CROSS NEURODEVELOPMENTAL DISORDER HOMOGENEITY

CROSS DISORDER HOMOGENEITY: AN EXAMINATION OF NEURODEVELOPMENTAL DISORDERS THROUGH BEHAVIOURAL CORRELATES AND FUNCTIONAL CONNECTIVITY

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree of Master of Science

McMaster University MASTER OF SCIENCE (2017) Hamilton, Ontario (Psychology)

TITLE: Cross disorder homogeneity: An examination of neurodevelopmental disorders through behavioural correlates and functional connectivity.

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NUMBER OF PAGES: ix; 81.

LAY ABSTRACT

The current study investigated the behaviour and brain functioning of children with neurodevelopmental disorders. We examined how children with autism spectrum disorder (ASD; n=90), attention-deficit hyperactivity disorder (ADHD; n=47) and obsessive-compulsive disorder (OCD; n=32) group together based on their difficulties with social skills, inattention, and behavioural flexibility. We then associated their symptoms to brain functioning at rest. We found that groupings based on difficulties and symptoms did not correspond with diagnosis, and that rigidity was associated with brain activity in the attention networks and social networks of the brain for different groups. This study supports the use of biological systems, rather than solely observable behaviour, to further our understanding of neurodevelopmental disorders.

ABSTRACT

Over 300,000 children in Ontario are diagnosed with neurodevelopmental disorders, which are defined as mental disorders with an onset in the developmental period. Autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD) are three neurodevelopmental disorders with symptom overlap including difficulties with social skills, inattention, and behavioural flexibility. The National Institute of Mental Health (NIMH) proposed the Research Domain Criteria (RDoC) to address these overlaps by examining symptoms at a biological, as well as observable, level. This study investigated how children with diagnoses of ASD (n=90), ADHD (n=47), and OCD (n=32) group together based on their symptom scores on the Social Communication Questionnaire (SCQ), the inattention subscales of the Child Behaviour Checklist (CBCL), and the behaviour flexibility subscales of the Repetitive-Behaviour Scale-Revised (RBS-R). Correlations between cluster groupings and functional connectivity were then evaluated. Children were clustered into 3 groups: (1) a group characterized by high inattention; (2) a group characterized by moderate impairment across social skills, inattention, and behavioural flexibility; and (3) a group characterized by high impairment in all measures. Functional connectivity between the anterior cingulate cortex and intraparietal sulcus was positively correlated with symptom scores on behavioural flexibility in group 1. Connectivity between the right amygdala and both the left superior temporal gyrus and the lateral parietal region were negatively correlated with symptom scores on behavioural flexibility in group 3. This study was the first to collapse across diagnostic groups of

neurodevelopmental disorders, and examine the correlation between symptom severity and functional connectivity. Findings support the use of the RDoC framework.

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AUTHOR'S DECLARATION OF ORIGINALITY

I hereby certify that I am the sole author of this thesis.

This thesis consists of five chapters. Chapters 1 and 2 provide background information and a literature review which frame the current study. Chapter 2 includes an outline of the current research questions and hypotheses. Chapter 3 describes components of the study design and methods, and chapter 4 reviews the results of these methods. The final chapter discusses the findings of the thesis, along with limitations, implications, and future research methods.

This thesis was conducted under the supervision of Dr. Geoffrey Hall, with secondary supervision by committee members Dr. Noam Soreni and Dr. Scott Watter.

CHAPTER I

INTRODUCTION

Research Domain Criteria Framework (RDoC Framework)

The field of mental health is dynamic and changing. Evidence-based assessments with strong psychometrics replace outdated strategies to address clinical needs. Also under revision are diagnostic classification systems, including the Diagnostic and Statistical Manual – 5th Edition (DSM-5; American Psychiatric Association (APA), 2013), and the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization (WHO), 2010). Both the ICD-10 (2010) and the DSM-5 (2013) categorically organize diagnoses, and conceptualize diagnoses as discrete categories rather than viewing psychopathology along a continuum (Sonuga-Barke, 2014). Diagnoses are made by assessing certain symptom criteria, of which a set number must be met for an individual to be given a diagnosis (Sanislow et al., 2010).

Clinically, the classification system within the DSM-5 (2013) addresses a need for consistency for mental health clinicians (Sonuga-Barke, 2014), allowing for a common framework and language that facilitates communication across healthcare professionals. The DSM-5 (2013) has many purposes through a range of disciplines, including insurance coverage, access to care, legal decision-making, and psychology research. However, where other diagnostic tools have improved in recent years, the DSM-5 (2013) is lagging, with fewer improvements that result in more accurate diagnoses (Cuthbert, 2014).

Many criticisms of the Text Revision of the Fourth Edition of the DSM (DSM-IV-TR; American Psychiatric Association, 2000) were raised before the DSM-5 revision was

finalized and published, and many are still relevant with the current DSM-5 (2013). For example, we do not yet understand the high rates of comorbidity between disorders (Regier, Narrow, Kuhl, & Kupfer, 2009). Comorbidity could be the result of two co-occurring disorders, or different presentations of the same core problem (Regier et al., 2009). One common case is with major depressive disorder and anxiety disorders, which often co-occur within the same individual. This co-occurrence may be the presentation of two distinct disorders, or may represent a specific subtype of major depressive disorder that includes anxiety, or vice versa (Regier et al., 2009). To answer this question, a thorough understanding of the core problems within each disorder, and the underlying neural systems and genetics, is necessary. Another problem unaddressed by DSM-5 is the heterogeneity of symptom presentation within disorders (Regier et al., 2009). Diagnoses are organized into lists of symptom criteria, for which a certain number must be present at an impairing or distressing level to be diagnostically significant. This systematically results in individuals with highly variable presentations receiving the same diagnoses. For example, a diagnosis of major depressive disorder requires six symptoms from a list of nine criteria to be present for two weeks. The six criteria met can differ substantially between individuals diagnosed, and thus their overall symptom presentation will differ. An additional complication is the number of symptoms that present two ends of a spectrum as inclusion criteria. For example, sleep disruption can take the form of insomnia or excessive sleeping to fulfill criteria for major depressive disorder (APA, 2013). Two individuals can therefore have *opposing* symptoms, and yet receive the same diagnoses, and in most cases, the same intervention.

To address all of the conflicts in diagnostic assessment, the National Institute of Mental Health (NIMH) initiated the Research Domain Criteria (RDoC) framework in 2009 (Cuthbert, 2014). The goal of the RDoC framework is a shift in the classification of disorders from being based solely on observable behaviours and objective diagnoses to include neurological and biological measures (Sonuga-Barke, 2014). This framework proposes the integration of research about genes, cells, neural circuits with knowledge about cognition, emotion and behaviour (Sanislow et al., 2010). Rather than continuing to narrow research to individual diagnostic constructs such as major depression and anxiety disorders, it is suggested that research should focus on five domains: negative affect, positive affect, cognition, social processes, and regulatory systems (Cuthbert, 2014; Sanislow et al., 2010). Investigating the five domains will be useful, as direct connections between neural networks or genetics and DSM diagnoses has not been effective. This integrative organization stresses the importance of categorizing and treating impairments commonly expressed across disorders, rather than specific classifications (NIMH, 2007). To advance research, investigators can examine the overlapping symptoms in different disorders, and explore the high comorbidity rates between them (Kendler, 2008). The RDoC framework will provide a more holistic understanding of neurodevelopmental disorders, and allow us to understand the developmental trajectories of these systems across the lifespan (Cuthbert, 2014). Other potential benefits of the RDoC framework include the identification of risk markers for early intervention (Sonuga-Barke, 2014), and the eventual integration of these markers into clinical use (Insel et al., 2010).

The Province of Ontario Neurodevelopmental Disorders Network

Over 300,000 children in Ontario are diagnosed with neurodevelopmental disorders (NDs) (POND, 2011). NDs are mental disorders which have an onset in the developmental period, and include diagnoses such as autism spectrum disorders (ASDs), obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), Tourette syndrome, and childhood-onset schizophrenia (Rumsey, 2008). Due to the developmental onset, NDs can impair skill acquisition in early developmental areas including attention, learning, and emotion regulation (Rumsey, 2008). Impairments become more severe through development due to the increasing gap in the developmental trajectories of children with NDs compared to their typically developing peers (Rumsey, 2008). These skill and ability deficits increase the cost of NDs for both families and society as a whole.

Research with NDs is further complicated by the overlap in presentation found across diagnoses. For example, many NDs are characterized by difficulties in areas including inattention, social communication, hyperactivity, emotion regulation, and repetitive behavior (Anholt et al., 2010; van der Meer et al., 2012; Zandt, Prior, & Kyrios, 2007; Baribeau et al., 2015). The symptom presentation and long-term outcomes within specific NDs is also characteristically heterogenous—wherein children with the same diagnosis can present as vastly different. This makes effective diagnoses and assessments difficult, and poses a barrier to treatment selection and response. NDs often co-occur as well (DSM-5). For example, children with ASD are often also diagnosed with an

intellectual disability, and children with ADHD are often also diagnosed with a specific learning disorder (APA, 2013).

The Province of Ontario Neurodevelopmental Disorders (POND) Network is an Ontario-wide initiative, including professionals from top research institutions and healthcare settings. The multidisciplinary team of scientists and practitioners share the goal of improving long-term outcomes for children with NDs. A priority for the POND Network is developing new assessment and intervention methods based on the integration of data collected from families with NDs in Ontario. Sub-studies include clinical trials, behavioural phenotyping, cognitive phenotyping, epigenetics, family studies (specifically with high risk infants), mouse and cell models, and neuroimaging. The current project focuses on the result of the neuroimaging sub-study.

Three POND sites are collecting data for the neuroimaging sub-study: the Hospital for Sick Children in Toronto, the Lawson Health Research Institute in London, and McMaster University and the Offord Centre for Child Studies in Hamilton (imaging at St. Joseph's Healthcare Hamilton).

Scope of the Thesis Work

There were two separate but related roles involved in the development of this thesis work. The first involved recruiting and scanning children with ASD at the Hamilton site during the second half of the third fiscal year (i.e., September 2015-March 2016), the full fourth fiscal year (i.e., March 2016-March 2017), and the first half of the fifth fiscal year (i.e., March 2017-September 2017). A summary of scanning progress is provided below (Table 1).

Table 1

Completed scans by fiscal year at the Hamilton imaging site.

Fiscal Year	Number of Completed Scans
1 (April 2013-March 2014)	0*
2 (April 2014-March 2015)	8
3 (April 2015-March 2016)	7 (5)
4 (April 2016-March 2017)	12 (12)
5 (April 2017-March 2018)	2 (2)
TOTAL	29 (19)

*Note: During the first fiscal year, recruitment for imaging in the ASD population had not yet begun. Numbers in brackets indicate those scanned by the author.

A full review of the POND intake procedure is discussed in the methods section. Families who were enrolled in the POND study, completed the required intake protocols, and consented to learning more about the neuroimaging sub-study are referred to the imaging sub-project. Families were contacted via e-mail or telephone, and given a description of the study protocol. This included the purpose of the study, and information about the fMRI. Families were also informed of the format of the visits—one primary teaching visit where families reviewed consent forms, children learned the computerized tasks, and participated in a modelled fMRI scan through a mock-scanner (approximately 1 hour), and a second session which involved the fMRI scan (approximately 1.5 hours). Parents gauged whether their child would be able to participate and indicated whether they were still interested in booking. If so, visits were booked approximately one week apart. If for any reason the child was unable to complete the primary visit (i.e., was upset by the sensory feeling of ear plugs, or demonstrated too much movement in the mock scanner), the second visit would be cancelled.

The second role involved analyzing resting state (RS) data collected throughout POND sites for children with ASD, ADHD, and OCD. The remainder of this thesis will focus on the analysis. It will begin with an introduction to core topics including ASD, ADHD, and OCD, RS data and functional connectivity, and a review of functional connectivity literature for each diagnosis. This will be followed with the research questions and hypotheses, methods, results, and discussion of the current study.

CHAPTER II

REVIEW OF LITERATURE

Introduction to Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder diagnosed in 1 of every 68 children (CDC, 2014), affecting approximately 1% of the population (Brugha et al., 2011). ASD is a highly heterogeneous disorder with core deficits in social communication and interaction, and restricted repetitive behaviour patterns. Examples of social communication difficulties include deficits in social-emotional reciprocity or initiating interactions, deficits in nonverbal communication such as eye contact and body language, and deficits in developing and maintaining relationships or engaging in imaginative play (APA, 2013). Restricted, repetitive patterns of behaviour include stereotyped body movements, insistence on sameness, difficulties with cognitive flexibility, and hyper-or-hypo-reactivity to sensory stimuli (APA, 2013). To receive a diagnosis of ASD, both core deficits must be present early in development and cause significant impairment in a child's functioning (APA, 2013). ASD is often associated with intellectual impairment and language impairment, which are also noted in a diagnosis (APA, 2013). Notably, a lack of intellectual and language impairment is associated with more positive long-term outcomes (APA, 2013).

ASD is typically identifiable during the second year of life, although earlier identification has been reported after given symptom severity (APA, 2013). Symptoms that typically manifest early include delayed language skills and unusual communication

patterns, and odd play patterns. However, an impairment in these behaviours needs to be differentiated from typical toddler development (APA, 2013).

Some groups are at a higher risk than others of being diagnosed with the disorder (Newschaffer et al., 2007), including males being diagnosed 4.3 times more often (Fombonne, 2005). Social impairments are considered within the context of an individual's cultural norms, rather than a universally accepted level of impairment (APA, 2013). Diagnoses are usually stable through the lifespan, with stability reported between 84-100% of children (Kim, Macari, Koller, & Chawarska, 2016).

Learning, adaptive skills, and sleep habits may be negatively impacted in ASD due to social communication difficulties, a lack of cognitive flexibility, sensory sensitivities and difficulty in novel situations. Due to these functional difficulties, individuals with ASD often have poorer outcomes in regards to independent living and employment opportunities (Howlin, Goode, Hutton, & Rutter, 2004). Further, the cost of caring for a child with ASD is substantially higher than for a typically developing child, with estimates in the United States ranging from 85-550% higher (Jacobson & Mulick, 2000).

ASD is highly heterogeneous both genetically and phenotypically. Heritability estimates range from 37% to higher than 90% (Geschwind, 2011). Although the genetic components are not yet understood, they are hypothesized to play a large role. Multiple potential genetic markers and mutations have been identified, but no single marker has emerged and most evidence identifies ASD as being polygenic (APA, 2013). Phenotypic heterogeneity is observed in symptom severity, verbal ability, IQ, social attention, and

response to treatment (Kim et al., 2016), which makes generalizing the prognosis for individuals with ASD difficult.

Further contributing to the heterogeneity of ASD is the spectrum of diagnoses that it encompasses. Prior to the DSM-5, autistic disorder was considered a separate diagnosis from pervasive developmental disorder-not otherwise specified (PDD-NOS) and Asperger's disorder. Autistic disorder was considered to have three core deficits: social interaction, language and communication, and repetitive or stereotyped behaviours (APA, 2000). Asperger's disorder differed in that it did not include a deficit in language, or a lower than average IQ (Newschaffer et al., 2007). Finally, PDD-NOS was diagnosed when the criteria for autistic disorder were not met, or there was a late age of onset (APA, 2000). However, factor analyses performed using common ASD assessment data have consistently clustered social and communication difficulties into one deficit (Constantino et al., 2004; Snow, Lecavalier, & Houts, 2009). This has contributed to the new single diagnostic category with the DSM-5. DSM-5 now combines the three neurodevelopmental disorders into one overarching ASD category, therefore resulting in a heterogeneous population with a wide range of cognitive and language abilities (Newschaffer et al., 2007).

As there are no genetic or biological diagnostic tools for the disorder, the most accepted assessments involve behavioural observations and parent or teacher reports (for example, the gold standard is the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) and the Autism Diagnostic Interview – Revised (ADI-R)) (Newschaffer et al., 2007).

Introduction to Attention-Deficit Hyperactivity Disorder

Diagnosis of ADHD requires consistent inattention and/or hyperactivity and impulsivity to be present for at least six months (APA, 2013). Inattention is characterized by the presence of six symptoms, including: making careless mistakes, difficulty sustaining attention, appearing distracted when spoken to, not finishing tasks, difficulty organizing oneself, avoiding tasks that require sustained attention, losing thing, easily distracted, or is forgetful in daily activities (APA, 2013). An individual who meets criteria for inattention, but does not for hyperactivity and impulsivity would be diagnosed with ADHD-inattentive subtype (ADHD-I). Hyperactivity and impulsivity is characterized by the presence of six symptoms as well, including: fidgeting or squirming, leaving situations where sitting is expected, running and climbing in inappropriate situations, an inability to play in activities quietly, appearing 'driven by a motor', talking excessively, not waiting turn in conversations and other situations, and interrupting others (APA, 2013). An individual who meets criteria for hyperactivity or impulsivity, but does not for inattention, would be diagnosed with ADHD-hyperactive/inattentive subtype (ADHD-HI). The third and final subtype is for individuals who demonstrate difficulties in both areas, and it is the ADHD-Combined subtype (ADHD-C). To receive a clinical diagnosis, symptoms must be present in at least two settings (i.e., home and school) and be present before the age of 12. Finally, the symptoms of inattention or hyperactivity and impulsivity must interact with the child's ability in social, academic, or other areas of functioning. Due to the distinct subtype populations, ADHD is by definition a heterogeneous disorder.

Approximately 5% of children (Polanczyk, 2007) and 2.5% of adults (Simon, Czobor, Balint, Meszaros, & Bitter, 2009) are diagnosed with ADHD, with the prevalence rates consistent cross-culturally. ADHD is often diagnosed in pre-and-school-aged children, as hyperactivity and inattention may be disruptive to the learning of children and their peers (APA, 2013). It is difficult to distinguish normal behaviour and impairing activity before school aged, but the course is relatively stable through the lifespan after a child is diagnosed (APA, 2013). In children, there is a 2:1 sex bias, with more males being diagnosed than females (Polanczyk et al., 2007). Males are more frequently identified in the ADHD-HI and females in the ADHD-I subtypes, which may contribute to a gender bias that is consistently found in literature: more males are identified and diagnosed since their symptoms are often more externalizing behaviours and disruptive than those of an inattentive individual (Castle, Aubert, Verbrugge, Khalid, & Epstein, 2007; Rowland, Lesesne, & Abramowitz, 2002).

Individuals with ADHD often also experience other developmental delays that are not exclusively related to the diagnosis. For example, many children have delays in language, motor, or social skill development, low frustration tolerance, and irritability (APA, 2013). Lifelong difficulties are often reported in academic performance (Frazier et al., 2007), and long-term employment attainment and performance difficulties (Kessler et al., 2006). Later in life, individuals with ADHD are more likely than their peers to engage in subsequent substance abuse or to exhibit conduct disorders (Klein et al., 2012), to be incarcerated (APA, 2013) or injured in traffic or other accidents (Merrill, Lyon, Baker, &

Gren, 2009; Pastor & Reuben, 2006) or to attempt or die by suicide (Agosti, Chen, & Levin, 2011).

Introduction to Obsessive-Compulsive Disorder

In DSM-5, obsessive-compulsive disorder (OCD) is characterized by the presence of behaviours identified as obsessions, compulsions, or both (APA, 2013). Obsessions are recurrent and persistent thoughts which are experienced as unwanted, and which cannot be suppressed or neutralized by another action or thought (APA, 2013). Compulsions are repetitive behaviours that are carried out in response to an obsession. These repetitive behaviours are aimed at minimizing anxiety or distress experienced as part of the obsessive thoughts (APA, 2013). Diagnostically, obsessions and compulsions must be time consuming, in that they take more than an hour per day, or they must significantly distress or impair an individual's ability to function socially, occupationally, or otherwise (APA, 2013). Two specifiers exist with OCD which provide clinicians with a better understanding of an individual's profile: a level of insight (i.e., good, poor, or absent/delusional beliefs) specifier, and whether an individual has a current or past tic-related disorder (APA, 2013).

Obsessions and compulsions often fall into specific themes. For example, cleaning (i.e., contamination obsessions or cleaning compulsions), symmetry (i.e., symmetry obsessions and counting compulsions), forbidden or taboo thoughts (i.e., aggressive obsessions and related compulsions), and harm (i.e., harming self or others) are frequently reported (APA, 2013). Females are more likely to exhibit compulsions concerning cleanliness, while males are more likely to exhibit those in the symmetry or forbidden

thoughts dimensions (APA, 2013). The variation across these themes, along with the aforementioned insight specifier, contribute to the heterogeneity of the disorder.

OCD has a prevalence rate of about 2-3% in the general population (Naaijen, Lythgoe, Amiri, Buitelaar, & Glennon, 2015), and additional people with sub-clinical symptomatology who also access care (Leckman et al., 2010). The sex discrepancies in OCD can be described by a bimodal age distribution, with males more commonly diagnosed in childhood, and females more commonly diagnosed in adulthood (Kessler et al., 2006; Ruscio, Stein, Chiu, & Kessler, 2010). More specifically, almost 25% of males have an onset before the age of 10 (Ruscio et al., 2010). Males are also more likely than females to be diagnosed with a co-occurring tic-disorder, especially with an earlier age at onset. These gender distributions and age of onset are relatively consistent cross-culturally (Lewis-Fernández et al., 2010), along with the typical themes of obsession and compulsions (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008).

OCD can be episodic or chronic, depending on the individual, with symptom count and severity differing across the lifespan (Ravizza et al., 1997; Skoog and Skoog, 1999). Regardless, OCD typically involves impairment in multiple areas of life, including social and occupational impairment due to the avoidance of triggering situations, the amount of time an individual may engage in obsessions/compulsions, and potential health problems which, for example, may occur due to over-cleaning (i.e., due to excessively using bleaches to clean) (APA, 2013). Impairment in childhood is further related to developmental difficulties in social skills and independence, and therefore impacts on

forming significant relationships, being autonomous, and attaining financial independence (APA, 2013).

The categorization and diagnostic criteria of OCD underwent numerous changes between DSM-IV-TR (1994) and DSM-5 (2013). For example, OCD now stands as an obsessive-compulsive and related disorder, rather than being subsumed under anxiety disorders. This is in part due to evidence suggesting that OCD is related to many other disorders, rather than just anxiety related disorders (APA, 2013).

Overlap in Presentation

Although ASD, ADHD, and OCD are separated into three distinct neurodevelopmental disorders in DSM-5 (2013), there are many overlapping features which are commonly shared across the disorders and make distinguishing them from one another difficult. For example, social skill difficulties are often reported in all three populations. By definition, an individual with ASD will have difficulties with social communication. Children with ADHD are often reported to lack friendships and experience problems in the friendships they do have (Wehmeier, Schacht, & Barkley, 2010a). Difficulty turn taking, being impulsive, and being intrusive are a few reasons why up to 70% of children with ADHD are reported as having no close friends by the third grade (Wehmeier et al., 2010a). Individuals with OCD often have few close friendships and show social difficulties as well (APA, 2013). Pallanti and colleagues further noted that individuals with OCD who do not respond positively to pharmaceutical intervention often present with more severe social deficits (Pallanti et al., 2002).

Another overlapping area of impairment is in inattention and hyperactivity. Between 24-50% of individuals with a diagnosis of ASD will exhibit impairing levels of impulsivity, inattentiveness, or hyperactivity (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010). This is important to note, as prior to the DSM-5 (2013), ADHD and ASD could not be co-occurring diagnoses. Further, impairing symptoms of ADHD have been reported in approximately 30% of children with OCD (Geller et al., 2000). Finally, stereotyped behaviour in ASD and obsessions/compulsions have also been related to one another, demonstrating an overlap in symptom presentation on a third dimension. Specifically, deficits in behavioural flexibility, involving a marked preference for a predictable environment (D'Cruz et al., 2013) can be seen in all three populations (Anholt et al., 2010; Cath, Ran, Smit, van Balkom, & Comijs, 2007; Cepeda et al., 2000; Oades & Christiansen, 2008). For example, one study demonstrated that individuals with co-occurring ASD and OCD demonstrated the most difficulty with behavioural flexibility, but that individuals with OCD alone scored significantly higher than controls on a measure of behavioural flexibility (Cath et al., 2007).

Thus, the categorical distinctions between ASD, ADHD, and OCD are less discrete than they appear, resulting in a large overlap in symptom presentation, and in comorbidities. The RDoC framework addresses this overlap through conceptualizing the deficits as areas of impairment, rather than elements of distinct disorders. Rather than operating through the DSM-5 (2013) categories which demonstrate this diagnostic symptom overlap, the framework suggests an examination of key areas of deficit and their underlying neurological foundations. It is proposed that a greater understanding of these

underlying mechanisms can lead to stronger diagnostic categories, assessment strategies, and interventions.

fMRI and Resting State

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique, making it ideal for use with pediatric populations and studying neurodevelopment (Bookheimer, 2000). fMRI uses the observed changes in regional blood flow and blood volume associated with neuronal activity during a task to understand brain function (Heeger and Ress, 2002). The blood oxygen level dependent contrasts (BOLD contrasts) use the resulting magnetic susceptibility difference between oxygenated and deoxygenated blood to detect brain activity. The Echo Planar Imaging (EPI) scan sequence used to acquire fMRI images is sensitive to levels of oxygenated to deoxygenated blood. Throughout an fMRI scan, images of the brain are collected in a series of 'slices'. By comparing the blood oxygen levels of slices of the brain across time, we can infer changes in the level of neuronal activation within specific voxels (volume pixels) in fMRI images. MRI is a popular neuroimaging technique, as both structural and functional data can be collected in a relatively short amount of time.

There are many known limitations to fMRI research in pediatric populations. It requires that a child is awake and still, and that across the scan there is minimal movement of the head or body. fMRI typically acquires multiple slices of the brain, and a whole series of slices is acquired for full brain coverage (volume). Therefore, an individual's movement between slices or between volumes introduces noise to the data. Scan sessions are typically an hour in duration, and although the amount of data collected

within this time can be substantial, it is difficult for children to remain laying still, making movement a real concern. Another limitation is introduced by the fMRI environment. fMRI scanners are loud, with a small space for an individual to lay in. Children bothered by loud noises or small spaces may be unable to complete an fMRI scan. Further complicating the fMRI environment is the sheer amount of safety and research equipment necessary. This includes ear plugs, a call bell (in case of emergency), a button-box for item response, headphones, and blankets. The combination of the novel and controlled environment, the strict requirement for laying still, and the introduction of a large amount of equipment can therefore impact a child's ability to participate in an MRI session.

Resting state (RS) research uses the same BOLD signal as task based fMRI research to understand the spontaneous activity in the brain (Fox & Raichle, 2007; Raichle et al., 2001). Rather than measuring BOLD signals during task or stimulus presentation, RS provides information about the large-scale networks in the brain that are active when the individual is asked to rest quietly and is not engaged in any tasks. Temporally synchronous activations across functionally separable regions of the brain are then identified as networks. To differentiate spontaneous brain activity from noise or artifacts of breathing and cardiac events, the low-frequency fluctuations (< 0.1 Hz) in BOLD signal are used (Fransson, 2005).

One advantage to RS research is its complementary nature to task-based fMRI research. It allows us to further understand the organization and connectivity within the brain by providing us with baseline patterns of activation (Fransson, 2005). It also has methodological advantages for pediatric populations, in that there is no task for a child to

learn or perform while in the scanner. With reduced demands, movement can therefore theoretically be minimized, and the pre-requisite of a child understanding a task can be removed. Lower-functioning children, and younger children, can be included in data sets, making research more generalizable. Finally, due to the lack of specific task or stimulus presented to participants, RS data can more easily be pooled across sites (Cherkassky, Kana, Keller, & Just, 2006). Neuroimaging studies characteristically include a low number of participants due to the high cost of scans and recruitment challenges. Combining RS data with other research teams can therefore provide larger data sets, and a more robust understanding of the large-scale networks in the brain.

Historically when trying to understand neuropsychiatric disorders, research focused on the identification of specific brain regions. Recent models use a systems or networks approach to understand these same disorders (Sergeant et al., 2006). Functional connectivity (FC) uses the temporal correlation of activation across regions or nodes throughout the brain to infer neural networks (Konrad & Eickhoff, 2010). In typically developing populations, a number of neural networks have been consistently found and replicated.

One consistently replicable network found in RS fMRI is the default mode network (DMN). The DMN is believed to consist of multiple sub-systems (Kennedy, Redcay, & Courchesne, 2006; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009) involving the medial prefrontal cortex (mPFC), the rostral anterior cingulate cortex (rACC), posterior cingulate cortex (PCC) and the precuneus (PrC) (Kennedy et al., 2006). The DMN has been theorized to play a role in episodic memory, social processes, and

general task-unrelated processes (Uddin et al., 2009), as well as emotional processing (Cato et al., 2004; Maddock, Garrett, & Buonocore, 2003; Whalen et al., 1998), perception of social interactions (Iacoboni et al., 2004), theory of mind (Gallagher & Frith, 2003; Gallagher, Jack, Roepstorff, & Frith, 2002; Vogeley et al., 2001), experience of joint attention (Williams et al., 2005), and person familiarity (Maddock, Garrett, & Buonocore, 2001; Pierce, Haist, Sedaghat, & Courchesne, 2004). Historically, the main point of interest regarding the DMN was its anti-correlation to task-related activation patterns and networks. Not only does the DMN appear active during RS, but it is also down-regulated when other networks are active.

Another network described in RS data is the salience network (SN). The main nodes of the SN are the anterior insula (AI) and the dorsal anterior cingulate cortex (dACC), with additional activations also in the amygdala, ventral striatum, and substantia nigra/ventral tegmental area (Menon, 2015). As apparent from the name, the SN is involved in filtering stimuli and focusing attention on salient ones (Menon, 2015). What individuals focus their attention on, or find salient, can differ between populations, and therefore the SN is useful to consider in the context of neurodevelopmental disorders. For example, Volkmar (2005) found that with populations with ASD, social stimuli were less salient. This in turn can lead to less focused attention on social stimuli, therefore misunderstanding or misattributing them, and poorer social skills. An additional role of the SN is in attention switching, specifically when an external stimulus has been identified as salient. Sridharan and colleagues (2008) described the role of the SN as a moderator between external attention to stimuli, and internal mental processes.

Another RS network, the dorsal attention network (DAN) involves the intraparietal sulcus (IPS) and the frontal eye field (FEF; within the dorsal frontal cortex, where the precentral and superior frontal sulci intersect) (Corbetta & Shulman, 2002). The DAN, along with the associated but separate ventral attention network, interact and play a role in focusing attention.

Finally, the social brain network is a large collection of brain regions that appear to play a role in social processing (Gotts et al., 2012). The social brain, which is activated in a range of social tasks (Gotts et al., 2012), is of particular importance for the neurodevelopmental disorders being examined in this thesis. One area of overlap between ASD, ADHD, and OCD symptomatology discussed previously is in social communication difficulties when compared to typically developing peers. The social brain consists of classic limbic areas such as the amygdala (Adolphs & Spezio, 2006), and anterior hippocampus (Fanselow & Dong, 2010), the ventral and medial regions of the prefrontal cortex (Carmichael & Price, 1995; Amodio & Frith, 2006; Frith, 2007), the posterior cingulate and precuneus (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Cavanna & Trimble, 2006), and the posterior superior temporal sulcus and temporo-parietal junction (Castelli et al., 2002; Beauchamp, Lee, Haxby, & Martin, 2003; Samson et al., 2004; Deen & McCarthy, 2010).

In the extant literature, functional connectivity research has indicated an anti-correlation between task-positive and task-negative networks (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016). More recently, however, this framework has been called into question. Dixon and colleagues have examined the effect sizes of negative FC

between the DMN and the DAN in the available literature, describing the relationship as a weak negative coupling or independent relationship, rather than an anti-correlation (Dixon et al., 2017). The coupling between the two networks may depend on cognitive state, and therefore be variable depending on a presented task, however it is not a strict anti-correlation (Dixon et al., 2017). This finding has implications in the interpretation of FC data, and may contribute to the mixed reports of correlations between networks (Dixon et al., 2017).

Resting State Networks in ASD

Results of resting state networks and functional connectivity in ASD are presently quite variable and inconsistent. Both under-connectivity and over-connectivity have been reported (Hull, Jacokes, Torgerson, Irimia, & Van Horn, 2017; Monk et al., 2009). As a neurodevelopmental disorder, ASD is often associated with abnormal connectivity between brain structures (Belmonte et al, 2004), rather than neuropathology localized to one region (Gotts et al., 2012). Previous literature has strongly pointed to the DMN abnormally functioning in ASD. As previously mentioned, the DMN is associated with emotional processing, social interaction, theory of mind, and person (Kennedy et al., 2006)–each of which are typically associated with deficits in ASD.

Early research strongly supported the under-connectivity hypothesis of ASD, and was initially based on results in task-based fMRI research. RS data reinforced this underconnectivity hypothesis. Specifically, underconnectivity has been consistently reported between the anterior and posterior regions in the default network in children, adolescents, and adults with ASD, whether researchers use a priori seed based or data-

driven analysis methods (Cherkassky et al., 2006; Kennedy & Courchesne, 2008; Monk et al., 2009; Weng et al., 2010; Wiggins et al., 2011). The anterior and posterior DMN regions are of particular interest, given their potential role in self-referential and emotional processing (Ochsner et al, 2005; Vogt & Laureys, 2005) during rest. This underconnectivity during rest in ASD may contribute to social skill and theory of mind difficulties in the population, as it represents a lack of coherence across the regions in the network overall.

Cherkassky and colleagues were the first to examine resting-state functional connectivity in ASD, and did so by measuring 24-second rest periods between tasks (Cherkassky et al., 2006). They found a pattern of pervasive underconnectivity in the adolescents and adults with ASD in comparison to controls, such that 94% of 66 pairwise comparisons showed less connectivity (Cherkassky et al., 2006). They also reported underconnectivity between the anterior and posterior medial cortex. Kennedy and colleagues had a similar procedure, wherein participants performed a colour-word stroop (words were either emotional, neutral, or number words; methods described in (Kennedy et al., 2006)) and three 21-second rest blocks. Compared to controls, the ASD participants did not demonstrate underconnectivity between the mPFC and rACC, and the PCC and PrC during the number vs. rest condition.

Methodological concerns arise in the previously discussed studies, as resting state was considered during a few small blocks throughout the task-based protocol. Monk and colleagues used one ten-minute conventional RS sequence, where participants were asked just lie still with their eyes open, not thinking of anything in particular. It was

demonstrated that ASD participants have weaker connectivity between the PCC and the right superior frontal gyrus (rSFG), but stronger connectivity between the PCC and right temporal lobe and right parahippocampal gyrus (rPHG). Underconnectivity was also found in children and adolescents between the posterior hub of the DMN and the rSFG (Wiggins et al., 2011). Further, this study also looked at development and age as a factor in connectivity in children and adolescents 10 to 18 years old, finding that healthy controls have larger increases in connectivity with age than ASD subjects do (Wiggins et al., 2011). Social brain regions involved in social behavior, language, and communication also show decreased activation in youth with high-functioning ASD than in same-aged controls (Gotts et al., 2012). Limbic-related regions associated with social processing show more underconnectivity between them than those associated with language or sensorimotor processing (Gotts et al., 2012). An effect of age has been found in a study examining whether ASD is marked by global underconnectivity and local overconnectivity (Washington et al., 2014). In healthy controls, the between-node connectivity increased with age across adolescence, which was not as strong in the ASD subjects (Washington et al., 2014). Together, these examples demonstrate the importance of considering age and development as a variable in functional connectivity research.

Washington and colleagues did find both overconnectivity and underconnectivity in their sample of children and adolescents with ASD (2014). Specifically, they found overconnectivity within DMN brain regions, and inter-region underconnectivity (Washington et al., 2014). A somewhat opposite pattern of connectivity has also been reported, with inter-region underconnectivity between the mPFC an PCC (Yerys et al.,

2015). Yerys and colleagues also described a pattern of overconnectivity between regions of the DMN and ones that lie outside of it (Yerys et al., 2015). Simultaneous overconnectivity between the PCC and retrospinal cortex (primarily the medial and anterolateral cortices), and underconnectivity found between the PrC and visual cortex, basal ganglia, and posteriormedial cortex has also been reported (Lynch et al., 2013). Lynch and colleagues proposed the possibility of childhood ASD being characterized by overconnectivity, given that it was more prevalent in their data overall (2013).

Overconnectivity has been reported in frontostriatal connections (Delmonte, Gallagher, O'Hanlon, McGrath, & Balsters, 2013), between the striatum and superior temporal gyrus, between the striatum and pons, between the striatum and insular cortex, and between the pons and insular cortex (Di Martino et al., 2011).

Given the heterogeneity of ASD presentation, and the spectrum of symptom severity, it is important to consider functional connectivity within the context of symptom. Assaf and colleagues found higher scores on the ADOS measure of social skills were correlated with DMN underconnectivity (Assaf et al., 2010). The same finding was replicated by Weng and colleagues using the ADI-R subscale of social skills (Weng et al., 2010). Similar results were also reported by Monk et al, (2009), although they used the ADI-R for measure of social skills. Social functioning in their adult population was correlated with weaker connectivity between the posterior cingulate cortex and the superior frontal gyrus (Monk et al., 2009). The ASD population was also presented with a clinical measure of social impairment (social subscale score on the ADI-R), which was

found highly correlated with less deactivation in the ventral MPFC—greater scores of impairment were correlated with greater functional abnormality (Kennedy et al., 2006).

Given the behavioural heterogeneity found across individuals with ASD, it is not surprising that the existing literature is highly variable. Many studies include individuals with Asperger's (or high-functioning ASD), ASD, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) in their subject pool. In some cases, intelligence quotient cut-offs or age ranges are instated as inclusion criteria, however, these do not capture the variability in verbal and nonverbal communication, social skill, and restrictive repetitive behaviours present.

Resting State Networks in ADHD

Fronto-striatal circuitry has been strongly implicated in task-based fMRI research, (Durston et al, 2003; MacMaster, Carrey, Sparkes, & Kusumakar, 2003; Perlov et al., 2010**)**, and consequently has been a focus of RS research as well. Regions that comprise the fronto-striatal circuit overlap with those activated in resting state networks, including the anterior cingulate cortex (ACC), prefrontal cortex (PFC), and the anterior insula (AI) of the SN (Castellanos & Proal, 2012). It is further hypothesized that the DMN, SN, VAN, and DAN may be involved in ADHD due to their roles in attention switching and maintenance. However, literature reports both increased and decreased connectivity across these networks in ADHD.

In children and youth with ADHD, underconnectivity within regions of the DMN have been reported when compared to controls (Fair et al., 2009, 2010; Konrad & Eickhoff, 2010). Regions of the DMN were not only weakly connected to one another,

but were strongly connected to other regions which were close in anatomical proximity (Fair et al., 2009). These connections appeared to weaken over development, and maturation lead to an increased connectivity between DMN regions (Fair et al., 2010). However, functional connectivity within the DMN may remain weak in adults with ADHD compared to controls as well, specifically between the dACC and PCC, and the dACC and PrC (Castellanos et al., 2008). In contrast, ADHD has been characterized by increased connectivity within regions of the DMN during childhood and adolescence (Cortese et al., 2012; Tian et al., 2006), and in adulthood (Cortese et al., 2012; McCarthy et al., 2013).

Sonuga-Barke & Castellanos suggested an Interference Hypothesis to explain the symptoms found in ADHD (2007). The Interference Hypothesis postulates that the disturbances seen in ADHD are due to interference from the DMN when connectivity should have diminished (Sonuga-Barke & Castellanos, 2007). Specifically, when an individual is transitioning from a resting state to a 'task-based' state, DMN activity would also transition, as it is down regulated with task-based networks. However, in the Interference Hypothesis, the DMN is not attenuating appropriately, and interference from activity in the DMN interrupts other functional networks. Evidence for this theory is mainly from task-based fMRI research (Helps et al, 2010; Liddle et al, 2011; Peterson et al, 2009). For example, unsuccessful attenuation of the DMN has been associated with poor task performance in a stop signal task (Li et al, 2007) longer reaction times, and more errors in attention control tasks (Weissman et al., 2006).

Aberrant organization has been reported in other networks as well, including the DAN (Cubillo, Halari, Smith, Taylor, & Rubia, 2012; McCarthy et al., 2013; Zhu et al., 2008). McCarthy and colleagues (2013) found increased connectivity between the bilateral FEF and occipital areas in adults with ADHD compared to controls, which may be related to poor inhibition of sensory perception seen in ADHD. They also found reduced functional connectivity between the right IPS and right fusiform gyrus (NS; McCarthy et al., 2013). In terms of ADHD presentation, connectivity within the DAN has been reported to be significantly correlated with higher levels of ADHD symptoms compared to control participants. The precuneus (associated with the DMN) and the sensory motor regions have also been reported to be hyperconnected in individuals with ADHD compared to controls (McCarthy et al., 2013; Tian et al., 2008).

As with ASD, the heterogeneity found within ADHD diagnoses is likely contributing to the highly variable results in the literature. Many protocols do not categorize participants by DSM-5 (2013) subtypes of ADHD. Therefore, the functional connectivity of brain regions in children with different areas of impairment, and different symptom presentation, is being analyzed together.

Resting State Networks in OCD

fMRI research in OCD is predominantly task-based, with limited research addressing resting-state functional connectivity. Of the resting-state literature available, most surrounds the cortical-striatal-thalamic-cortical (CSTC) circuit implicated in OCD. Furthermore there is a dearth of child-based RS research in OCD.

Although not a core resting state network, the CSTC circuit does share common brain regions implicated in other resting state networks. Several neural pathways or loops make up the CSTC circuit, of which the sensorimotor, associative, and limbic loops are most reliably reported and agreed upon (Posner et al., 2014). Of specific interest in OCD is the limbic loop, which is composed of the orbitofrontal cortex (OFC) and the ACC (Posner et al., 2014). Over-activity in the loop is consistently reported in OCD in the OFC, ACC, anterior thalamus, and basal ganglia (Posner et al., 2014). The ACC, which plays a crucial role in both the CSTC circuit and the DMN, was explored by Zhang and colleagues (2017). They found decreased connectivity between the rostral ACC (rACC) and the DLPFC, and increased connectivity between the dorsal ACC (dACC) and the caudate in OCD (Z. Zhang et al., 2017). Further, the connectivity between the dACC and the caudate was positively correlated with clinical scores from the Yale-Brown Obsessive-Compulsive Scale (Y-BOCs; Zhang et al., 2017).

A recent study investigated the coupling between the DMN, SN, and central executive network (CEN) in OCD resting state networks. Increased functional connectivity was reported within several subsystems in each network, as well as atypical connectivity between the SN and anterior DMN, and the SN with the dorsal CEN (Fan et al., 2017). Further, trait anxiety was significantly correlated with the connectivity between the SN and dorsal CEN (Fan et al., 2017). Stern and colleagues found increased connectivity between the anterior insula and a number of DMN regions, including the PCC/PrC, medial frontal cortex (MFC), posterior inferior parietal lobule, and the parahippocampus compared to controls (Stern, Fitzgerald, Welsh, Abelson, & Taylor,

2012). Greater symptom severity was associated with reduced connectivity between the right anterior insula and the right thalamus (Stern et al., 2012).

Functional connectivity is under-researched in children with OCD. However, Fitzgerald and colleagues have reported reduced connectivity between the dorsal ACC and the right anterior operculum, as well as reduced connectivity between the ventral MFC (vMFC) and the posterior cingulate cortex (PCC) in OCD youth compared to healthy controls (Fitzgerald et al., 2010). A follow up study by these authors compared the performance of adults as well as youth with OCD to healthy controls (Fitzgerald et al., 2011). In children, reduced connectivity between the dorsal striatum and rACC, and reduced connectivity between the medial dorsal thalamus and the dACC were reported (Fitzgerald et al., 2011). The reduced connectivity between the dorsal striatum and rACC was further correlated with increased symptom severity (Fitzgerald et al., 2011).

In adults, reduced connectivity of the orbitofrontal cortex (OFC) has also been associated with OCD, specifically in the connectivity between the OFC and the dorsal medial cortex (Meunier et al., 2012). Higher scores on the Y-Bocs was negatively associated with activity in the right superior OFC (Meunier et al., 2012). Also exhibiting decreased functional connectivity was the posterior temporal region to both the left anterior fusiform and the left anterior prefrontal cortex (T. Zhang, 2011), and between the rACC and the dorsolateral prefrontal cortex (DLPFC) (Z. Zhang et al., 2017). Regions exhibiting increased connectivity reported in OCD include between the dACC and caudate (Z. Zhang et al., 2017), between the ventral striatum and each of the OFC,

vMPFC, and the DLPFC (Sakai et al., 2011), and between the right anterior prefrontal cortex and each of the right insula and middle cingulate cortex (Li et al., 2012).

Understanding the Variable Results

Functional connectivity literature for each of the neurodevelopmental disorders is variable and complex. Contradictory evidence may be due to a number of confounds, including differences in age and sex of participants, severity of symptoms, and methods of data collection (Pua, Bowden, & Seal, 2017). It is important to consider the effects of age and developmental trajectories in functional connectivity research, given that resting state networks are still undergoing developmental changes across childhood and adolescence (Fair et al., 2008, 2009; Stevens et al., 2009, Supekar et al., 2010). Often the methods employed across sites are as variable as results are, with differences in the type of scanner used (and therefore the types scan acquisition parameters), experimental protocols (eg. Resting State with eyes open or eyes closed), and different analyses packages used in the preprocessing of data.

PURPOSE OF THE PRESENT STUDY

As we have seen, the heterogeneity found in the symptom presentation of each disorder is also evident in the imaging literature. The POND study is aligned with the RDoC framework, and therefore is studying neurodevelopmental disorders under one umbrella. As part of the POND imaging sub-study, children with ASD, ADHD, and OCD have been scanned using a range of neuroimaging techniques (MRI, fMRI, DTI, and magnetic resonance spectroscopy), and studying the differences and similarities of the functional connectivity between and within each disorder. The current study is part of the

fMRI sub study, and set out to correlate symptom severity on a range of measures with functional connectivity in neurodevelopmental disorders. Symptom severity was measured on a set of instruments selected to provide information common to all three diagnoses in the areas of social skills, inattention, and behavioural flexibility. The measures selected were the Social Communication Questionnaire (SCQ; Rutter et al., 2003), subscales of the Repetitive Behaviour Scale-Revised (RBS-R; Bodfish, Symons & Lewis, 2000) and the Child Behaviour Checklist (CBCL; Achenbach & Rescorla, 2001). A cluster analysis was conducted using the behavioural measures, and resulted in three separate clusters based on how symptom scores grouped together. Finally, functional connectivity within each cluster was examined. Similar methods have been carried out to examine candidate genes for schizophrenia, where a cluster analysis was conducted, followed by genetic association to the clusters (Wessman et al., 2009). The ultimate goal of the present study was to use symptom-based clusters to explore functional connectivity in children with neurodevelopmental disorders.

Research Questions and Hypotheses

Research Question #1: Will symptom clusters correspond with the DSM-5 diagnoses currently provided to children?

Hypothesis #1: Given the overlap in diagnostic criteria between ASD, ADHD, and OCD, and the high comorbidity between them, we predicted the cluster analysis would not correspond with current diagnostic categories.

Research Question #2: Within clusters, what is the relationship between symptom severity and functional connectivity?

Hypothesis #2: Given the RDoC framework, we predicted that cross-diagnostic symptom clusters will be reflected in group differences in the functional connectivity profiles. However, given that this is the first study to look at cross-diagnostic symptom clusters and functional connectivity, no concrete hypotheses regarding the specific group differences in functional connectivity profiles were made.

CHAPTER III

METHODS

Participants and Procedure

Participants involved in the neuroimaging sub-study were previously recruited and studied as volunteers in the Province of Ontario Neurodevelopmental Disorders (POND) study. As POND is a province-wide collaborative study, participants were recruited from one of the participating hospitals: The Hospital for Sick Children and Holland Bloorview Kids Rehabilitation Hospital in Toronto, McMaster University and the Offord Centre for Child Studies in Hamilton, and Lawson Health Research Institute in London. To facilitate recruitment, there were many mechanisms in place including postings in doctor's offices and partner organizations, and mail-out pamphlets to previous patients. Participants were invited to join the study at any age after diagnosis, until 21 years and 11 months, and must have a formal DSM-5 diagnosis for one of the neurodevelopmental disorders under study. The neurodevelopmental disorders include: Autism Spectrum Disorder (ASD, Attention Deficit Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), pediatric Bipolar Disorder, Childhood-onset Schizophrenia, Tourette's syndrome, or a disorder with a known genetic etiology such as Fragile X and 22q deletion. In order to procure a database that can be maximally generalizable to individuals with neurodevelopmental disorders in Ontario, POND set a non-restrictive exclusion and inclusion criteria. Therefore, the only inclusion criteria were a formal DSM-5 diagnosis, speaking and understanding English, and the agreement to contribute a genetic sample to the POND research team, and subsequently to the Ontario Brain Institute (OBI).

Participants who had been given a formal diagnosis of a neurodevelopmental disorder at their home site were then referred to the neuroimaging sub-study at the same site. Exclusion criteria for the neuroimaging sub-study differ from those of the full POND study for safety reasons—for example, individuals with metal in their body such as braces or other medical devices were excluded. The Hospital for Sick Children Research Ethics Board, Holland Bloorview Research Ethics Board, and Hamilton Integrated Research Ethics Board approved this study. Children provided written and informed consent or assent if 16 years or older, and legal guardians provided written and informed consent for children unable to provide it.

***POND Intake Procedure*:** Before being referred to the neuroimaging sub-study, participants participated in four general POND study stages. Stages 1 and 2 were collection of parent measures; stage 3 involved clinical and diagnostic measures, including IQ and language testing, for the participant; and stage 4 involved cognitive testing. Stage 3 of the POND intake procedure is used to validate DSM-5 diagnoses, with assessments completed by trained research personal such as a research assistant or coordinator, under the supervision of a licensed clinical psychologist. For participants with ASD, diagnostic assessments included the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, Dilavore & Risi, 2008), the Autism Diagnostic Interview – Revised (ADI-R; Rutter et al., 2008), and the Vineland Adaptive Behaviour Schedule – Second Edition (VABS-II; Sparrow, Cicchetti, & Balla, 2005). For participants with ADHD, diagnostic assessments included the Kiddie-Schedule for Affective Disorder (K-SADS; Kaufman, Birmaher, Rao, & Ryan, 1996) and the Parent Interview for Child Symptoms-6

(PICS-6; The Hospital for Sick Children, 2013). For participants with OCD, diagnostic assessments included the K-SADS and the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; Goodman et al., 1989). Following completion of the POND intake procedure, participants were invited to learn more about the POND neuroimaging sub-study. Those who expressed interest were contacted by the neuroimaging team.

***Current Study*:** Resting state data for 208 participants was initially obtained. Primary data-cleaning involved removing participants who were controls (n=9), and outside of the ages of 6-15 years old (n=30; 8 OCD, 22 ASD). There were two reasons for limiting our population by age. First, age was not included as a co-variate during the cluster analysis, as the goal was to understand how symptom scores group together. By including age, we would be interfering with this analysis. Second, of these 30 participants who were removed, behavioural data was only available for 5. Therefore, we felt comfortable removing them. After cleaning both the resting state imaging data and the behavioural measures which were missing too many scores, both of which are explained in detail below, our sample contained 169 participants (131 males, 38 females). The mean age of participants was 10.6 years (SD=2.24, range=8.8). Sex and diagnosis distributions were not equal. The ASD group was the largest sample, containing 71 males and 19 females (79% males), while the ADHD group contained 40 males and 7 females (85% males), and the OCD group contained 20 males and 12 females (63% males). These distributions will be further reviewed in the discussion. On average, the three samples had similar mean ages.

Neuroimaging

All imaging was done on a Siemens 3T MAGNETOM Trio, a Tim (total imaging matrix) MRI system, using a twelve-channel head coil (Siemens Healthcare, Erlangen, Germany). Each scanning session involved a localizer scan (40 seconds), a high-resolution 3D magnetization prepared rapid gradient echo (MP-RAGE) sagittal T1-weighted imaging sequence (repetition time (TR) = 2300 ms, echo time (TE) = 2.96 ms, inversion time (TI) = 900 ms, flip angle = 9 degrees, matrix size = 192x240x256, 1 mm isotropic voxels, 192 acquired slices; duration = 5.03 min) and a T2*-weighted interleaved echo-planar imaging sequence (TR = 2340 ms, TE = 30 ms, flip angle = 70 degrees, receiver bandwidth per pixel = 2694 Hz, Matrix size = 64x64x224 mm, 40 axial slices, slice thickness = 3.5 mm, 120 image volumes; duration = 4.68 minutes).

Participants were asked to remain as still as possible throughout the scan. Typical resting state paradigms have participants fixating on a single point. However, this method has many limitations when used with small children (Yerys et al., 2009), and more so with younger children with neurodevelopmental disorders. We therefore presented films as a constant visual display during the rest scan. This may be a preferred method for resting state data collection in children because it allows for the investigation of both the DMN and the SN. Passive viewing of a film would activate the DMN (Gleran et al., 2015), while simultaneously placing demands on the integration of external information with the internal processes that are expected to engage the SN (Gleran et al., 2015). A final benefit to this method is its potential to reduce the risk of fatigue, attrition, and data loss due to excessive motion during scanning of children with neurodevelopmental

disorders. Children were able to select their own film and were encouraged to not pick something they would either engage in repetitive behaviour to or laugh at, due to the added motion that would occur.

fMRI Preprocessing

Imaging was preprocessed using Statistical Parametric Mapping (SPM12) software (Welcome Department of Imaging Neuroscience, London, UK) running under Matlab *R2012a) (Mathworks Inc., New York, USA). MRI preprocessing began with slice-timing correction, which accounts for differences in sampling times of fMRI slices. Following, fMRI time series were motion corrected using registration to mean volume in a two-stage process, in order to quantify and correct inter-scan movement. Functional images were co-registered with the T1-weighted structural scans, and both were normalized. Structural images were bias corrected, normalized, and segmented by tissue type using SPM's algorithm and a pediatric tissue map generated by the Template-O-Matic (TOM) Toolbox. TOM provides templates in MNI (ICBM152) space customized to a study sample by age and sex based on imaging data from the NIH study of normal brain development (http://www.bic.mni.mcgill.ca/nihpd/info/) (Wilke et al., 2008). Lastly, fMRI data was smoothed with an isotropic 5 mm FWHM Gaussian kernel.

Head Motion

Scanning children often presents more movement in scans, which in turn impacts on data quality (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Small frame-to-frame displacements can introduce noise and incorrect correlations in analyses (Van Dijk, Sabuncu, & Buckner, 2012). Therefore, motion artifacts in the scans were examined. We

applied settings previously reported as conservative, at 0.5 mm frame-to frame motion (z-stat=3 for frame-to-frame signal change) (Power et al., 2012). The ArtRepair toolbox was used to identify problematic frames for scrubbing (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Frames were removed from the analysis using covariates (one per frame). After the initial scrubbing, subjects with a large number of scrubbed frames (>30 scrubbed frames) were eliminated entirely. Subject data used in subsequent analysis had at least 3.5 minutes of resting state data remaining.

Data Analysis

Functional connectivity analysis was carried out with the CONN toolbox (https://www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2014). Denoising involved three corrections: the regression of confounding signals from white matter, cerebrospinal fluid, motion parameters, and scrubbing; the application of a 0.01-0.08 Hz bandpass filter to remove noise from unrelated physiological signals; and linear detrending to remove noise from the baseline drifts from the MRI scanner (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Fransson & Marrelec, 2008; Zou, Wu, Stein, Zang, & Yang, 2009). Following denoising, Region of interest-to-region of interest (ROI-to-ROI) connectivity was assessed using bivariate correlation with hemodynamic response function (HRF) weighting among 31 functional and anatomical regions making up the four networks of interest (default mode network, salience network, dorsal attention network, and social brain; see Appendix A for ROI details).

Measures

The clinical measures used in the study were those which assess common difficulties reported in each of ASD, ADHD, and OCD. The Social Communication Questionnaire (SCQ; Rutter, Bailey & Lord, 2003) was used for measures of social communication, the attention problems and ADHD problems sub-scales of the Child Behaviour Checklist (CBCL; Achenbach & Rescorla, 2001) were used to measure attention difficulties, and the ritualistic and sameness behaviour sub-scales of the Repetitive Behaviour Scale-Revised (RBS-R) were used to measure behavioural flexibility. It is important to note that the analyses conducted, and the choice of assessments, were limited by those administered to *all* participants in the POND intake procedure. Other potentially useful assessments (i.e., the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; Goodman et al., 1989)) were only administered in a sub-group of children, therefore these measures could not be used in an analysis which collapses across diagnostic categories.

SCQ. Measurements of social communication were collected via the SCQ (Rutter, Bailey, & Lord, 2003). The SCQ is a parent-report measure which contains 40 yes/no items. The items are used to assess three domains: reciprocal social interaction (15 total items; i.e., offering to share), communication (13 total items; i.e., pointing to express interest), and restricted, repetitive, and stereotyped patterns of behaviour (8 items; i.e., verbal rituals). There is a "current" and a "lifetime" form, with "current" focusing on the last 3 months. Because we were interested broadly in the child's life, we used the lifetime form. A total score can be compiled by adding the endorsed items (some are reverse

coded), with a total possible score of 39. Higher scores indicate a higher symptom count, and a cut-off score of 15 or more indicates that further assessment is recommended. The yes/no format of the questionnaire limits its use, as there is no way to assess individual symptom severity or frequency. The SCQ has strong reported sensitivity (0.88) and specificity (0.72) between ASD and non-ASD cases (Chandler et al., 2007).

The SCQ was originally developed for use with the Autism Diagnostic Interview – Revised (ADI-R), and therefore items are focused on behaviours that are common in ASD. We chose to include the SCQ as a measure of social communication because it fit the goal of the RDoC framework and the POND study. Our goal is to further understand the homogeneity of symptoms across neurodevelopmental disorders. Although the SCQ was developed to use with ASD populations, it also measures difficulties which are present in children with ADHD or OCD. A measure of social communication was important to include due to the overlapping social skills deficit found in ASD (APA, 2013), ADHD (Coghill et al., 2006; Hoza et al., 2005; Reiersen, Constantino, Volk, & Todd, 2007; Wehmeier, Schacht, & Barkley, 2010b) and OCD (Cath et al., 2007)**.**

CBCL. The CBCL (Achenbach & Rescorla, 2001) is another parent-report form, and is used for children aged 6-18. It includes problem items and competence items; problem items are answered on a 3-point Likert scale (i.e., 0 indicating the item is not true for their child, 2 if the item is very/often true of their child) for the past six-months. Competence items ask the respondent to consider their child in comparison of same-aged peers (Rescorla et al., 2012). The CBCL scoring provides scores for DSM-oriented scales and syndrome scales. Syndrome scales are based on factor-analyses on the forms, and

include: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behaviour, and sleep problems. DSM-oriented scales are based on DSM criteria for diagnoses, including: affective problems, anxiety problems, pervasive developmental problems, attention-deficit/hyperactivity problems, stress problems, autism spectrum problems, and oppositional defiant problems.

Considering the overlap between ASD, ADHD, and OCD in symptoms of inattention and hyperactivity (Geller et al., 2000; Rommelse et al., 2010), we included the attention-deficit/hyperactivity problems DSM-oriented scale and the attention problems syndrome scale from the CBCL in our analysis.

RBS-R. The RBS-R (Bodfish et al., 2000) is also an informant-based scale, which was designed to measure domains of restrictive, repetitive behaviours observed in ASD (Lam & Aman, 2007). There are six independent sub-scales included in the RBS-R: stereotyped behaviour, self-injurious behaviour, compulsive behaviour, ritualistic behaviour, sameness behaviour, and restricted behaviour (Lam & Aman, 2007). A total of 43-items are scored from 0-3 (0 = *the behaviour does not occur,* 3 = *the behaviour occurs and is a severe problem*). The RBS-R is organized from selected items from a variety of scales, including the ADI-R, the Childhood Routines Inventory (Evans et al., 1997), the Sameness Questionnaire (Prior & MacMillan, 1973), and the Abnormal Focused Affections Checklist (Schultz & Berkson, 1995).

Impairments in behavioural flexibility have been consistently demonstrated across ASD, ADHD, and OCD, and as such, it may represent a common etiological factor

underlying the three diagnoses (Anholt et al., 2010). Lam & Aman found a five-factor model of the RBS-R fit better than the six sub-scales which are currently used (Lam & Aman, 2007). Their model collapsed ritualistic and sameness behaviour, where ritualistic behaviour is defined as "performing activities of daily living in a similar manner," and sameness behaviour is defined as "resistance to change, insisting that things stay the same," (Lam & Aman, 2007). Performing activities in a rigid manner is related to the need for sameness, so combining the two sub-scales is both empirically and clinically applicable. We combined the scores from the two sub-scales into one behavioural flexibility subscale as in Lam & Aman (2007), which will here-in be referred to as the RBS-bf (RBS-behavioural flexibility) sub-scale. The RBS-bf included 12 items, and a total possible score of 36.

Cluster Analysis

All statistical analyses were completed in IBM Statistical Package for the Social Sciences (SPSS) for Mac (Version 21.0). First, measurement scores were transformed into z-scores in order to compare across different behavioural measures. The cluster analysis required scores from all four measures to be included, and therefore participants with incomplete data were removed. A Ward method cluster analysis was computed. The Ward method begins with each participant in their own group, and calculates the sum of squares for each possible combination. Clusters are based on the solution which results in the lowest sum of squares. The solutions were computed for 2-8 clusters. Frequencies and means were calculated for the 2-4 cluster models in order to explore their composition of sex, age, diagnosis, and symptom measure distributions.

CHAPTER IV

RESULTS

Sample Characteristics.

The data for all participants included in the sample (N=169) are provided in Table 2**.** The full sample consisted of 169 participants aged 6-15 years old with a confirmed diagnosis of ASD (mean age (SD)=10.51 (2.3)), ADHD (10.15 (2.1)), or OCD (11.48 (2.2)). One-way ANOVAs conducted demonstrated a significant difference of age between groups ($F(2,166)=3.58$, $p=0.03$), and no significant differences of IQ between groups ($F(2, 78) = 2.98$, $p=0.57$).

Cluster Analysis.

Missing data. Behavioural data for all participants who were between 6-15 years old were input into the cluster analysis. The broad age range was selected to ensure our clusters could be the most representative of children with neurodevelopmental disorders, and coincides with POND study protocol of having very few exclusion criteria. Of the 169 participants included, data for all measures of interest (i.e., the SCQ, CBCL, and the RBS-bf) were available for 93 participants (55%). Specifically, 67 participants were missing the SCQ, 73 were missing both measures of the CBCL, and 67 were missing the RBS-bf. Therefore, the total sample size used in the cluster analysis was 93 participants. Demographic information for the cluster distribution is presented in Table 3, and mean scores and standard deviations for each cluster are presented in Table 4**.**

Table 2

Participant characteristics organized by diagnosis.

Diagnosis	N	% Males	Variable	Minimum	Mean	Maximum	SD
ASD	90	79	Age	6.2	10.51	15	2.3
			IQ	0.09	40.29	99.9	27.56
ADHD	47	85	Age	6.7	10.15	14.7	2.1
			IQ	5	50.4	98	28.73
OCD	32	63	Age	6.3	11.48	14.9	2.2
			IQ	19	67.5	96	36.36

Note: ASD = autism spectrum disorder; ADHD = attention deficit/hyperactivity disorder; OCD = obsessive-compulsive disorder; SD= Standard Deviation; Age is in years; IQ is in percentile rank.

Table 3

Demographics of each cluster

Cluster	N	% Males	Variable	Minimum	Mean	Maximum	SD	% of cluster removed due to motion
1	41	82.9	Age	6.7	10.573	14.7	2.07	17.1
			IQ	5	50.7	95	28.72	
2	28	67.9	Age	7.7	11.568	15.4	2.34	21.4
			IQ	9	46.2	82	29.73	
3	24	70.8	Age	6.7	11.479	15	2.39	20.8
			IQ	0.4	43.7	99.9	33.25	

Note: SD= Standard Deviation; Age is in years; IQ is in percentile rank.

Table 4

Means and standard deviations for the behavioural measures

	Cluster 1	Cluster 2	Cluster 3
SCQ			
Mean	7.9	10.18	24.63
St. Dev	4.58	8.41	4.39
CBCL-attention problems			
Mean	95.93	72.04	95.42
St. Dev	2.53	12.50	3.01
CBCL- ADHD problems			
Mean	94.80	67.11	92.08
St.Dev	4.66	12.07	6.51
RBS-bf			
Mean	6.59	11.21	16.25
St. Dev	4.91	9.20	10.46

Ward Method Solution. The three-group solution through the Ward Method cluster analysis yielded the most meaningful organization of the data. In the four-and-more group solutions, cluster groups were combining less meaningfully, and had too few participants to further analyze (i.e., cluster 2 broke into a group of 20 and a group of 8 participants).

Research Question #1: Will symptom clusters correspond with the DSM-5 diagnoses currently provided to children?

As demonstrated in Table 5 and Figure 1, the cluster groups did not correspond directly with diagnostic groups. Interestingly, each cluster was heavily weighted (composed of >45%) to a specific diagnosis.

Neuroimaging data:

***Data cleaning*.** During this stage, 19 participants (7 from cluster 1; 6 from cluster 2; 6 from cluster 3) included in the cluster analysis were removed from the analysis due to motion (e.g., >30% scrubbed frames). There was no statistical difference in behavioural measures between those who were removed from the FC analysis and those who remained (SCQ: ($F(1, 91) = 1.235$, $p=0.27$); CBCL-attention problems: ($F(1, 91) = 0.268$, $p=0.61$); CBCL-ADHD problems: ($F(1, 91) =0.502$, $p=0.48$); RBS-bf : ($F(1, 91) = 0.129$, $p=0.72$)).

***Functional Connectivity*.** Correlations between functional connectivity and behavioural measures were calculated for each cluster group through CONN (Whitfield-Gabrieli & Nieto-Castanon, 2014). The analyses revealed patterns of correlations between the RBS-bf in two clusters. In cluster one, the RBS-bf symptom scores were positively

Table 5

Distribution of diagnoses across clusters

	Cluster 1	Cluster 2	Cluster 3	Total
ASD - *N*	10	13	22	45
% of cluster	24.4	46.4	91.7	48.4
% within dx	22.2	28.9	48.9	100
ADHD- *N*	27	1	2	30
% of cluster	65.9	3.6	8.3	32.3
% within dx	90.0	3.3	6.7	100
OCD- *N*	4	14	0	18
% of cluster	9.8	50.0	0.0	19.4
% within dx	22.2	77.8	0.0	100
Total- *N*	41	28	24	93
% of cluster	100	100	100	100
% within dx	44.1	30.1	25.8	100

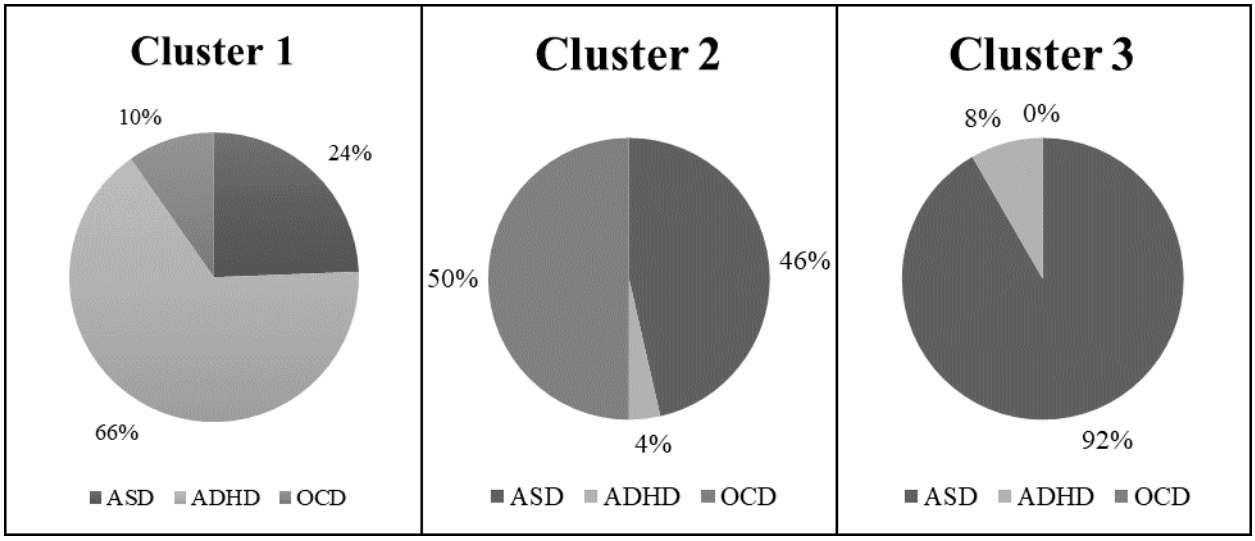

Figure 1: Visual distribution of diagnoses across clusters.

correlated with the functional connectivity between the ACC and the IPS. In cluster three, the RBS-bf symptom scores positively correlated with the functional connectivity between the right amygdala and both the LP and the STGl. There were no significant correlations between FC and other measures (i.e., SCQ and CBCL) or other clusters. These findings are summarized below, and demonstrated in Figure 2.

Research Question #2: Within clusters, what is the relationship between symptom severity and functional connectivity?

ACC and IPS: FC between the ACC and IPS was positively correlated with symptom scores on the RBS-bf (R^2= 0.36, p=0.000186). Therefore, increased scores (i.e., increased impairment) on the RBS-bf were associated with increased connectivity between the ACC and IPS for cluster group 1.

Amygdala and STGI*:* The right amygdala and STGl were negatively correlated with symptom scores on the RBS-bf (R^2= 0.53, p=0.000436). So, as scores increased on the RBS-bf, decreased connectivity was seen between the regions in cluster group 3.

Amygdala and LP*:* The right amygdala and LP were also negatively correlated with symptom scores on the RBS-bf (R^2= 0.54, p=0.000365). In this case, increased scores on the RBS-bf were also associated with decreased connectivity between brain regions in cluster group 3.

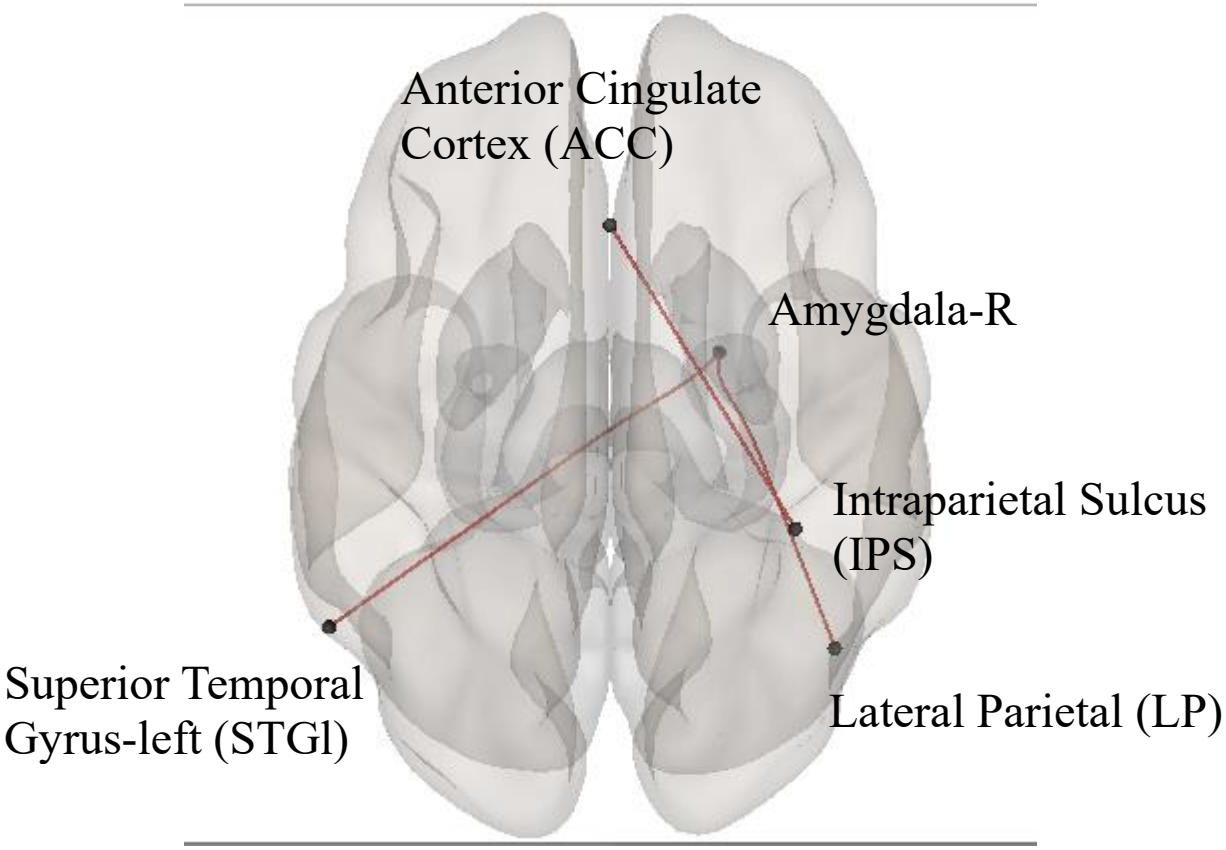

Figure 2: Patterns of functional connectivity.

CHAPTER IV

DISCUSSION

Review of Study Design

The purpose of the present study was to explore the overlapping symptomatology of children with neurodevelopmental disorders, and how symptom profiles correspond with functional connectivity. First, this study examined how scores on behavioural measures of overlapping problem areas cluster and correspond with current DSM-5 (APA, 2013) diagnoses. Second, the clusters were used to examine the relationship between symptom profile and FC in resting state data. The analyses controlled for factors such as missing psychometric data and the noise introduced by subject movement in the fMRI data.

Sample Characteristics

Our initial sample did not have equal group size for the three diagnoses included. There were 90 children with ASD, 47 with ADHD, and only 32 with OCD. There are many factors which may influence this considerable difference in sample size, including the prevalence rate of the diagnoses. Another influence on group size may be the children's ability to participate in the fMRI portion of the study. The 169 children included in our sample were required to have under gone both the resting state and structural MRI scans as well as parents having completed the behavioural measures. However, there are many common barriers to children participating in an fMRI study. For example, the fMRI scanner is very loud, and therefore can be highly aversive to children. Indeed, many children with ASD have heightened sensory sensitivities and find loud

noises aversive. In addition, the loud noises and closed-in spaces of the MRI may also cause considerable anxiety for a child, and affect their ability to participate in the fMRI scan. This may be of particular importance when scanning children with OCD. Although OCD this is no longer considered an anxiety disorder in DSM-5 (APA, 2013), heightened anxiety is still part of the symptom profile for these children. Another barrier to participation in the fMRI portion of the study is the requirement of minimal movement. In our sample, 21 participants were removed due to excessive motion, which illustrates the difficulty children may have with the requirement. Children with ADHD, specifically ADHD-HI subtype, may find it difficult to restrict their movements. This can have an impact on recruitment, as those children who demonstrated difficulty laying still during the screening visit may be excluded from the MRI session.

There was a significant difference ($F(2,166)=3.58$, $p=0.03$) in mean age between the three groups. Specifically, OCD had a greater mean age than either ASD or ADHD. This may be due to the later age of diagnosis or onset that is seen with OCD compared to ASD and ADHD. As previously discussed, ASD is typically identified by 2 – 3 years of age and ADHD by school age (APA, 2013). OCD, on the other hand, has a mean age of onset of 19.5 years (APA, 2013), although approximately 25% of males have an onset before 10 years of age (Ruscio et al., 2010).

Importantly, there were no significant differences in IQ between the three groups. However, there were more males within each diagnosis than females. ASD is diagnosed 4 times more often in males than it is in females (APA, 2013), where our sample demonstrated approximately a 3.5:1 ratio. Therefore, it is relatively reflective of the

population. ADHD, however, is diagnosed 2 times more often in males than females (APA, 2013), and our sample reflected a much higher 6:1 ratio. This could be a result of many factors, including ADHD-HI being more often diagnosed in males than in females at younger ages, and also being easier to identify in males (Castle, Aubert, Verbrugge, Khalid & Epstein, 2007; Rowland et al., 2002). This greater gender disparity may be due to different presentations in females than males, wherein females are more likely to present with the ADHD-I subtype, and therefore be later diagnosed**.** The gender distribution of OCD is typically described as bimodal, with more than 25% of males having an onset before 10 years old. Our sample being made up of 63% males may be a consequence of the higher likelihood of males being diagnosed at a younger age, and the average age of our sample.

Cluster Analysis

To our knowledge, this is the first study to re-organize children with ASD, ADHD, and OCD into new groupings based on their symptom scores. This project is in line with the NIMH RDoC framework and POND study goals.

It is interesting to note which areas of impairment appear to group together. For example, cluster 1, which was characterized by the highest impairment on inattention measures, while having the lowest impairment in social communication and behavioural flexibility. Cluster 2 was characterized by moderate impairments across all behavioural measures, and was primarily composed of children with OCD and ASD. Finally, cluster 3 was characterized by the highest impairment across all measures, and 92% of the cluster was composed of children with ASD.

Cluster 1 appeared most similar to ADHD as it is conceptualized in the DSM-5 (APA, 2013). Core deficits of attention and ADHD problems presented around the 95th percentile, while measures of social communication and behavioural flexibility are lower.

Examining cluster 2, we see that children with ASD and OCD can present very similarly. Although inattention may not be the largest area of impairment for some children in this cluster, they are still above the 50th percentile and therefore are an area to consider in diagnosis and intervention. Social communication and behavioural flexibility difficulties are prevalent and characteristic.

Finally, cluster 3 appeared to be the most impaired in all areas measured. This cluster consisted only of children with ASD and ADHD. One reason for this may be the relatively low number of children with OCD included in the study, compared to those of ASD and ADHD. As mentioned previously, the children with OCD included in the fMRI portion would be ones able to sit still, and able to tolerate the aversive noises and environment of the scanner. Overall, these children therefore may have different symptom profiles than other children with OCD who were unable to participate.

Functional Connectivity

ACC and IPS: Symptom scores on the RBS-bf were positively correlated with FC between the ACC and IPS for cluster group 1. Cluster group 1, as detailed above, was characterized by high inattention, and composed largely of children with ADHD (66%), followed by ASD (24%), and OCD (9%).

The Salience Network (SN) ACC activation was co-activated with a Dorsal Attention Network (DAN) region; the IPS. The SN functions to filter environmental

stimuli in order to direct attention to salient and important information (Menon, 2015). The DAN, in contrast, is involved in focusing and maintaining attention (Corbetta & Shulman, 2002). Typically, the two networks are not activated simultaneously—the SN is theorized to operate as a switch between the DMN and the DAN. The SN acting as a switch functions in the coordination of functional networks in the brain (Alnaes et al., 2015). Large-scale networks in the brain are task-modulated based on attentional load (Alnaes et al., 2015).

Behavioural flexibility—drawn from the RBS-bf—refers to an individual's ability to adjust to changing tasks and goals (Hanania & Smith, 2009) and a pervasive pattern of rigidity in activities. This measure of behavioural flexibility includes items such as, "becomes upset if interrupted in what he/she is doing," and "insists that specific things take place at specific times," (RBS-R). Anholt and colleagues previously reported a high correlation between measures of attention switching and the inattention subdomain of ADHD (Anholt et al., 2010). They noted that this correlation is interesting, because at face value, the areas of impairment in behavioural flexibility appear to contradict those of inattention—however, individuals with ADHD have also been reported to exhibit difficulties in attention switching (Cepeda et al., 2000; Oades and Christiansen, 2008). Our result can be interpreted similarly, as individuals in cluster 1 were characterized by higher scores in the inattention measures.

Therefore, high levels of impairment in behaviour flexibility being associated with co-activation of two regions from separate networks (i.e., the ACC from the SN, and the IPS from the DAN) may suggest that networks are less coherent or less well fractionated

in individuals with high impairment. As previously discussed, neural networks are developing in childhood and adolescence. Developmental changes include increases in specialization of specific networks or nodes over time. Specifically, increased coherence of networks, and segregation of networks from one another, occurs over development (Fair et al., 2008; 2010). The segregation between the DAN and the SN may therefore be impaired in this population. It is important to note, however, that cluster 1 was not characterized by the highest scores on the RBS-bf. Participants in Cluster 3 demonstrated the highest mean scores on all measures. Consequently, it appears that the dysregulation between the SN and DAN may be present in cases with moderate attention switching difficulties, but not those with severe ones. Given that this is a preliminary finding, it will be important to examine whether the correlation is present with a larger group size.

Amygdala and STGl/LP: Functional connectivity between the right amygdala and both the STGl and the LP were negatively correlated with symptom scores on the RBS-bf for cluster group 3. For both the Amygdala-STG1 and the Amygdala-LP connectivities, higher scores on the RBS-bf were associated with reduced connectivity between regions. Cluster 3 was characterized by participants with the high scores across all the behavioural measures, including social communication.

The amygdala, STGl, and LP regions are all a part of the social brain. As previously discussed, the social brain plays a role in social processing (Gotts et al., 2012), which is impaired in all diagnoses included in the current sample. It is unclear exactly how the social brain is related to behavioural flexibility in this relationship, however, it is interesting to note that higher impairment on the RBS-bf *was* found in the same

individuals with weaker connectivity in the social brain. This suggests that the two areas of impairment may be strongly inter-related, and supports the examination of neurodevelopmental disorders through the RDoC framework. The goal of the RDoC framework is to examine neurodevelopmental disorders at the biological and neurological levels, which has been done in this sample through functional connectivity. The profile of connectivity in the social brain and symptom scores on the RBS-bf would not be accessible without a deeper examination of neurodevelopmental disorders. Again, it would be interesting to note what correlations would occur between behavioural measures and the social brain with a larger sample.

Strengths, Limitations, and Implications

There were a number of strengths in the methodology of the current study. First, it was the first to collapse across DSM-5 (APA, 2013) diagnostic categories and distinguish groups of children based on behavioural measures. By definition, then, this study was also the first to examine the functional connectivity of these clustered groups. By investigating how functional connectivity correlates with behavioural measures, we found support for the notion that there substantial overlap in symptom presentation across ASD, ADHD, and OCD. A second strength is the inclusion of fMRI data with behavioural measures. It is difficult to collect fMRI data from children with neurodevelopmental disorders due to the loud noises, confined space, and requirement of minimal movements during the scan. However, due to the neurological nature of neurodevelopmental disorders, fMRI can provide a valuable tool to examine brain function in these disorders. By allowing participants to watch a video during the resting state and anatomical scans, we were able

improve the tolerability of the scan session and successfully scan a number of individuals with neurodevelopmental disorders.

There are also some limitations in the present study that should be addressed. The first is the use of a video during the resting state. As mentioned, this allowed us to include children in the study who otherwise would have found it difficult to sit still or participate in the fMRI portion. However, this also presents a limitation due to the a lack of 'true' resting state as is convention (Biswal et al., 1995).

Limitations exist for the study sample as well. For example, our group sizes for ASD, ADHD, and OCD were uneven, and did not closely match population prevalence rates. Our cluster analysis, therefore, reflects the available data and participants. It is possible that with a more representative sample, there would be a stronger or different clustering of behavioural measures. Overall, having a larger sample size would be beneficial in analyzing resting state data as well, and differentiating between artifacts of motion and true connectivity found in the analysis. Further, 45% of our original sample did not have all of the behavioural measures required for the cluster analysis, and were subsequently removed from the functional connectivity analysis. This may be due to the multi-step POND intake procedure, which involves data being collected at different points (i.e., not all completed at the same time point as the neuroimaging data). Since data is continuously being collected for the POND study, a larger are more robust sample will likely be available in the future to investigate. Finally, the data being collected at different time points can be considered a limitation. In many cases, children who are referred to the neuroimaging sub-study may not be able to participate immediately. Numerous barriers

exist, such as having braces or another metal implant in the body, as well as aversions to small spaces, loud noises, or sitting still. In these cases, families may have been contacted later (eg after braces are removed, or the child more likely to hold still) to participate in the neuroimaging sub-study, introducing a large gap of time between the collection of behavioural data and neuroimaging data. However, it is important to note that the measures used were based on lifetime symptomatology, and are therefore likely still representative of the individuals challenges at the time of the neuroimaging study participation.

Future Directions

Future research could explore many of the results of this study. First, including a larger sample size that is more representative of community and clinical rates of diagnoses would solidify how behavioural measures cluster in children with neurodevelopmental disorders. This could be an important first step in addressing the vast overlap in symptoms and comorbidity between ASD, ADHD, and OCD. Second, a longitudinal study could be beneficial. As pointed out previously, neural networks differ between children and adults. What appears to be one cohesive network in adulthood may present as multiple independent ones in childhood (Weber, Soreni, & Noseworthy, 2014). Therefore, looking at how connectivity changes over time for children with neurodevelopmental disorders in these clusters may be another area to examine. Additionally, a longitudinal design which re-clustered participants could provide more information on the development of neurodevelopmental disorders, and how stable they may be.

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APPENDIX

APPENDIX 1: ROI information

Network and Region	MNI 152 Co-ordinates
1. DMN – medial prefrontal cortex	(1,55,-3)
2. DMN – lateral parietal (left)	(-39,-77,33)
3. DMN – lateral parietal (right)	(47,-67,29)
4. DMN – posterior cingulate cortex	(1,-61,38)
5. SN – anterior cingulate cortex	(0,22,35)
6. SN – anterior insula (left)	(-44,13,1)
7. SN – anterior insula (right)	(47,14,0)
8. SN – rostral prefrontal cortex (left)	(-32,45,27)
9. SN – rostral prefrontal cortex (right)	(32,46,27)
10. SN – supramarginal gyrus (left)	(-60,-39,31)
11. SN – supramarginal gyrus (right)	(62,-35,32)
12. DAN – frontal eye field (left)	(-27,-9,64)
13. DAN – frontal eye field (right)	(30,-6,64)
14. DAN – intraparietal sulcus (left)	(-39,-43,52)
15. DAN – intraparietal sulcus (right)	(39, -42, 54)
16. Frontoparietal – lateral prefrontal cortex (left)	(-43,33,28)
17. Frontoparietal – posterior parietal cortex (left)	(-46,-58,49)
18. Frontoparietal – lateral prefrontal cortex (right)	(41,38,30)
19. Social brain – fusiform gyrus – face	
20. Social brain – fusiform gyrus – social attribution task area	
21. Social brain – medial prefrontal cortex (left)	
22. Social brain – medial prefrontal cortex (right)	
23. Social brain – superior temporal gyrus (left)	
24. Social brain – superior temporal gyrus (right)	
25. Social brain – temporoparietal junction	
26. Social brain – inferior frontal gyrus (left)	
27. Social brain – inferior frontal gyrus (right)	
28. Social brain – amygdala (left)	
29. Social brain – amygdala (right)	
30. Social brain – dorsal medial prefrontal cortex	
31. Social brain – ventral medial prefrontal cortex	