=0.036, r=-0.191) are the most positively correlates with the strength of connectivity between the ROI seed and MFG.

The strength of these correlations are very weak (r<0.3) but its promising that the regions of association are those that have multiple function, therefore the defects observed as a result of ADOS test may not be representative of the severity of the defects seen in ASD.

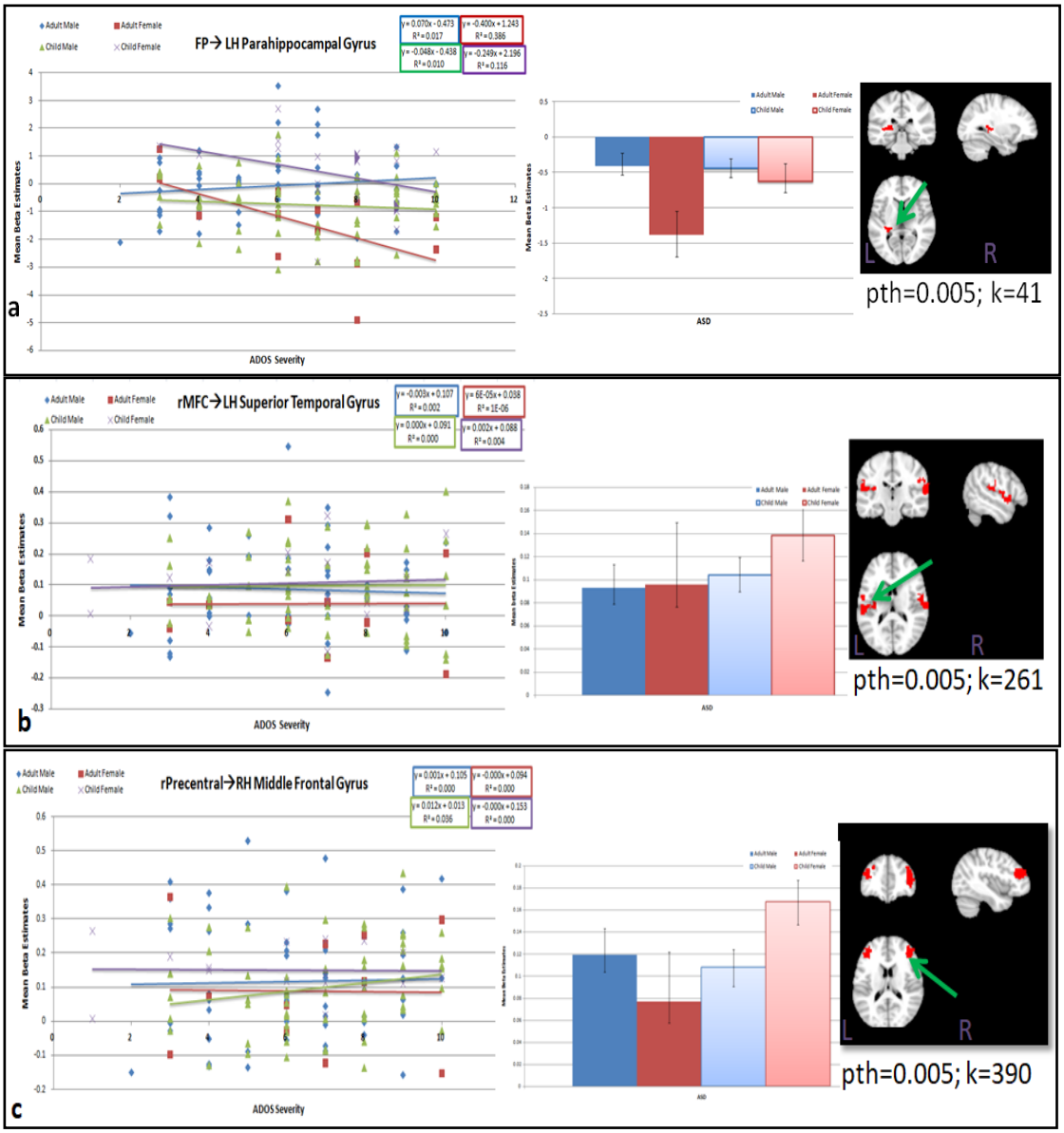


Figure 5.2 Behavioral Correlations Resting-state Functional Connectivity Results: (a) Patterns of connectivity are seen in Dual Regression, show correlation between ASD severity and memory encoding regions (b-c) . ROI analysis show trends in STG and MFG are strongest in male children.

5.3 Behavioral Correlations in Graph Theory Metrics

144 out of 168 ASD subjects have ADOS scores available. We report that interactions effects of developmental stage-by-sex-diagnosis are reported for path length, clustering

coefficient, local efficiency, and between centrality. We do not include correlation analysis for path length due to the reservations presented by Powers et al 2013 "in correlation networks, where degree is a problematic measure, and where path lengths are often created from thresholded correlation matrices, it is less clear how to interpret these measures (Power, Schlaggar et al. 2013)". What we find is that their exist little correlation between these GT metrics and ADOS scores. This suggest to us that the GT Metrics and what is reported by clinicians does not necessary coincides with the ADOS scores reported.

Correlation of ADOS severity and local efficiency in adult females is the highest (r^2=0.106, r=0.326). It is in this same group where we report the lowest level of local efficiency in sensorimotor network this may explain the higher correlation seen in the scores. Clustering Coefficient plots reveal that in all groups clustering coefficient is negatively correlated. The most significant cluster is localized around the temporal parietal junction (TPJ) which has been implicated in ASD patient ability to identify socially awkward situation, as it has been implicated in social cognition and perception (Pantelis, Byrge et al. 2015). Betweeness centrality describes the importance of a node to the network, we had previously reported that the most significant Hub, sensory motor area (SMA). The highest positive correlation is seen in female children (r^2=0.087, r=0.295)

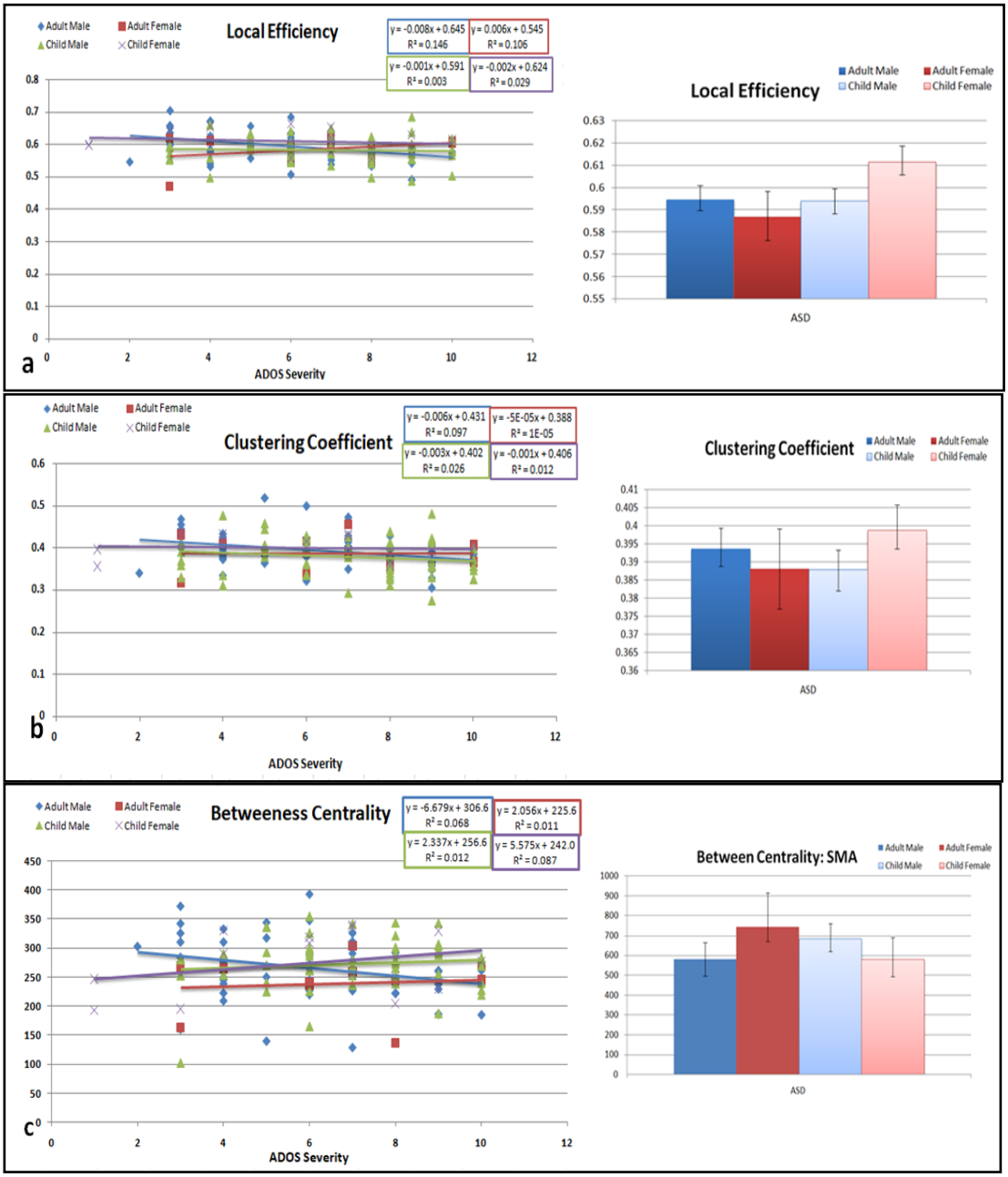


Figure 5.3 Behavioral Correlations Graph Theory Metrics Results: Correlations of GT metrics with ADOS scores. (a)We see high local efficiency in sensorimotor network of adult females. (b)The greatest clustering coefficient is localized around the temporal parietal junction (TPJ).(c)The strength of sensory motor area (SMA), Hub is highest in female children.

5.4 Behavioral Conclusions

The primary analysis of this research was to quantify alterations in that occur in ASD as a result if of the interactions of neurodevelopment and sex. We reported in three investigations various regions that are significant in this three-way interaction. With the availability of ADOS scores from the ABIDE data base we able to perform our secondary analysis, which attempts to merge the results reported in Projects 1-3 with the observational clinical assessment. Assessments that are used to diagnose, characterize severity, and ultimately inform treatment options. We find overall ADOS sores are very weakly correlated to neuroimaging results, no single score has a correlations coefficients greater than 0.5, which implies little to no associations with neuroimaging measures; cortical thickness, surface area, mean beta estimates and various GT metrics.

As seen in Table 1.2, ADOS scores are not significant different between ASD groups (adult/children and male/female). However, when these scores are correlated with specific brain regions, we find that the most powerful and meaningful clinical conclusions can be seen in female children. The severity and obviousness of defects in communication and social interactions, is expected in children who are developmentally immature. Publications have reported that females with ASD have more severe delays in language and fewer incidences of observed repetitive stereotyped behavior (Lai, Lombardo et al. 2011, Mandy, Chilvers et al. 2012).

Significant modulations in cortical thickness of the rostral middle frontal cortex (rMFC), a cite of emotional processing. Communication scores of female children (r^2=0.270,r=0.520) are the highest. The resting-state functional connectivity between the rMFC and the bilateral STG; a multisensory integration site, that is heavily associated

with communication functions. We see that in female children communication scores have the greatest correlation (r^2=0.283, r=-0.531), with mean beta estimates of the STG.

In our assessment of GT metrics, the function-sub score analog does not easily apply, however we so see that female children have longest path and the strongest correlation to social scores (r^2=0.278, r=0.527) which implies weaker function integration and presentation of more obvious social defects. We see similarly high correlations in repetitive behaviors (r^2=0.278, r=0.527) of local efficiency of female children in the sensorimotor network. Analysis of clustering coefficients show that most significant network cluster is centered at the TPJ, a site that has long been investigated in the "social awkwardness," classical to ASD. We see this conformation in the high correlation of social scores if once again females children. Lastly, Hubs of centrality localized to the SMA, a region that can be evidently characterized by stereotypical behavioral scores, and like all the GT metrics report female children with ASD are the most correlated.

At the start of the research we hypothesized that the subjective scores of clinical assessment may not be enough for a accurate diagnosis. We suspected that unintentionally bias, resulting in missed/late diagnosis, may be responsible for the alarming sex disparity reported in ASD. What we have found is that correlation between scores are too weak to confidently discount the accuracy of ADOS scores. It also possible that the assessment itself is not capable of capturing macro-neuronal changes caused by the presence of ASD, altered developmental trajectory and natural biological sex differences. It should also be noted the population in this research is high-functioning and therefore, ADOS scores may not accurately characterize ASD symptoms due to their self awareness. Whatever the case, what we find in our Behavioral evaluation, female

children have scores that are the most correlated. This simply demonstrates the need for various alternative methods for diagnosis, which will untimely improve the long-term treatment outcomes for those with ASD.

CHAPTER 6

STUDY CONCLUSIONS

The goal of this research was to investigate the interactions of developmental stage and sex on the neurological presentation of ASD. We hope the various neuroimaging techniques reveal alterations that can be seen anatomically, resting state connectivity and GT metrics. The highlight of this research are these interactions and the methodologies used. We lie in the intersection of increased awareness of ASD, as there is a growing interest in the unexplained sex differences that persist in the populations.

We find clusters of significance in our inquiries of cortical thickness, in the left rostral middle frontal cortex and surface area, over the left paracentral and right precentral gyrus. Changes in the connectivity between the frontoparietal network and the left parahippocampal gyrus seen using the Dual Regression approach. *A priori* ROI-based correlation analysis using, ROI's from Project 1; an analysis of morphological differences at the intersection of developmental stage-diagnose-by sex revealed regions on the cortex, rostral middle frontal gyrus (CTh) and right precentral gyrus (SA). Bilateral superior frontal gyrus (STG) and middle frontal gyrus (MTG) are the accompanying regions that report strong correlations. Altered connections are seen in the interactions of all three factors, Path Length, Cluster Coefficient, Local Efficiency, and Betweeness Centrality. We also perform a simple correlation analysis in which we plot quantitative measures against the observational measures made by trained professions used during the ADOS assessment.

Table 6.1 Summary of Study Results

Interactions	**Project 1: Morphology**	**Project 2:Resting State FC**	**Project 3: GT Metrics**
Developmental stage-by-diagnosis-by-sex	**(CTh)** LH Rostral Middle Frontal Cortex **(SA)** LH Paracentral Gyrus RH Precentral Gyrus	**(DR)** FP→ LH Parahippocampal Gyrus **(ROI)** LH rMF(CTh) →LH&RH Superior Temporal Gyrus RH Precentral Gyrus(SA) →LH&RH Middle Frontal Gyrus	Functional Connectivity Path Length Cluster Coefficient Local Efficiency Between Centrality

6.1 Study Discussion

We hypothesized that interactions of developmental stage-by-diagnoses-by-sex can be observed in each Project, and to this our hypothesis is true. The genetically and phenotypically independent morphological measures, cortical thickness and surface area report in regions associated with interpretation of emotion stimuli, somotosensory and primary motor functions (Chouinard and Paus 2006, Winkler, Kochunov et al. 2010, Roy, Shohamy et al. 2012). Both regions are heavily influences by age and sex. Classical symptoms seen in ASD patients include struggles with the interpretation of emotional stimuli and aversions to specific somatosensory stimuli and of repetitive motor behaviors.

BOLD based resting-state functional connectivity has used signal processing techniques for the past 25 years many methods have been derived all of which have their pros and cons (Biswal, Zerrin Yetkin et al. 1995, Cole, Smith et al. 2010, Azeez and Biswal 2017, Hull, Dokovna et al. 2017). Using an ICA approach, we see that connections between a frontoparietal network, one associated with language comprehension, high level executive functions, memory retrieval, and visual-spatial processing (Talati and Hirsch 2005, Smith, Fox et al. 2009, Zevin 2009, Rosazza and Minati 2011, Borsook, Maleki et al. 2015, Sturm, Haase et al. 2016). The

parahippocampal gyrus, a region for memory encoding, visual-spatial processing and episodic memory (Aminoff, Kveraga et al. 2013). The seed-based approach using the seeds from Project1 reveal bilateral superior temporal gyurs, a multisensory interaction site and middle temporal gyrus, which plays an important role in reorienting internal and external attention control (Japee, Holiday et al. 2015). Again as we see in anatomical data, the regions revealed in our analysis are seen to be altered by all three factors. With normal age come improvements in language, memory, improved sensory functions and attention. Recorded natural biological sex effects have revealed that females outperform male socially and cognitively in language, communication, and attention task. Impairments in all of these functions are seen in ASD groups; clinically. Notable among all groups Project 2 are females with ASD who report the strongest connections Dual Regression showing strongest anti-correlation in adult females with ASD while ROI analysis strong positive connections exist in female children with ASD.

Graph Theory metrics have demonstrated that alterations in network integration and segregation are abnormal in ASD, and the inclusion of developmental stage and sex further results in a completely altered topology. Interestingly, we see in female children the most meaningful alterations in GT Metric. They report longest path lengths, implying weaker whole brain integration. Higher clustering coefficient particularly in the temporal parietal junction which has been implicated in the social awkwardness is seen in ASD (Pantelis, Byrge et al. 2015). Female children with ASD have the most efficient local information transfer. We see a loss of Hubs in ASD populations. The most powerful Hub is seen in the sensory motor area likely to be affected most by repetitive motor behavior. What we conclude from Project 3 is that changes in GT metrics can be used to

characterized a population, that frankly is underrepresented in current literature. This is promising finding maybe useful in furthering our understanding for the differences in presentation from one clinical population to the next.

In our final attempt to fully understand the results of our data within the confides of current scientific findings of ASD, we conduct behavioral correlations, between the measures taken in all the Project. To try and place the neuroimaging results with those of clinical behavioral assessments, ADOS sub scores are correlated with regions and whose function fall in to one of three, ASD categories; social defects, language impairments and stereotypical repetitive behaviors. What we find is that overall correlation coefficients are weak ($r<0.05$). However they are promising as the strongest correlations lie in female children. This suggest the perhaps the specific regions that have been revealed throughout the research are better biological markers of the modifications seen by the interactions of development and sex.

All in all what we can take away is that the areas on the cortex that are affected by age, sex and diagnoses of ASD are localized to regions of emotional processing, language comprehension, and sensory integration. We see these findings in all three methodologies; morphology, resting-state, and graph theory.

6.2 Limitations

The research while unique, controlled, and carefully conducted does have limitations. The subject pool although a powerful resource in size and availability, does have limits; they are sourced from 11 different imaging intuitions and lack female subjects with ASD

(n=45). We have attempted to circumvent this with a series of strict statistical test for each project to the best of our scientific ability.

Project 1-Morphological Analysis: We limited our investigation of developmental stage to those of children aged (<11) and adults (>18). This leaves us with an average age of 9 and 25 in children and adults. In skipping over adolescence, a stage that is rapidly changing and growing due to influences of sex hormones, we are limited by information pertaining to this major interactive factor. ABIDE does not provide onset ages of puberty or any gonadocorticoid blood levels. We also in our subject criteria choose subjects whose full IQ are greater than 70, high functioning ASD patients in an attempt to have some uniformity. Therefore, the alterations seen in morphology may a result of a subdued clinical dataset. We also must note at the 11 sites that the data was sourced from, this systematic scanner variability introduces unaccounted for effects to our data.

Project 2-Resting State Functional Connectivity: We choose to implore a mostly data driven-approach to avoid as many investigator biases. In doing so, we must acknowledge the pitfalls of each methodology. While seed-based ROI is a priori approach, it is the most commonly used and oldest method of analysis. It is limited by its inability to inspect connectivity of regions outside of the chosen seeds, therefore potential alterations may be overlooked. Dual Regression, uses ICA to created distinct resting state networks from spectral decomposition of correlation matrix. A drawback is that single brain regions can be found in multiple networks, which can lead to network correlations that are orthogonal due to mathematical handing. We also, in an attempt to reduce motion artifacts, limit the age of our subject pool. The youngest patient in our research study is 7

years old, this intentional avoiding of young subjects is due to the challenge of scanning children in a MR scanner, a loud and tightly closed space, resulting in motion artifacts.

Project 3-Graph Theory: New to the field of neuroscience, the complex mathematical approach, originally developed to characterize social networks. In recent years has been applied to the study of the human brain. While an innovative approach to understanding a complex heterogeneous disorder, characterized by a spectrum does have some pitfalls. The complexity of the methodology requires many assumptions; the functional relevance of the nodes defined by the parcellation. The proliferation and continued interest highlight that there is no "perfect" parcellation and the creation of these atlases is are subjective to the statistic used in the resting state analysis used to crate them (Wang, Wang et al. 2009), which ultimately limits the power of interpretation of results. Thus revealing the larger issue, connecting GT metrics to biological phenomena. "This represent the current state of this field, which requires highly sophisticated network computational approaches that need to be tested systematically before being fully exploited to understand the function and development of brain systems (Ernst, Torrisi et al. 2015)."

6.3 Future Directions

In the future, we would also like to address some of the pitfalls that we acknowledge in our study. Firstly, we still want a better understanding of the sex disparity in ASD diagnose. Therefore, having more MR scans of females with ASD would help immensely, as currently this group only represents 10% of the mean sample sizes in published literature (Hull, Dokovna et al. 2017). If possible, acquiring MR scans and

hormone levels during adolescents, so that we may see the transition in morphology, network changes and GT metrics as a result of the interaction of hormonal changes. Further studies into the developmental changes particular in adolescent girls, who are experiencing puberty; the rapid developmental changes, emotional and social. We would also like to explore the same effects in low functioning ASD patients, it quite possible that the effects we have reported maybe more severe. We would also want to include more images of younger children 3-8 years old as they are not well represented (Hull, Dokovna et al. 2017) to better observe changes in resting state networks. While ABIDE provides many phenotype information, we do not have any information as to the types of behavioral or occupational therapy that subjects are or have participated in would be interesting to see if the effects of these therapies can be seen in neuroimaging analysis.

So much of what have been learned of ASD is through the observation of clinical, and family of those afflicted. While the work of these clinicians have expanded our understanding, there are limitations to this singular approach to the etiology. Behavioral measures and test are typically made for children. This subjectivity and unintentional bias is a possible explanation for the sex disparity and lack of reach in Adults with ASD. For all Projects of the research, we wanted to acquire quantifiable measures that may provide insight to ASD. Still a rather new approach, machine learning, a subset of artificial intelligence (AI) is the scientific study of algorithms. A computer algorithm can be provided with test data and allowed to run over a series of iterations, without being manually programmed These software's can be used this to make predict outcomes. The algorithm learns and improves from previous iterations until it reaches a accuracy acceptable to the programmer. Researchers have proved the power of Machine Learning

in automatic diagnose in Alzheimer's and Parkinson's disease (Chen, Ward et al. 2011, Kazeminejad, Golbabaei et al. 2017, Talai, Boelmans et al. 2017). Its success in neurodegenerative disorders has encouraged scientist to begin to investigate its potential in automatic ASD diagnosis (Kazeminejad and Sotero 2019). We hope going further the regions of significant extracted from Projects 1 and 2 along with the GT biomarkers calculated can be used as classifiers for machine learning algorithm to best distinguished between health and disease states for different sex and developmental stages. Machine learning used in conjunction with pharmacological, and behavioral therapies may help to better determine diagnosis as well as points of intervention so maximum positive prognosis is achieved, for individual patients.

This Dissertation begin as an inquire into the effects of biological sex on ASD and we would later include the effect of development. We have reported interaction effects of all these factors using a variety of methodological approaches. On the 75th anniversary of Dr. Kranner's seminal publication, we acknowledge the many strides that have been made by clinical and health professionals who have used observational and subjective clinical measures in the aid of their patients. As we begin to understand the heterogeneity of the spectrum disorder and as technological advancements in neuroimaging have improved in the last 25 years, we now are able to calculate quantitative measures to help in the characterization of ASD. Now, in an age of hyper-awareness of the disorder many pop-cultural examples have reduced the stigma. Prevalence has also increased in recent years, and alarming sex statistics have added to more research into the workings of the disorder. Ours is one, that attempts to approach the intersection of neurodevelopment and biological sex in ASD from many facets; morphology, connectivity and network

topology. We report effects for each approach suggesting that the disorder should be investigated from all angles. The large subject pool, ABIDE, provide strong statistical power, and our use of strict statically test give us confidence in our results. However, we do note the limitations, and hope that they can be addressed in future studies. Ultimately, we hope that one day clinicians, radiologist, and data scientist can combine their expertise to aid in early diagnosis, which will inform treatment options and eventually improve the outcome of patients with Autism Spectrum Disorder, continuing the work that started from a of a simply case study, with 11 children, conducted over 75 years ago.

REFERENCES

Achard, S. and E. Bullmore (2007). "Efficiency and cost of economical brain functional networks." PLoS computational biology **3**(2): e17.

Akshoomoff, N., C. Corsello and H. Schmidt (2006). "The Role of the Autism Diagnostic Observation Schedule in the Assessment of Autism Spectrum Disorders in School and Community Settings." The California School Psychologist: CASP **11**: 7-19.

Alaerts, K., S. P. Swinnen and N. Wenderoth (2016). "Sex differences in autism: a resting-state fMRI investigation of functional brain connectivity in males and females." Social Cognitive and Affective Neuroscience **11**(6): 1002-1016.

Aldunate, N. and R. González-Ibáñez (2017). "An Integrated Review of Emoticons in Computer-Mediated Communication." Frontiers in Psychology **7**(2061).

Allison, T., A. Puce and G. McCarthy (2000). "Social perception from visual cues: role of the STS region." Trends in Cognitive Sciences **4**(7): 267-278.

Amaral, D., C. Schumann and l. C. Nordah (2008). "Neuroanatomy of autism." Trends in Neruoscience: 137-145.

Aminoff, E. M., K. Kveraga and M. Bar (2013). "The role of the parahippocampal cortex in cognition." Trends in Cognitive Sciences **17**(8): 379-390.

Aron, A. R., P. C. Fletcher, E. T. Bullmore, B. J. Sahakian and T. W. Robbins (2003). "Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans." Nature Neuroscience **6**(2): 115.

Association, A. P. (2013). Diagnostic and statistical manual of mental disorders : DSM-5. Arlington, VA, American Psychiatric Association.

Attwood, T. and T. Grandin (2006). Asperger's and Girls: World-renowned Experts Join Those with Asperger's Syndrome to Resolve Issues that Girls and Women Face Every Day!, Future Horizons.

Azeez, A. K. and B. B. Biswal (2017). "A Review of Resting-State Analysis Methods." Neuroimaging Clinics of North America **27**(4): 581-592.

Baio, J. (2012). "Prevalence of Autism Spectrum Disorders: Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. Morbidity and Mortality Weekly Report. Surveillance Summaries. Volume 61, Number 3." Centers for Disease Control and Prevention.

Baio, J., L. Wiggins, D. L. Christensen, M. J. Maenner, J. Daniels, Z. Warren, M. Kurzius-Spencer, W. Zahorodny, C. R. Rosenberg and T. White (2018). "Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014." MMWR Surveillance Summaries **67**(6): 1.

Baron-Cohen, S. (2000). "Theory of mind and autism: A fifteen year review." Perspectives from developmental cognitive neuroscience **2**: 3-20.

Baron-Cohen, S. (2002). "The extreme male brain theory of autism." Trends in Cognitive Sciences **6**(6): 248-254.

Baron-Cohen, S. (2002). "The extreme male brain theory of autism." Trends Cogn Sci **6**.

Bassett, D. S. and E. Bullmore (2006). "Small-world brain networks." The Neuroscientist **12**(6): 512-523.

Bauer, D. J., B. A. Goldfield and J. S. Reznick (2002). "Alternative approaches to analyzing individual differences in the rate of early vocabulary development." Applied Psycholinguistics **23**(3): 313-335.

Beckmann, M., H. Johansen-Berg and M. F. Rushworth (2009). "Connectivity-based parcellation of human cingulate cortex and its relation to functional specialization." Journal of Neuroscience **29**(4): 1175-1190.

Biswal, B., F. Zerrin Yetkin, V. M. Haughton and J. S. Hyde (1995). "Functional connectivity in the motor cortex of resting human brain using echo-planar mri." Magnetic Resonance in Medicine **34**(4): 537-541.

Biswal, B. B., M. Mennes, X.-N. Zuo, S. Gohel, C. Kelly, S. M. Smith, C. F. Beckmann, J. S. Adelstein, R. L. Buckner, S. Colcombe, A.-M. Dogonowski, M. Ernst, D. Fair, M. Hampson, M. J. Hoptman, J. S. Hyde, V. J. Kiviniemi, R. Kötter, S.-J. Li, C.-P. Lin, M. J. Lowe, C. Mackay, D. J. Madden, K. H. Madsen, D. S. Margulies, H. S. Mayberg, K. McMahon, C. S. Monk, S. H. Mostofsky, B. J. Nagel, J. J. Pekar, S. J. Peltier, S. E. Petersen, V. Riedl, S. A. R. B. Rombouts, B. Rypma, B. L. Schlaggar, S. Schmidt, R. D. Seidler, G. J. Siegle, C. Sorg, G.-J. Teng, J. Veijola, A. Villringer, M. Walter, L. Wang, X.-C. Weng, S. Whitfield-Gabrieli, P. Williamson, C. Windischberger, Y.-F. Zang, H.-Y. Zhang, F. X. Castellanos and M. P. Milham (2010). "Toward discovery science of human brain function." Proceedings of the National Academy of Sciences **107**(10): 4734.

Boddaert, N., N. Chabane, H. Gervais, C. Good, M. Bourgeois, M. Plumet, C. Barthelemy, M. Mouren, E. Artiges and Y. Samson (2004). "Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study." Neuroimage **23**(1): 364-369.

Bonnelle, V., R. Leech, K. M. Kinnunen, T. E. Ham, C. F. Beckmann, X. De Boissezon, R. J. Greenwood and D. J. Sharp (2011). "Default Mode Network Connectivity Predicts Sustained Attention Deficits after Traumatic Brain Injury." The Journal of Neuroscience **31**(38): 13442.

Borsook, D., N. Maleki and R. Burstein (2015). Chapter 42 - Migraine. Neurobiology of Brain Disorders. M. J. Zigmond, L. P. Rowland and J. T. Coyle. San Diego, Academic Press**:** 693-708.

Bullmore, E. and O. Sporns (2009). "Complex brain networks: graph theoretical analysis of structural and functional systems." Nature Reviews Neuroscience **10**: 186.

Bullmore, E. and O. Sporns (2012). "The economy of brain network organization." Nature Reviews Neuroscience **13**: 336.

Burman, D. D., T. Bitan and J. R. Booth (2008). "Sex differences in neural processing of language among children." Neuropsychologia **46**(5): 1349-1362.

Calvert, G. A. (2001). "Crossmodal Processing in the Human Brain: Insights from Functional Neuroimaging Studies." Cerebral Cortex **11**(12): 1110-1123.

Cascio, C., F. McGlone, S. Folger, V. Tannan, G. Baranek, K. A. Pelphrey and G. Essick (2008). "Tactile Perception in Adults with Autism: a Multidimensional Psychophysical Study." Journal of Autism and Developmental Disorders **38**(1): 127-137.

Casey, B. J., N. Tottenham, C. Liston and S. Durston (2005). "Imaging the developing brain: what have we learned about cognitive development?" Trends in Cognitive Sciences **9**(3): 104-110.

CDC. (2018, November 15, 2018). "Data & Statistics on Autism Spectrum Disorder." from https://www.cdc.gov/ncbddd/autism/data.html.

CDC. (2018, February 26, 2015). "Screening and Diagnosis." Autism Spectrum Disorder(ASD), 2018, from https://www.cdc.gov/ncbddd/autism/screening.html#1.

Chen, G., B. D. Ward, C. Xie, W. Li, Z. Wu, J. L. Jones, M. Franczak, P. Antuono and S.-J. Li (2011). "Classification of Alzheimer disease, mild cognitive impairment, and normal cognitive status with large-scale network analysis based on resting-state functional MR imaging." Radiology **259**(1): 213-221.

Chouinard, P. A. and T. Paus (2006). "The Primary Motor and Premotor Areas of the Human Cerebral Cortex." The Neuroscientist **12(**2): 143-152.

Christensen, D. L., K. V. N. Braun, J. Baio, D. Bilder, J. Charles, J. N. Constantino, J. Daniels, M. S. Durkin, R. T. Fitzgerald and M. Kurzius-Spencer (2018). "Prevalence and characteristics of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2012." MMWR Surveillance Summaries **65**(13): 1.

Cole, D. M., S. M. Smith and C. F. Beckmann (2010). "Advances and pitfalls in the analysis and interpretation of resting-state FMRI data." Frontiers in Systems Neuroscience **4**: 8-8.

Cosgrove, K. P., C. M. Mazure and J. K. Staley (2007). "Evolving knowledge of sex differences in brain structure, function, and chemistry." Biological Psychiatry **62**(8): 847-855.

Cox, R. W. (1996). "AFNI: software for analysis and visualization of functional magnetic resonance neuroimages." Computers and Biomedical Research **29**(3): 162-173.

Craddock, R. C., G. A. James, P. E. Holtzheimer III, X. P. Hu and H. S. Mayberg (2012). "A whole brain fMRI atlas generated via spatially constrained spectral clustering." Human Brain Mapping **33**(8): 1914-1928.

Cross, C., L. Copping and A. Campbell (2011). Sex Differences in Impulsivity: A Meta-Analysis.

Davey, J., H. E. Thompson, G. Hallam, T. Karapanagiotidis, C. Murphy, I. De Caso, K. Krieger-Redwood, B. C. Bernhardt, J. Smallwood and E. Jefferies (2016). "Exploring the role of the posterior middle temporal gyrus in semantic cognition: Integration of anterior temporal lobe with executive processes." NeuroImage **137**: 165-177.

De Bellis, M. and M. Keshavan (2001). "Sex differences in brain maturation during childhood and adolescence." Cerebral Cortex: 552-557.

de Bie, H. M., M. Boersma, S. Adriaanse, D. J. Veltman, A. M. Wink, S. D. Roosendaal, F. Barkhof, C. J. Stam, K. J. Oostrom and H. A. Delemarre-van de Waal (2012). "Resting-state networks in awake five-to eight-year old children." Human Brain Mapping **33**(5): 1189-1201.

Del Giudice, M. (2015). Gender Differences in Personality and Social Behavior**:** 750-756.

Dennis, E. L. and P. M. Thompson (2013). "Typical and atypical brain development: a review of neuroimaging studies." Dialogues in clinical neuroscience **15**(3): 359-384.

DeRamus, T. P., B. S. Black, M. R. Pennick and R. K. Kana (2014). "Enhanced parietal cortex activation during location detection in children with autism." Journal of Neurodevelopmental Disorders **6**(1): 37-37.

Dereu, M., P. Warreyn, R. Raymaekers, M. Meirsschaut, G. Pattyn, I. Schietecatte and H. Roeyers (2010). "Screening for Autism Spectrum Disorders in Flemish Day-Care Centres with the Checklist for Early Signs of Developmental Disorders." Journal of Autism and Developmental Disorders **40**(10): 1247-1258.

Desikan, R. S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J. (2006). "An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest." NeuroImage **31**(3): 968 - 980.

Di Martino, A., D. O'Connor, B. Chen, K. Alaerts, J. S. Anderson, M. Assaf, J. H. Balsters, L. Baxter, A. Beggiato, S. Bernaerts, L. M. E. Blanken, S. Y. Bookheimer, B. B. Braden, L. Byrge, F. X. Castellanos, M. Dapretto, R. Delorme, D. A. Fair, I. Fishman, J. Fitzgerald, L. Gallagher, R. J. J. Keehn, D. P. Kennedy, J. E. Lainhart, B. Luna, S. H. Mostofsky, R.-A. Müller, M. B. Nebel, J. T. Nigg, K. O'Hearn, M. Solomon, R. Toro, C. J. Vaidya, N. Wenderoth, T. White, R. C. Craddock, C. Lord, B. Leventhal and M. P. Milham (2017). "Enhancing studies of the connectome in autism using the autism brain imaging data exchange II." Scientific Data **4**: 170010.

Di Martino, A., C.-G. Yan, Q. Li, E. Denio, F. X. Castellanos, K. Alaerts, J. S. Anderson, M. Assaf, S. Y. Bookheimer, M. Dapretto, B. Deen, S. Delmonte, I. Dinstein, B. Ertl-Wagner, D. A. Fair, L. Gallagher, D. P. Kennedy, C. L. Keown, C. Keysers, J. E. Lainhart, C. Lord, B. Luna, V. Menon, N. Minshew, C. S. Monk, S. Mueller, R.-A. Müller, M. B. Nebel, J. T. Nigg, K. O'Hearn, K. A. Pelphrey, S. J. Peltier, J. D. Rudie, S. Sunaert, M. Thioux, J. M. Tyszka, L. Q. Uddin, J. S. Verhoeven, N. Wenderoth, J. L. Wiggins, S. H. Mostofsky and M. P. Milham (2014). "The Autism Brain Imaging Data Exchange: Towards Large-Scale Evaluation of the Intrinsic Brain Architecture in Autism." Molecular Psychiatry **19**(6): 659-667.

Di Martino, A., C. Yan, Q. Li, E. Denio, F. Castellanos and K. Alaerts (2013). "The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. ." Molecular Psychiatry.

Di, X., S. Gohel, E. Kim and B. Biswal (2013). "Task vs. rest—different network configurations between the coactivation and the resting-state brain networks." Frontiers in Human Neuroscience **7**(493).

Dosenbach, N. U. F., B. Nardos, A. L. Cohen, D. A. Fair, J. D. Power, J. A. Church, S. M. Nelson, G. S. Wig, A. C. Vogel, C. N. Lessov-Schlaggar, K. A. Barnes, J. W. Dubis, E. Feczko, R. S. Coalson, J. R. Pruett, Jr., D. M. Barch, S. E. Petersen and B. L. Schlaggar (2010). "Prediction of individual brain maturity using fMRI." Science **329**(5997): 1358-1361.

Ecker, C., A. Shahidiani, Y. Feng and E. Daly (2014). "The effect of age, diagnosis, and their interaction on vertex-based measures of cortical thickness and surface area in autism spectrum disorder." Neural Transmission: 1157-1170.

Engvig, A., A. M. Fjell, L. T. Westlye, T. Moberget, Ø. Sundseth, V. A. Larsen and K. B. Walhovd (2010). "Effects of memory training on cortical thickness in the elderly." Neuroimage **52**(4): 1667-1676.

Ernst, M., S. Torrisi, N. Balderston, C. Grillon and E. A. Hale (2015). "fMRI functional connectivity applied to adolescent neurodevelopment." Annual review of clinical psychology **11**: 361-377.

Fair, D. A., A. L. Cohen, J. D. Power, N. U. Dosenbach, J. A. Church, F. M. Miezin, B. L. Schlaggar and S. E. Petersen (2009). "Functional brain networks develop from a “local to distributed” organization." PLoS computational biology **5**(5): e1000381.

Fair, D. A., N. U. Dosenbach, J. A. Church, A. L. Cohen, S. Brahmbhatt, F. M. Miezin, D. M. Barch, M. E. Raichle, S. E. Petersen and B. L. Schlaggar (2007). "Development of distinct control networks through segregation and integration." Proceedings of the National Academy of Sciences **104**(33): 13507-13512.

Fischl, B. and A. M. Dale (2000). "Measuring the thickness of the human cerebral cortex from magnetic resonance images." Proceedings of the National Academy of Sciences of the United States of America **97**(20): 11050-11055.

Floris, D. L., M.-C. Lai, T. Nath, M. P. Milham and A. Di Martino (2018). "Network-specific sex differentiation of intrinsic brain function in males with autism." Molecular Autism **9**: 17-17.

Fuster, J. M. (2009). Prefrontal Cortex. Encyclopedia of Neuroscience. L. R. Squire. Oxford, Academic Press**:** 905-908.

Gage, N. M. and B. J. Baars (2018). Chapter 4 - The Art of Seeing. Fundamentals of Cognitive Neuroscience (Second Edition). N. M. Gage and B. J. Baars. San Diego, Academic Press**:** 99-141.

Gao, W., H. Zhu, K. S. Giovanello, J. K. Smith, D. Shen, J. H. Gilmore and W. Lin (2009). "Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects." Proceedings of the National Academy of Sciences **106**(16): 6790.

Geerligs, L., R. J. Renken, E. Saliasi, N. M. Maurits and M. M. Lorist (2014). "A brain-wide study of age-related changes in functional connectivity." Cerebral Cortex **25**(7): 1987-1999.

Gerrish, A. C., A. G. Thomas and R. A. Dineen (2014). "Brain White Matter Tracts: Functional Anatomy and Clinical Relevance." Seminars in Ultrasound, CT and MRI **35**(5): 432-444.

Geschwind, D. H. and P. Levitt (2007). "Autism spectrum disorders: developmental disconnection syndromes." Current Opinion in Neurobiology **17**(1): 103-111.

Giedd, J. N., J. Blumenthal, N. O. Jeffries, F. X. Castellanos, H. Liu, A. Zijdenbos, T. Paus, A. C. Evans and J. L. Rapoport (1999). "Brain development during childhood and adolescence: a longitudinal MRI study." Nature Neuroscience **2**: 861.

Gilliam, J. E. (1995). "Gilliam autism rating scale: Examiner's manual." Pro-ed.

Gogtay, N., J. N. Giedd, L. Lusk, K. M. Hayashi, D. Greenstein, A. C. Vaituzis, T. F. Nugent, D. H. Herman, L. S. Clasen, A. W. Toga, J. L. Rapoport and P. M. Thompson (2004). "Dynamic mapping of human cortical development during childhood through early adulthood." Proceedings of the National Academy of Sciences of the United States of America **101**(21): 8174.

Gogtay, N. and P. M. Thompson (2010). "Mapping gray matter development: Implications for typical development and vulnerability to psychopathology." Brain and Cognition **72**(1): 6-15.

Gong, G., Y. He and A. C. Evans (2011). "Brain connectivity: gender makes a difference." The Neuroscientist **17**(5): 575-591.

Gong, G., P. Rosa-Neto, F. Carbonell, Z. J. Chen, Y. He and A. C. Evans (2009). "Age- and Gender-Related Differences in the Cortical Anatomical Network." The Journal of Neuroscience **29**(50): 15684-15693.

Gotham, K., S. Risi, A. Pickles and C. Lord (2007). "The Autism Diagnostic Observation Schedule: revised algorithms for improved diagnostic validity." Journal of Autism and Developmental Disorders **37**(4): 613.

Gourley, S. L., K. S. Zimmermann, A. G. Allen and J. R. Taylor (2016). "The Medial Orbitofrontal Cortex Regulates Sensitivity to Outcome Value." The Journal of Neuroscience **36**(16): 4600.

Green, S. A. and L. Hernandez (2016). "Salience Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Overresponsivity." Journal of the American Academy of Child & Adolescent Psychiatry: 618-626.

Ha, S., I.-J. Sohn, N. Kim, H. J. Sim and K.-A. Cheon (2015). "Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan." Experimental Neurobiology **24**(4): 273-284.

Haines, D. E. and G. A. Mihailoff (2018). Chapter 16 - The Telencephalon. Fundamental Neuroscience for Basic and Clinical Applications (Fifth Edition). D. E. Haines and G. A. Mihailoff, Elsevier**:** 225-240.e221.

Halladay, A. K., S. Bishop, J. N. Constantino, A. M. Daniels, K. Koenig, K. Palmer, D. Messinger, K. Pelphrey, S. J. Sanders, A. T. Singer, J. L. Taylor and P. Szatmari (2015). "Sex and gender differences in autism spectrum disorder: summarizing evidence gaps and identifying emerging areas of priority." Molecular Autism **6**: 36-36.

Hampshire, A., S. R. Chamberlain, M. M. Monti, J. Duncan and A. M. Owen (2010). "The role of the right inferior frontal gyrus: inhibition and attentional control." NeuroImage **50**(3): 1313-1319.

Hampson, E. (1992). "Sex differences and hormonal influences on cognitive function in humans." Behavioral endocrinology.

Hanaie, R., I. Mohri, K. Kagitani-Shimono, M. Tachibana, J. Azuma, J. Matsuzaki, Y. Watanabe, N. Fujita and M. Taniike (2013). "Altered microstructural connectivity of the superior cerebellar peduncle is related to motor dysfunction in children with autistic spectrum disorders." The Cerebellum **12**(5): 645-656.

He, Y., Z. Chen and A. Evans (2008). "Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease." The Journal of Neuroscience **28**(18): 4756-4766.

Hill, E. L. (2004). "Executive dysfunction in autism." Trends in Cognitive Sciences **8**(1): 26-32.

Hobson, R. P. (1993). "The emotional origins of social understanding." Philosophical psychology **6**(3): 227-249.

Hoff, G. E. A.-J., M. Van Den Heuvel, M. J. N. L. Benders, K. J. Kersbergen and L. S. de Vries (2013). "On development of functional brain connectivity in the young brain." Frontiers in Human Neuroscience **7**(650).

Hu, S., J. S. Ide, S. Zhang and C.-s. R. Li (2016). "The Right Superior Frontal Gyrus and Individual Variation in Proactive Control of Impulsive Response." The Journal of Neuroscience **36**(50): 12688.

Hull, J. V., L. B. Dokovna, Z. J. Jacokes, C. M. Torgerson, A. Irimia and J. D. Van Horn (2017). "Resting-State Functional Connectivity in Autism Spectrum Disorders: A Review." Frontiers in Psychiatry **7**: 205-205.

Hus, V., K. Gotham and C. Lord (2014). "Standardizing ADOS domain scores: separating severity of social affect and restricted and repetitive behaviors." Journal of Autism and Developmental Disorders **44**(10): 2400-2412.

Hus, V. and C. Lord (2014). "The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores." Journal of Autism and Developmental Disorders **44**(8): 1996-2012.

Ingalhalikar, M., A. Smith, D. Parker, T. D. Satterthwaite, M. A. Elliott, K. Ruparel, H. Hakonarson, R. E. Gur, R. C. Gur and R. Verma (2014). "Sex differences in the structural connectome of the human brain." Proceedings of the National Academy of Sciences **111**(2): 823-828.

Itahashi, T., T. Yamada, H. Watanabe, M. Nakamura, D. Jimbo, S. Shioda, K. Toriizuka, N. Kato and R. Hashimoto (2014). "Altered network topologies and hub organization in adults with autism: a resting-state fMRI study." PLoS one **9**(4): e94115-e94115.

Jacquemont, S., B. P. Coe, M. Hersch, M. H. Duyzend, N. Krumm, S. Bergmann, J. S. Beckmann, J. A. Rosenfeld and E. E. Eichler (2014). "A higher mutational burden in females supports a “female protective model” in neurodevelopmental disorders." The American Journal of Human Genetics **94**(3): 415-425.

Japee, S., K. Holiday, M. D. Satyshur, I. Mukai and L. G. Ungerleider (2015). "A role of right middle frontal gyrus in reorienting of attention: a case study." Frontiers in Systems Neuroscience **9**(23).

Johns, P. (2014). Chapter 3 - Functional neuroanatomy. Clinical Neuroscience. P. Johns, Churchill Livingstone**:** 27-47.

Jolles, D. D., M. A. van Buchem, E. A. Crone and S. A. R. B. Rombouts (2011). "A Comprehensive Study of Whole-Brain Functional Connectivity in Children and Young Adults." Cerebral Cortex **21**(2): 385-391.

Just, M., T. Keller, V. Malave, R. Kana and S. Varma (2012). "Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity." Neuroscience and Biobehavioral Reviews: 1292-1313.

Kanner, L. (1943). "Autistic disturbances of affective contact." Nervous Child: 217-250.

Kazeminejad, A., S. Golbabaei and H. Soltanian-Zadeh (2017). Graph theoretical metrics and machine learning for diagnosis of Parkinson's disease using rs-fMRI. 2017 Artificial Intelligence and Signal Processing Conference (AISP).

Kazeminejad, A. and R. C. Sotero (2019). "Topological Properties of Resting-State fMRI Functional Networks Improve Machine Learning-Based Autism Classification." Frontiers in Neuroscience **12**(1018).

Keown, C. L., M. C. Datko, C. P. Chen, J. O. Maximo, A. Jahedi and R.-A. Müller (2017). "Network organization is globally atypical in autism: A graph theory study of intrinsic functional connectivity." Biological Psychiatry: Cognitive Neuroscience and Neuroimaging **2**(1): 66-75.

Kern, J. K., M. H. Trivedi, C. R. Garver, B. D. Grannemann, A. A. Andrews, J. S. Savla, D. G. Johnson, J. A. Mehta and J. L. Schroeder (2006). "The pattern of sensory processing abnormalities in autism." Autism **10**(5): 480-494.

Khundrakpam, B. S., A. Reid, J. Brauer, F. Carbonell, J. Lewis, S. Ameis, S. Karama, J. Lee, Z. Chen, S. Das, A. C. Evans and G. Brain Development Cooperative (2013). "Developmental changes in organization of structural brain networks." Cerebral Cortex **23**(9): 2072-2085.

Kim, K. W., S. W. Lee, J. Choi, T. M. Kim and B. Jeong (2016). "Neural correlates of text-based emoticons: a preliminary fMRI study." Brain and Behavior **6**(8): e00500-e00500.

Kim, Y. S., B. L. Leventhal, Y.-J. Koh, E. Fombonne, E. Laska, E.-C. Lim, K.-A. Cheon, S.-J. Kim, Y.-K. Kim and H. Lee (2011). "Prevalence of autism spectrum disorders in a total population sample." American Journal of Psychiatry **168**(9): 904-912.

Kimura, D. (2000). Sex and cognition, MIT press.

Lai, M.-C., M. V. Lombardo, G. Pasco, A. N. V. Ruigrok, S. J. Wheelwright, S. A. Sadek, B. Chakrabarti, M. A. Consortium and S. Baron-Cohen (2011). "A Behavioral Comparison of Male and Female Adults with High Functioning Autism Spectrum Conditions." PLoS one **6**(6): e20835.

Lecavalier, L. (2005). "An Evaluation of the Gilliam Autism Rating Scale." Journal of Autism and Developmental Disorders **35**(6): 795.

Leech, R. and D. J. Sharp (2014). "The role of the posterior cingulate cortex in cognition and disease." Brain **137**(Pt 1): 12-32.

Lenroot, R., N. Gogtay and D. Greenstein (2007). "Sexual dimorphism of brain developmental trajectories during childhood and adolescence." NeuroImage: 1065-1073.

Lenroot, R. K. and J. N. Giedd (2006). "Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging." Neuroscience & Biobehavioral Reviews **30**(6): 718-729.

Levy, J. (1972). "Lateral specialization of the human brain, behavioral manifestations and possible evolutionary basis." The Biology of Behavior.

Li, C.-s. R., S. Zhang, J.-R. Duann, P. Yan, R. Sinha and C. M. Mazure (2009). "Gender Differences in Cognitive Control: an Extended Investigation of the Stop Signal Task." Brain Imaging and Behavior **3**(3): 262-276.

Lin, W., Q. Zhu, W. Gao, Y. Chen, C. H. Toh, M. Styner, G. Gerig, J. K. Smith, B. Biswal and J. H. Gilmore (2008). "Functional Connectivity MR Imaging Reveals Cortical Functional Connectivity in the Developing Brain." American Journal of Neuroradiology **29**(10): 1883.

Lord, C., S. Risi, P. S. DiLavore, C. Shulman, A. Thurm and A. Pickles (2006). "Autism From 2 to 9 Years of Age." JAMA Psychiatry **63**(6): 694-701.

Mandy, W., R. Chilvers, U. Chowdhury, G. Salter, A. Seigal and D. Skuse (2012). "Sex Differences in Autism Spectrum Disorder: Evidence from a Large Sample of Children and Adolescents." Journal of Autism and Developmental Disorders **42**(7): 1304-1313.

Mansouri, F. A., D. J. Fehring, A. Gaillard, S. Jaberzadeh and H. Parkington (2016). "Sex dependency of inhibitory control functions." Biology of Sex Differences **7**: 11-11.

Marco, E. J., L. B. N. Hinkley, S. S. Hill and S. S. Nagarajan (2011). "Sensory processing in autism: a review of neurophysiologic findings." Pediatric research **69**(5 Pt 2): 48R-54R.

Marek, S. and N. U. F. Dosenbach (2018). "The frontoparietal network: function, electrophysiology, and importance of individual precision mapping." Dialogues in clinical neuroscience **20**(2): 133-140.

Martin, A. and L. L. Chao (2001). "Semantic memory and the brain: structure and processes." Current Opinion in Neurobiology **11**(2): 194-201.

Martinez-Murcia, F., M. Lai, J. Górriz and J. Ramírez (2016). "On the brain structure heterogeneity of autism: Parsing out acquisition site effects with significance-weighted principal component analysis." Human Brian Mapping.

Mather, M. and N. R. Lighthall (2012). "Risk and reward are processed differently in decisions made under stress." Current directions in psychological science **21**(1): 36-41.

McGugin, R. W., A. E. Van Gulick and I. Gauthier (2016). "Cortical thickness in fusiform face area predicts face and object recognition performance." Journal of Cognitive Neuroscience **28**(2): 282-294.

Mechelli, A., M. L. Gorno-Tempini and C. J. Price (2003). "Neuroimaging Studies of Word and Pseudoword Reading: Consistencies, Inconsistencies, and Limitations." Journal of Cognitive Neuroscience **15**(2): 260-271.

Medaglia, J. D. (2017). "Graph Theoretic Analysis of Resting State Functional MR Imaging." Neuroimaging Clinics of North America **27**(4): 593-607.

Menary, K., P. F. Collins, J. N. Porter, R. Muetzel, E. A. Olson, V. Kumar, M. Steinbach, K. O. Lim and M. Luciana (2013). "Associations between cortical thickness and general intelligence in children, adolescents and young adults." Intelligence **41**(5): 597-606.

Menon, V. and L. Q. Uddin (2010). "Saliency, switching, attention and control: a network model of insula function." Brain Structure and Function **214**(5-6): 655-667.

Meunier, D., S. Achard, A. Morcom and E. Bullmore (2009). "Age-related changes in modular organization of human brain functional networks." Neuroimage **44**(3): 715-723.

Miller, L. M. (2016). Chapter 41 - Neural Mechanisms of Attention to Speech. Neurobiology of Language. G. Hickok and S. L. Small. San Diego, Academic Press**:** 503-514.

Miller, M., K. L. Bales, S. L. Taylor, J. Yoon, C. M. Hostetler, C. S. Carter and M. Solomon (2013). "Oxytocin and vasopressin in children and adolescents with autism spectrum disorders: sex differences and associations with symptoms." Autism Research **6**(2): 91-102.

Monaco, A. P. and A. J. Bailey (2001). "The search for susceptibility genes." The Lancet **358**: S3.

Monk, C. S., S. J. Peltier, J. L. Wiggins, S.-J. Weng, M. Carrasco, S. Risi and C. Lord (2009). "Abnormalities of intrinsic functional connectivity in autism spectrum disorders." NeuroImage **47**(2): 764-772.

Murray, A. D., J. Johnson and J. Peters (1990). "Fine-tuning of utterance length to preverbal infants: Effects on later language development." Journal of child language **17**(3): 511-525.

Murray, H. A. (1938). Explorations in personality: a clinical and experimental study of fifty men of college age. Oxford, England, Oxford Univ. Press.

Nickerson, L. D., S. M. Smith, D. Öngür and C. F. Beckmann (2017). "Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses." Frontiers in Neuroscience **11**: 115-115.

Nomi, J. S. and L. Q. Uddin (2015). "Developmental changes in large-scale network connectivity in autism." NeuroImage: Clinical **7**: 732-741.

Noriuchi, M. and Y. Kikuchi (2010). "Altered white matter fractional anisotropy and social impairment in children with autism spectrum disorder." Brain Research: 141-149.

Oldehinkel, M., M. Mennes, A. Marquand, T. Charman, J. Tillmann, C. Ecker, F. Dell'Acqua, D. Brandeis, T. Banaschewski, S. Baumeister, C. Moessnang, S. Baron-Cohen, R. Holt, S. Bölte, S. Durston, P. Kundu, M. V. Lombardo, W. Spooren, E. Loth, D. G. M. Murphy, C. F. Beckmann, J. K. Buitelaar, J. Ahmad, S. Ambrosino, B. Auyeung, T. Banaschewski, S. Baron-Cohen, S. Baumeister, C. F. Beckmann, S. Bölte, T. Bourgeron, C. Bours, M. Brammer, D. Brandeis, C. Brogna, Y. de Bruijn, J. K. Buitelaar, B. Chakrabarti, T. Charman, I. Cornelissen, D. Crawley, F. Dell'Acqua, G. Dumas, S. Durston, C. Ecker, J. Faulkner, V. Frouin, P. Garcés, D. Goyard, L. Ham, H. Hayward, J. Hipp, R. Holt, M. H. Johnson, E. J. H. Jones, P. Kundu, M.-C. Lai, X. Liogier D'ardhuy, M. V. Lombardo, E. Loth, D. J. Lythgoe, R. Mandl, A. Marquand, L. Mason, M. Mennes, A. Meyer-Lindenberg, C. Moessnang, N. Mueller, D. G. M. Murphy, B. Oakley, L. O'Dwyer, M. Oldehinkel, B. Oranje, G. Pandina, A. M. Persico, B. Ruggeri, A. Ruigrok, J. Sabet, R. Sacco, A. S. J. Cáceres, E. Simonoff, W. Spooren, J. Tillmann, R. Toro, H. Tost, J. Waldman, S. C. R. Williams, C. Wooldridge and M. P. Zwiers (2019). "Altered Connectivity Between Cerebellum, Visual, and Sensory-Motor Networks in Autism Spectrum Disorder: Results from the EU-AIMS Longitudinal European Autism Project." Biological Psychiatry: Cognitive Neuroscience and Neuroimaging **4**(3): 260-270.

Pantelis, P. C., L. Byrge, J. M. Tyszka, R. Adolphs and D. P. Kennedy (2015). "A specific hypoactivation of right temporo-parietal junction/posterior superior temporal sulcus in response to socially awkward situations in autism." Social Cognitive and Affective Neuroscience **10**(10): 1348-1356.

Park, H. R., J. M. Lee, H. E. Moon, D. S. Lee, B.-N. Kim, J. Kim, D. G. Kim and S. H. Paek (2016). "A Short Review on the Current Understanding of Autism Spectrum Disorders." Experimental Neurobiology **25**(1): 1-13.

Parsons, T. D., A. R. Rizzo, C. v. d. Zaag, J. S. McGee and J. G. Buckwalter (2005). "Gender Differences and Cognition Among Older Adults." Aging, Neuropsychology, and Cognition **12**(1): 78-88.

Pelphrey, K. A., J. P. Morris and G. McCarthy (2005). "Neural basis of eye gaze processing deficits in autism." Brain **128**(5): 1038-1048.

Perrin, J., G. Leonard and M. Perron (2009). "Sex differences in the growth of white matter during adolescence." NeuroImage: 1055-1066.

Perry, A., R. A. Condillac, N. L. Freeman, J. Dunn-Geier and J. Belair (2005). "Multi-site Study of the Childhood Autism Rating Scale (CARS) in Five Clinical Groups of Young Children." Journal of Autism and Developmental Disorders **35**(5): 625-634.

Petrides, M. (2016). Chapter 3 - The Ventrolateral Frontal Region. Neurobiology of Language. G. Hickok and S. L. Small. San Diego, Academic Press**:** 25-33.

Pilowsky, T., N. Yirmiya, C. Shulman and R. Dover (1998). "The Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale: Differences Between Diagnostic Systems and Comparison Between Genders." Journal of Autism and Developmental Disorders **28**(2): 143-151.

Platt, M. L. and H. Plassmann (2014). Chapter 13 - Multistage Valuation Signals and Common Neural Currencies. Neuroeconomics (Second Edition). P. W. Glimcher and E. Fehr. San Diego, Academic Press**:** 237-258.

Power, J. D., K. A. Barnes, A. Z. Snyder, B. L. Schlaggar and S. E. Petersen (2012). "Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion." NeuroImage **59**(3): 2142-2154.

Power, J. D., A. L. Cohen, S. M. Nelson, G. S. Wig, K. A. Barnes, J. A. Church, A. C. Vogel, T. O. Laumann, F. M. Miezin and B. L. Schlaggar (2011). "Functional network organization of the human brain." Neuron **72**(4): 665-678.

Power, Jonathan D., Bradley L. Schlaggar, Christina N. Lessov-Schlaggar and Steven E. Petersen (2013). "Evidence for Hubs in Human Functional Brain Networks." Neuron **79**(4): 798-813.

Ptak, R. (2011). "The Frontoparietal Attention Network of the Human Brain: Action, Saliency, and a Priority Map of the Environment." The Neuroscientist **18**(5): 502-515.

Rajan, C. S. and H. B. Joseph (2019). "Self esteem and emotional maturity among adolescents." International Journal of Nursing Care **7**(1): 27-29.

Raznahan, A., P. Shaw, F. Lalonde, M. Stockman, G. L. Wallace, D. Greenstein, L. Clasen, N. Gogtay and J. N. Giedd (2011). "How does your cortex grow?" The Journal of Neuroscience **31**(19): 7174-7177.

Righart, R., P. Schmidt, R. Dahnke, V. Biberacher, A. Beer, D. Buck, B. Hemmer, J. S. Kirschke, C. Zimmer, C. Gaser and M. Mühlau (2017). "Volume versus surface-based cortical thickness measurements: A comparative study with healthy controls and multiple sclerosis patients." PLoS one **12**(7): e0179590-e0179590.

Ritvo, E. R., L. B. Jorde, A. Mason-Brothers, B. Freeman and C. Pingree (1989). "The UCLA-University of Utah epidemiological survey of autism: Recurrence risk estimates and genetic counseling." The American journal of psychiatry **146**(8): 1032.

Rosazza, C. and L. Minati (2011). "Resting-state brain networks: literature review and clinical applications." Neurological Sciences **32**(5): 773-785.

Roulstone, S., S. Loader, K. Northstone and M. Beveridge (2002). "The speech and language of children aged 25 months: Descriptive data from the Avon Longitudinal Study of Parents and Children." Early Child Development and Care **172**(3): 259-268.

Roy, M., D. Shohamy and T. D. Wager (2012). "Ventromedial prefrontal-subcortical systems and the generation of affective meaning." Trends in Cognitive Sciences **16**(3): 147-156.

Rubia, K., L. Lim, C. Ecker, R. Halari, V. Giampietro, A. Simmons, M. Brammer and A. Smith (2013). "Effects of age and gender on neural networks of motor response inhibition: From adolescence to mid-adulthood." NeuroImage **83**: 690-703.

Rubinov, M. and O. Sporns (2010). "Complex network measures of brain connectivity: Uses and interpretations." NeuroImage **52**(3): 1059-1069.

Rudie, J. D., J. A. Brown, D. Beck-Pancer, L. M. Hernandez, E. L. Dennis, P. M. Thompson, S. Y. Bookheimer and M. Dapretto (2013). "Altered functional and structural brain network organization in autism." NeuroImage: Clinical **2**: 79-94.

Ruigrok, A. N., G. Salimi-Khorshidi, M.-C. Lai, S. Baron-Cohen, M. V. Lombardo, R. J. Tait and J. Suckling (2014). "A meta-analysis of sex differences in human brain structure." Neuroscience & Biobehavioral Reviews **39**: 34-50.

Satterthwaite, T. D., D. H. Wolf, D. R. Roalf, K. Ruparel, G. Erus, S. Vandekar, E. D. Gennatas, M. A. Elliott, A. Smith, H. Hakonarson, R. Verma, C. Davatzikos, R. E. Gur and R. C. Gur (2015). "Linked Sex Differences in Cognition and Functional Connectivity in Youth." Cerebral Cortex **25**(9): 2383-2394.

Saul, L. J. (1947). Emotional maturity: The development and dynamics of personality. Oxford, England, Lippincott.

Schmidt, E. L., W. Burge, K. M. Visscher and L. A. Ross (2016). "Cortical thickness in frontoparietal and cingulo-opercular networks predicts executive function performance in older adults." Neuropsychology **30**(3): 322.

Schultz, H., T. Sommer and J. Peters (2015). "The Role of the Human Entorhinal Cortex in a Representational Account of Memory." Frontiers in Human Neuroscience **9**: 628-628.

Seghier, M. L. (2013). "The angular gyrus: multiple functions and multiple subdivisions." The Neuroscientist **19**(1): 43-61.

Silani, G., C. Lamm, C. C. Ruff and T. Singer (2013). "Right Supramarginal Gyrus Is Crucial to Overcome Emotional Egocentricity Bias in Social Judgments." The Journal of Neuroscience **33**(39): 15466-15476.

Singh-Curry, V. and M. Husain (2009). "The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy." Neuropsychologia **47**(6): 1434-1448.

Smalley, S. L., R. F. Asarnow and M. A. Spence (1988). "Autism and Genetics: A Decade of Research." Archives of General Psychiatry **45**(10): 953-961.

Smith, S. M., P. T. Fox, K. L. Miller, D. C. Glahn, P. M. Fox, C. E. Mackay, N. Filippini, K. E. Watkins, R. Toro, A. R. Laird and C. F. Beckmann (2009). "Correspondence of the brain's functional architecture during activation and rest." Proceedings of the National Academy of Sciences of the United States of America **106**(31): 13040-13045.

South, M., B. J. Williams, W. M. McMahon, T. Owley, P. A. Filipek, E. Shernoff, C. Corsello, J. E. Lainhart, R. Landa and S. Ozonoff (2002). "Utility of the Gilliam Autism Rating Scale in Research and Clinical Populations." Journal of Autism and Developmental Disorders **32**(6): 593-599.

Sowell, E. R., B. S. Peterson, P. M. Thompson, S. E. Welcome, A. L. Henkenius and A. W. Toga (2003). "Mapping cortical change across the human life span." Nature Neuroscience **6**: 309.

Sowell, E. R., P. M. Thompson, C. M. Leonard, S. E. Welcome, E. Kan and A. W. Toga (2004). "Longitudinal Mapping of Cortical Thickness and Brain Growth in Normal Children." The Journal of Neuroscience **24**(38): 8223.

Speaks, A. (2018, April 26, 2018). "CDC increases estimate of autism's prevalence by 15 percent, to 1 in 59 children: Autism Speaks calls on nation's leaders to adequately fund critically needed research and support services." from https://www.autismspeaks.org/science-news/cdc-increases-estimate-autisms-prevalence-15-percent-1-59-children.

Sporns, O., D. R. Chialvo, M. Kaiser and C. C. Hilgetag (2004). "Organization, development and function of complex brain networks." Trends in Cognitive Sciences **8**(9): 418-425.

Sridharan, D., D. J. Levitin and V. Menon (2008). "A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks." Proceedings of the National Academy of Sciences **105**(34): 12569-12574.

Stavropoulos, K. K. M. and L. J. Carver (2013). "Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention." Journal of Child Psychology and Psychiatry **54**(6): 603-618.

Stigler, K. A. and C. J. McDougle (2013). Chapter 3.1 - Structural and Functional MRI Studies of Autism Spectrum Disorders. The Neuroscience of Autism Spectrum Disorders. J. D. Buxbaum and P. R. Hof. San Diego, Academic Press**:** 251-266.

Sturm, V. E., C. M. Haase and R. W. Levenson (2016). Chapter 22 - Emotional Dysfunction in Psychopathology and Neuropathology: Neural and Genetic Pathways. Genomics, Circuits, and Pathways in Clinical Neuropsychiatry. T. Lehner, B. L. Miller and M. W. State. San Diego, Academic Press**:** 345-364.

Tadevosyan-leyfer, O., M. Dowd, R. Mankoski, B. Winklosky, S. Putnam, L. McGrath, H. Tager-flusberg and S. E. Folstein (2003). "A Principal Components Analysis of the Autism Diagnostic Interview-Revised." Journal of the American Academy of Child & Adolescent Psychiatry **42**(7): 864-872.

Talai, S., K. Boelmans, J. Sedlacik and N. D. Forkert (2017). Automatic classification of patients with idiopathic Parkinson's disease and progressive supranuclear palsy using diffusion MRI datasets. Medical Imaging 2017: Computer-Aided Diagnosis, International Society for Optics and Photonics.

Talati, A. and J. Hirsch (2005). "Functional specialization within the medial frontal gyrus for perceptual go/no-go decisions based on “what,”“when,” and “where” related information: an fMRI study." Journal of Cognitive Neuroscience **17**(7): 981-993.

Thompson, P. M., E. R. Sowell, N. Gogtay, J. N. Giedd, C. N. Vidal, K. M. Hayashi, A. Leow, R. Nicolson, J. L. Rapoport and A. W. Toga (2005). Structural MRI and Brain Development. International Review of Neurobiology, Academic Press. **67:** 285-323.

Tian, L., J. Wang, C. Yan and Y. He (2011). "Hemisphere- and gender-related differences in small-world brain networks: A resting-state functional MRI study." NeuroImage **54**(1): 191-202.

Tzourio-Mazoyer, N., B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, B. Mazoyer and M. Joliot (2002). "Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain." NeuroImage **15**(1): 273-289.

Uddin, L. Q., J. S. Nomi, B. Hébert-Seropian, J. Ghaziri and O. Boucher (2017). "Structure and Function of the Human Insula." Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society **34**(4): 300-306.

Uddin, L. Q., K. S. Supekar, S. Ryali and V. Menon (2011). "Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development." The Journal of neuroscience : the official journal of the Society for Neuroscience **31**(50): 18578-18589.

van den Heuvel, M. P. and H. E. Hulshoff Pol (2010). "Exploring the brain network: A review on resting-state fMRI functional connectivity." European Neuropsychopharmacology **20**(8): 519-534.

van den Heuvel, M. P. and O. Sporns (2013). "Network hubs in the human brain." Trends in Cognitive Sciences **17**(12): 683-696.

Van Essen, D. C. (1997). "A tension-based theory of morphogenesis and compact wiring in the central nervous system." Nature **385**(6614): 313.

Vander Ghinst, M., M. Bourguignon, M. Op de Beeck, V. Wens, B. Marty, S. Hassid, G. Choufani, V. Jousmäki, R. Hari, P. Van Bogaert, S. Goldman and X. De Tiège (2016). "Left Superior Temporal Gyrus Is Coupled to Attended Speech in a Cocktail-Party Auditory Scene." The Journal of Neuroscience **36**(5): 1596-1606.

Vinckier, F., S. Dehaene, A. Jobert, J. P. Dubus, M. Sigman and L. Cohen (2007). "Hierarchical coding of letter strings in the ventral stream: dissecting the inner organization of the visual word-form system." Neuron **55**(1): 143-156.

Von dem Hagen, E. A. H. e. a. (2013). "Reduced functional connectivity within and between 'social' resting state networks in autism spectrum conditions." Social Cognitive and Affective Neuroscience: 94-701.

Wang, J., L. Wang, Y. Zang, H. Yang, H. Tang, Q. Gong, Z. Chen, C. Zhu and Y. He (2009). "Parcellation-dependent small-world brain functional networks: A resting-state fMRI study." Human Brain Mapping **30**(5): 1511-1523.

Wang, J., X. Zuo and Y. He (2010). "Graph-based network analysis of resting-state functional MRI." Frontiers in Systems Neuroscience **4**: 16-16.

Waye, M. M. Y. and H. Y. Cheng (2018). "Genetics and epigenetics of autism: A Review." Psychiatry and Clinical Neurosciences **72**(4): 228-244.

Werling, D. M. and D. H. Geschwind (2013). "Sex differences in autism spectrum disorders." Current Opinion in Neurobiology **26**(2): 146-153.

Wiggins, L. D., D. L. Robins, R. Bakeman and L. B. Adamson (2009). "Breif report: sensory abnormalities as distinguishing symptoms of autism spectrum disorders in young children." Journal of Autism and Developmental Disorders **39**(7): 1087-1091.

Winkler, A. M., P. Kochunov, J. Blangero, L. Almasy, K. Zilles, P. T. Fox, R. Duggirala and D. C. Glahn (2010). "Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies." NeuroImage **53**(3): 1135-1146.

Yamaura, A., K. Kansaku and S. Kitazawa (2000). "Sex Differences in Lateralization Revealed in the Posterior Language Areas." Cerebral Cortex **10**(9): 866-872.

Zevin, J. (2009). Word Recognition. Encyclopedia of Neuroscience. L. R. Squire. Oxford, Academic Press**:** 517-522.

Zhang, C., N. D. Cahill, M. R. Arbabshirani, T. White, S. A. Baum and A. M. Michael (2016). "Sex and Age Effects of Functional Connectivity in Early Adulthood." Brain connectivity **6**(9): 700-713.

Zielinski, B. A., M. B. Prigge, J. A. Nielsen, A. L. Froehlich, T. J. Abildskov, J. S. Anderson, P. T. Fletcher, K. M. Zygmunt, B. G. Travers and N. Lange (2014). "Longitudinal changes in cortical thickness in autism and typical development." Brain **137**(6): 1799-1812.