Functional Neural Architecture Associated with Autism Spectrum Disorder, Psychopathy, and Related Social Cognitive Trait Dimensions

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DECLARATION

I, Rachel E. W. Smith, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

The overarching aim of this thesis was to deepen our understanding of the relationship between functional brain organization and disorders of social cognition (and their related trait dimensions). The empirical chapters outlined below addressed outstanding research questions and contribute novel resting-state fMRI findings to the study of ASD, developmental risk for psychopathy, and individual differences within these two trait domains. **Chapter 2** provided a contextual foundation for the subsequent studies by detailing the main methodological tool used throughout this thesis: resting-state fMRI. Relevant resting-state findings in ASD, psychopathy, and CP were also reviewed. In **Chapter 3**, resting-state functional connectivity was compared in males and females with ASD, as existing research is biased towards males. Results revealed a diagnosis-by-sex interaction in cortico-cerebellar connectivity, whereby females and males showed opposite patterns of connectivity, or increases versus decreases, respectively. In **Chapter 4**, widespread increases in functional connectivity within- and between networks was found to be associated with higher levels of psychopathic traits in a large (n=924) community sample of young adults. Reduced empathic concern partly accounted for this association. However, a significant relationship between ASD traits and resting-state functional connectivity was not found. **Chapter 5** demonstrated widespread increases in within-and between- network functional connectivity in boys who are at increased risk of developing psychopathy (CP/HCU) relative to TD boys. The overlap between findings in Chapters 4 and 5 motivated **Chapter 6,** which directly compared results from the two studies. We detected both spatial commonalities and statistically significant similarity after permutation tests. Common regions were located in areas related to socioemotional and somatomotor function. Taken together, it is clear that baseline functional brain organization is an important correlate of socioemotional function in both normal and clinical populations, and that resting-state fMRI can extend our understanding the mechanisms underlying disorders of social cognition.

IMPACT STATEMENT

Together with structural and task-based neuroimaging, resting-state fMRI allows researchers to tap further into neural mechanisms underlying psychiatric disease states as well as individual differences in static traits. Through this lens, the findings from this thesis are of substantial value, as they contribute to a (brain-based) reconceptualization of disorders such as ASD and psychopathy, which have been heavily stigmatized. This thesis also contributes novel information to a growing body of literature that could help to inspire new avenues for intervention or treatment.

Sex differences in ASD are not clearly understood, and literature is heavily biased towards male samples. This thesis demonstrated that males and females with ASD exhibit unique, opposing patterns of atypical functional connectivity between the cortex and cerebellum. When considered in light of genetic and morphological findings in the cerebellum, this observed divergence in functional brain organization between the sexes in ASD may offer clues that ultimately help researchers tease apart the disorder's pathophysiology.

There appears to be a significant relationship between widespread functional connectivity increases and higher levels of psychopathic traits, and this pattern of hyperconnectivity was observed in both healthy adult and at-risk child samples. This directional consistency across studies suggests that differences in functional neural architecture are reliable associations and may help explain atypical social cognition seen in individuals with high levels of psychopathic traits. Further studies motivated by this research should examine whether poor network differentiation/segregation may contribute to the development of psychopathic traits via altered or competing streams of information processing. A subset of regions mainly subserving limbic/paralimbic and sensorimotor functions was also implicated in both samples (healthy young adults and at-risk boys), indicating that to some extent, there is a common factor underlying continuous variation in psychopathic traits.

The fact that a broad range of functionally diverse regions were involved in the resting-state findings across all studies outlined in this thesis underscores the advantages of employing a data-driven analytic approach. Unbiased findings can help move the field

forward by shining a light on overlooked corners of the brain, such as the somatomotor regions implicated in the analyses of psychopathic traits and risk for psychopathy. Future studies should continue to strive for thorough and inclusive experimental designs.

A primary goal for future research should be to elucidate the interplay between aberrant structure, aberrant activation, and aberrant functional connectivity and determine effective relationships. Is there a reliable mechanistic pattern that can relate these three measures? For example, is increased functional coupling between brain regions a compensatory adaptation to congenital hypoplasia? Or alternatively, could aberrant neural wiring between brain regions encourage local tissue to proliferate or atrophy? To what extent can very fine-grained phenotypes be predicted by resting-state functional connectivity? Can baseline brain activity predict task-based activation? In particular, these questions of mechanistic interplay should be addressed from a developmental angle, given that atypicalities across neuroimaging modalities have been identified in children with neurodevelopmental disorders (e.g. ASD), or who are at heightened risk for developing clinical syndromes in adulthood (e.g. CP/HCU).

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KEY ABBREVIATIONSF

ACC	Anterior cingulate cortex
AFNI	Analysis of Functional NeruoImages (software)
ASPD	Antisocial personality disorder
ASD	Autism spectrum disorders
AQ	Autism Quotient
CP	Conduct Problems
CP/HCU	CP with high levels of CU traits
CP/LCU	CP with low levels of CU traits
CU	Callous unemotional
fMRI	Functional magnetic resonance imaging
FDR	False detection rate
EC	Empathic concern
HCU	High levels of CU traits
IFG	Inferior frontal gyrus
IRI	Interpersonal Reactivity Index
LCU	Low levels of CU traits
MRI	Magnetic resonance imaging
MTG	Middle temporal gyrus
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
SES	Socioeconomic status
SMA	Supplementary motor area
SRS	Social Responsiveness Scale
SRP-SF	Self-Report Psychopathy Scale -Short Form
STG	Superior temporal gyrus
STS	Superior temporal sulcus
TD	Typically developing
ToM	Theory of mind
vmPFC	Ventromedial prefrontal cortex

CHAPTER 1

GENERAL INTRODUCTION

Humans live in dynamic, social worlds where a vast amount of the incoming information is social in nature. From the earliest days of life, infants begin taking social cues from others in order to learn about their environments, and this social learning is a crucial tool for survival (Adolphs, 1999; Frith, 2008). The centrality of social behavior to the human experience persists throughout the lifespan, and many significant events such as forging friendships, finding a mate, gaining an education, securing a job, and becoming a parent, require a reasonable degree of social understanding and interaction. To successfully meet these interpersonal demands, humans must be able to interpret social information by inferring the thoughts, feelings, and intentions of others while often simultaneously reflecting on their *own* thoughts, feelings, and intentions (Frith & Frith, 2007; Gallese et al., 2004). Furthermore, they must also be able to determine the most appropriate and effective ways to communicate across an infinite number of contextual scenarios. These psychological capacities, which allow humans to accomplish such impressive interpersonal feats, form the core of what is referred to as social cognition (Fiske & Taylor, 2013).

1.1 Why is Social Cognition Important?

Social cognition encompasses the processes by which humans make sense of their social environments, and it is an important precursor for relationships, beginning with early attachment to caregivers (Thompson, 2008). Social psychology research has demonstrated that having healthy attachments and sufficient socio-emotional support are strong predictors of resilience in the face of stress, and positive physical health outcomes throughout the

lifespan (Coffman & Gilligan, 2002; Hale et al., 2010; Russell & Cutrona, 1991). The value of social competence extends beyond the individual as well, and exerts significant facilitative and productive power at the group- or even societal-level. At this larger scale, researchers refer to the effectiveness of reciprocal relationships degrees of social aptitude as 'social capital,' which draws on the economic power of strong interpersonal networks (Bourdieu, 1986; Coleman, 1990; Kawachi & Berkman, 2000).

On a more basic evolutionary level, social cognition and reciprocal social bonds can increase chances of survival, while isolation can lead to vulnerability (Hall-Lande et al., 2007). Although humans' social capabilities may be more advanced and social rewards may be more nuanced than those of other species, many other animals, including nonhuman primates, display some social and pair-bonding behaviors (Hecht et al., 2012), which indicates some degree of shared physiological mechanisms. Decades of research into the underlying biology of these social behaviors have found that a common, adaptive, neuro-endocrine system featuring the peptide hormone oxytocin plays a leading physiological role in social motivation and social reward (Adolphs, 2010; Anacker & Beery, 2013; Insel, 2010; Norman et al., 2012; Young & Wang, 2004).

More recently, scientists have also begun to explore how the human brain responds to social stimuli such as emotional faces, interpersonal exchanges, and interactive games (Adolphs, 2009; Singer, 2012). These studies have led researchers to identify a set of brain regions that are reliably involved in such tasks, which are now referred to as the 'social brain' (Adolphs, 2009; Dunbar, 1998; Lieberman, 2007). The social brain develops throughout childhood and adolescence, as social demands also continue to grow (Blakemore, 2008). While it seems clear that as a species, humans have an advanced capacity for complex social

behavior, degrees of social aptitude still vary from person to person. It remains unclear how the variability in those prosocial capacities are reflected in the underlying brain's functional organization. One extreme of that variability is compromised social cognition and diminished prosociality. Atypicalities like these can make it exceedingly difficult to meet the demands associated with employment, relationships, parenthood, etc., which likely leads to poor outcomes across these domains.

A number of psychiatric disorders including—and perhaps most notably—autism spectrum disorder (American Psychiatric Association [APA], 2013) involve marked problems with social cognition. Because of the challenges they face in social situations, individuals with ASD are particularly vulnerable to becoming lonely, isolated, depressed, and even suicidal (Hedley et al., 2017). In fact, studies have demonstrated that one of caregivers' greatest concerns in people with ASD is their persistent lack of social relationships (Operto et al., 2017). Even in childhood, patients themselves report high levels of loneliness and social exclusion (Lasgaard et al., 2009). Despite many improvements in inclusive schooling and ongoing support, follow-up longitudinal studies still paint a bleak picture of long-term dependence on parents or other caregivers and relatively poor career prospects in ASD, even for some higher-functioning individuals (Chamak & Bonniau, 2016; Howlin, 2005). This implicates the related social-cognitive deficits as a major barrier to professional success and independence.

Psychopathy is another clinical disorder that is characterized by social-cognitive atypicalities (Cleckley, 1976). Like ASD, psychopathy is also associated with poor interpersonal outcomes, but unlike ASD, some psychopathic individuals may also engage in impulsive, aggressive, and violent criminal behavior, which can lead to incarceration (Hare,

1999). Some elements of psychopathy such as low levels of empathy, reduced guilt, and increased fearlessness, can also be adaptive in certain career paths (Babiak & Hare, 2006), and under the right socioeconomic circumstances, this may lead some psychopathic adults to find success (Glenn et al., 2011). However, these individuals still experience persistent interpersonal difficulties (Benning et al. 2018). Psychopathy also stems from very different socio-emotional deficits than those seen in people with ASD (Bird & Viding, 2014; Lockwood et al., 2013a; Jones et al., 2010; Rogers et al., 2006). More specifically, psychopathic individuals struggle to resonate with others emotions and therefore lack affective empathy, whereas individuals with ASD are able to resonate (and in some cases, resonate too heavily), but struggle to see things from another person's perspective. Psychopathy and ASD represent the extreme, clinical ends of a complex spectrum of social and empathic abilities, and even within healthy populations, there is a great degree of individual variability in autistic and psychopathic traits.

To reduce and eventually eliminate the unfavorable outcomes associated with social-cognitive difficulties in clinical and healthy populations alike, it is imperative that researchers gain a more comprehensive understanding of the functional neurobiology, including resting-state neural profiles associated with social aptitude, or lack thereof. With respect to disorders of social cognition such as ASD and psychopathy, studies have begun to map atypicalities in functional brain organization, but the picture is limited. For example, while resting-state neuroimaging studies of ASD have amassed in recent years the vast majority of these studies consists exclusively of male participants, thereby preventing many findings from being extrapolated to females with ASD. Likewise, studies of resting-state brain activity in psychopathy have accumulated as well, albeit more slowly than in the ASD literature. However, little is known about these baseline brain characteristics of youths who are at

increased risk of developing psychopathy. With respect to psychiatrically healthy populations, it remains unclear whether individual differences in psychopathic or autistic traits can be reliably linked to resting-state activity in particular brain networks, and whether those network dynamics mirror findings from in clinical populations.

The aim of this thesis is to provide novel empirical findings that will address the aforementioned limitations and gaps in the existing literature. The following sections will first provide overviews of ASD and psychopathy, respectively, as well as an introduction to resting-state fMRI, which is the main neuroimaging approach used in the current thesis, before moving on to each of the empirical studies performed.

1.2 Autism Spectrum Disorder: An Overview

1.2.1 *General Definition*

The autism spectrum encompasses a heterogenous group of neurodevelopmental disorders characterized by abnormalities in social communication, repetitive or stereotyped physical behaviors, restricted interests, rigid adherence to routines, and altered sensitivity to sensory stimuli (APA, 2013; Centers for Disease Control and Prevention [CDC], 2021). There is a wide range of intellectual ability seen in ASD, with some individuals who are profoundly impaired and others who are exceptionally creative and intelligent (Charman et al., 2010; Chiang & Lin, 2007; Hetzroni et al., 2019). The repetitive motor behaviors seen in ASD may present as rocking, shaking, or hand flapping, and sensory abnormalities may manifest as extreme aversion to loud or unexpected noises, bright lights or colors, and strong tastes or smells (Leekam et al., 2011; Robertson & Baron-Cohen, 2017). The social and

communicative difficulties associated with ASD often present as a lack of interest in or attachment to caregivers in early childhood, delayed onset of language, discomfort with physical affection, difficulty relating to others, and a preference for solitude (Lord et al., 2006).

It is important to note that there is a high degree of phenotypic heterogeneity across individuals with ASD, and that symptomatic presentation and degree of functioning can vary widely (Georgiades et al., 2013). Unfortunately, given the apparent differences social-communicative behavior and generalizations about an 'impaired social brain' in ASD, there are pervasive stereotypes about individuals with ASD that detract focus from the more unique abilities and strengths associated with the disorder and may impede further study into the more nuanced social processing differences (Hamilton & Krendl, 2007). There is much work being done in academic settings and advocacy groups alike to highlight these strengths and emphasize that some interpersonal differences need not always be seen as problem in need of 'fixing.'

Recent epidemiological studies suggest that about 1 out of every 59 children will be diagnosed with ASD by 8 years of age, and that males are 3-4 times more likely than females to receive this diagnosis (Baio et al., 2018). While most ASD diagnoses are given between the ages of 4-6, new research suggests that the disorder can be reliably identified in children as young as 24 months (Daniels & Mandell, 2014).

1.2.2. *Social-Affective Profile of ASD*

At the behavioral level, the social-communicative difficulties seen in ASD can present as emotional detachment from parental figures early in childhood, disinterest in social

interaction, unusual or inappropriate expressions of affect, and lack of empathy towards others (APA, 2013). These clinical symptoms can be very difficult both for individuals with ASD, as well as for their families and friends. However, many researchers believe that the social, emotional, and communicative challenges faced by people with ASD are due, in part, to an inability to assume the cognitive (and visual) perspectives of other people, rather than a lack of general empathy, as seen in psychopathy (Bird & Viding, 2014; Hamilton et al., 2009). Simply put, people with ASD are not easily able to infer or anticipate what another person is thinking or experiencing, which naturally makes bidirectional interaction confusing and difficult.

This phenomenon of thinking about others' mental states is referred to as mentalizing or theory of mind (ToM) (Baron-Cohen et al., 1985). Typically developing (TD) individuals differentiate between the self and other on a virtually automatic basis, and are able to mentalize with minimal effort, whereas people with autism struggle to imagine another's point of view or to hold multiple perspectives in mind at once. Early studies demonstrated these ToM deficits in children with ASD using a classic experimental paradigm called the 'Sally-Anne task' (Baron-Cohen et al., 1985). In this task, experimenters create a vignette with two dolls or puppets: Sally and Anne. Each doll has a covered box or basket, and Sally has a marble in her basket. Sally leaves briefly and while she is away, Anne moves the marble to her own basket (unbeknownst to Sally). When Sally returns, experimenters ask the children where Sally will first look for her marble. The majority of TD children will correctly identify that as far as Sally knows, the marble should be where she left it—in her own basket. However, children with ASD are unable to separate their own knowledge of the marble's relocation from Sally's lack of that knowledge, and they incorrectly point to the marble's new location (Baron-Cohen et al., 1985). More recent studies suggest that where

possible, children may rely on more heavily on spatial cues to compensate for difficulties in embodying the experience of another individual (Pearson et al., 2016).

Researchers have also designed studies to explore the extent to which ASD influences social attention or interest, as it has been suggested that ASD is associated with reduced social motivation (Chevallier et al., 2012). One such investigation found that children with ASD attended significantly less to socially-relevant imagery compared to healthy counterparts (Gale et al., 2019). There is also evidence to suggest that adolescents with ASD have a clear preference for viewing non-social visual stimuli, while TD adolescents do not show a strong preference for either social versus non-social imagery (Dubey et al., 2017). Studies of gaze orientation and eye movements have noted abnormal saccade patterns in ASD when viewing faces, indicating that even at the featural level, social information may be processed differently in ASD (Dalton et al., 2005). Indeed, researchers noted that participants with ASD tended to fixate on more neutral parts of the face, rather than features like the eyes, which convey the majority of socially relevant information (Benson et al., 2009; Neumann et al., 2006; Spezio et al., 2007). These featural information-processing deficits have also emerged in studies of biological motion and hidden faces, where participants with ASD were unable to identify human-like forms within ambiguous visual scenes (Pavlova et al., 2017; Todorova et al., 2019).

Another common but controversial experimental finding is poor performance on facial emotion recognition tasks in individuals with ASD, and these deficits appear to be most prominent when identifying negative emotions such as fear (Uljarevic & Hamilton, 2013). Behavioral findings like these may appear to suggest that ASD features prominent deficits in empathy, but this branch of affective research is hotly debated and experts have warned

against conflating the empathic deficits seen in ASD with those seen in psychopathy (Bird & Viding, 2014). Indeed, poor perspective-taking abilities may play a key role in these emotion-recognition difficulties, and this may be compounded with co-occurring alexithymia, a sub-clinical trait dimension characterized by difficulty understanding and labeling emotions (Bird & Cook, 2013).

1.2.3 *Etiology*

A wide range of etiological factors have been associated with ASD, including hormonal imbalances in utero, prenatal exposure to various teratogens (valproic acid, thalidomide, ethanol, misoprostol, and other organic pollutants such as common pesticides), parental age, rare neurogentetic conditions such as fragile X syndrome, epilepsy, and congenital or sustained damage to the cerebellum (Bölte et al., 2019; Wang et al., 2014). The heritability of ASD has also been studied with increasing rigor and a large number of candidate genes have been identified (Huguet et al., 2013). Given the phenotypic heterogeneity of this disorder, it is not surprising that such a wide range of genes have been implicated, and it may be the case that many play a role in ASD's epidemiology. In light of extensive research from multiple scientific disciplines, there is not currently a universal determining cause of ASD, but rather a number of significant risk factors, some of which may be working in concert (Bai et al., 2019).

1.3 Neuroimaging in Autism

One of the most informative ways to bridge the mechanistic gap between molecular and genetic factors and the behavioral phenotype of ASD is by imaging the brain. From the

earlier days of electrophysiology to the advent of functional magnetic resonance imaging (fMRI), a substantial amount of neuroimaging literature has accumulated to deepen our understanding of ASD from a neurobiological perspective.

1.3.1 *Structural imaging*

The suggestion that ASD may be associated with altered brain structure actually predated any modern neuroimaging, and was introduced by Kanner (1943), who noted a link between ASD and enlarged heads. Over the following decades, a handful of other research teams published similar findings, relating increased cranial circumference to participants with ASD (e.g. Elder et al 2007; Lainhardt et al., 1997; Torrey et al., 2004). The emergence of MRI allowed scientists to determine whether those crude markers of cranial size were indicative of structural brain abnormalities. While studies have consistently reported increased brain volume (white *and* grey matter) in infants and young children with ASD, this effect appears age-specific (Hazlett et al., 2005; Sacco et al., 2015). Studies suggest that this ASD-related neural overgrowth is most prominent between the ages of 12 months and 4-5 years, and is evident across the cortex and subcortex, especially in frontal, temporal, and cingulate cortices as well as the amygdala, basal ganglia, and corpus callosum (Mosconi et al., 2009; Nichl-Jockschat et al., 2011; Schumann et al., 2009; Schumann et al., 2010; Sparks et al., 2002; Wolff 2018). More recent studies have suggested that early (<12 months) acceleration of surface area growth is responsible for the volumetric increases and is highly predictive of ASD (Hazlett et al., 2017).

In adolescence, structural differences associated ASD are typically at their peak, with many changes now following the opposite pattern of *reductions* in volume and cortical

thickness (Zielinski et al., 2014; van Rooij et al., 2018). In both adolescents and adults with ASD, this pattern is particularly prominent in subcortical regions such as the basal ganglia and amygdala, and in regions involved in social cognition, including the superior temporal sulcus (STS), temporo-parietal junction(TPJ), inferior frontal gyri, cingulate gyri, supramarginal gyri, prefrontal cortex (PFC), and inferior/middle temporal cortex (Wallace et al. 2010; Scheel et al. 2011; Greimel et al. 2013; van Rooij et al., 2018; Sato et al. 2017). Reductions in grey matter and increased cortical thinning have also been reported in somatomotor regions such as the pre- and post- central gyri (Wallace et al., 2010; Greimel et al., 2013). In addition, increases in cortical thickness in frontal regions have also been observed by some researchers (Ecker et al. 2013; van Rooij et al. 2018). While the degree of structural divergence from healthy controls appears to peak around adolescence, research suggests that the precise trajectories of ASD-related morphological changes are also region-specific (Zielinski et al., 2014; van Rooij et al., 2018).

There have been inconsistent reports about the nature of structural changes in the cerebellum in ASD (Traut et al., 2018). For instance, some researchers have found volumetric decreases in cerebellar vermal structures in children and adults with ASD (Hashimoto et al., 1995; Webb et al., 2009; D'Mello et al., 2015), while others have reported *increases* in anterior lobule size as well as increased cerebellar white matter in children with ASD (Akshoomoff et al., 2004). Meanwhile, some have failed to find any significant differences at all after correcting for total brain volume (Hazlett et al., 2005; Sparks et al., 2002; Traut et al. 2018). A number of factors could have contributed to these inconsistencies. Findings from one study, which observed grey matter reductions only in *female children* with ASD, indicated that sex may also play a role in ASD-related cerebellar abnormalities (Bloss & Courschesne, 2007). Yet, the aforementioned studies were not all

comparable with respect to the ratio of males and females in their participant groups. In addition, some studies had significantly smaller samples than others, which means that the findings from those studies could be treated more cautiously, and some included participants with varying degrees of intellectual disability, whereas others excluded individuals with more severe cognitive impairment, making it difficult to draw firm conclusions regarding the possible impact of cognitive ability on the findings. Interestingly, one study that found white matter increases but no grey matter differences associated with ASD also reported a dissociation in posterior cerebellar vermis morphology between children diagnosed with high- versus low-functioning ASD (Akshoomoff et al., 2004). This suggests that including samples with varying degrees of intellectual disability could obscure or dilute study findings. Authors of the same study also observed a greater degree of variability in cerebellar morphology among those with ASD diagnoses, irrespective of intellectual disability (Akshoomoff et al., 2004), which casts doubt on the reliability and implications of ASD-related changes cerebellar structure.

Despite the heterogeneity of these structural findings, the cerebellum remains consistently implicated in ASD literature, and the potential etiological relevance of this particular structure in the pathogenesis of ASD, especially as it may pertain to sex differences, will be explored in depth in Chapter 3.

1.3.2 *Task-Based Functional Imaging*

To gain insights into the functional neurobiology of ASD, and to identify the neural correlates of aberrant social processing, researchers have turned to fMRI, which measures acute changes in brain activity during a task or event. Functional neuroimaging studies of ASD have employed a range of experimental tasks—both explicit and implicit—, which are

intended to evoke and measure meaningful responses in the brain. Given the pervasive social-cognitive deficits seen in ASD, many tasks have aimed to address socially relevant neural computations. For example, reduced attention to, or interest in human faces is a prominent feature of ASD (Bird et al., 2006), so a number of fMRI studies have utilized visual paradigms that display images of human faces while participants are inside the scanner. According to these studies, in both active and passive tasks, participants with ASD exhibited reduced local activation compared to controls in social and face-processing brain areas while viewing neutral faces (for review, see Nomi and Uddin, 2015). These social and face-processing areas include the STS, amygdala, and fusiform gyrus. Because there is also evidence that individuals with ASD may have difficulty identifying expressions of emotion, some face studies have also manipulated the stimuli to depict different emotions, and monitored brain response while participants passively viewed images or performed more explicit tasks (Pelphrey et al., 2007). While there have not always been consistent group differences during passive viewing of emotional faces, more demanding explicit tasks typically evoke reduced activation in the same areas implicated in prior face studies (e.g. fusiform gyrus, amygdala, and STS) in ASD participants, compared to healthy controls (Bird et al., 2006; Corbett et al., 2009; Critchley et al., 2000; Kleinhans et al., 2010). Interestingly, although a majority of studies reported task-based hypo-activation in ASD, gender identification tasks with emotional faces have elicited the opposite pattern of amygdala and STS hyper-activation in ASD compared to controls (Critchley et al., 2000; Weng et al., 2011). These findings suggest that the cognitive demands of a given task may further compound the already aberrant streams of face processing in ASD (Nomi and Uddin, 2015).

Difficulties with perspective-taking in ASD have also been examined under the task-based neuroimaging microscope. During ToM or mentalizing tasks, social brain areas such

as the PFC and TPJ have shown reduced activity and connectivity in children and adults with ASD compared to controls (Kana et al. 2009; Shulte-Rüther et al., 2010; Murdaugh et al. 2014; O'Nions et al., 2014; Nijhof et al. 2018). However, the disorder's overall heterogeneity combined with discrepancies in task performance have made these investigations difficult to interpret conclusively (Lenroot & Yeung, 2013). Furthermore, subtle differences in the content of perspective-taking tasks could introduce elements of affective processing rather than pure perspective-taking, thereby further complicating the picture.

It is important to consider the ecological validity of the common fMRI tasks given to participants with ASD. In order for a task to be suitable for the scanner, it must be sufficient in length, must involve sensory information that is provided via computer screens projected onto mirrors, must use unobtrusive tools for making responses, and must not induce excess motion on the part of the participant. Of course, setups like these are inorganic and unlike any other naturalistic experience, which challenges the applicability of any findings to real events outside the scanner. Furthermore, when studying social-communicative difficulties, researchers might want to employ tasks that involve interaction, but these present motion-related challenges inside the scanner. A handful of researchers are attempting to broaden the scope of what fMRI can capture and have attempted to study phenomena such as verbal communication (Jasmin et al., 2019) and taste (Avery et al., 2018), albeit via expertly rigged contraptions that deliver tiny amounts of fluid to the mouth or with audio and visual feedback from someone outside of the scanner. Of course, these still do not even approach real-life gustatory or social experiences. So, while task-based fMRI can provide information about specific differences in neural computations and highlight particular brain regions or networks for further study, they do have a number of limitations.

1.4 Psychopathy: An Overview

1.4.1 *General Definition*

Psychopathy is a personality disorder that is characterized by profound deficits in empathy, lack of guilt or remorse, deviant antisocial behavior, callousness, disinhibition, manipulation, and self-centeredness (Cleckley, 1976; Hare, 1999). Epidemiological studies estimate that psychopathy affects approximately 1% of the general population (Neumann & Hare, 2008; Coid et al., 2009), but the prevalence rate in prison populations is much higher, with some reports as high as 25% (Neumann & Hare, 2008; Kiehl & Hoffman, 2011). This discrepancy highlights the propensity for psychopaths to become criminal offenders, and these high rates of incarceration impose a significant financial burden on society. In fact, although psychopathy is far less common than major depression, psychopathy is associated with 10 times the societal cost of depression (Viding, 2019). Psychopathy is also more prevalent in males than females, which either indicates a biologically relevant sex difference or a bias in the identification and diagnosis of female psychopaths (Wynn et al., 2012).

Although they are often conflated outside of clinical or academic settings, psychopathy, antisocial personality disorder (ASPD), and sociopathy are not synonymous, and it is important to carefully differentiate these terms (Viding 2019). The broader category of ASPD is included in the Diagnostic and Statistical Manual Fifth Edition ([DSM-5] APA, 2013) and is used for clinical and diagnostic purposes. To meet the criteria for ASPD, an individual must display a number of antisocial, impulsive, callous, uncaring, or aggressive

tendencies, and these behavioral features must have been present before or by the age of 15 (DSM-5, APA, 2013). A formal diagnosis of psychopathy can only be made in adults over the age of 18, using the clinician-administered Psychopathy Checklist, Revised ([PCL-R]; Hare, 2003), however, other measures of psychopathic traits have been used to assess prevalence rates and individual variability in larger, non-incarcerated groups.

Psychopathic individuals display the core features of ASPD, but only a smaller subset of those diagnosed with ASPD will also meet the criteria for psychopathy (Viding 2019). Psychopathy can therefore be thought of as a subgroup under the ASPD umbrella, comprised of individuals who also engage in persistent, violent, criminal behavior (Werner et al., 2015; Viding 2019). The term 'sociopathy' has been used in the media and entertainment industries to refer to individuals with ASPD or psychopathy, but the term lacks specificity and a rigorous operational definition. 'Sociopathy' is therefore not commonly used in clinical or academic settings, and research is typically conducted using the gold standard measures such as the DSM-5 or PCL-R, which clearly and reliably define ASPD and psychopathy, respectively.

The most notable developmental precursor of persistent antisocial behavior and adult psychopathy is the presence of conduct problems and high levels of callous-unemotional (CU) traits during childhood/adolescence (Blair et al., 2014; Frick et al., 2014; Pardini & Fite, 2010). Conduct disorder refers to the clinical syndrome associated with conduct problems and is characterized by hostile, rule-breaking behavior, bullying, dishonesty, theft, and risky or nonconsensual sexual activity (APA, 2013). However, many children and adolescents who exhibit persistent conduct problems fail to secure a referral to services and receive a formal diagnosis, so research instruments such as the Child Behavior Checklist

([CBCL]; Achenbach & Ruffle, 2000), Strengths and Difficulties Questionnaire ([SDQ]; Goodman, 2001), and Child and Adolescent Symptom Inventory ([CASI]; Gadow & Sprafkin, 2009) are often used to assess conduct problems for the purpose of empirical study. These instruments allow researchers to identify and study behaviorally similar children, without having to exclude those who have not been assessed for a clinical diagnosis.

A subset of children and adolescents with conduct problems also exhibit high levels of CU traits, which mirror the affective deficits seen in psychopathy (Frick et al., 2014; Viding & Kimonis, 2018). More specifically, CU traits include a profound lack of empathy or concern for others, shallow, blunted affect, absence of guilt or remorse, and cruelty towards others. The DSM-5 makes reference to CU traits under the diagnostic criteria for conduct disorder, but uses the phrase "limited prosocial emotions" instead (APA, 2013). When they emerge early and occur together, conduct problems and CU traits are associated with the most persistent and severe forms of antisocial and criminal behavior (Blair et al., 2014; Fontaine et al., 2011; Longman et al., 2016; Viding & Kimonis, 2018). Conduct problems with high levels of CU traits will be examined in greater depth through an empirical, neuroimaging lens in Chapter 5.

1.4.2. *Social-Affective Profile of Psychopathy*

Reduced empathy is a hallmark of psychopathy, but the empathic deficits seen in psychopathy are unlike those associated with ASD. For psychopaths, affective resonance or emotional contagion is profoundly diminished, but perspective-taking abilities remain mostly intact (Bird & Viding, 2014; Lockwood et al., 2013a). In a recent experimental study,

Drayton and colleagues (2018) found that although individuals with high levels of psychopathic traits may not automatically attend to others thoughts or mentalize— perhaps because they are more focused on themselves—, they are easily able to engage in perspective-taking when asked or when doing so provides some sort of reward. There is also substantial empirical evidence that due to their empathic deficits, psychopaths are less susceptible to distraction when presented with extraneous emotional information during a task, and this can lead to better goal-directed task performance than healthy controls (Mitchell et al., 2006). Together, these findings offer support for psychopaths' tendency to manipulate and tune others out when necessary for personal gain.

Psychopaths' lack of guilt removes another barrier that would have discouraged them from engaging in deviant or harmful means of achieving this personal gain. In experimental tasks using hypothetical moral dilemmas, psychopaths and individuals with high levels of psychopathic traits make more utilitarian judgments, and are less hesitant or emotionally reactive to choices that inflict harm on others (Koenigs et al., 2012; Pletti et al., 2016). In addition, multiple studies have indicated that psychopathic individuals are able to deliberately lie or deceive more easily than their healthy counterparts (Fullam et al., 2009; Glenn et al., 2017; Shao & Lee, 2017). Glenn and colleagues (2010) theorized that unlike most healthy adults, morality is simply not a relevant component of personal identity in individuals with psychopathy, and surely their freedom from guilt contributes to this.

Individuals with high levels of psychopathic traits also tend to display blunted responses to others' fear, distress, and pain (Blair 2013; Blair et al., 2005). In facial affect recognition tasks, psychopaths are able to identify the emotions presented, but tend to respond slower and less reliably to fearful or distressed faces, especially when the affective

cues are subtle (Blair et al., 2004). Furthermore, psychopaths display reduced physiological arousal when viewing others in distress, and lack the same startle response as their healthy counterparts when viewing unpleasant images (Patrick et al., 1993). Aiming to find a mechanism responsible for this insensitivity, Brislin and colleagues (2016) also correlated psychopathic traits with pain tolerance, and found that high levels of psychopathic traits were predictive of higher pain tolerance and lower anticipatory fear of painful stimuli. The researchers concluded that an increased pain tolerance in psychopathy may be partially responsible for their insensitivity to pain experienced by others (Brislin et al., 2016). However, another similar study found weaker, and inconsistent correlations between pain tolerance and levels of psychopathy (Miller et al., 2014). It is therefore likely that in psychopathy, a combination of increased pain tolerance, decreased fearfulness, ego-centricity, and absence of empathy may all contribute to the observed lack of sensitivity to others' pain.

1.4.3. *Etiology*

Although individual candidate genes have not been identified, converging evidence from a number of twin studies suggests that heritability plays a significant role in the development of antisocial behavior and psychopathic personality traits (Forsman et al., 2008; Mann et al., 2015; Viding et al., 2005; Viding et al., 2008). Likewise, a number of environmental factors have also been highlighted, including early adversity, maltreatment, harsh or dysfunctional parenting, low parental warmth, and low socioeconomic status, all of which have been associated with risk for psychopathy (Fairchild et al., 2019; Hyde et al., 2016). A number of studies have found positive associations between childhood abuse or neglect and levels of psychopathic traits in adolescent and adult male offenders (Craparo et

al., 2013; Kimonis et al., 2013; Lansford et al., 2007; Poythress et al., 2006), suggesting that trauma and emotional deprivation during early development can play a significant role in the development of psychopathy. Although they do not suffer physical abuse or neglect, children with parents who exhibit harsh, intrusive styles of discipline or who fail to bond with their infants, may also be at increased risk for persistent antisocial behavior (Kochanska & Kim, 2012; Mills-Koonce et al., 2016; Wagner et al., 2015) Until the genetic and mechanistic pathophysiology of psychopathy are more precisely elucidated, it may be difficult to differentiate between genetic and parental environmental risk factors, as the genetic predisposition to behave antisocially may have been inherited from a cold, harsh, disciplinarian parent.

Socioeconomic status (SES) may be another important environmental factor associated psychopathy. According to a study by Sadeh and colleagues (2010), poverty and its related disadvantages or lack of resources, compounded by a genetic predisposition, were associated with increased antisocial behavior in youths. It may also be the case that privileges associated with material wealth and higher education serve as protective factors that make adaptation more accessible and incarceration less likely (Persson & Lilienfeld, 2019). Psychopathic individuals who utilize their immorality and lack of empathy for personal or professional gain—while evading law enforcement—are referred to as 'successful psychopaths' (Benning et al., 2018).

In summary, it appears that a complex interplay between underlying genetic vulnerability and specific environmental risk factors together determine an individual's chances of becoming a psychopath. In addition to raising awareness about all potential risk

factors, researchers are now beginning to elucidate the neurobiological changes underlying psychopathy in adults as well as its developmental precursors in children and adolescents.

1.5 Neuroimaging in Psychopathy

1.5.1 *Structural imaging*

Given the host of cognitive and behavioral abnormalities associated with psychopathy, it is not surprising that researchers have also found differences in brain structure in individuals with high levels of psychopathic traits. The most well replicated morphological finding associated with psychopathy in adults has been reductions in regional brain volume, most notably in the PFC or orbitofrontal cortex (OFC) (Yang & Raine, 2009). Group comparison studies have reported cortical thinning or decreases in grey matter volume in the middle frontal, cingulate, parahippocampal, and superior temporal gyri (STG) in psychopathic individuals, compared to controls (Müller et al., 2008a; Yang et al., 2009). Within groups of violent offenders, levels of psychopathic traits have been also negatively correlated with prefrontal and limbic/paralimbic (e.g. PFC, OFC, anterior and posterior cingulate [ACC/PCC], amygdala, temporal pole, and parahippocampus/hippocampus) volumes (Cope et al., 2014; Ermer et al., 2012; Gregory et al. 2012; Leutgeb et al. 2015). However, the striatum has exhibited the opposite structural pattern of grey matter *increases* in psychopaths compared to controls (Glenn et al., 2010), and in prison populations, *positive* correlations have also been reported between psychopathic traits and grey matter in the cerebellum, supplementary motor area (SMA), and basal ganglia (Glenn et al., 2012; Korponay et al. 2017; Leutgeb et al., 2015).

Results from morphological studies carried out in children and adolescents who are at risk for developing psychopathy have echoed the adult studies. In children with conduct problems, very similar abnormalities in grey matter and cortical thickness in the OFC, PFC, anterior cingulate cortex (ACC), temporal cortex, amygdala, and insula have been reported (Fahim et al., 2011; Fairchild et al., 2011; Huebner et al., 2008; Hyatt et al., 2012; Rogers & De Brito, 2016; Sebastian et al., 2016; Sterzer et al., 2007; Wallace et al., 2014). It has been suggested that many of these structural differences are directly correlated with or mediated by levels of CU traits (Caldwell et al., 2019; Cardinale et al., 2019; Cohn et al., 2016; Sebastian et al., 2016; Wallace et al., 2014). For example, one study in children with conduct problems reported a significant negative correlation between CU scores and amygdala grey matter (Cohn et al., 2016). Another study that split participants into groups with high versus low CU traits found that significantly reduced grey matter (in the OFC, ACC, amygdala, and insula) was unique to just the HCU group (Sebastian et al., 2016). In addition, much like in adult offenders, in incarcerated male adolescents, psychopathic traits have been negatively associated with limbic/paralimbic volumes (e.g. in the OFC, PCC, temporal pole, and parahippocampus; Ermer et al., 2013). However, Ermer and colleagues (2013) noted an inconsistency, whereby these incarcerated adolescents exhibited a *positive* correlation between medial PFC volume and psychopathic traits. The researchers suggest that this could represent an artifact of development given that some impulsive, deviant behaviors may peak in adolescence. Overall, the parallel structural findings from adult and child/adolescent studies provide compelling evidence that to at least some degree, psychopathy may be viewed as a neurodevelopmental disorder.

1.5.2. *Task-Based Functional Imaging*

Neuroimaging researchers have used a range of tasks to tap into the behavioral abnormalities seen in psychopathy, from emotion recognition paradigms, to moral dilemmas, to reward processing, to firsthand and vicarious experience of pain or distress. Not surprisingly, many of the limbic/paralimbic candidate regions identified in structural studies of psychopathy have either been used as regions of interest, or have also emerged in group contrasts or continuous analyses of psychopathic traits in these task-based fMRI studies (for reviews, see: Del Casale et al., 2015; Seara-Cardoso & Viding, 2015). A number of studies have displayed images of emotional faces, scenes, or words during scans to interrogate implicit or explicit brain responses to affective stimuli in psychopathic individuals. Compared to healthy controls, psychopathic adults have typically shown reduced activation to emotional stimuli in visual and limbic regions (e.g. fusiform gyrus, amygdala, ACC, and hippocampus/parahippocampus), suggesting that psychopathic adults attend to and process emotional information differently from their TD counterparts (Deeley et al., 2006; Kiehl et al., 2001; Mier et al., 2014; Müller et al., 2008b). Reinforcing this idea, two different research groups found that although criminal psychopaths did not differ from non-psychopathic participants in their performance on explicit emotion recognition and ToM tasks, they displayed reduced activation in the amygdala, fusiform gyrus, STS, and inferior frontal gyrus (IFG), and increased activation in the OFC, medial PFC, and TPJ relative to controls or non-psychopathic criminals during these tasks (Mier et al., 2014; Sommer et al., 2010). This supports the idea that psychopaths may employ different neural processing streams when computing affective information.

Other researchers who focused specifically on psychopathic neural responses related to empathy for pain (or lack thereof) have found that compared to healthy controls (Meffert et al., 2013) or to offenders with low levels of psychopathic traits (Decety et al., 2013a; 2013b),

psychopathic offenders display diminished neural responses the dorsal ACC, IFG, amygdala, and anterior insula when viewing images of others experiencing pain. However, when participants were instructed to imagine that body parts in the painful scenarios were their own, these same regions displayed higher activation in psychopathic offenders than in offenders with low levels of psychopathic traits (Decety et al., 2013b). Meffert et al. (2013) explicitly asked psychopathic offenders to empathize with the individuals in the images, and during this task, their neural responses became less divergent from those seen in the healthy control group. This offers compelling evidence that psychopathic offenders may be able to upregulate their empathic response if prompted.

During moral tasks, psychopathic inmates exhibit reduced activation in the medial PFC, angular gyri, PCC, and hippocampus, compared to healthy controls, despite responding normally during moral judgments (Pujol et al., 2012). In a community sample, psychopathic traits were negatively associated with responses in these same regions as well as the amygdala during moral dilemma tasks, but were also positively associated with activity in the dorsolateral PFC (Glenn et al., 2009a; 2009b). This may be indicative of a psychopathy-driven dependence on logical rather than affective neural systems in order to make moral judgments.

Results from task-based studies in children and adolescents with conduct problems and high levels of CU traits have been consistent with the adult literature, and are typically characterized by reduced neural responsiveness to others' emotions, particularly fear and distress. A large number of studies have reported blunted activation in the amygdala, ACC, insula, and medial PFC in children/adolescents with conduct problems and high levels of CU traits compared to TD controls while observing negative emotions versus neutral faces

(Ewbank et al., 2018; Finger et al., 2008; Jones et al., 2009; Marsh et al., 2008; Viding et al., 2012; White et al., 2012) or others experiencing pain (Cheng et al. 2012; Lockwood et al., 2013b; Marsh et al., 2013; Michalska et al., 2016; Yoder et al., 2016). Diminished responsiveness in the amygdala has also been observed in children with conduct problems and high levels of CU traits during moral evaluations or decisions (Marsh et al., 2011). Interestingly, a recent study found that among male youths with conduct disorder, levels of CU traits were positively associated with task-based connectivity between the amygdala and ACC while viewing angry versus neutral faces (Ewbank et al., 2018). This finding emphasizes the importance of investigating the potential role of altered functional organization in the overall picture of CU-trait related neurobiology.

There is some room for improvement with respect to task-based fMRI in psychopathic populations and in children at increased risk of developing psychopathy. For instance, the field would benefit from more explicit and consistent task parameters in order to ensure that in studies aiming to measure the same constructs are indeed getting participants to engage the same information processing systems. Consistency in task parameters would also help to control for inter-study variation in degree of task demands. In addition, many experimental paradigms suffer from a lack of validation and poor sensitivity to individual differences, as they were primarily designed to assess larger group differences. This may hinder studies' ability to use functional neuroimaging findings to reliably predict clinical outcomes across development (Viding & McCrory, 2020).

Despite these challenges, it is clear that structural and functional neuroimaging can still provide a wealth of information about the neurobiology social-cognitive disorders such as ASD and psychopathy. The following chapter will introduce resting-state fMRI, which is

another, more recent approach to neuroimaging, and will provide the methodological foundation for the subsequent empirical chapters in this thesis. After reviewing resting-state fMRI findings within these clinical populations, Chapter 2 will identify gaps in the resting-state literature of ASD and psychopathy and outline how the empirical chapters will address outstanding research questions that have been identified.

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CHAPTER 2

WHAT IS RESTING-STATE FMRI? WHY IS IT USEFUL?

2.1 Methodological Overview

Recent years have witnessed a shift towards a more connectivity-based approach to understanding the link between brain and behavior, and studies using resting-state fMRI have begun to proliferate. Unlike task-based fMRI, which operates on a stimulus-and-response type premise, resting-state fMRI records natural, baseline fluctuations in brain activity that occur in the absence of any explicit or implicit task. While tasks are helpful in trying to simulate specific information processing demands, similar to those that may occur in real life, the brain is does not simply 'turn off' when explicit task demands are removed. Therefore, equal attention should be given to the brain's activity at baseline. This resting-state activity serves as a blueprint of the brain's functional architecture in as naturalistic of a state as possible, and can provide a stable and reliable index of brain function (Elliott et al., 2020; Gratton et al., 2018). This blueprint may help us understand whether differences in functional neural design relates to clinical disorders, behavioral traits, or the predisposition to respond to stimuli in a certain way, thereby making resting-state fMRI a particularly useful tool for studying individual differences.

Like all fMRI scans, Resting-state data are also collected by recording time series of blood-oxygenation level dependent (BOLD) changes throughout the brain (Hillman, 2014). However, instead of convolving those changes with task-related events, resting-state time series are compared (correlated) with one another to determine the level of coherence or synchrony across spatially distinct parts of the brain. This can be done with straightforward

correlations, and the result is referred to as functional connectivity. The premise of functional connectivity has its roots in Hebbian learning and the reinforcement of circuits via consistent, synchronous neural firing (Biswal et al., 1995; Hebb, 1949; Hillman, 2015).

During resting-state scans, participants are typically asked to lie quietly and fixate on a visual cross, but in some studies involving young children, resting-state scans have also been collected during natural sleep (Shen et al., 2016). This scanning protocol is far less taxing than most experimental paradigms, which demand sustained attention and often require participants to respond across many trials.

Another advantage of resting-state fMRI is that is inherently free from any bias with respect to task performance. When studying group differences in brain activation, it can be challenging to design an experimental paradigm that elicits the desired response in both groups but is not confounded by task effects or a difference between experimental groups in their ability to perform the task. Of course at the behavioral level, significant group differences in task performance give us valuable information, but large behavioral differences also present problems for interpreting neuroimaging data (e.g. researchers struggle to ascertain whether brain differences are associated with the disorder itself, or simply with the clinical group's inability to perform the task). Task designs appropriate for clinical groups and compatible with the limitations of fMRI tend to therefore be rather simplistic and of questionable ecological validity. Especially in disorders like ASD where social cognition is so severely impaired, it would be most valuable to have naturalistic, interactive tasks, but these would be extremely difficult to orchestrate and analyze in a setting where any sort of movement can compromise the integrity of the data (Jo et al, 2013; Van Dijk et al., 2012). The analysis of some task-based studies has reinforced a counterproductive 'new phrenology'

(Uttal, 2001), by focusing on individual a-priori brain regions and treating them as isolated nodes independently responsible for their designated functionality. Of course, approaches like these often fail to capture the bigger, whole-brain picture. Perhaps most crucially, findings from a recent review and meta-analysis suggest that findings from task-based fMRI studies show surprisingly poor reliability, which seriously challenges the appropriateness of using this imaging methodology as a means of identifying clinical disease biomarkers (Elliott et al., 2020).

Resting-state fMRI goes far beyond simply addressing the issues associated with task-based studies, because it more accurately reflects and represents of the immense complexity and interconnectedness of the brain, and does so in a reliable way. Resting-state fMRI has already had a significant impact in the neuroscientific field, and has fundamentally changed the way we think about the human brain. For example, Buckner et al. (2009) applied clustering algorithms to resting-state data from typically developing (TD) adults to better understand how the brain is functionally organized. This study revealed a number of stable 'networks' with coherent timeseries, such as the default mode network, which is most active at rest while not engaged in any explicit task, and is related to spontaneous, self-reflective thought (Buckner et al., 2009; Shen et al., 2013; Yeo et al., 2011). While this coarse network structure of the brain is reliable across studies and across individuals, subtle individual differences in degrees of connectivity within or between networks have been linked to personality traits, intelligence, and psychiatric health (Dubois et al., 2018a; 2018b; Nostro et al., 2018; Rosazza & Minati, 2011). For this reason, resting-state is beginning to be regarded by some scientists as a sort of neural 'fingerprinting,' which can be used to predict a range of traits and features (Finn et al., 2015). Indeed, with the advent of increasingly sophisticated machine learning approaches to resting-state data, the potential for resting-state fMRI and the

individual level may be within reach. Researchers have already been able to predict general intelligence (Dubois et al., 2018b), language fluency (Sun et al., 2019), neuroticism, extraversion (Hsu et al., 2018; Pang et al., 2016) and openness (Dubois et al., 2018a) using resting-state functional connectivity alone. Furthermore, in clinical studies, resting-state data was helpful in sub-categorizing heterogeneous disorders such as depression and anxiety (Drysdale et al., 2017; Rabany et al., 2017; Tokuda et al., 2018), and has even been used to predict the effectiveness of some treatment approaches (Dichter et al.. 2015; Klumpp et al., 2014; Reggente et al., 2018).

2.2 Preprocessing of Resting-State fMRI Data

While resting-state functional connectivity has a number of advantages over task-based fMRI, it also presents certain challenges. In task-based fMRI, measurement artifacts – such as head motion – are less of a problem because the artifacts are often unrelated in their timing to the timing of the trials. Trial averaging within each task condition also allows noise cancellation across trials, with progressively more accurate estimations of the BOLD response as trial number increases. In resting-state fMRI, there is no such opportunity; any source of temporal variation, be it real or artifactual, will have an impact on the measured correlations. This means that various noise sources have to be estimated and removed through other techniques, such as regression (Fox et al., 2005) and independent components analysis (ICA) (Beckmann et al., 2009). Regression-based techniques are the most common, transparent, and easy to implement. Typically, one extracts signals from non-neural tissues (e.g. ventricles, white matter) that will contain nuisance physiological signals (e.g. head motion and pulsatile motion due to cardiac and respiratory cycles). Some approaches further acquire simultaneous cardiac and respiratory waveforms during the resting-state scans for use

in modeling these artifacts (Glover et al., 2000; Birn et al., 2008; Jo et al., 2010). These signals are then regressed against the measured timeseries in each brain voxel, and the residuals of the nuisance model are saved and used for analyses. ICA techniques typically involve a spatial decomposition of the voxel timeseries, with some components identified as artifact (e.g. head motion) based on their spatial distribution. Analyses are then performed on the putative "good" components. However, each of these techniques has only limited success in comprehensively removing all artifacts at the subject-level regression or ICA decomposition (Power et al., 2012; Power et al., 2018; Satterthwaite et al., 2017). For this reason, some groups have recommended adding covariates (e.g. mean framewise displacement), in group-level analyses to more fully remove/model artifacts, employing ANCOVA or linear mixed effects models rather than simple ANOVA models (Gotts et al., 2013; Saad et al., 2013; Yan et al., 2013a,b; see Gotts et al., 2020, for discussion).

2.3 Resting-State Imaging in ASD

Resting-state functional connectivity is becoming a popular methodological tool in investigations of clinical disorders, and has been especially illustrative in the context of ASD. In fact, many researchers now refer to ASD as a disorder of atypical brain organization and connectivity (Belmonte et al., 2004; Castelli et al., 2002; Gotts et al., 2012; Just et al., 2012; Picci et al., 2016). Indeed resting-state fMRI studies conducted in ASD populations across a range of age groups have consistently found such alterations, but their directionality and spatial characteristics have not been completely consistent. This inconsistency is unsurprising, given the degree of phenotypic heterogeneity seen in ASD, the limited representation of females with ASD or those with poor cognitive ability, and subtle variation in methodological approaches (Hull et al., 2017). Perhaps one of the most consistent findings

has been diffuse reductions in functional connectivity between brain regions related to socio-emotional processing, language, and sensorimotor function (Alaerts et al., 2014; Anderson et al., 2011; ; Cheng et al. 2015; Gotts et al. 2012, 2019; Jung et al., 2014; Lee et al., 2016; Picci et al. 2016; Ramot et al. 2017; von dem Hagen et al., 2013). Researchers have also noted that many of these regions are involved in the default mode network (Fox et al., 2005), and for this reason, some studies have focused specifically on nodes from this network (e.g. Assaf et al., 2010; Monk et al., 2009; Weng et al., 2010).

In a landmark study, Gotts et al. (2012) used a novel whole-brain data-driven approach and found that compared to healthy adults, those with high-functioning ASD displayed significantly reduced resting-state functional connectivity between a large number of cortical regions including the such as the STG, STS, PCC, TPJ, fusiform gyri, pre/postcentral gyri, amygdala, hippocampus, precuneus, medial and inferior frontal cortex, and cerebellum. Clustering analyses based on the physiological data sorted these regions into clusters that subserved social-affective, communicative, and motor functions (Gotts et al., 2012). Importantly, Gotts et al. (2012) also found a negative relationship between the degree of functional connectivity within and between these clusters and ASD symptom severity as measured by the Social Responsiveness Scale (SRS). Functional connectivity in many of these same regions has also been negatively associated with scores on other clinical measures of ASD such as the Autism Diagnostic Observational Schedule (ADOS) (Assaf et al., 2010; Weng et al., 2010). These significant brain-behavior correlations helped to solidify the idea that the social-communicative deficits seen in ASD are directly related to a breakdown in functional brain organization.

It appears that some of these ASD-related organizational brain changes may be present from a very early age, as studies of children with ASD have reported similar patterns of hypoconnectivity. For example, a study conducted in preschool-aged children with ASD symptomatology found reduced functional connectivity between the amygdala and a range of cortical areas similar to those implicated in adult studies, including the temporal lobes, medial prefrontal cortex, and striatum (Shen et al., 2016). Echoing the adult literature, Shen et al. (2016) also found a negative correlation between amygdala-temporal and amygdala-medial PFC functional connectivity and severity of ASD symptoms in these young children.

In addition to the cortico-cortical hypoconnectivity often reported in ASD, some researchers have also found increases in functional connectivity in children and adults with ASD—most commonly between subcortical structures (e.g. thalamus and striatum/basal ganglia) and many of the same aforementioned cortical areas (Cerliani et al. 2015; Cheng et al. 2015; Di Martino et al. 2011, 2014). Researchers have suggested that this pattern is indicative of maturational delays in the developing brain's functional organization (Di Martino et al., 2011).

Importantly, many of these resting-state studies of ASD were conducted using predominantly male samples without severe intellectual disability, thereby limiting the extensibility of any findings. In fact, there is now some evidence to suggest that combining male and female participants with ASD could result in suppressor effects, as diagnosis-by-sex interactions in patterns of ASD-related functional connectivity have been reported (Alaerts et al., 2016; Smith et al. 2019; See Chapter 3). Additionally, methodological advances have cast doubt on earlier studies that utilized less optimal means of head motion correction, and

that have limited or biased analyses with selective a-priori seed regions informed by the task-based literature (Gotts et al., 2019).

Resting-state fMRI may also have incredible potential for both diagnostic and therapeutic applications in ASD. For example, several groups of researchers have built algorithms using machine learning and resting-state functional connectivity data to differentiate between individuals with ASD and healthy controls with relatively high accuracy (Dvornek et al., 2018; Plitt et al 2015; Zhou et al., 2018). Emerson et al. (2017) tested the predictive validity of resting-state functional connectivity in infants as young as 6 months, and determined that presymptomatic brain data from these infants was highly predictive (96% accuracy) of developing ASD symptoms by 24 months. This again underscores the notion that ASD is indeed a disorder of altered functional connectivity and demonstrates the utility of resting-state imaging as both an investigatory tool and potentially also as a means of early risk detection. However, resting-state as a diagnostic tool is still in its early stages, and ideally this method would be able to identify subtle differences among ASD brains, and reveal the various endophenotypes responsible for the disorder's heterogeneous symptomatology.

Because the aberrant functional connectivity seen in ASD has been directly correlated with symptom severity (Gotts et al., 2012), new treatment approaches are being geared towards a rewiring of the affected networks. Treatment approaches are now being researchers have begun to resting-state fMRI as a potential treatment approach with real-time neurofeedback (Ramot et al., 2017). Neurofeedback often involves a real-time feed of neural activation and participants are instructed to up- or down-regulate that activation in order to explicitly 'train' the brain. This can also be done passively using another task or game as a

surrogate. In ASD, neurofeedback has already yielded some promising findings (Ramot et al., 2017). In a recent clinical trial, Ramot and colleagues (2017) performed neurofeedback in a small group of boys with ASD who saw an obscured image and were instructed to try to reveal the image with their minds. The visibility of the image was determined by the strength of coherence among several nodes in the 'social brain' network that are typically underconnected in ASD. This attempt to train the rewiring of that network had significant effects, which persisted beyond the initial trial (Ramot et al., 2017). However, given that the sample consisted only of males, it is unclear whether this type of intervention would be appropriate or effective for females with ASD. Longer term training protocols, inclusion of female participants, additional follow-up scans, and evaluation of symptomatic improvement are all needed to determine the therapeutic efficacy of neurofeedback in ASD.

2.4 Resting-State Imaging in Psychopathy

Resting-state fMRI has also shed light on the relationship between functional brain organization and psychopathy. Studies have found a complex and somewhat inconsistent pattern of both increases and decreases in functional connectivity associated with high levels of psychopathic traits. For example, in a study comparing psychopathic and non-psychopathic criminals, researchers reported reduced functional connectivity between the amygdala and ventromedial PFC as well as between the ventromedial PFC and the PCC and precuneus in the psychopathic criminals (Motzkin et al., 2011). Another study in criminal offenders found that hypoconnectivity among the precuneus, insula, ACC, and lateral parietal cortex was associated with psychopathic traits (Philippi et al., 2015).

However in contrast, other researchers have found the opposite pattern of predominantly increased rather than reduced functional connectivity. In youth arrestees, high levels of CU traits were associated with hyperconnectivity in the PFC (Cohn et al., 2015). Leutgeb and colleagues (2016) found a similar pattern in violent adult offenders, whereby high levels of psychopathic traits were linked to increased prefrontal connectivity as well as hyperconnectivity between the amygdala and cerebellum (Leutgeb et al., 2016).

Reward-processing regions such as the striatum have also been implicated in studies of psychopathy, in addition to the aforementioned prefrontal, limbic/paralimbic, and lateral parietal regions (Korponay et al., 2017). More specifically, within-striatum functional connectivity was found to be positively associated with psychopathic traits in criminal offenders, as was functional connectivity between the striatum and PFC, but negative associations were reported between the striatum and parietal cortex (Korponay et al. 2017). Perhaps capturing a broader and more complex picture of the functional connectivity changes seen in psychopathy, Espinoza and colleagues (2019) found a relationship between psychopathic traits and *both* increases and decreases in functional connectivity throughout 7 different larger-scale resting-state networks.

Thus, while the nature of the changes in functional organization is not entirely clear, it does appear that the degree of coupling between a number of limbic/paralimbic and reward-processing regions is altered in psychopathy. These baseline changes may impact the integrity of affective information processing streams, which may in turn contribute to psychopathic trait symptomatology. Further clarification on the nature of these changes would be helpful, however given their propensity for violence and criminality, it is difficult

to study psychopathic individuals outside of prison populations, and therefore a challenge to compare with healthy adults.

Resting-state research is still nascent in child/adolescent samples who are at heightened risk developing psychopathy, and additional studies are needed in these populations. To date, only a small handful of peer-reviewed studies have used resting-state fMRI to explore the functional connectivity correlates of conduct problems (CP) and high levels of CU traits, and each with notable limitations. One study found relatively diffuse increases in functional connectivity, both within and between networks, in children with CP compared to TD boys (Pu et al., 2017). However, given that CU trait levels within the CP sample were relatively low (only 3 participants scored >20), and that CU scores in the control group were higher than expected, this study was inconclusive with respect to differentiating between CP with and without high levels of CU traits (Pu et al., 2017). A second study found increased functional connectivity within the anterior default mode network associated with CU traits, but the sample consisted of youths who had been arrested, and there was no comparison with TD youths (Cohn et al., 2015). A recent study by Werhahn and colleagues (2020), found hyperconnectivity a range of regions including the insula, ACC, posterior cingulate (PCC), precuneus, medial PFC, paracentral lobules, angular gyrus, and cerebellum in children and adolescents with disruptive behavior disorders and high levels of CU traits. However, Werhahn et al's (2020) a-priori selection of regions of interest limits the potential for findings unrelated to those seed regions.

Though the literature is extremely sparse, the directionality of the resting-state findings in children and adolescents with CP and high levels of CU traits appears to be more directionally consistent than that of adults. It is possible that the inconsistencies observed in

these network dynamics are a product of developmental changes. Further resting-state research with longitudinal designs would help to clarify this. Spatially, there appears to be good agreement across the adult psychopathy literature and that of children/adolescents at risk for psychopathy. There are far fewer published resting-state studies of children with CP and varying levels of CU traits than there are studies of children with ASD. Study replications and investigations in larger samples are warranted to bolster the literature base for CP and risk for persistent antisocial behaviors.

2.5 Review of Gaps in the Literature and Outstanding Research Questions

2.5.1. *Females with ASD and The Elusive Cerebellum*

Within the resting-state imaging literature on ASD, perhaps the greatest shortcoming is the dearth of data on females. This scarcity is understandable given the disorder's male-to-female sex ratio in terms of prevalence (4:1). Although females with ASD have garnered neuroimaging attention in recent years, a majority of the existing resting-state literature has used the same banks of neuroimaging data, thereby limiting the replicability of novel findings. One recent resting-state study reported a diagnosis-by-sex interaction between the left cerebellar vermis VIII, and the right precuneus and left inferior frontal gyrus, whereby females with displayed hyperconnectivity and males displayed hypoconnectivity (Aleaerts et al., 2016). This study also reported increased functional connectivity in females with ASD compared to controls between the a seed in the left STS and the cerebellum, but there was no substantive discussion of this finding (Alaerts et al., 2016).

The role of the cerebellum in ASD is another line of inquiry that is ripe for further investigation, and may be especially relevant in the context of sex differences. For example, studies have suggested that levels of sex steroid hormones may imapct neural growth in the cerebellum during development (Biamonte et al., 2009; Dean & McCarthy, 2008; Menashe et al., 2013; Willsey et al., 2013; Wang et al., 2014), and the local expression of ASD candidate genes may compound this interaction (Koibuchi & Ikeda, 2013). A number of resting-state fMRI studies of ASD have published cerebellar findings, but these results are not consistent and are rarely discussed, as the focus tends to lie more on robust cortical differences. Chapter 3 will explore this relationship between sex, cerebellum, and ASD in greater depth, and will use resting-state fMRI to investigate potential interactions.

2.5.2. *Functional connectivity related to psychopathic and ASD trait dimensions*

Researchers believe that many traits, including Psychopathic and ASD traits, exist along a dimensional spectrum with a normal distribution of individual variation, and clinical syndromes at the extreme end (Constantino & Todd 2003;Levenson et al. 1995; Hare & Neumann 2005; Walton et al. 2008; Wallace et al. 2012). Both psychopathic and ASD traits can indeed be found to varying degrees in TD populations, and this provides evidence for a continuous, quantitative model of phenotypic variation in each of these trait domains (Frick et al. 2000; Constantino et al. 2004; Edens et al. 2006; Murrie et al. 2007; Neumann & Hare 2008; Ronald & Hoekstra 2011; Skuse et al. 2005).

Given that both clinical syndromes have been associated with significant alterations in functional connectivity, it would be interesting to determine whether any of these differences can be seen—to some extent—sub-clinically, based on varying levels of psychopathic and

ASD traits in healthy individuals. It would also be interesting to directly compare the resting-state functional correlates associated with each trait domain, as there has been some spatial overlap in regions implicated in the clinical disorders, but little is known about these associations in community samples. To date, no large-scale studies have explored the link between resting-state functional connectivity and individual differences in psychopathic and ASD traits, nor have they directly compared resting-state correlates associated with each trait domain. Chapter 4 will follow this line of inquiry and investigate the relationship between functional brain organization and individual variation in psychopathic and ASD traits in a large (n=924) community sample.

2.5.3. *Resting-State Correlates of Risk for Psychopathy*

While many studies have found structural abnormalities in children/adolescents with conduct problems and CU (or psychopathic) traits (Rogers & De Brito, 2016), to date very few have examined abnormalities in resting-state functional connectivity in these at-risk children. There is a substantial amount of evidence pointing to aberrant patterns of resting-state functional connectivity, particularly in limbic/paralimbic brain regions in psychopathic adults (Espinoza et al., 2019). There is also some spatial overlap between structural differences observed in at-risk children, and brain areas implicated in resting-state studies of psychopathic adults.

It would assist researchers and clinicians alike to better understand the full extent of any neurobiological changes associated with developmental risk for psychopathy, including those present before late adolescence/early adulthood. Once we have a more firm grasp on the functional neural correlates of psychopathy risk, perhaps resting-state imaging could

serve as another tool for guiding differentiated treatment, including possible neurofeedback options. Additional research is therefore needed to determine whether any changes in functional organization can be seen in children with behavioral problems and high levels of CU traits. Chapter 5 of this thesis will focus on comparing resting-state functional connectivity in at-risk children and adolescents with that of TD peers. Then, Chapter 6 will consider the findings from Chapters 4 and 5, and will formally (spatially and quantitatively) compare the resting-state functional connectivity findings related to psychopathic traits in healthy young adults and those found to differ between boys with CP and high levels of CU traits and their TD peers.

2.6 Resting-State Summary

Resting-state fMRI is proving to be a valuable tool with multiple applications, from etiological investigation, to diagnostic assessment, to therapeutic intervention, but the field is still relatively nascent, with significant gaps in the current knowledge base on both ASD and psychopathy (or risk thereof), as well as their respective trait dimensions. Resting-state data can shed light on individual differences in healthy populations as well as inform our understanding of atypical network connectivity seen in clinical disorders such as ASD and psychopathy, and in individuals who are at a developmental risk trajectory with respect to these conditions.

2.7 Summary of Thesis Aims

The current thesis therefore provide substantive extension of the existing literature on functional neural connectivity in ASD by addressing these aforementioned gaps and

answering the following research questions: How do the resting-state profiles of males and females with ASD differ, and do these differences provide clues as to the disorder's etiology? Does the cerebellum play a role in these sex differences? What can resting state-profiles in the general population tell us about individual differences in psychopathic and ASD traits? Does functional organization differ earlier in development in children and adolescents with conduct problems and CU traits (who are at risk for developing psychopathy)? How similar are the resting-state profiles of these at-risk children and healthy young adults who simply have higher levels of psychopathic traits?

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CHAPTER 3

SEX DIFFERENCES IN RESTING-STATE FUNCTIONAL CONNECTIVITY IN ASD

This section is presented as an accepted journal article and is a copy of the author accepted version of the following publication:

Smith, R. E. W., Avery, J. A., Wallace, G. L., Kenworthy, L., Gotts, S. J., & Martin, A. (2019). Sex differences in resting-state functional connectivity of the cerebellum in autism spectrum disorder. *Frontiers in Human Neuroscience, 13,* Article 104. http://dx.doi.org/10.3389/fnhum.2019.00104

Supplementary material that is referenced in this chapter will appear in:
Appendix 1 (Age Histograms by Group)
Appendix 2 (Evaluating Noise Bias in Seed Voxel Selection)

Abstract

Autism Spectrum Disorder (ASD) is more prevalent in males than females, but the underlying neurobiology of this sex bias remains unclear. Given its involvement in ASD, its role in sensorimotor, cognitive, and socio-affective processes, and its developmental sensitivity to sex hormones, the cerebellum is a candidate for understanding this sex difference. The current study used resting-state functional magnetic resonance imaging (fMRI) to investigate sex-dependent differences in cortico-cerebellar organization in ASD. We collected resting-state fMRI scans from 47 females (23 ASD, 24 controls) and 120 males (56 ASD, 65 controls). Using a measure of global functional connectivity, we ran a linear

mixed effects analysis to determine whether there was a sex-by-diagnosis interaction in resting-state functional connectivity. Subsequent seed-based analyses from the resulting clusters were run to clarify the global connectivity effects. Two clusters in the bilateral cerebellum exhibited a diagnosis-by-sex interaction in global connectivity. These cerebellar clusters further showed a pattern of interaction with regions in the cortex, including bilateral fusiform, middle occipital, middle frontal, and precentral gyri, cingulate cortex, and precuneus. Post-hoc tests revealed a pattern of cortico-cerebellar *hyperconnectivity* in ASD females and a pattern of *hypoconnectivity* in ASD males. Furthermore, cortico-cerebellar functional connectivity in females more closely resembled that of control males than that of control females. These results shed light on the sex-specific pathophysiology of ASD, and are indicative of potentially divergent neurodevelopmental trajectories for each sex. This sex-dependent, aberrant cerebellar connectivity in ASD might also underlie some of the motor and/or socio-affective difficulties experienced by members of this population, but the symptomatic correlate(s) of these brain findings remain unknown.

3.1 Introduction

Autism spectrum disorder (ASD) is a heterogeneous, neurodevelopmental condition characterized by social-communicative impairments and restricted/repetitive or stereotyped behaviors (American Psychiatric Association, 2013). Diagnostic symptomatology can be reliably detected as early as 24 months (Daniels and Mandell, 2014), which suggests that etiological factors may be present very early in development. Epidemiologically, ASD also has a strong male preponderance, with only 1 female diagnosed for every 3 to 4 males (Centers for Disease Control and Prevention, 2017; Lai et al., 2015a). This uneven sex ratio has resulted in decades of ASD research that focuses almost exclusively on males, thereby

limiting the generalizability of published findings, and leaving females with this disorder underrepresented and poorly understood. However, recent years have witnessed an uptick in the number of clinical and preclinical studies probing the male bias in ASD's prevalence, and speculating about how it might be related to different neurobiological factors (Lai et al., 2015a, 2017), as well as numerous cultural and diagnostic biases (Dworzynski et al., 2012; Lai et al., 2015b).

Researchers have developed two theoretical biological hypotheses to explain the male prevalence in ASD diagnoses (Lai et al., 2015a, 2017). First, certain neurodevelopmental mechanisms may put males at a heightened risk for being diagnosed with ASD. Second, other mechanisms may play a protective role for females, thereby putting them at a comparatively lower risk (Robinson et al., 2013, or for review see Lai et al., 2015a, 2017; McCarthy and Wright 2017).

A substantial amount of research has accumulated, illustrating the heritability of ASD, highlighting a large number of candidate genes, and unraveling aberrant patterns of neural organization associated with this disorder, but mechanisms responsible for ASD's male preponderance remain poorly understood (McCarthy and Wright 2017; Taniai et al., 2008). Some studies have found ASD's heritability to be stronger in females than in males, and that females appear to require a larger number of genetic mutations or related polymorphisms to be present before they reach the threshold for an ASD phenotype (Jacquemont et al., 2014; Robinson et al., 2013). This increased genetic burden could be interpreted as evidence for a female protective effect in action (Lai et al., 2017; McCarthy and Wright 2017). However, males' vulnerability for developing ASD cannot be explained by any individual genetic risk factors or neurogenetic conditions such as fragile X syndrome, and there is a lack of a

conclusive sex bias in any of the implicated candidate genes (Hampson and Blatt 2015; Iossifov et al., 2014; Sanders et al., 2015). If individual genes and rare neurogenetic syndromes cannot successfully explain the heightened risk for ASD in males, what other neurodevelopmental mechanisms might help to account for the disorder's male-biased prevalence?

3.1.1 *The Cerebellum as a Candidate Region for Sex Differences in ASD*

While the answer to this question remains equivocal, some researchers are turning their empirical attention toward the cerebellum for several reasons (Dean and McCarthy 2008; Hampson and Blatt 2015; Lai et al., 2017). First, abnormalities in cerebellar histology, structure, and function have all been associated with ASD, as well as with other neurodevelopmental disorders whose prevalence or age of onset are determined by biological sex (e.g. attention-deficit hyperactivity disorder, or ADHD, schizophrenia, and dyslexia) (Courchesne et al., 1988; McCarthy and Wright 2017; Nguon et al., 2005). In fact, cerebellar pathology carries the highest risk ratio for ASD of any single, non-heritable factor (Wang et al., 2014). Postmortem and magnetic resonance imaging (MRI) studies of ASD have noted a reduction in Purkinje and granular cells, volumetric changes, and abnormal task-based activation patterns in this region (Bloss and Courchesne 2007; Hampson and Blatt 2015; Nguon et al., 2005). In addition, congenital or acquired cerebellar injury often results in cognitive and affective deficits similar to those seen in ASD (Hampson and Blatt 2015; Schmahmann 2010).

Another motivating factor for investigating the cerebellum in the context of sex differences in ASD is the simultaneous co-expression of ASD candidate genes and rising

gonadal steroids that promote neural growth (Koibuchi and Ikeda 2013) in this same region during development (Menache et al., 2013; Wang et al., 2014; Willsey et al., 2013). Studies conducted using selectively bred mice have suggested that sex steroids mediate cerebellar neurodegeneration, and also that estrogens may have a protective effect on localized neural development (Biamonte et al., 2009; Dean and McCarthy 2008). Human studies have also established a link between androgen levels in utero and ASD diagnoses, and have also noted endocrine abnormalities in people with this disorder (Baron-Cohen et al, 2015; Bejerot et al., 2012; Ingudomnukul et al., 2007; McCarthy and Wright 2017). Therefore, the coincidence of gene expression and sex-dependent fluctuations in gonadal steroids could be one mechanism by which early steroidogenic dysregulation can lead to ASD symptomatology.

Recent mapping of the cerebellum's functional organization has provided a rough framework for how these early chemical deviations can precipitate later widespread changes in cortical organization seen in this disorder (see Mash et al., 2017; Picci et al, 2016) for recent reviews of neuroimaging findings in ASD). Indeed, resting-statefunctional MRI (fMRI) has allowed researchers to spatially map functional connections across the cerebellum by measuring their baseline coherence with other parts of the cortex (Buckner et al., 2011). This has demonstrated that different subdivisions of the cerebellum are functionally connected to a range of cortical areas whose functions include: socio-affective processing (Baumann et al., 2015; Buckner 2013; Buckner et al., 2011), executive function, theory of mind, language, auditory discrimination (Baumann and Mattingley, 2010), visuospatial processing including biological motion (Baumann et al., 2015), and of course, somatomotor functions (Buckner et al., 2011; Wang et al., 2014). Individuals with ASD experience deficits in many, or all, of these behavioral domains, and sex-dependent alterations in cerebellar-cortical network dynamics could be partially responsible.

Researchers have used functional and microstructural data to explain the relationship between cerebellar development and the extensive cortical changes associated with ASD (D'Mello and Stoodley 2015; Wang et al., 2014). A popular theory is that injury to the cerebellum, either congenital or acquired via sex-dependent hormonal or environmental factors, interrupts closed-loop cerebellar-cortical circuits while the brain's functional architecture is still fragile. With compromised structural integrity, the cerebellum acts "upstream" (Wang et al., 2014) to reshape the brain's functional organization, and this ultimately leads to the "downstream" cortical and behavioral abnormalities seen in ASD (Olivito et al., 2017). Although studies are inconsistent with respect to directionality, there do appear to be sustained changes in cerebellar-cortical functional connectivity in ASD (Noonan et al., 2009; Olivito et al., 2017; Khan et al., 2015), but whether these changes manifest differently in ASD males and ASD females remains unknown.

There is limited functional neuroimaging data on females with ASD, and studies exploring how sex mediates resting-state functional connectivity between the cerebellum and the cortex are even more rare. Neuroimaging studies of ASD have reported findings in the cerebellum (Hull et al., 2016), but these results are inconsistent, often overshadowed by robust cortical differences, and exclusively representative of ASD males. In one study with a predominantly male sample, the cerebellum exhibited a pattern of reduced functional connectivity in ASD compared to controls, much like the connectivity reductions seen in social brain areas (Gotts et al., 2012). However, two other male-biased studies found the opposite pattern of increased cerebro-cerebellar functional connectivity, as well as atypical lateralization and "non-canonical" organization (Khan et al., 2015; Noonan et al., 2009).

One recent resting-state study reported increased functional connectivity between the cerebellum and a seed in the left superior temporal sulcus in females with ASD, compared to controls, but there was no subsequent discussion of this finding (Alaerts et al., 2016). The same study also reported diagnosis-by-sex interactions between the left cerebellar vermis VIII, and the right precuneus and left inferior frontal gyrus, whereby in ASD, females displayed increased functional connectivity and males showed decreased functional connectivity. While this specific finding was also not discussed, the authors concluded that connectivity profiles in females with ASD were consistent with "neural masculinization," or a shift towards the organizational patterns seen in healthy males, whereas males with ASD displayed a "neural feminization" or FC more similar to healthy females, also referred to as "gender incoherence" (Alaerts et al., 2016; see also Bejerot et al., 2012; Baron-Cohen, 2002 and Floris et al., 2018). These findings were inconsistent with the extant "extreme male brain" theory of ASD (Baron-Cohen 2002).

3.2 Aim of Study

The goal of the current study was to examine differences in cerebellar-cortical organization in males and females with ASD, by identifying areas that exhibit a diagnosis-by-sex interaction in their patterns of resting-state functional connectivity. However, given the paucity of information about the similarity of ASD male and female patterns of altered brain dynamics, we employed a data-driven, whole-brain approach to the analyses, permitting us to identify results outside of the cerebellum, if they were to exist.

3.3 Methods and Materials

3.3.1 *Participants*

Participants included 88 (24 female, 65 male) typically developing (TD) Individuals (mean age 21.51 ±7.54; age range 10-54), and 79 (23 female, 56 male) individuals diagnosed with ASD (mean age 21.63 ±10.79; age range 11-62) (see Table 1 for a summary of participant demographic information). While these age ranges appear extremely broad, they were matched across all experimental groups, and most participants in all groups ranged between 10 and 25 years of age (see Supplementary Figure for age histograms by group). Exclusion criteria included the presence of any neurogenetic disorders such as fragile X syndrome, congenital or traumatic brain injuries, full-scale intelligence quotient (FSIQ) scores below 80, and psychiatric disorders in the TD group. All ASD participants met DSM-5 diagnostic criteria for ASD as assessed by an experienced clinician. Additionally, all participants with ASD met diagnostic criteria for 'broader ASD' according to guidelines established by the National Institute of Child Health and Human Development/ National Institute on Deafness and Other Communication Disorders Collaborative Programs for Excellence in Autism (Lainhart et al., 2006), and based on scores from either the Autism Diagnostic Interview (ADI or ADI-R) (Le Couteur et al., 1989; Lord et al., 1994), or the Autism Diagnostic Observation Schedule (ADOS or ADOS-2) (Lord et al., 2000) administered by research-reliable clinicians.

Table 1. Participant Demographic Characteristics

	ASD Females (n=23)	ASD Males (n=56)	TD Females (n=24)	TD Males (n=65)	*P* value
Age (years)	21.84(13.94)	21.63(9.27)	21.80(10.30)	21.41(6.33)	$p = 0.1586$[i]
Head Motion[a]	0.072(.059)	0.073(.063)	0.067(.034)	0.069(.035)	$p = 0.9465$[i]
FSIQ	114.38(16.43)	109.62(16.13)	113.29(12.64)	116.32(11.18)	$p = 0.1324$[i]
Social Responsiveness Scale (sum)	96.90(26.68)[b]	88.30(31.17)[c]			$p = 0.3314$[j]
ADI Social	17.46(4.98)[d]	21.30(4.32)[e]			$p < 0.0505$[j]
ADI Verbal Communication	13.46(4.37)[d]	16.02(4.37)[e]			$p < 0.0494$[j]
ADI Restricted / Repetitive Behaviors	5.00(2.35)[d]	5.47(2.62)[e]			$p = 0.9337$[j]
ADOS Social + Communication	9.56(2.18)[f]	12.31(3.25)[g]			$p < 0.0106$[j]
ADOS Stereotyped Behaviors	1.39(1.14)[f]	1.47(1.47)[g]			$p = 0.6236$[j]
ADOS-2 Social Affect	12.25(5.50)[h]				
ADOS-2 Restricted / Repetitive Behavior	3.5(0.58)[h]				

Table 1: Participant Demographic Characteristics
FSIQ = full-scale intelligence quotient (Standard Score)
Data are mean (standard deviation) [a]: Motion is measured via frame-wise displacement in mm/TR. [b]: n = 20 [c]: n = 53 [d]: n = 16 [e]: n = 50 [f]: n = 18 [g]: n = 55 [h]: n = 3 [i]: Kruskal-Wallis Test [j]: Wilcoxon Rank Sum Test

The current study was approved by the NIMH Institutional Review Board, and informed consent and assent were obtained from all participants and/or their parent/guardian. Participants completed measures of FSIQ, using either the Wechsler Abbreviated Scale of Intelligence, the Wechsler Abbreviated Scale of Intelligence-II, the Wechsler Intelligence

Scale for Children-IV, or the Wechsler Intelligence Scale for Children-V. Due to the exclusion criteria mentioned above, the current study only examined cases of ASD where IQ scores were average or above average, which helped to maintain comparability of FSIQ across the ASD and TD groups.

3.4.2 *Imaging Acquisition*

Structural and Functional MRI data were acquired using a GE Signa 3 T whole-body MRI scanner at the NIH Clinical Center NMR Research Facility. During all scans, a GE 8-channel receive-only head coil was used, with an acceleration (SENSE) factor of 2. First, T1-weighted anatomical images (MPRAGE) were collected for each participant (124 axial slices, 1.2 mm slice thickness, field of view = 24 cm, 224 224 acquisition matrix), followed by resting-state scans, which measure slow, spontaneous, blood-oxygenation-level-dependent (BOLD) fluctuations. Participants were instructed to lie quietly and fix their gaze on a central cross. Each gradient-echo echo-planar rest scan lasted 8 minutes and 10 seconds (140 consecutive volumes with whole-brain coverage, repetition time = 3500 ms, echo time = 27 ms, 90 degree flip angle, 42 axial contiguous interleaved slices per volume, 3.0 mm slice thickness, 22 cm field of view, 128 x 128 acquisition matrix, 1.7 mm x 1.7 mm x 3.0 mm voxel size). Cardiac and respiratory signals were recorded during the resting-state scan for later regression during image preprocessing.

3.4.3 *fMRI Preprocessing*

Echo-planar images (EPIs) were preprocessed using the Analysis of Functional NeuroImages (AFNI) software package (Cox 1996). The first 3 EPI volumes were removed

from the scan, after which AFNI's 3dDespike was applied in order to attenuate any extreme deviations in the voxelwise signals. The remaining EPI volumes were then slice-time corrected (to slice-time 0) and co-registered with their respective anatomical scans (MPRAGEs). Scans were blurred using a 6mm isotropic full-width at half-maximum Gaussian kernel and rescaled to percent signal change by normalizing to each voxel's mean BOLD signal intensity. Finally, in preparation for statistical group comparisons, all scans were resampled to 3.0 mm^3 voxels, and transformed into standard Talairach-Tournoux (1988) space.

AFNI's ANATICOR protocol was used to regress nuisance artifacts from the EPI data (Jo et al., 2010; 2013; see also Berman et al., 2016; Gotts et al., 2012). This process began by segmenting the MPRAGE scans, which was done using FreeSurfer (Fischl et al., 2002). Masks were then made for ventricles and white matter, resampled to the EPI resolution, and eroded by 1 voxel to prevent partial volume effects with the grey matter. Before smoothing, a single average nuisance time series for the ventricles was calculated using the EPI data, along with a localized average of white matter, centered on each voxel and averaged within a 15mm-radius sphere. Including a localized average white matter signal has been shown to reduce the dependence of functional connectivity on transient motion, as reflected in motion-censoring analyses (e.g. Jo et al., 2013). Using the respiration and cardiac data collected during the scan, respiration volume per time (RVT) (Birn et al., 2009) and Retroicor (Glover et al., 2000) regressors were generated. Before least-squares model fitting to every voxel's time series, nuisance variables were detrended with fourth-order polynomials. The full nuisance regression model therefore contained 1 localized white matter time series, 1 average ventricle time series, 6 motion parameters, 8 Retroicor time series (4 cardiac, 4 respiration), 5 RVT time series, along with a 4th-order polynomial

baseline model. Residual time series were generated by subtracting the best fit time series of this nuisance model from the full, volume-registered time series.

3.4.4 *fMRI Analyses*

All analyses were performed using AFNI (Cox et al., 1996) and MATLAB. First, mean "connectedness" was calculated (Pearson's r) at every grey matter voxel for each participant (e.g Cole et al., 2010; Gotts et al., 2012; Salomon et al., 2011). This technique assigns each voxel a single value representing the mean of all correlations between that voxel and the rest of the voxels in the grey matter brain mask. Using Fisher-z transformed subject-level whole-brain connectedness-maps, a 2 x 2 linear mixed effects analysis (AFNI's 3dLME) was run in order to identify any regions showing a diagnosis-by-sex interaction, by specifying the following model: (ASD males – ASD Females) x (TD males – TD females). Age, motion (AFNI's @1dDiffMag, comparable to mean frame-wise displacement in units of mm/TR), and global correlation level (GCOR) (Saad et al., 2013) were all included in the model as nuisance covariates. Small volume correction was performed for the cerebellum using AFNI's 3dClustSim with empirical autocorrelation function (ACF) parameters using cluster size (Cox et al., 2017). The cerebellum mask used for this correction was comprised of only those voxels that contained full EPI data in at least 85 percent of the participants in all groups.

To elucidate the initial connectedness findings, surviving clusters from the first linear mixed effects analysis were then used as seed regions for subsequent analyses by creating a 6mm radius sphere around their peak coordinates (see Berman et al., 2016; Gotts et al., 2012; Stoddard et al., 2016 for further discussion). Mean time series within the spherical masks

were extracted from the cleaned residual time series for every subject. These average time series were then correlated with the rest of the voxels in a whole-brain mask. An additional 2 x 2 linear mixed effects analysis was run for each cerebellar seed on the resulting seed-based correlation maps, to determine which other cortical or subcortical regions might be driving the interaction effect found in the primary analysis of connectedness. This approach is analogous to post-hoc testing following the detection of a significant main effect in an ANOVA, as the locations driving connectedness effects remain unclear without further seed testing. The seed tests were corrected for multiple comparisons using cluster size within a whole-brain mask (Cox et al., 2017), with the adjustment that the maps were corrected to P<.05 divided by the number of seed tests being performed (Bonferroni), thereby adjusting for whole-brain voxel-wise tests and the number of seed tests at the same time (see Gotts et al., 2012 for further discussion). The seed tests were also evaluated for any noise bias in the voxel selection using a leave-one-out cross validation approach (see Supplementary Materials).

Lastly, pairwise correlations were calculated among all possible region-to-region pairs for three contrasts: ASD - TD within each sex, and diagnosis-by-sex. To do this, masks were created for the 13 regions that survived correction, and average time series were extracted for each. With 2 cells for the cerebellar seeds included, the 15x15 correlation matrices were thresholded below false discovery rate (FDR)-corrected levels (P<.0069 for q<.05). For the within-sex correlation matrices, p-values only within those region-to-region combinations that exhibited an FDR-corrected diagnosis-by-sex interaction were considered.

To investigate the extent to which the data support prevailing theories of either "gender incoherence" (Alaerts et al., 2016; Bejerot et al. 2012) or extreme masculinization

(Baron-Cohen, 2002; Baron-Cohen et al, 2015) of the brain in ASD, two different measures were applied to the set of region-to-region pairs exhibiting a significant diagnosis-by-sex interaction: 1) Pearson correlation of each individual ASD participant with the mean pattern of TD males and females, and 2) the Euclidean distance between each ASD participant with the mean pattern of TD males and females. The correlation measure differs mainly from the Euclidean distance measure in that the mean region-by-region functional connectivity values were removed, evaluating only the pattern similarity rather than the mean differences that helped to define the diagnosis-by-sex interactions in each region-by-region combination. Correlations and Euclidean distances from TD males and females were compared by paired *t-tests* after checking for normality.

3.4 Results

Matching across the experimental groups on nuisance variables was evaluated with the Kruskal-Wallis Test. Results indicated that the four groups were indeed adequately matched on age, head motion, and IQ (p=0.1586, p=0.9465, and p=0.1324, respectively; See Table 1). When comparing ADOS and ADI subscale scores between males and females with Wilcoxon Rank Sum tests (also in Table 1), some modest significant differences emerged, most notably in the Social + Communication subscale of the ADOS (p<0.0106). In this case, ASD males appeared to have more severe deficits in this category than ASD females, although both groups exhibited impairment. However, these differences were not observed in the scores on the Social Responsiveness Scale (SRS), which is designed to be a more cardinal measure for use in correlational and other behavioral analyses.

In the primary analysis of global connectedness, significant diagnosis-by-sex effects were initially found in 4 clusters (voxel-wise threshold of $p < .005$, uncorrected): two in the

bilateral cerebellum (left crus II and right lobule VIIIA/B, just lateral to the vermis), and two in the bilateral superior temporal gyri. While none of these clusters survived whole-brain cluster-size correction, after small volume correction for the cerebellum, both left and right cerebellar clusters survived (corrected to $p < .05$) (Figure 1). To establish the direction of the interaction, average time courses were extracted for each cerebellar cluster. Both clusters exhibited a similar crossover interaction pattern of mean connectedness with the rest of the cortex, whereby males with ASD displayed significantly *reduced* functional connectivity compared to their TD male counterparts, and females with ASD displayed significantly *increased* connectivity compared to TD females (Figure 2). Subsequent seed-based analyses were only performed on the two significant cerebellar clusters.

Figure 1. Cerebellar Clusters Exhibiting a Diagnosis-by-Sex Interaction

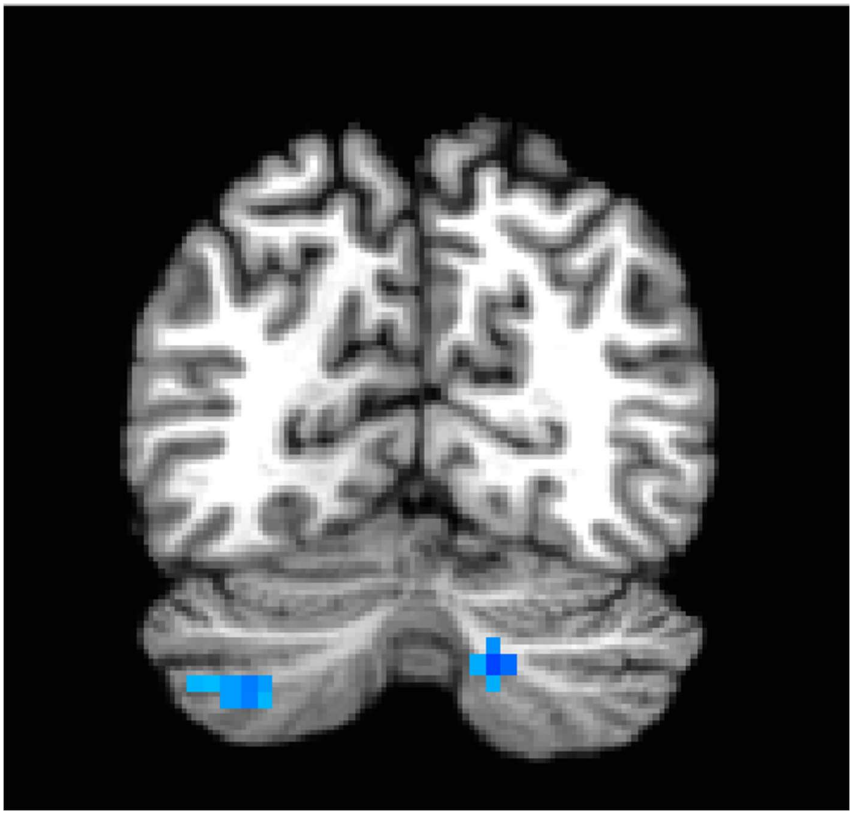

Figure 1. Cerebellar Clusters Exhibiting a Diagnosis-by-Sex Interaction
Shown in standard Talairach Tournoux space. Left is shown on the left. Mode contrast= (ASD males – ASD Females) x (TD males – TD females). Clusters shown were significant at $p<.05$ with small volume correction for the cerebellum.

Figure 2. Mean Global Connectedness Values for Left and Right Cerebellar Clusters

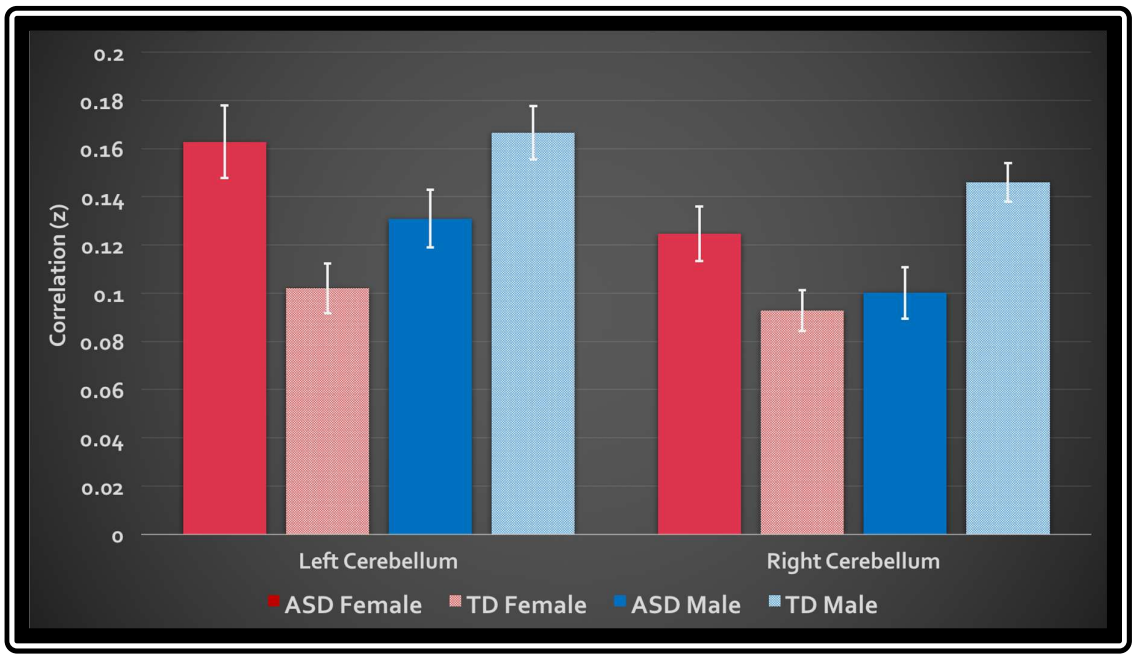

Figure 2: Mean Global Connectivity Values for Left and Right Cerebellar Clusters. The y-axis displays the average z-transformed correlation coefficient of the cluster's mask with every other voxel in the brain. White bars denote standard error.

When seeding from the right (VIII) cerebellar cluster, 12 predominantly bilateral regions emerged, exhibiting a corresponding diagnosis-by-sex interaction. These were located in the bilateral precentral, middle occipital, middle frontal, fusiform, and cingulate gyri, as well as the left cuneus, precuneus, and inferior temporal gyrus (Table 2, Figure 3). When seeding from the left (crus II) cerebellar cluster, an additional region emerged in the right precuneus. These seed-based tests only assessed relationships between the seeds in the cerebellum and the cortex.

Table 2. Numbered List of Resulting Regions from Each Cerebellar Seed

Region #	Region Label	Peak Coordinates[a]
1	R. Precentral Gyrus	(41, -13, 44)
2	R. Precuneus	(17, -79, 35)
3	L. Precentral Gyrus	(-37, -10, 47)
4	L. Precuneus	(-28, -46, 59)
5	R. Fusiform Gyrus	(23, -58, -19)
6	R/L. Cingulate Gyrus	(2, 11, 44)
7	R. Middle Frontal Gyrus	(38, 32, 29)
8	L. Fusiform Gyrus 1	(-25, -49, -7)
9	L. Cuneus	(-4, -76, 17)
10	L Middle Frontal Gyrus	(-37, 32, 32)
11	L. Middle Occipital Gyrus	(-22, -85, 20)
12	L. Fusiform Gyrus 2	(-28, -67, -16)
13	R. Middle Occipital Gyrus	(53, -61, 2)
14	R. Cerebellum VIII	(14,-61, -37)
15	L. Cerebellum Crus II	(-31, -67, -40)

Table 2. Numbered key of cortical regions resulting from seed-based tests. Numbers in parenthesis refer directly to those used in Figures 3-5.
[a] Coordinates are (*x, y, z)*, in standard Talairach-Tournoux space, *left-posterior-inferior* orientation, peaks from cluster-size corrected seed-based maps.

Figure 3. Regions Resulting from Seed-Based Analysis Showing Diagnosis-By-Sex Interaction

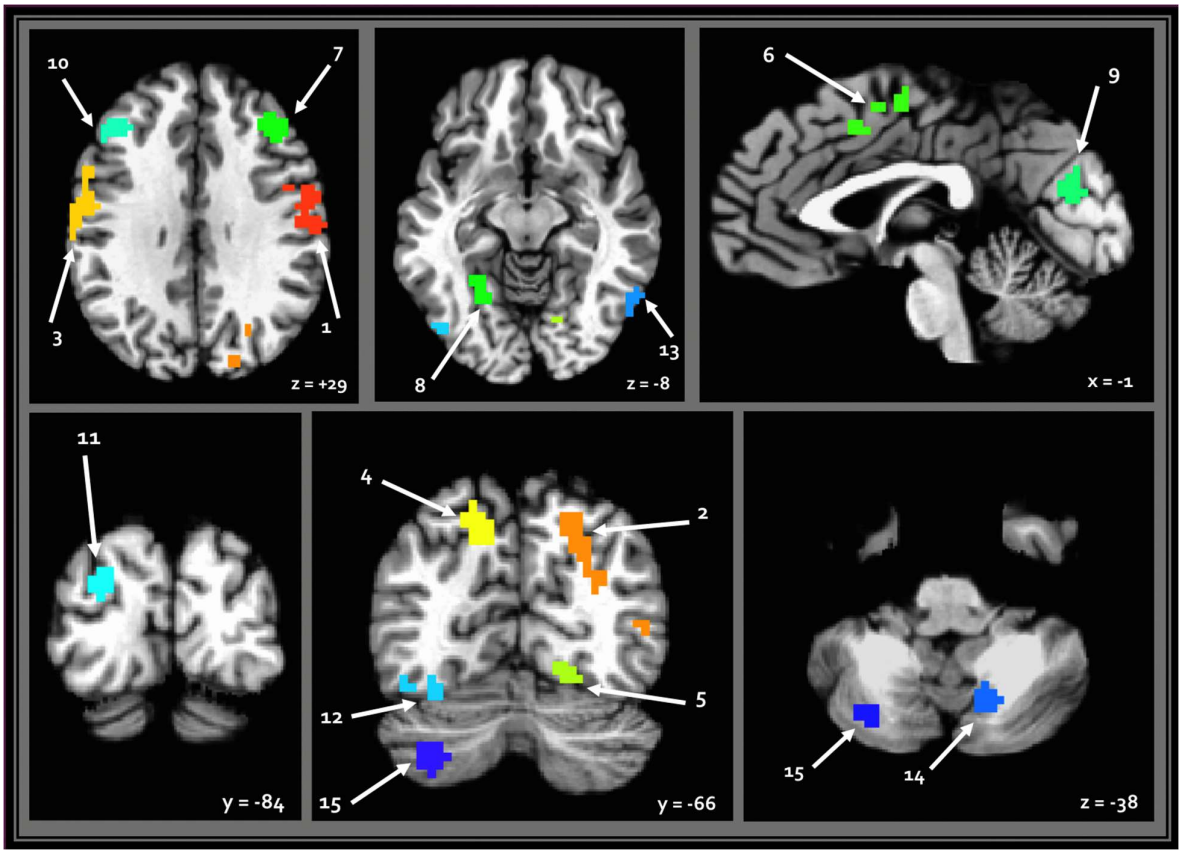

Figure 3. Resulting cortical regions whose functional connectivity with cerebellar seeds showed a diagnosis-by-sex interaction. Cerebellar seeds are pictured in the lower right panel. Left is shown on the left, and results are in standard Talairach-Tournoux space. Refer to Table 2 for key of numeric region labels.

All possible regional inter-relationships were then assessed in the full region-to-region correlation matrices. However, only the cerebellum-to-cortex relationships identified in the seed-based tests survived FDR correction ($q<.05$), and these detected diagnosis-by-sex interactions were qualitatively similar to those identified in the earlier analyses of whole-brain connectedness (see Figure 4A), with correlation decreases observed in ASD males compared to TD males and correlation increases observed in ASD females compared to TD females. For the ASD-TD contrasts in females, all region-to-region pairs showing a

significant diagnosis-by-sex interaction also showed significant increases in ASD females (Figure 4B). In contrast, for the ASD-TD contrasts in males, decreases were observed in ASD males between the right cerebellar VIII seed and the bilateral precuneus, bilateral fusiform, bilateral middle occipital gyri, left cuneus, and left inferior temporal gyrus (Figure 4C).

Figure 4(A-C). Cerebellar-Cortical Region Correlation Matrices

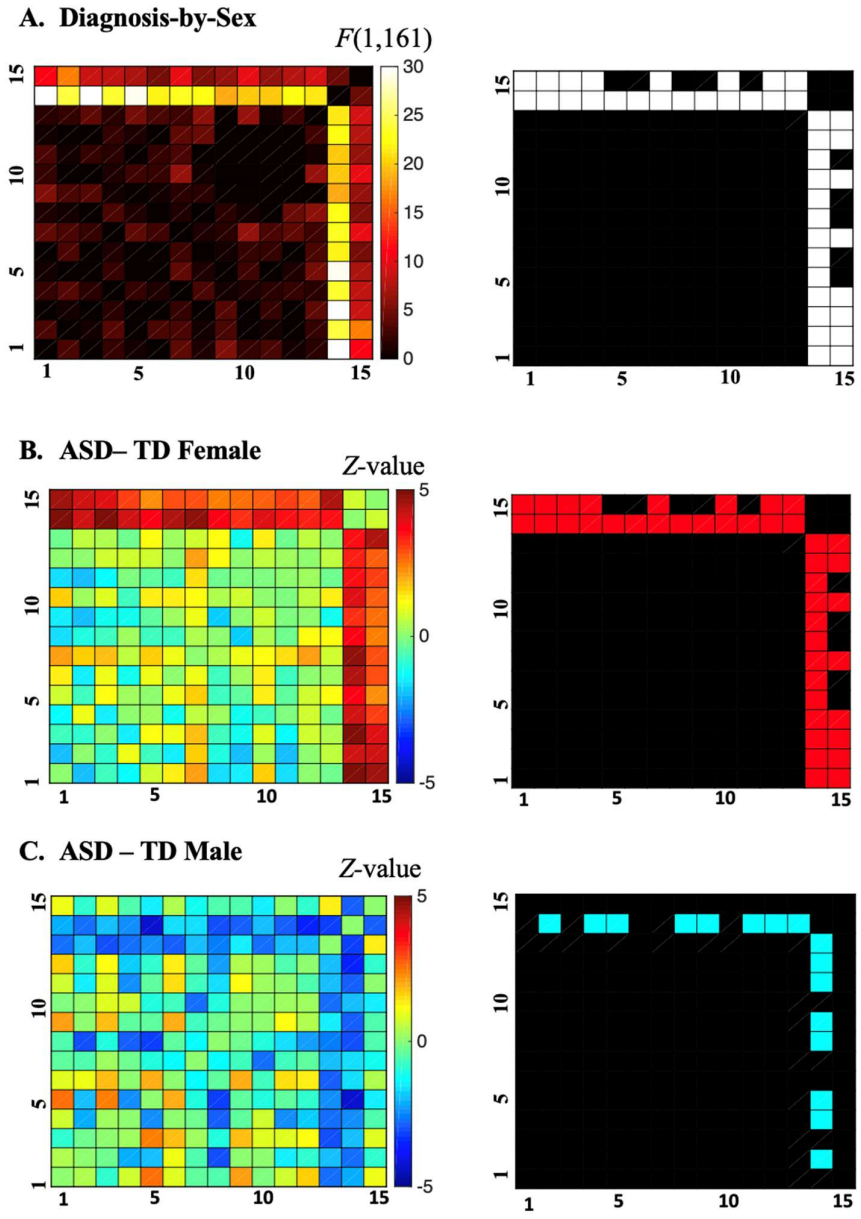

Figure 4(A): F-values for diagnosis-by-sex interaction (left), and surviving pairs at *P*<.0069 after FDR correction to q<.0 shown in white (right).
Figure 4(B): Z-values for ASD – TD contrast in females (left), and surviving pairs at *P*<.0216 (FDR-corrected to *q*<.05 within those combinations already FDR-corrected in the diagnosis-by-sex contrast) shown in red (right).
Figure 4(C): Z-values for ASD – TD contrast in males (left), and surviving pairs at *P*<.0216 (FDR-corrected to *q*<.05 within those combinations already FDR-corrected in the diagnosis-by-sex contrast) shown in blue (right).

Given the modest differences in the subscales of the ADI and ADOS shown in Table 1, we examined whether there might be a correspondence between the ASD male/female subscale scores and the diagnosis-by-sex interactions observed in functional connectivity. No significant correlations were observed with the ADOS social+communication score and region-to-region pairs exhibiting interactions, even at a $p<.05$ (uncorrected) level, nor were there any differences in slope of these relationships by group (ASD male/female). Corresponding analyses using SRS sum score also failed to yield significant results.

Finally, functional connectivity of the region-to-region pairs exhibiting a diagnosis-by-sex interaction were examined to evaluate the gender incoherence and extreme male brain theories. The gender incoherence theory predicts that ASD males should be more similar to TD females and ASD females should be more similar to TD males, whereas the extreme male brain theory predicts that both ASD males and females should be more similar to TD males - and that ASD males are further away from TD females on the sex continuum than TD males are (i.e. they are extreme male). Results for the Pearson correlation measure are shown in Table 3. On average, the pattern of cerebellar-cortical FC in ASD females was more similar to TD males rather than to TD females [paired *t*-test(22): 2.3457, $p<.0284$], and this result remained significant when using Euclidean distance to compare groups [paired *t*-test(22): -4.1914, $p<6.4891e-05$] (see Table 4). ASD males had FC patterns more similar to TD males than to TD females [paired *t*-test(55): 3.3597, $p<.0014$], however, this effect was no longer significant or apparent when using Euclidean distance as a means of comparison. It is also worth noting that ASD females were numerically closer to TD males than ASD males were to their same-sex controls, though this failed to reach significance [$p<.1974$]. Additionally, the numeric distance between TD males and TD females was greater than the distances between ASD males and TD females [paired *t*-test(143): -2.4207, $p<.0167$], and ASD males and TD

males [paired *t*-test(143): -2.3234, *p*<.0216], indicating that ASD males lie *between* TD males and TD females with respect to pattern and magnitudes of FC.

Table 3. Mean Correlations and Tests of Male/Female Similarity

Clinical Group	TD Female	TD Male	Paired *t*-Test
ASD Female	0.3321 (0.2354)	0.3675 (0.2065)	*t*(22) = 2.3457 P<.0284*
ASD Male	0.2552 (0.2010)	0.2981 (0.1722)	*t*(55) = 3.3597 P< .0014*

Table 3. Correlations are mean (SD) and paired *t*-tests are *t*-statistic (degrees of freedom)
*statistically significant

Table 4. Euclidean Distances and Tests of Male/Female Similarity

Group	TD Female	TD Male	Paired *t*-Test
ASD Female	1.5231 (0.5853)	1.0847 (0.3110)	*t*(22) = -4.1914 *p*<6.4891e-05*
ASD Male	1.2032 (0.5151)	1.2202 (0.4575)	*t*(55) = 0.2253 *p*< .8225
TD Female	1.0214 (0.3479)	1.3988 (0.5160)	
TD Male	1.4515 (0.6276)	1.1228 (0.4293)	

Table 4. Distances are mean (SD) and paired *t*-tests are *t*-statistic (degrees of freedom)
*statistically significant

3.5 Discussion

The current study sought to build upon existing literature that has explored the neurophysiology of the sex bias associated with ASD, and to focus, in particular, on the cerebellum. Early, localized co-expression of ASD candidate genes (wang et al., 2014), regional sensitivity to the action of sex steroids (Dean and McCarthy 2008), well-mapped connections with the rest of the cortex (Buckner et al., 2011), and consistent involvement in sex-dependent neurodevelopmental disorders (Hampson and Blatt 2015) are all motivating factors for further investigation of cerebellum in this context. Although the current study employed a data-driven approach over the entire brain to investigate sex differences in ASD, the findings indeed highlight the role of the cerebellum.

By probing sex differences in resting-stateFC, the current study found that cortical-cerebellar connectivity profiles looked strikingly different in males and females with ASD. In fact, there was a significant diagnosis-by-sex interaction in mean connectedness between two sub-regions of the cerebellum and the rest of the brain. These regions (in right lobule VIII and left crus II) exhibited *hyper*-connectivity with the cortex in ASD females, and an opposing pattern of *hypo*-connectivity in ASD males. These current findings are in line with similarly opposing FC patterns that were recently reported by Alaerts et al (2016). No cerebellar regions showed significant differences in FC that were directionally similar across sexes in the clinical groups.

Elucidation of the initial interaction implicated a range of functionally diverse cortical areas. In follow-up correlation analyses, both ASD males and ASD females in the current study exhibited levels of region-to-region connectivity that more closely resembled that of

TD males than TD females. However, when comparing Euclidean distances between experimental groups, the FC pattern and magnitudes of ASD males actually appeared to fall somewhere between that of TD males and TD females, rather than at the extreme end of the TD males. Therefore, with respect to ASD-related changes in cerebellar-cortical functional connectivity, the current results align more with "gender incoherence" than with an "extreme male brain" (Baron-Cohen, 2002).

Multiple theories have been proposed to account for ASD's male preponderance. Researchers believe that male-specific risk factors, and/or female-specific protective mechanisms help to drive the imbalanced diagnostic rate (Lai et al., 2017). With those predispositions in mind, it has been proposed that females who meet the diagnostic threshold for ASD would present with more severe neurophysiological impairments than males (Lai et al., 2015a, 2017). However, results from the current study, in conjunction with other recent publications, suggest that ASD's pathophysiology is qualitatively, rather than simply quantitatively, different in females relative to males (Alaerts et al., 2016; Lai et al., 2017).

Because alterations in androgens and estrogens have been noted in both early developmental and later phenotypic stages of ASD (Lai et al., 2017), researchers have interpreted organizational brain changes as "neural masculinization" or "feminization" (Alaerts et al., 2016; Bejerot et al., 2012; Lai et al., 2015a; 2017) or as a shift toward an "extreme male brain" (Baron-Cohen 2002). The current study does not find clear evidence for an "extreme male brain" (Baron-Cohen, 2002) in ASD, but it does provide support for "masculinization" in the cerebellar-cortical connectivity patterns of *females* with ASD. However in males, the picture is less straightforward, which may be a byproduct of the relatively small sample of females to which they were compared. ASD males in the current

study had FC *patterns* (excluding the mean functional connectivity values) that were more similar to those of TD males than TD females, but when taking magnitude into account (Euclidean distances), this was no longer true. In addition, ASD females were actually numerically closer to TD males than ASD males are, though this failed to reach significance. Furthermore, the distance between ASD males and TD females is less than the distance between TD males and TD females, again emphasizing that they actually lie somewhere between TD males and females in terms of FC magnitudes and patterns rather than at the extreme male end of the continuum. This finding is inconsistent with the "extreme male brain" theory, and while it does not provide robust, unequivocal evidence for the "gender incoherence" reported in other studies, it is more in line with "gender incoherence" theory than with the former theoretical framework for ASD.

Other studies have offered support for the "gender incoherence" theory (Alaerts et al., 2016; Bejerot et al, 2012) rather than the "extreme male brain" (Baron-Cohen, 2002). In addition to patterns of neural activity, Bejerot et al. (2012) also saw a pattern of male/female "gender incoherence" in the physical appearance and endocrine profiles of participants with ASD, noting in a study that females had less feminine facial features, and higher levels of testosterone than controls, while males had less masculine voices and body characteristics, but no change in testosterone levels. In contrast, another recent study reported exaggerated masculine features in both males and females with the disorder (Tan et al., 2017), so the link between gendered brain organization, hormonal dysregulation, and external features is not straightforward. It is likely that multiple converging mechanisms are responsible for the sex-based divergence in brain organization and physical features in ASD.

In the current study, diagnosis-dependent sex differences in cerebellar organization were found in two clusters, in the right lobule VIII and the left crus II. Studies have previously linked volumetric changes in these regions with ASD, consistently reporting grey matter reductions in lobule VIII (D'Mello and Stoodley 2015), and also correlating diagnosed children's communication difficulties with decreased grey matter in bilateral crus II and VIII (Riva et al., 2013).

The seed-based tests from each cerebellar cluster in the current study yielded a total of 13 predominantly bilateral regions underlying the interaction effects. Functional organization in the cerebellum and cortex tends to follow a predictably contralateral pattern, so the current finding of bilateral cortical regions for a unilateral (right) cerebellar seed is suggestive of broadly altered cortical-cerebellar circuitry in ASD, which is consistent with existing literature (Khan et al., 2015; Noonan et al., 2009). Cerebellar crus II is reliably connected to cortical areas involving both sensorimotor and social abilities, and previous studies have found aberrant connectivity among crus II and these regions in ASD. However, the current study only found diagnosis-dependent sex differences in FC between this cerebellar sub-region and the right precuneus. When seeding from the right lobule VIII, the remaining regions were in cortical areas associated with somatomotor, visuospatial, perceptual, and executive functions. Lobule VIII-A/B, also overlaps with areas previously shown to be involved in auditory processing and discrimination (Baumann and Mattingley 2010), which is also often impaired in ASD.

It is doubtful that the results found in the current study provide a full picture of the sex-based cortical-cerebellar abnormalities in ASD, and based on the disorder's symptomatic heterogeneity, there may be individual differences in the specific subdivisions of the

cerebellum that are most affected. It is important to note that the current sample was only representative of ASD phenotypes *without* intellectual disability, and this limits the generalizability of the current findings to only a subset of the broader ASD population. Cerebellar structure and function have both been linked with IQ (Hogan et al., 2011), and importantly, a recent study also noted significant sex differences in the degree to which cerebellar-cortical connectivity corresponded with IQ in the general population (Pezoulas et al., 2017). These researchers found that only females showed a significant correlation between cerebellar network efficiency and IQ. Neuroimaging studies that incorporate more cognitively diverse ASD populations would help to shed light on whether sex differences in cerebellar architecture look different in groups with more severe cognitive deficits.

There is extensive evidence to suggest that the cerebellum, through its functional relationship with the cortex, plays an important role in a range of behaviors, from auditory processing, to perceiving biological motion, to labeling emotional faces (Baumann et al., 2015; Baumann and Mattingley 2010; Buckner 2013; Jack et al., 2017). The right cerebellar cluster, in VIII-A/B (Buckner et al, 2011) partially overlaps with areas previously shown to be involved in auditory processing (Baumann and Mattingley 2010). This has interesting implications, given that over- or under-sensitivity to auditory stimuli is a very common ASD symptom. Unfortunately, without behavioral measures or an experimental task to probe this in the current study, it remains unclear whether there is a direct relationship between the degree of cerebellar-cortical connectivity and the ASD sensory phenotype.

Because there is limited clinical literature on sex differences in ASD phenotypes, it is difficult to speculate about potential behavioral correlates for the current study's brain-based results. In a recent qualitative analysis, clinicians reported that sex differences were more

exaggerated in certain domains of ASD symptomatology (Halladay et al., 2015; Jamison et al., 2017). In particular, there were larger behavioral discrepancies in repetitive, restricted behaviors, and fewer in social communication, with males tending to exhibit more severe motor symptoms (Halladay et al., 2015; Jamison et al., 2017). Another recent study found that in parent reports of executive function, females with ASD showed greater difficulties than males (White et al., 2017). Naturally, it is important to consider the role that social expectations play in assessing males and females with ASD, and it is also important to remember that ASD diagnostic measures were not developed or normed with female samples, which is yet another limitation in the accurate identification of sex differences in this disorder.

Given the multitude of higher functions in which the cerebellum is involved, including social and motor processes, it would be useful to probe sex-based behavioral differences further and attempt to relate them to resting-stateand task-based activity in different sub-regions of the cerebellum. This will eventually provide a more complete picture of the cortical-cerebellar changes associated with ASD, and will also delineate those changes that differ significantly between males and females.

3.6.1 *Limitations*

The first major limitation of the current study was the relatively small sample of females who were recruited and scanned. Given the disproportionate number of males and females diagnosed with ASD, the uneven sex ratio seen in the current sample is not surprising, and the smaller number of females may help to explain the lack of other

significant cortical findings in the initial diagnosis-by-sex interaction analysis (i.e. producing an expectation of Type II rather than Type I errors).

Another limiting factor was the exclusion of ASD participants with cognitive impairments. This exclusion criteria allowed for the comparison of clinical and healthy control groups without the confound of IQ discrepancies, but it also compounded the challenge of recruiting a sufficient number of eligible female ASD participants. The participants included in the current study therefore represent only a subgroup of the broader ASD population, and the current results should not be extrapolated to the full, heterogeneous spectrum of ASD. This is particularly relevant in light of the current study's cerebellar findings, as IQ has been linked to cerebellar structure, function, and connectivity profiles (Hogan et al., 2011; Pezoulas et al., 2017). In future studies, it would be helpful to investigate whether the same crossover interaction pattern observed in the current study persists in a more heterogeneous ASD sample, or in a set of low-IQ samples.

In addition to exploring cerebellar-cortical organization in ASD within a subgroup that *does* have intellectual disability, it would also be informative to gather similar data during early childhood, or across multiple time points in a longitudinal design. The current sample consisted predominantly of adults and included no young children, so this study's findings only provide a static snapshot of cerebellar-cortical organization in adults with this disorder. Without developmental context, it cannot be determined wither these sex-dependent changes are stable in ASD, or whether they diverge in males and females earlier in development. Furthermore, given the potential influence of sex steroids on early cerebellar development, it would also be worthwhile to relate the functional architecture of the

cerebellum to reproductive hormone levels and to establish whether there is a direct relationship between the two at any point in development.

An important limitation of the current study is that it does not provide insight into the symptomatic correlates of the observed sex differences cerebellar-cortical connectivity. It would be difficult to select a single behavioral domain for investigation as a correlate of the brain-based findings, due to the functional diversity of cortical regions implicated, and the wide range of behaviors that the cerebellum subserves. Additionally, the measures by which both males and females are assessed have been designed and normed using male samples, which calls into question their validity and sensitivity to a specifically female ASD phenotype.

3.6 Conclusions

To summarize, the current findings are in agreement with recent studies that have found functional *hyper*-connectivity in the brains of ASD females, and *hypo*-connectivity in ASD males (Alaerts et al., 2016), and when focusing specifically on cerebellar-cortical functional connectivity, are more consistent with the "gender incoherence theory" (Alaerts et al., 2016; Bejerot et al., 2012) than with the "extreme male brain" (Baron-Cohen 2001). The current results also provide support for the ongoing investigation of the cerebellum as a hub for both early and sustained sex differences in ASD, and finally, they raise questions about the possible behavioral correlates of sex-dependent abnormalities in cortical-cerebellar organization that warrant further exploration.

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CHAPTER 4

FUNCTIONAL CONNECTIVITY ASSOCIATED WITH NORMAL VARIATION IN PSYCHOPATHIC AND AUTISM SPECTRUM DISORDER TRAITS

Abstract

Psychopathy and autism spectrum disorder (ASD) traits can be found to varying degrees in typically developing populations, however little is known about the neurobiological features that underlie these traits. The current study used resting-state functional magnetic resonance imaging (fMRI) to determine whether, in a large community sample, psychopathic and ASD traits could be related to specific patterns of resting-state functional connectivity. Trait measures and resting-state fMRI scans were collected from 924 healthy young adults (535 females, mean age 19.68). Global functional connectivity was correlated with psychopathic and ASD traits. After performing a leave-one-out cross validation, 10 regions emerged, showing positive associations between psychopathic trait levels and mean connectivity. No significant relationship between ASD traits and functional connectivity was found. Follow-up seed testing revealed that increased functional connectivity between a total of 18 regions was associated with related to higher levels of psychopathic traits. These regions were functionally diverse, but predominantly located in somatomotor, limbic, default mode, and cerebellar networks. Reduced empathic concern partially accounted for these findings, and was significantly associated with connectivity between the left inferior temporal pole and the right temporo-parietal junction. The overall findings suggest that the observed increased coupling or decreased network segregation might inhibit the typical flow of information during socio-effective processing, and contribute to behaviors seen in individuals with higher levels of psychopathic traits.

4.1 Introduction

Traits associated with psychopathologies such as psychopathy and autism spectrum disorders (ASD) are believed to exist along a dimensional continuum, with the clinical syndrome representing the extreme end of individual variability (Constantino & Todd, 2003; Hare & Neumann, 2005; Levenson et al., 1995; Wallace et al., 2012; Walton et al., 2008). ASD traits can indeed be found to varying degrees in typically developing populations (Ronald & Hoekstra, 2011; Skuse et al., 2005), and this provides support for considering ASD symptomatology to be a continuous, quantitative trait (Constantino et al., 2004). Likewise, psychopathic and antisocial traits have also been investigated outside of clinical populations, and similar individual variation has been reported, indicating its trait dimensionality (Edens et al., 2006; Frick et al., 2000; Hare, 1998; Murrie et al., 2007; Neumann & Hare, 2008)

At higher levels, psychopathic or ASD traits can lead to behavior that is suggestive of a profound lack of empathy towards other people (Blair, 2005; Jones et al., 2010), and this may impact an individual's ability to communicate or develop healthy relationships with others. However, the nature and neurobiological origin of this unempathetic behavior are likely different in individuals with high levels of psychopathic traits versus those with high levels of ASD traits (Jones et al., 2010; Lockwood et al. 2013; Schwenck et al. 2012). More specifically, individuals with high levels of psychopathic traits lack empathic concern, or the ability to affectively resonate with others, whereas individuals with high levels of ASD traits struggle to assume the perspectives of other people, and therefore cannot anticipate others' feelings or respond appropriately (Bird & Viding, 2011; Lockwood et al., 2013; Mazza et al., 2014; Seara-Cardoso et al., 2012).

This means that although individuals with ASD traits might behave in ways that suggest a lack of empathic concern, such behavior could have its origins in different socio-cognitive difficulties from those that characterize individuals with high levels of psychopathic traits. Lockwood and colleagues (2013) conducted an experimental investigation of the dissociation between these components of empathic processing. Their study demonstrated that in a community sample, psychopathic traits were associated poorer performance on tasks measuring *affective* empathy, while in contrast, ASD traits were associated poorer performance on *cognitive* empathy tasks. These findings help to reinforce the notion that empathic difficulties associated with high ASD and psychopathic traits, respectively, are products of distinct cognitive processes.

Evidence from structural neuroimaging studies in clinical/forensic populations also suggests that these trait domains may be related to at least partially distinct neurobiological correlates. Structural magnetic resonance imaging (MRI) studies have reported reduced gray matter volume (GMV) or thinning in prefrontal and temporal regions (Müller et al., 2008; Yang et al., 2009), as well as GMV *increases* in the striatum (Glenn et al., 2010) in psychopathic individuals compared to controls. Similarly, in violent criminal offenders, high levels of psychopathic or antisocial traits have been negatively associated with GMV in the prefrontal cortex (PFC) and limbic/paralimbic structures (Cope et al., 2014; Ermer et al., 2012, 2013; Gregory et al., 2012;; Leutgeb et al., 2015), but positively associated with GMV in the cerebellum, supplementary motor area (SMA), and basal ganglia (Glenn et al., 2012; Korponay et al., 2017; Leutgeb et al., 2015;).

In contrast, structural MRI studies in ASD have found complex, age-dependent alterations in cortical development, characterized by reduced GMV or cortical thinning in parts of the brain related to social cognition. These areas include the superior temporal sulcus (STS), dorsomedial PFC, inferior/middle temporal cortex, inferior frontal gyrus, temporo-parietal junction(TPJ)/supramarginal gyrus, and cingulate gyri (Greimel et al., 2013; Sato et al., 2017; Scheel et al., 2011; Wallace et al., 2010). Progressive thinning/GMV reductions have been observed in sensorimotor areas such as the pre- and postcentral gyri (Greimel et al., 2013; Wallace et al., 2010), and age-dependent changes in cerebellar structure have also been consistent features of ASD (Wang et al., 2014). Finally, several studies have also noted thicker cortex in frontal and parietal regions in individuals with ASD, compared to healthy controls (Ecker et al., 2013; van Rooij et al., 2018).

Because psychopathic and ASD traits are also present in neurotypical individuals, a handful of researchers have extended their investigations of structural brain differences into healthy populations, but research is sparse when compared to the clinical literature. In a study of neurotypical youths, Wallace and colleagues (2012) directly compared cortical changes related to ASD traits versus psychopathic traits, and found largely distinct patterns of cortical thinning, which mirrored those identified in clinical samples. In a small sample of healthy adults, Vieira and colleagues (2015) found overall psychopathic traits to be negatively associated with GMV in the left putamen and amygdala. In a more recent study of healthy youths, Raschle and colleagues (2018) reported a link between insula volumes and callous unemotional traits, but this relationship was not found in the female participants.

In studies examining ASD traits, researchers have reported alterations in both gray matter (Geurts et al., 2013; Saito et al., 2014) and white matter (Iidaka et al., 2012; Von dem

Hagen et al., 2011) that partially parallel the clinical findings, but with some inconsistencies and caveats. For Saito and colleagues (2014), the effects were only seen in males, and for Iidaka and colleagues (2012), effects were only seen for one AQ subscale, which was not representative of ASD traits overall. Other studies have failed to identify any significant differences in brain structure that could be related to ASD traits (Koolschijn et al., 2015; Watanabe et al., 2014;).

Task-based functional neuroimaging studies in participants with psychopathy or ASD have also found differences in activation in areas that overlap with the structural findings. Implicit and explicit tasks involving moral, empathic, or reward processing have linked psychopathy and/or psychopathic traits to altered activation in affect-related (limbic/paralimbic) regions such as the amygdala, ACC, vmPFC, and insula, as well as in areas related to reward processing (e.g. the striatum) (for reviews, see: Del Casale et al., 2015; Seara-Cardoso & Viding, 2015). For example, criminal offenders with high levels of psychopathic traits tend to display reduced neural responses to others' expressions of emotion or pain, compared to healthy controls (Meffert et al., 2013) or to offenders with low levels of psychopathic traits (Decety et al., 2013a, 2013b, 2014). However, when cognitively attributing emotions to others, offenders with high levels of psychopathic traits have exhibited increased activation in the vmPFC and temporo-parietal areas compared to offenders with low levels of psychopathic traits (Sommer et al., 2010). Evidence from a number of fMRI studies in community samples suggests that these stimulus-based activation effects can also be seen in the general population, where higher levels of psychopathic traits are associated with reduced neural responses to other people's distress for example (Seara-Cardoso & Viding, 2015).

Tasks probing socio-affective processing in ASD have identified extensive differences in activation in regions ranging from the cerebellum, to the thalamus/hypothalamus, to the PFC, to the medial temporal lobes (Aoki et al., 2014; Minshew & Keller, 2010; Philip et al., 2012). For example, in studies with face stimuli or facial expressions of emotion, individuals with ASD typically exhibit reduced activation in the fusiform gyri and sometimes also in the amygdala, compared to healthy control participants (Corbett et al., 2009; Dalton et al., 2005; Deeley et al., 2007). In addition, during mentalizing tasks, social brain areas such as the PFC and TPJ have shown reduced activity and connectivity in individuals with ASD compared to controls (Kana et al., 2009; Murdaugh et al., 2014; Nijhof et al., 2018). However, the disorder's overall heterogeneity combined with discrepancies in task performance have made these investigations difficult to interpret conclusively (Lenroot & Yeung, 2013).

The emerging popularity of resting-state fMRI is beginning to shed additional light on the neural underpinnings of psychopathy and ASD. This methodology allows researchers to establish whether task-free (baseline) brain activity, or intrinsic coherence among brain regions (also known as functional connectivity), is altered in clinical groups compared to their healthy counterparts. Identifying any clinically relevant baseline changes could help to provide a functional blueprint for these disorders and present an arena for new treatment approaches such as neurofeedback that target aberrant connectivity (e.g. Ramot et al., 2017). Resting-state fMRI studies of both psychopathy and ASD have proliferated, offering support for the idea that alterations in functional brain organization are highly relevant in the disorders' pathophysiology. Functional connectivity findings in these clinical syndromes show considerable spatial overlap with earlier structural studies, with some additional brain areas also emerging via resting-state analyses.

In criminal and psychiatric populations, psychopathy has been associated with a varied picture of both increases and decreases in functional connectivity. For example, Leutgeb and colleagues (2016) found that in violent criminal offenders, high levels of psychopathic traits were linked to hyperconnectivity within the dorsolateral PFC and between the amygdala and cerebellum. A similar pattern of increased prefrontal FC was found in youth arrestees with high levels of callous-unemotional (CU) traits, compared to those with low CU traits (Cohn et al., 2015). In contrast, Motzkin and colleagues (2011) reported *hypo*connectivity between the ventromedial PFC and amygdala, as well as between the ventromedial PFC and precuneus/PCC in psychopathic versus non-psychopathic criminals. A similar study in prison inmates found psychopathic traits to be associated with significantly reduced FC between the lateral parietal cortex, precuneus, ACC, and insula (Philippi et al., 2015). In addition to alterations in prefrontal, lateral parietal, and limbic/paralimbic FC, the striatum's connectivity has also been linked to psychopathic traits in incarcerated males (Korponay et al. 2017). More specifically, within-striatum FC was positively associated with psychopathic traits, as was FC between the striatum and PFC, but negative associations were reported between the striatum and parietal cortex (Korponay et al. 2017). In a recent, large (n=985) inmate study, Espinoza and colleagues (2019) found that a complex picture of both increases and decreases in FC across 7 resting-state networks were all associated with psychopathic traits.

In ASD, the resting-state research landscape is also complex, and this is not surprising given the disorder's phenotypic heterogeneity. A large number of studies have amassed, and while there is no universal consensus among researchers, there do appear to be some consistent patterns of altered functional connectivity (Gotts et al. 2019; Picci et al. 2016).

The most well-replicated resting-state features of ASD include diffuse reductions in FC across the cortex, particularly in social brain areas, including the superior temporal gyrus, STS, fusiform gyri/ventral temporal cortex, inferior frontal cortex, and PCC, and somatosensory cortex. These reductions in functional connectivity have also been successfully correlated with symptom severity (Cheng et al., 2015; Gotts et al., 2012, 2019; Jung et al., 2014; Picci et al., 2016; Ramot et al., 2017). In parallel, studies have also found *increases* in FC between subcortical structures (e.g. thalamus and striatum) and many of the same aforementioned cortical regions (Cerliani et al., 2015; Cheng et al., 2015; Di Martino et al., 2011, 2014). Importantly, these findings are from predominantly male samples, and recent studies have reported significant differences in FC between males and females with ASD, further complicating the picture of ASD pathophysiology (Alaerts et al., 2016; Smith et al., 2019).

Outside of clinical populations, individual differences in resting-state functional connectivity have also been linked to normal variation in a range of trait dimensions including impulsivity (Angelides et al., 2017; Davis et al., 2013;), emotional intelligence (Killgore et al., 2017), general intelligence (Dubois et al., 2018), openness (Dubois et al., 2018; Wang et al., 2018); neuroticism (Hsu et al., 2019), and extraversion (Hsu et al., 2018; Tian et al., 2018). However, no larger-scale studies employing commonly used behavioral measures have used resting-state fMRI to investigate psychopathic or ASD traits in typical adults. Only one small study (n = 25) reported a significant negative association between ASD traits (as measured by the social responsiveness scale (SRS)) and functional connectivity between the mid-insula and pregenual anterior cingulate cortex (Di Martino et al., 2009). The study had significant limitations, including a small sample size, a limited

number of a priori regions of interest investigated, and reliance on informant reports for the behavioral data.

4.2 Aim of Study

Taken together, the current literature suggests that neurocognitive profiles associated with these two trait domains are likely to be at least partially distinct, but little is known about whether, in healthy populations, the functional organization of the brain may be differentially related to psychopathic and ASD traits. To date no studies have directly compared the resting-state functional connectivity correlates of psychopathic and ASD traits in the same population. The current study will provide a novel extension of the existing literature by directly comparing potential resting-state correlates of psychopathic and ASD traits in the same large community sample. In addition, the current study includes an exploratory element to test whether any functional connectivity related to psychopathic or ASD traits might be accounted for by reduced empathic concern. Both psychopathic and ASD traits have been related to behaviors that are suggestive of reduced empathic concern, but the reason for this may not be identical for the two disorders (Bird & Viding, 2011).

We hypothesized that resting-state functional connectivity associated with psychopathic and ASD traits would be at least partially distinct. We predicted that higher psychopathic traits would be related to altered connectivity between prefrontal and limbic/paralimbic areas, as well as within/between the lateral parietal lobes, cerebellum, and striatum. We did not predict the direction of these effects, given the inconsistencies in the current resting-state literature on psychopathic traits. We predicted that ASD traits would be related to mainly reduced functional connectivity, particularly in the temporal lobes. We also

anticipated that there could be some overlap in the regions implicated for psychopathic traits and autism spectrum traits, particularly in the temporal and cingulate cortices as well as in sensorimotor areas and the cerebellum. These areas have all been implicated in clinical resting-state literature for both disorders. Finally, we conducted exploratory analyses to examine whether reduced empathic concern contributed to explaining any resting-state functional connectivity features associated with psychopathic or ASD traits.

4.3 Materials and Methods

4.2.1 *Participants*

Behavioral, anatomical, and resting-state imaging data were derived from 924 young adult participants (535 women, mean age 19.68 ± 1.25 years) who took part in the Duke Neurogenetics Study (DNS), which is a multimodal investigation of behavioral and biological traits among healthy university students. The DNS was approved by the Duke University School of Medicine Institutional Review Board, and all participants provided written informed consent prior to participation. Additional information about recruitment and exclusion criteria can be found elsewhere (Davis et al., 2013; Prather et al., 2013; Swartz et al., 2016).

4.2.2 *Behavioral Assessments*

The Self Report Psychopathy, Short Form (hereafter referred to as SRP; Neumann & Pardini, 2014; Paulhus et al., 2017), is a 29-item adaptation of the Psychopathy Checklist-Revised (PCL-R; Hare, 2003). The SRP is rated on a 5-point scale from "Disagree Strongly" to "Agree Strongly," and includes items such as "People often say that I am cold-hearted."

Higher scores therefore indicate increased impairment. While the PCL-R is mainly used as a clinical instrument, the SRP was developed for use in community samples where self-reporting is appropriate, and has good reliability and construct validity (Dotterer et al., 2017; Gordts et al., 2017; Neumann et al., 2015; Seara-Cardoso et al., 2019; Tew et al., 2015). SRP data was available for 924 participants with resting-state scans. The SRP total/summary score was used in the current study to measure general levels of psychopathic traits rather than individual factor scores, as total scores show good internal reliability and validity (Neal & Sellbom, 2012), and some recent papers have reported potential inconsistencies in dimensionality and factor structure across males and females (Boduszek & Debowska, 2016;; Debowska et al., 2014; Dotterer et al., 2017; Seibert et al., 2011).

The Autism Spectrum Quotient (AQ) (Baron-Cohen, 2001) was collected in a smaller subset of the DNS sample (n = 459, 264 women, mean age 19.60 ± 1.22 years). The AQ is a 50-item, self-report instrument designed to capture individual differences in ASD traits within typically developing populations. Items on the AQ measures abilities in the following areas: social skill, communication, attention switching, attention to detail, and imagination (Baron-Cohen, 2001). Responses range from "definitely agree" to "definitely disagree" on a 4-point scale. Item-level scoring is binarized, after grouping "definitely agree" with "slightly agree" and "definitely disagree" with "slightly disagree". In order to capture the greatest amount of variance and dimensionality, total scores were used, rather than Baron-Cohen's (2001) original binarized scores (Kuenssberg et al., 2014; Lockwood et al., 2013).

Lastly, scores from the Empathic Concern (EC) subscale of the Interpersonal Reactivity Index (IRI) (Davis, 1983) were also obtained from the full (n = 924) sample. The EC subscale of the IRI consists of 7 questions (e.g. "I often have tender, concerned feelings for people less fortunate than me") that measure feelings of empathy or sympathy for others,

and is scored on a 5-point Likert-type scale from “does not describe me well” to “describes me very well.” (Davis, 1983).

4.2.3 *Image Acquisition*

Anatomical and functional scans were collected at the Duke-UNC Brain Imaging and Analysis Center on a GE MR750 3 Tesla scanner with 50 mT/m gradients at 200 T/m/s slew rate. During all scans, an 8-channel head coil (for parallel imaging) and a high-order shimming program (for optimal field homogeneity) were used. High-resolution 3-dimensional anatomical images were acquired with the functional scans in 34 axial slices coplanar (repetition time[TR] = 7700 ms, echo time[TE] = 3.0 ms, flip angle [α] = 12°, field of view[FOV] = 240 mm, voxel size = 0.9 x 0.9 x 4 mm). For each 4 min, 16 s resting-state scan, which measured slow, spontaneous, blood oxygenation-level-dependent (BOLD) fluctuations, a series of 34 interleaved axial functional slices aligned with the anterior/posterior commissure plane were acquired for whole-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact (TR = 2000 ms, TE = 30 ms, α = 60°, FOV = 240 mm, voxel size = 3.75 x 3.75 x 4 mm). Four initial radiofrequency excitations were performed (and discarded) to achieve steady-state equilibrium. Participants were shown a blank gray screen and instructed to lie still with their eyes open, think about nothing in particular, and remain awake.

4.2.4 *fMRI Preprocessing*

Raw resting-state scans were preprocessed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). After removing the initial three BOLD volumes from the scan, AFNI’s 3dDespike was run in order to attenuate any extreme

deviations in the voxel-wise signals. Next, the remaining volumes were slice-time corrected (to slice-time 0) and co-registered with their respective anatomical scans. Functional scans were blurred using a 6 mm isotropic full-width at half-maximum Gaussian kernel and rescaled to percent signal change by normalizing to each voxel's mean BOLD signal intensity. Finally, all scans were resampled to 4.0 mm^3 voxels, and transformed into standard Talairach and Tournoux (1988) space.

AFNI's ANATICOR protocol was used to regress nuisance artifacts from the BOLD data (Jo et al., 2010, 2013; see also Berman et al., 2016; Gotts et al., 2012). First, anatomical scans were segmented using using FreeSurfer (Fischl et al., 2002), and masks were made for ventricles and white matter. These masks were resampled to match the functional scan's resolution, and eroded by 1 voxel to prevent partial volume effects with the gray matter. Prior to smoothing, a single average nuisance time series for the ventricles was calculated using the BOLD data, along with a localized average of white matter, centered on each voxel and averaged within a 40mm-radius sphere (e.g., Jo et al., 2013). Before least-squares model fitting to every voxel's time series, nuisance variables were detrended with fourth-order polynomials. Because physiological data, such as heart rate or respiration, was not collected, the first 3 principal components of the signal from white matter and ventricles were included as nuisance regressors (e.g. aCompCor; see Behzadi et al., 2007 and Muschelli et al., 2014; Stoddard et al., 2016). The full nuisance regression model, therefore, contained one localized white matter time series, one average ventricle time series, six motion parameters, and the first 3 principal components from white matter/ventricular voxels, along with a 4th-order polynomial baseline model. Residual time series were generated by subtracting the best fit time series of this nuisance model from the full, volume registered time series. All scans met a conservative motion cutoff of less than 0.2 mm/TR of mean framewise displacement.

4.2.5 *fMRI Analysis*

All analyses were performed using AFNI (Cox, 1996) and MATLAB. We employed a data-driven, tiered approach to the analyses, and began by calculating mean "connectedness" maps for every participant (AFNI's 3dTcorrMaps, e.g. Cole et al., 2010; Gotts et al., 2012; Salomon et al., 2011; Smith, et al., 2019). To create these whole-brain, subject-level maps, each gray matter (GM) voxel was correlated (Pearson's r) with every other GM voxel in the subject's brain mask (which contained only those voxels with high signal quality [tSNR > 40]). Each GM voxel was then assigned a single value representing the mean of all those correlations. Next, a 3-dimensional Student's *t*-test (AFNI's 3dttest++) was run on the Fischer's Z-transformed connectedness maps with SRP sum scores covaried in order to determine whether global connectivity in any part of the brain could be related to continuous variation in SRP score.

Seed-based tests were then run to elucidate the nature and direction of the functional connectivity effects in the primary connectedness analysis. In the context of the current, nested analytic approach, these seed tests are analogous to the post-hoc testing typically performed during an ANOVA, to clarify the otherwise ambiguous connectedness findings. However, because initial seed detection and post-hoc seed tests were run within the same sample, noise bias in individual participant data could theoretically impact the regions identified during subsequent seed testing. Therefore, to control for such potential bias, the initial connectedness tests were run with leave-one-out cross-validation (LOOCV; e.g. each subject was excluded for one iteration), thresholding maps at $P<.0005$ on each iteration and correcting for whole-brain comparisons to $P<.05$ using cluster size using AFNI's empirical spatial autocorrelation approach (Cox et al., 2017). Only voxels that remained significant

when excluding each individual participant's data over all participants were included in seed masks for post-hoc analyses (see also Smith et al., 2019).

Masks of the resulting, robust clusters were then used as seeds for post-hoc seed-based tests, and subject-level averages of the cleaned residual time series within each seed were computed. The average seed time series were then correlated with all remaining voxels' time series within the group brain mask. SRP scores were then correlated with the resulting whole-brain seed-based correlation maps across subjects, using a voxelwise threshold of $P<5.0x10^{-6}$. Multiple comparisons correction then combined voxelwise testing with multiple seed tests by applying Bonferroni correction to the familywise corrected alpha (e.g. individual seed-based correlation maps were corrected to $P<.05$ divided by the number of seed tests; see also Gotts et al., 2012; Berman et al., 2016). For further data reduction and manageability, resulting regions also had to reach this level of significance in at least 2 of the 10 seed tests. Final resulting regions were then merged with the original seeds to create a composite set of regions.

A correlation matrix was then computed using every possible pair of final significant regions from this composite set. Within the matrix, standard deviation and motion (AFNI's @1dDiffMag, comparable to mean frame-wise displacement in units of mm/TR) were partially correlated with each region-pair to control for any excess noise in the findings (Gotts et al., 2020). To make better sense of relevant patterns of functional organization, the matrix was reorganized according to each region's membership in one of Yeo et al.'s (2011) 7 brain networks. This was done by superimposing a mask of the networks onto the significant regions and then categorizing each region based on the network membership of their peak coordinates.

The same multi-tiered analysis protocol described above was followed for the AQ analysis, which was carried out in a smaller subset of participants (n = 459) who had completed the behavioral measure. To test for any significant sex differences in the effects, separate correlation matrices were created for males and females and slopes between FC and behavioral score were compared. The same matrix-level correlation analysis was carried out to determine whether functional connectivity in regions associated with psychopathic traits could be specifically related to empathic concern (or lack thereof), using the EC subscale of the IRI. An additional exploratory partial correlation analysis was run using EC scores as nuisance covariates, in order to determine which region pairs remained significantly associated with SRP after accounting for lack of empathic concern.

4.4 Results

Descriptive statistics for the SRP and AQ can be found in Table 1 and Figures 1-2. The two measures showed very weak correlation (r=0.101) with one another, indicating that they are largely independent constructs.

Table 1. Behavioral Measure Summary Statistics

Measure	Mean	Min, Max	Correlation (r)	Shared variance (r^2)
SRP-SF (n=924)	47.98(13.23)	29, 93		
			0.101	0.010
AQ (n=459)	104.68(12.23)	68, 151		

Table 1. Descriptive statistics for behavioral measures. Means are mean(standard deviation). Correlations reported for those 459 participants with both measures.

Figure 1. Distribution of SRP-SF Total Scores

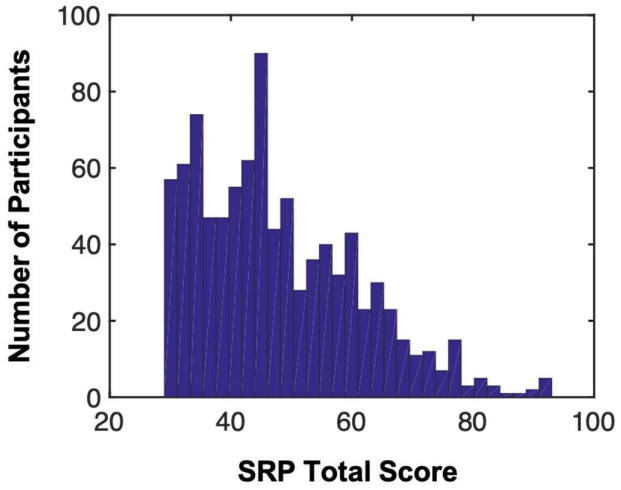

Figure 1. Histogram displaying SRP-SF total scores across the full sample (n = 924) of participants.

Figure 2. Distribution of AQ Sum Scores

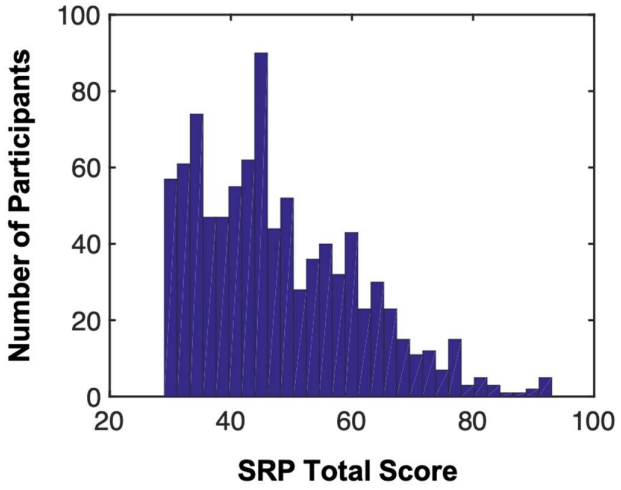

Figure 2. Histogram displaying AQ sum scores across the sub-sample (n = 459) of participants for whom AQ scores were collected.

In the initial mean connectedness analysis for psychopathic traits, significant FC effects were found in 10 clusters after the LOOCV and whole-brain correction (see Table 2). All 10 clusters displayed positive correlations between mean global connectedness and SRP score. Anatomically, these clusters were located in the bilateral paracentral lobules, right

precuneus, right cerebellum, and left superior frontal gyrus, left SMA, left angular gyrus, and throughout the left temporal cortex (see Figure 3). However, in the initial mean connectedness analysis for ASD traits, no clusters were significantly correlated with AQ score after whole-brain correction. Subsequent seed testing was therefore only performed for the SRP, as no potential seeds could be detected for the AQ. Direct comparison of potential regions associated with both psychopathic and ASD traits was addressed by correlating AQ scores within the matrix of regions associated with the SRP (see below).

Table 2. Numbered List of Seed Regions

Seed #	Seed Label	Peak Coordinates[a]
1	R. paracentral lobule & precuneus	(22, -25, 56)
2	L. paracentral lobule	(-46, -17, 48)
3	L. pSTS	(-42, -29, 4)
4	L. angular gyrus	(-42, -65, 36)
5	L. inferior temporal pole	(-54, -5, -28)
6	L. SMA	(-10, -21, 52)
7	L. Superior Frontal Gyrus	(-14, 39, 44)
8	L. MTG	(-66, -37, 0)
9	R. cerebellum crus 1 / VIII	(18, -61, -28)
10	L. STG / rolandic opurculum	(-54, -9, 8)

Table 2. Seeds with mean connectedness displaying significant positive correlations with SRP-SF score, robust to LOOCV. SMA: supplementary motor area, pSTS: posterior superior temporal sulcus, MTG: middle temporal gyrus, STG: superior temporal gyrus
[a]Coordinates are (*x, y, z*) in standard, Taliarach-Tournoux space, peaks based on *T*-statistics.

Post-hoc seed-based tests were performed using each of the above 10 significant clusters as seeds. Regions that survived correction in at least two of the seed tests were

merged with the original seeds in a final map, as some resulting regions overlapped with the seeds. The final map was comprised of a total of 18 regions, including the original seeds. Outside of the seed regions, 8 new areas emerged from the seed tests, including: the bilateral mid-cingulate cortices, bilateral fusiform gyri, right middle frontal gyrus (MFG), right TPJ/middle temporal gyrus, right superior temporal pole, and an additional node in the right cerebellum (lobule VI) (see Table 3 and Figure 4). All 18 regions were then organized into networks according to the Yeo et al. (2011) 7-network parcellation. With the exception of the two cerebellar nodes (which are hereafter categorized as the "cerebellar network"), the regions intersected with 5 out of 7 of the Yeo et al. (2011) networks: visual, somatomotor, ventral attention (VAtt), limbic, and default mode (DMN) (refer to Table 3).

Figure 3. Seed regions associated with SRP

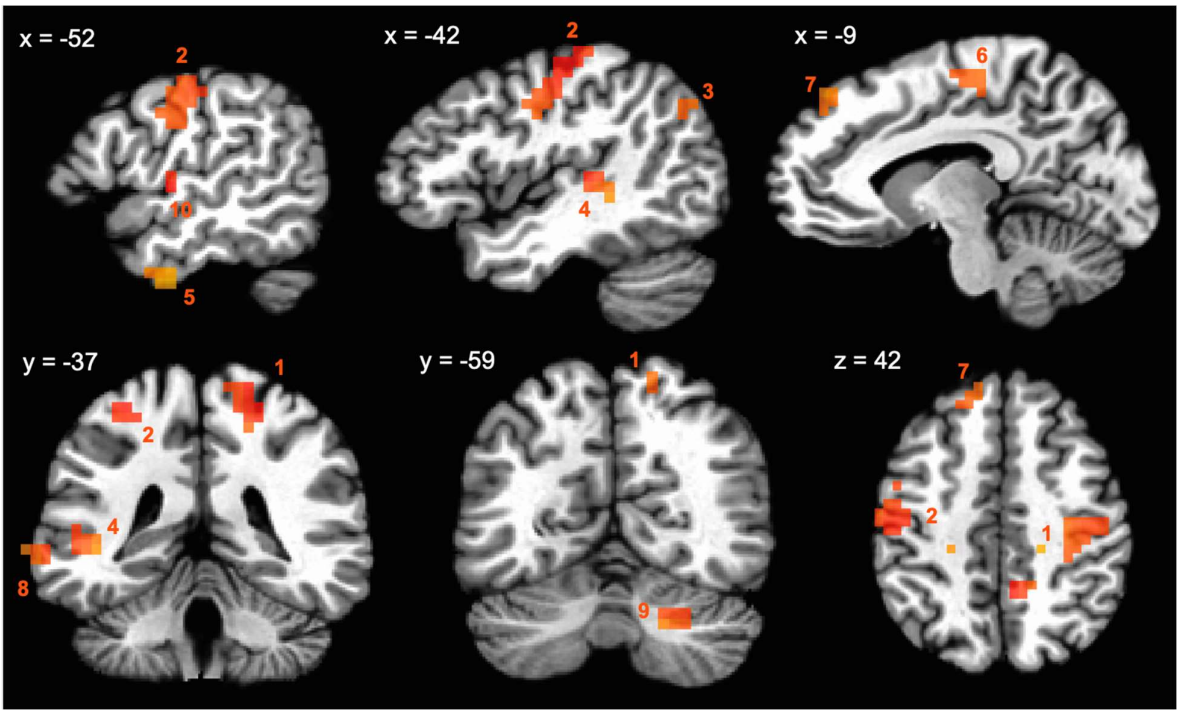

Figure 3. Seed regions detected with significant positive correlations between global connectedness and SRP-SF score, after LOOCV. Numbered regions correspond to those listed in Table 1.

Table 3. Final 18 Resulting Regions

Region #	Region Label	Peak Coordinates[a]	Network[b]
1	L. fusiform gyrus	(-42, -57, -16)	Visual
2	R. fusiform gyrus	(50, -61, -12)	Visual
3	R. paracentral lobule & precuneus	(46, -9, 24)	Somatomotor
4	L. paracentral lobule	(-50, -1, 28)	Somatomotor
5	L. STG/rolandic operculum	(-54, -9, 4)	Somatomotor
6	R. mid-cingulate cortex	(10, -5, 36)	Somatomotor
7	L. mid-cingulate cortex	(-10, -9, 36)	Somatomotor
8	R. superior temporal pole	(54, 11, -4)	Somatomotor
9	L. precuneus & SMA	(-14, -41, 40)	Ventral Attention
10	R. MTG/TPJ	(54, -53, 8)	Ventral Attention
11	L. inferior temporal pole	(-50, -5, -32)	Limbic
12	L. pSTS	(-42, -37, 0)	Default Mode
13	L. angular gyrus	(-42, -65, 32)	Default Mode
14	R. middle frontal gyrus	(27, 27, 36)	Default Mode
15	L. superior frontal gyrus	(-10, 43, 40)	Default Mode
16	L. MTG	(-66, -41, -8)	Default Mode
17	R. cerebellum crus I/VIII	(26, -61, -32)	Cerebellar
18	R. cerebellum lobule VI	(30, -53, -20)	Cerebellar

Table 3. Numbered Key of regions resulting from seed-based tests combined with original seeds. Regions correspond to figures 3-4. STG: superior temporal gyrus, SMA: supplementary motor area, MTG: middle temporal gyrus, TPJ: temporoparietal junction, pSTS: posterior superior temporal sulcus.
[a]Coordinates are (x, y, z) in standard Talairach-Tournoux space, peaks from corrected conjunction map of seeds and resulting regions.
[b]Aside from cerebellar, networks refer to those defined by Yeo et al (2011).

Figure 4. Final 18 regions associated with SRP

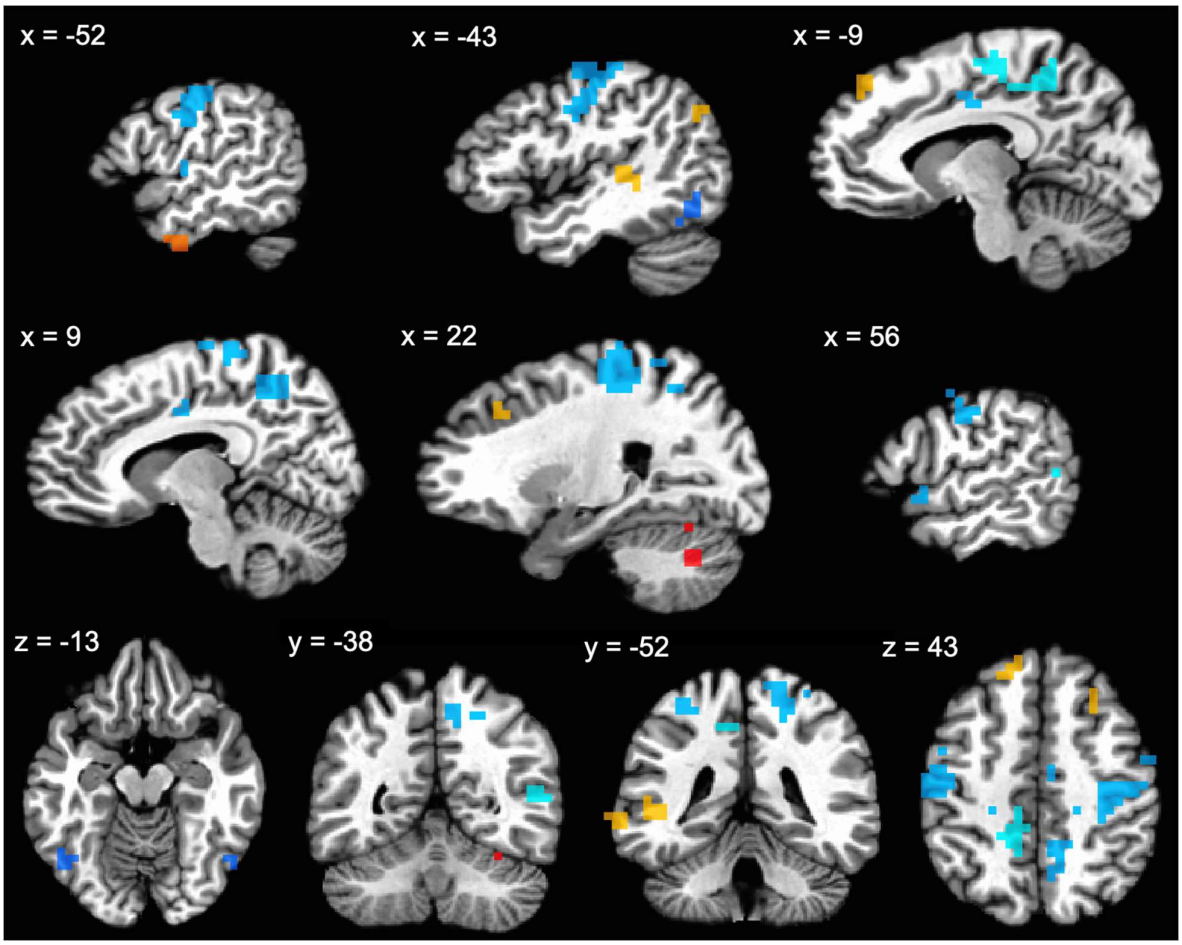

Figure 4. Merged map of all 18 regions with FC significantly (positively) related to SRP score. Regions are individually listed in Table 3. Colors correspond to network membership (also listed in Table 3). Dark blue = visual, light blue = somatomotor, cyan = ventral attention, yellow = default mode, orange = limbic, red = cerebellum.

Next, a full (18x18) pairwise correlation matrix, with motion and standard deviation covaried, was generated to examine all possible inter-region combinations whose FC could be associated with SRP score. The resulting heatmap of *r*-values revealed a widespread pattern of positive associations between SRP score and pairwise FC, and these positive relationships remained significant in 62 of the possible region combinations, after correcting for false discovery rate (FDR; $q<.05$; see Figure 5A-B). Increased FC was observed within and between networks, most prominently featuring the limbic, default mode, and cerebellar

networks. In fact, 52 of the 62 significant region pairs had nodes in these 3 networks. Within- and between-network connectivity of somatomotor regions accounted for the remaining 10 pairs.

Figure 5A. SRP correlation matrix

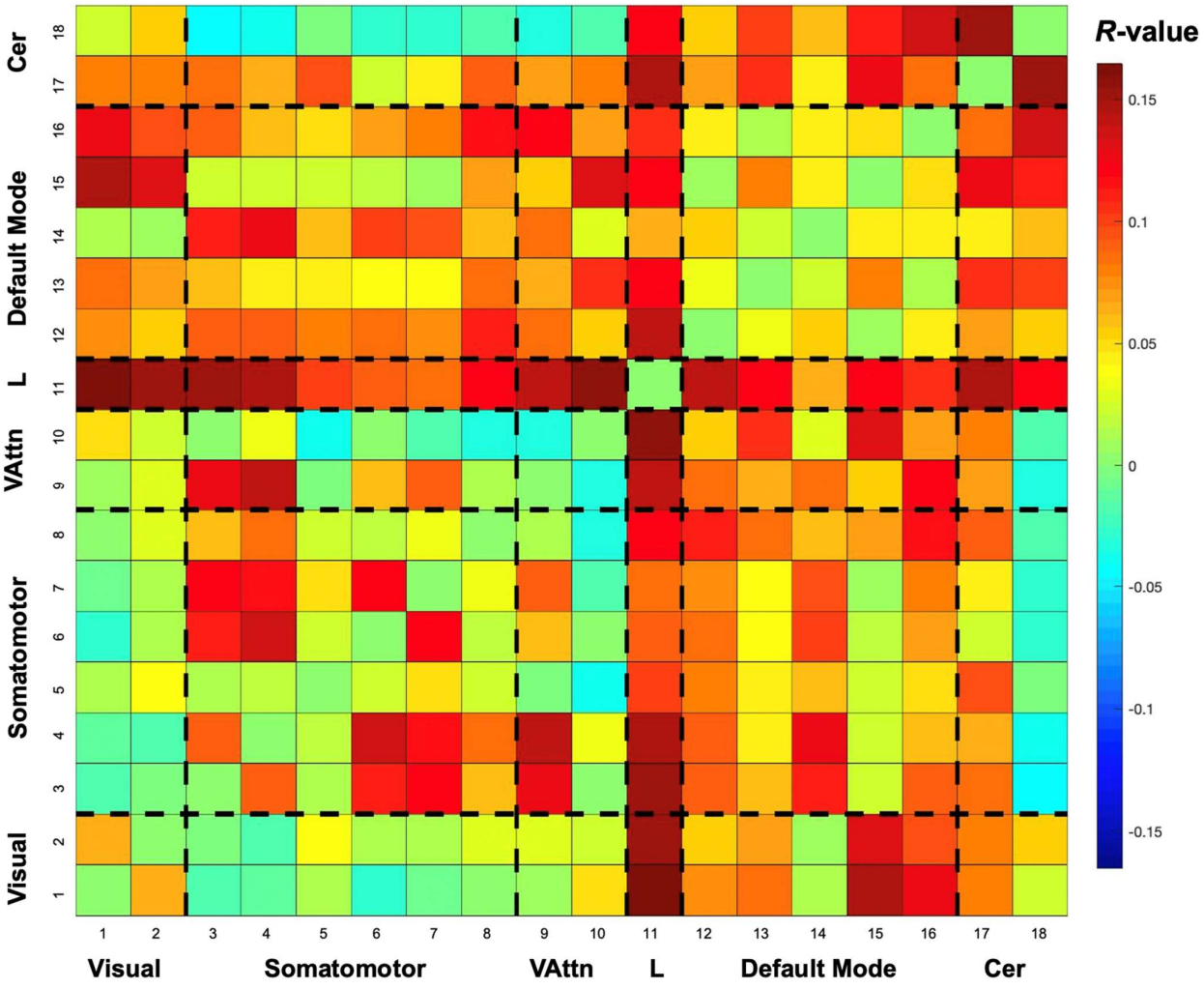

Figure 5A. Pairwise correlation matrix for SRP score with standard deviation and motion covaried. Dashed lines demarcate networks. VAttn: ventral attention network, L: limbic network, Cer: cerebellar network. Colors correspond to partial *r*-values. Axis numbers correspond to each of the final 18 regions listed in Table 2.

Figure 5B. SRP-SF significant *P*-value matrix

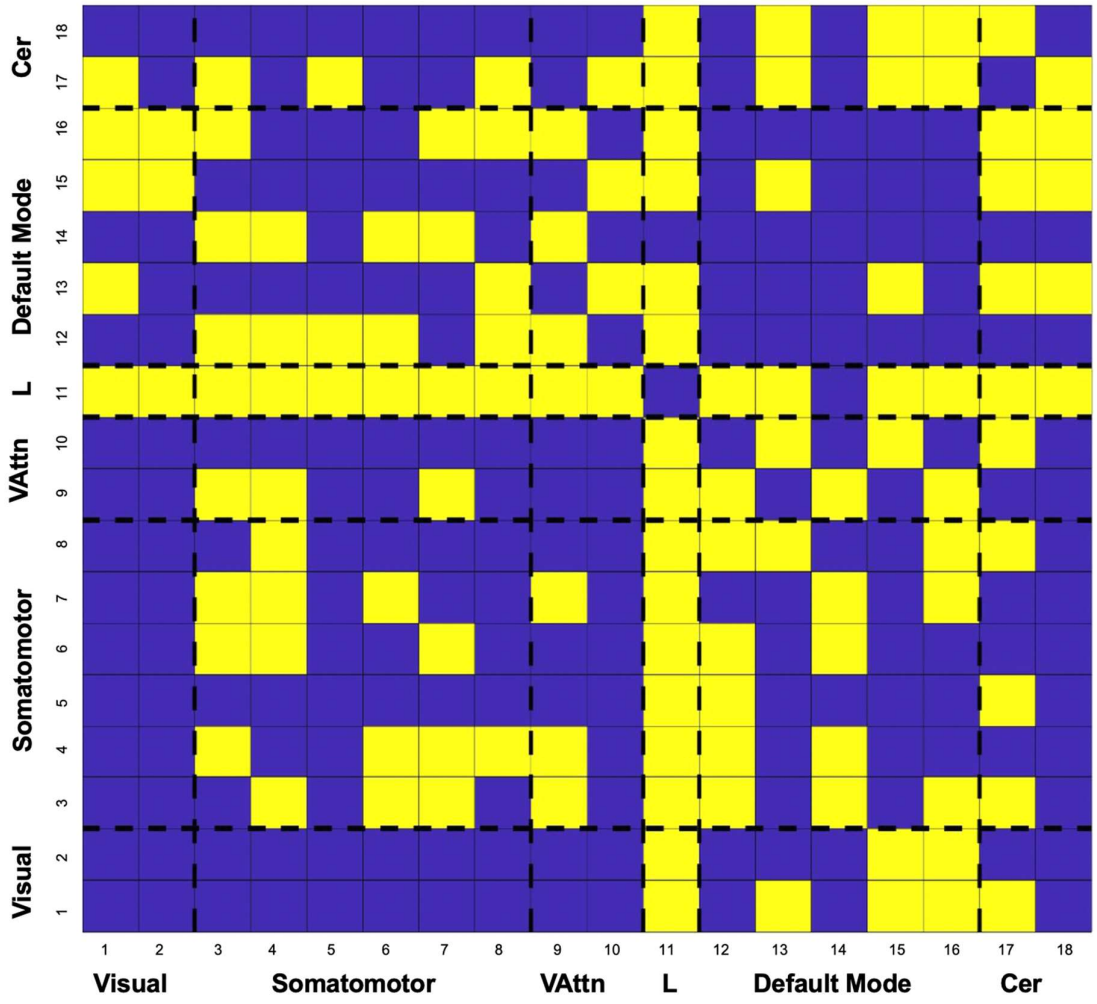

Figure 5B. FDR-corrected *P*-value matrix based on pairwise correlation matrix (Figure 5A). Yellow cells indicate significant region pairs (*P*<.0181). Dashed lines demarcate networks. VAttn: ventral attention network, L: limbic network, Cer: cerebellar network. Colors correspond to partial *r*-values. Axis numbers correspond to each of the final 18 regions listed in Table 2.

While it was not possible to directly compare regions associated with psychopathic and ASD traits due to the lack of results for the AQ measure, a secondary comparison was done at the matrix level. Within the 18-regions resulting from the SRP analyses, functional connectivity data from those participants with AQ scores was correlated with AQ score, with motion and standard deviation covaried. Across all region pairs, there were no significant relationships between functional connectivity and AQ score that survived FDR correction.

To further probe the degree of difference between the AQ and SRP at this matrix-level, the summed squared distance was calculated between correlation values in the AQ and SRP matrices. This value was then compared to chance-level distances obtained via permutation testing (by randomly shuffling behavioral scores across participants). The distance between correlation values in the AQ and SRP matrices was significantly greater than chance-level distances ($P<.0073$, 2-tailed by permutation).

To probe for any potential sex differences in the main SRP findings, separate correlation matrices were computed for males and females, and were tested for significant differences. Across all region pairs, there were no FDR- or Bonferroni-corrected differences between males and females with respect to the slope of functional connectivity and SRP score.

In order to determine whether functional connectivity in any regions associated with psychopathic traits was specifically related to a lack of empathy, an additional 18x18 correlation matrix was computed using EC scores from the IRI. The resulting connectivity heatmap of *r*-values consisted of primarily negative, rather than positive associations with EC scores (Figure 6A). Only one pair of regions (whose functional connectivity was negatively related to EC score) survived FDR correction ($q<.05$): the left inferior temporal pole (limbic network), and right MTG/TPJ (ventral attention network). EC scores were also used as nuisance covariates in a follow-up analysis of the initial SRP effects, and 44 of the 62 original region pairs remained significantly associated with the SRP after FDR correction ($P<.0122$, $q<.05$). The regions that were no longer significant spanned across all networks involved (see Figure 6B),

Figure 6A. IRI-EC correlation matrix

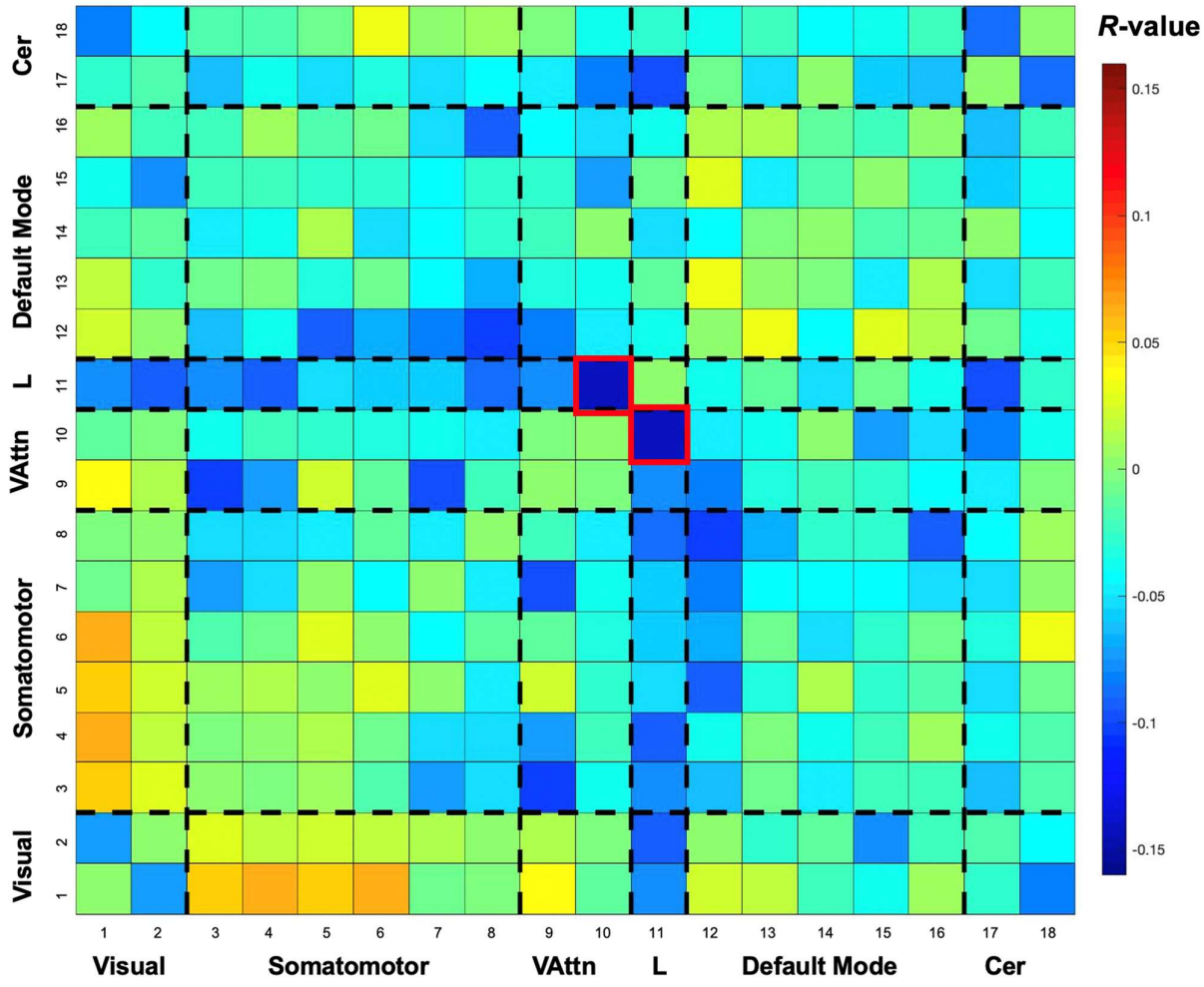

Figure 6A. Pairwise correlation matrix for IRI-EC score in regions derived from SRP analysis, with standard deviation and motion covaried. Cells outlined in red are significant after FDR correction. Dashed lines demarcate networks. VAttn: ventral attention network, L: limbic network, Cer: cerebellar network. Colors correspond to partial *r*-values. Axis numbers correspond to each of the final 18 regions listed in Table 2.

Figure 6B. Significant Region Pairs related to SRP after Covarying EC

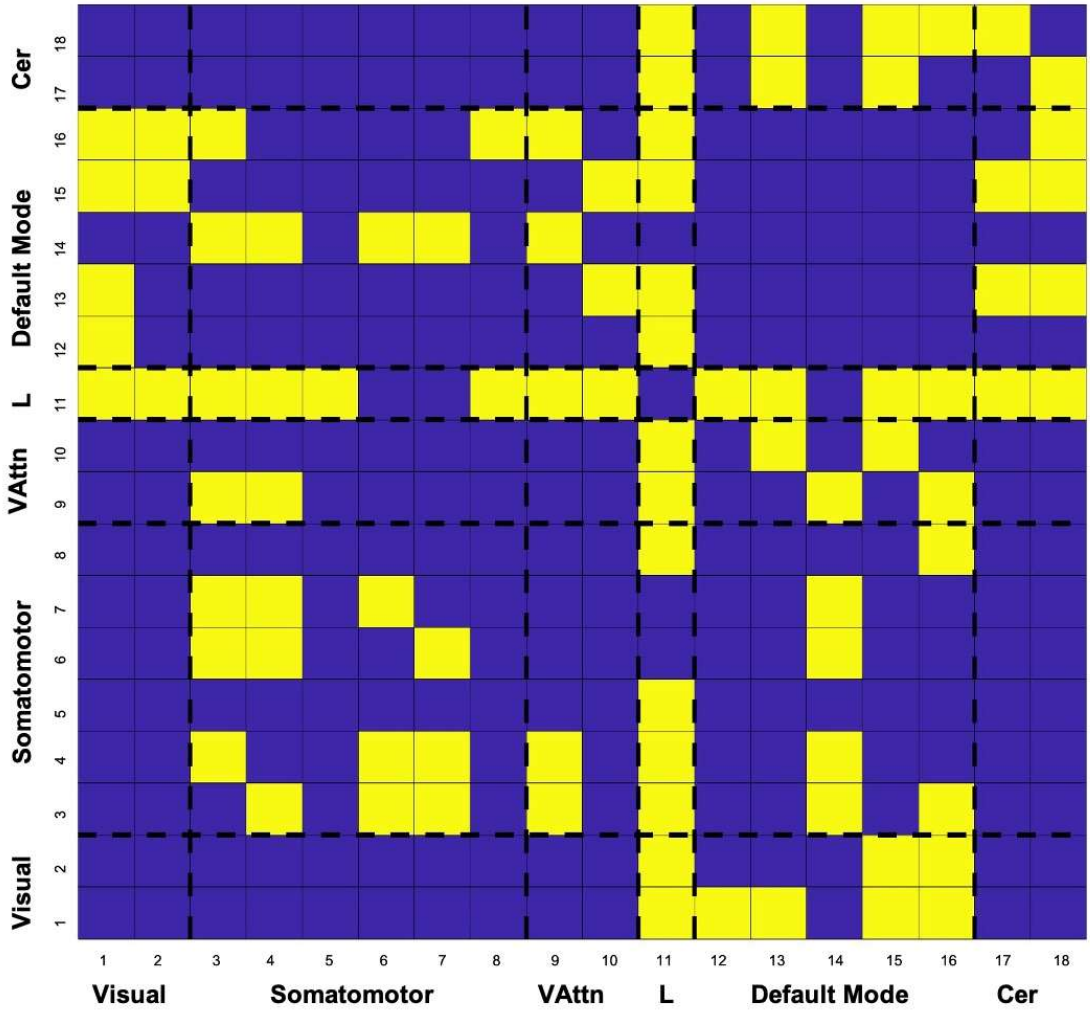

Figure 6B. Matrix indicating regions pairs with FC that remain significantly related to SRP after empathic concern (EC), standard deviation, and motion are covaried. Yellow cells represent pairs where $p<.0122$ and $q<.05$. Dashed lines demarcate networks. VAttn: ventral attention network, L: limbic network, Cer: cerebellar network. Axis numbers correspond to each of the final 18 regions listed in Table 2.

4.5 Discussion

The aim of the current study was to identify the resting-state functional correlates of continuous variation in psychopathic and ASD traits in a large community sample. The study also aimed to directly compare the regions or networks whose functional connectivity was implicated in each trait domain. Finally, measurement of empathic concern was also included in order to investigate whether reduced empathic concern contributed to explaining any resting-state functional connectivity features associated with psychopathic or ASD traits.

In the investigation of psychopathic traits, initial connectedness analyses revealed 10 seeds with positive associations between global connectedness and SRP scores. After follow-up seed testing, a total of 18 regions across 6 different networks emerged with this same relationship, and the predicted prefrontal, paralimbic, and motor areas were all represented. Although resting-state findings in the clinical/forensic literature have been mixed with respect to whether psychopathic traits are mainly related to functional connectivity increases (Cohn et al., 2015; Leutgeb et al., 2016), decreases (Motzkin et al., 2011; Philippi et al., 2015), or both (Korponay et al., 2017; Espinoza et al., 2019), the current study found only increases in functional connectivity to be associated with higher levels of psychopathic traits in healthy young adults. The current results show moderate agreement with some prior resting-state findings, particularly in the cingulate cortex, cerebellum lobule IV, and prefrontal cortex, where increases in functional connectivity have been associated with levels of psychopathic traits (Cohn et al., 2015; Espinoza et al., 2019; Leutgeb et al., 2016). However, other studies have found the opposite pattern of functional connectivity decreases in these same areas (Motzkin et al., 2011; Philippi et al., 2015).

Motor and default mode networks have both been implicated in prior resting-state studies of psychopathy (Cohn et al., 2015; Espinoza et al., 2019; Philippi et al. 2015), but these effects were specific to individual sub-components of psychopathy rather than overall psychopathic traits. Furthermore, two studies (Espinoza et al., 2019; Philippi et al., 2015) observed functional connectivity decreases in these areas, rather than the increases seen in the current study.

Clinical/forensic resting-state studies have not emphasized associations between overall levels of psychopathic traits and atypicalities in temporal lobe functional connectivity, but the current study revealed a positive association between psychopathic traits and functional connectivity in healthy young adults across multiple temporal regions including the STS, STG, MTG, TPJ, and temporal poles. It is important to note that the extant resting-state studies of psychopathy and psychopathic traits have been conducted in prison populations with no healthy, non-incarcerated comparison groups.

Contrary to our predictions, reward-related areas such as the striatum were not found to be associated with overall psychopathic traits. It is therefore possible that disruptions to resting-state reward circuitry are only apparent in clinical populations who suffer from impulse control and substance use disorders.

One prevailing theory of psychopathy, referred to as the impaired integration theory, frames functional connectivity findings in the context of larger resting-state networks, and proposes that in combination with underlying genetic or biochemical vulnerability, functional disorganization and reduced modularity of associative brain networks, disrupts efficient perceptual integration (Hamilton et al., 2015). This ultimately impairs empathic processing

and leads to the psychopathic/antisocial phenotype. When examined through a similar brain-network lens, the current findings are characterized by increased between-network connectivity, or reduced network segregation. The limbic, cerebellar, and default mode networks were featured most prominently in this pattern, but functional connectivity between the somatomotor and ventral attention networks was also positively associated with psychopathic traits. Increased within-network functional connectivity was observed as well, in all but the visual and ventral attention networks. Although the impaired integration theory was based on findings of mainly decreased connectivity, the current study's finding of increased connectivity within and between networks could still impact the efficiency with which certain cognitive and affective computations related to the empathic process are performed, thereby resulting in higher degrees of psychopathic-like behavior. For example, it is possible that increased functional connectivity between associative and somatomotor regions reduces appropriate inhibition, and contributes to increases in the impulsive, aggressive elements of psychopathic traits. Interestingly, alterations in functional network structure have also been linked to other types of psychopathology, including depression, anxiety, bipolar disorder, and schizophrenia (Menon, 2011; Stoddard et al., 2016).

In the exploration of empathic concern's contribution to the functional connectivity findings in psychopathic traits, the overall pattern of negative associations with empathic concern where positive associations were observed for psychopathic traits was not surprising given that the EC subscale measures the strength of an individual's empathic concern. Higher scores indicate greater levels of empathy, whereas higher SRP scores theoretically indicate lower levels of empathy. Based on the current findings, functional connectivity between the left temporal pole and the right MTG/TPJ appears to be significantly associated with both empathic concern and psychopathic traits, whereby reduced connectivity is related

to higher levels of empathy and increased connectivity is related to higher levels of psychopathic traits (e.g. lower levels of empathy). It remains unclear whether this is a network-level phenomenon involving the limbic and ventral attention networks or is limited to these specific nodes. The right TPJ has been implicated in the process of understanding others' mental states (Saxe & Kanwisher, 2003; Saxe & Wexler, 2005; Sommer et al., 2010), moral decision-making (Young et al., 2010) and competition versus cooperation (Bitsch et al., 2018). The temporal pole has also been implicated in social and affective processing, and may serve a role in integrating perceptual information with socio-affective responses (Olson et al., 2007; Ross & Olson, 2010). However, the specific mechanism by which levels of functional connectivity between these two regions contribute to trait-level empathic abilities remains unclear. While no other regions were significantly related to EC, a number of region pairs were lost after covarying EC score in the psychopathic trait analysis. This indicates that empathic concern helps to partially account for the initial findings.

No seeds (and therefore no resulting regions) were extracted from the analysis of ASD traits using the AQ. There is little precedent to help interpret the lack of findings related to ASD traits, but one potential factor could be the particular measure used to assess this trait domain. For example, in the one resting-state study that examined ASD traits in healthy adults, the researchers used the SRS rather than the AQ as a measurement tool (Di Martino et al., 2009). The current null findings could also indicate an all-or-nothing pattern of neural alterations in ASD. At least in the context of resting-state functional connectivity, it appears that significant changes may not be seen unless ASD traits fall closer to or within the clinical range. Further resting-state research using alternative measures of ASD traits is warranted in order to determine whether any relationship with functional connectivity exists at the subclinical level.

It is also of note that no significant relationships were found between functional connectivity and ASD traits in any of the regions that were associated with psychopathic traits. Additionally, within these regions, correlation values between functional connectivity and ASD traits were significantly different (based on Euclidean distance permutation tests) from those observed for psychopathic traits. This suggests that these two trait domains have largely distinct resting-state neural underpinnings.

4.4.1 *Limitations*

There were some limitations to the current study. While the relatively narrow age range in the current sample could also be seen as a strength in that it helps to control for developmental artifacts, the current results still only pertain to well-functioning young adults and inferences cannot be made about individuals in other life stages. It would be valuable to explore the relationship between resting-state functional connectivity and psychopathic and ASD traits longitudinally or across the lifespan, with a particular focus on the initial development of resting-state networks and origination of psychopathic and ASD traits. We were unable to detect any link between ASD traits and resting-state functional connectivity, and it may be the case that in typically developing populations, ASD traits cannot be measured with as much specificity as psychopathic traits. Additional research with alternative ASD-trait measurement tools is also warranted, in order to determine whether ASD traits can be reliably linked to resting-state network organization or regional variations in connectivity. On their own, the current findings are difficult to interpret mechanistically, so it would also be valuable to explore task-based changes in the observed patterns of functional connectivity, paying particular attention to the order of activation in the regions currently implicated.

4.6 Conclusions

The current study provides novel information about the resting-state neural underpinnings of individual variation in psychopathic traits. Increased within- and between-network connectivity, particularly across nodes of the limbic, cerebellar, and default mode networks was associated with higher levels of psychopathic traits, and reduced empathic concern partially accounted for these findings. Both psychopathic traits and empathic concern were directly related to functional connectivity between the temporal pole and TPJ. The positive association between connectivity and psychopathic traits could be reflective of altered integration of sensory stimuli, altered motor inhibition, or altered streams of neural information processing. The current study did not find any regions whose functional connectivity could be related to ASD traits, nor did it find any shared functional connectivity features between psychopathic and ASD traits. This supports the idea that these two trait dimensions are underpinned by partially distinct patterns of functional neural architecture. Additional research in neurotypical children and adults is warranted to gain a more comprehensive understanding of the neural correlates underlying psychopathic and ASD traits throughout development.

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CHAPTER 5

ALTERED RESTING-STATE FUNCTIONAL CONNECTIVITY IN MALE YOUTHS WITH CONDUCT PROBLEMS AND CALLOUS-UNEMOTIONAL TRAITS

Abstract

Children and adolescents with conduct problems (CP) and high levels of callous unemotional (CU) traits are at increased risk of developing psychopathy in adulthood. While structural and task-based neuroimaging studies have reported patterns of atypical volume and activation in these children, to date, few studies have used resting-state functional magnetic resonance imaging (fMRI) to investigate the functional connectivity correlates of psychopathy risk. The current study sought to identify any atypicalities in baseline brain activity in children at greatest risk for pervasive antisocial behavior. Resting-state fMRI scans were collected from 73 boys: 20 with CP and high CU traits (CP/HCU), 18 with CP and low CU traits (CP/LCU), and 35 typically developing (TD) controls. High and low CU groups were determined using a median split approach. Global functional connectivity was compared across groups. A total of 8 seed regions emerged, with significantly increased global functional connectivity in boys with CP/HCU relative to TD boys. No significant differences were found between the CP/LCU and TD boys. Follow-up seed testing revealed that increased functional connectivity between a total of 22 regions across functional networks was driving the significant difference between CP/HCU and TD groups. Results particularly highlighted nodes from limbic and somatomotor regions including the OFC, vmPFC, temporal poles, insula, and paracentral gyri. These findings appear to converge with those reported in Chapter 4, and suggest also suggest that overconnectivity or network

disorganization might impact socio-affective information processing contribute to the CP/HCU phenotype.

5.1 Introduction

Conduct problems (CP) are comprised of persistent aggressive, defiant, and antisocial behaviors that emerge during childhood or adolescence (Frick, 2016). Children with CP not only struggle academically and interpersonally, but they are also at an increased risk of engaging in reckless, law-breaking behavior and consequently spending time in juvenile detention, or later, prison (with higher rates of recidivism) (Erskine et al., 2016). Youths with CP are also more likely to develop a range of other mood, personality, and substance use disorders (Erskine et al., 2016; Wertz et al., 2018). The public health (and economic) burden related to these aggressive and disruptive issues in children has been met with growing concern (D'Amico et al., 2014; Erskine et al., 2014; Frick, 2016; Rivenbark et al., 2017). In recent years, a great deal of research has been aimed at understanding the heterogeneity observed in the presentation of CP, and at finding ways to identify neurobiological abnormalities associated with CP and its poor long-term outcomes.

Under the heterogeneous umbrella of CP, some children possess high levels of callous unemotional (CU) traits while others do not (Frick & Viding 2009; Frick et al., 2014). High levels of CU translate to a profound lack of empathy, lack of remorse, blunted affect, and cruel, violent inclinations (Frick et al., 2014; Viding & McCrory, 2018). It has been suggested that CU traits stem from deficits in basic cognitive-affective mechanisms, including reinforcement- or outcome-based learning, and responding to others' distress (Blair 2013; Blair et al., 2014; Lockwood et al., 2013; Pardini & Byrd, 2012). While all children

with CP exhibit aggressive and defiant behavior to some degree, those with CP and high CU traits (CP/HCU) are more likely to engage in deliberate violent or illegal actions without any guilt or remorse, and to exhibit more severe and persistent antisocial behavior than those with lower levels of CU traits (CP/LCU) (Kahn et al., 2013; Longman et al., 2016). Furthermore, because CU traits often persist beyond childhood, children with CP/HCU are also believed to be at a heightened risk of developing psychopathy later in adulthood (Lynam et al., 2007; Viding & McCrory, 2018; Viding & Kimonis, 2018). Twin studies have also found higher degrees of heritability in antisocial behavior in children with CP/HCU compared to those with CP/LCU, underscoring the notion that CU traits are distinct from CP as a whole (Viding et al. 2005; Viding, Larsson, & Jones, 2008).

Given that CP/HCU is associated with such poor and pervasive outcomes, it is of interest to develop a comprehensive understanding of different features associated with this group of children, including related neurobiological characteristics. It is also important to evaluate the degree to which such characteristics differ from those observed in children with CP/LCU, or in typically developing (TD) peers without concerning behavioral problems. Neuroimaging studies have begun to characterize atypicalities in the brain associated with CP, and have also begun to differentiate between the aforementioned CP subgroups.

Abnormalities in limbic/paralimbic grey matter and cortical thickness have been reported in a number of structural magnetic resonance imaging (MRI) studies of children with CP (e.g. in amygdala, temporal cortex, orbitofrontal cortex [OFC], ventromedial prefrontal cortex [vmPFC], insula, and anterior cingulate cortex [ACC]) (Fahim et al., 2011; Fairchild et al., 2011; Huebner et al., 2008; Hyatt et al., 2012; Rogers & De Brito, 2016; Sebastian et al., 2016; Sterzer et al., 2007; Wallace et al., 2014). However, studies that have

taken CU traits into consideration suggest that many of these structural abnormalities are particularly characteristic of individuals with high levels of these traits (Caldwell et al., 2019; Cardinale et al., 2019; Cohn et al., 2016; Sebastian et al., 2016; Wallace et al., 2014). One study noted an interesting interaction whereby CP scores were positively associated with grey matter concentration (GMC) in the amygdala, while CU scores showed the opposite (negative) relationship with amygdala GMC (Cohn et al., 2016). In a study that viewed high CU traits categorically rather than continuously, significantly reduced grey matter in the OFC, ACC, amygdala, and insula were reportedly unique to the CP/HCU group alone, but did not characterize the participants with CP/LCU (Sebastian et al., 2016). Widespread microstructural (white matter) connectivity abnormalities have also been identified in individuals with CP/HCU, including in tracts that connect many of the regions above (Breeden et al., 2015; Puzzo et al., 2017)

In functional MRI (fMRI) studies of CP and CU traits that have employed emotion-processing or reinforcement-learning-based tasks, these same limbic/paralimbic regions (e.g. amygdala, ACC, insula, vmPFC, etc.) emerge, often exhibiting blunted task-related activation patterns compared to what is seen in healthy controls (Finger et al., 2008; Jones et al., 2009; Lockwood et al., 2013; Marsh et al., 2008; Viding et al., 2012; White et al., 2012). In one such study, youths with CP showed reduced responses to others' pain in the insula, ACC, and inferior frontal gyrus, compared to controls, and response reductions in the ACC and insula were directly linked to levels of CU traits (Lockwood et al., 2013). However, while task-based fMRI studies have provided clues regarding the neural basis of CP behaviors, they only capture a limited part of the broader neurobiological picture and can suffer from poor reliability and blunted ability to capture individual differences (Elliott et al., 2020).

Resting-state fMRI is a potentially valuable tool for investigating functional neural atypicalities associated with CP and CU traits. This imaging approach focuses on baseline brain function and examines the degree of coherence in spontaneous activity across the brain (referred to as functional connectivity). It has been shown to have reasonable reliability and sensitivity to individual differences that appears more robust than that found for task-based fMRI (Elliott et al., 2020). Resting-state functional connectivity provides a blueprint for the brain's dynamic 'wiring' and this functional organization is thought to underlie individual differences in behavior. Although resting-state fMRI studies have proliferated in the exploration of psychopathology, to date very few peer-reviewed studies have applied this methodology to CP, and even fewer to understand potential heterogeneity driven by CU traits. Further investigation of CP samples that afford differentiation based on HCU vs. LCU may provide insights into candidate developmental risk factors for psychopathy. Such insights have the potential to inform early interventions that modulate neurobiological characteristics, an approach that is already showing promise in other clinical disorders (Gonzalez-Castillo et al., 2020). For example, resting-state findings have guided development of neurofeedback interventions for autism spectrum disorders with encouraging initial results (Ramot et al., 2017).

To date, few peer-reviewed studies have used resting-state fMRI to explore the functional connectivity correlates in samples with CP that include measurement of CU traits. One study carried out in a youth arrestee sample found that CU traits were associated with increased FC within the anterior default mode network, but no healthy comparison group was included in the study, making it difficult to interpret the findings (Cohn et al., 2015). A second study found relatively widespread increases in FC within and between networks in the CP group compared to typically developing (TD) adolescents, but also found higher levels of

CU traits to be associated with *reduced* frontoparietal-default mode network connectivity (Pu et al., 2017). However, the authors mention that CU trait levels (as measured by the Antisocial Personality Screening Device [APSD], Vitacco et al., 2003) within their CP sample were relatively low, with only 3 participants scoring >20, and that CU scores in the control group were higher than expected (Pu et al., 2017). In addition, the common use of group independent components analysis (ICA) to process data involving clinical samples may not be optimal. In ICA, all data is aggregated and denoised together, which makes the assumption that intrinsic dimensionality of the signal is equivalent across groups/participants, and this may not be the case, especially when comparing clinical and TD samples.

In a very recent study, Werhahn and colleagues (2020), observed reduced functional connectivity between the PCC and frontal pole, and between the anterior insula, OFC, and frontal pole in children and adolescents with disruptive behavior disorders and varying comorbid attention deficit/hyperactivity disorder (ADHD), compared to healthy controls. However, within the clinical group, high levels of CU traits were actually found to be associated with significant *increases* in FC among a range of regions including the insula, ACC, posterior cingulate (PCC), precuneus, medial PFC, paracentral lobules, angular gyrus, and cerebellum. There is notable spatial overlap between these regions and those implicated in much of the existing structural and functional imaging literature of CP and CU traits. It is worth noting that Werhahn et al (2020) were interested mainly in aggression subtypes and therefore selected a-priori regions of interest related to aggression specifically, which limits the potential for findings to emerge beyond those seed regions. Furthermore, the study used CU traits as a continuous rather than a categorical variable.

Although many previous studies have included CU traits as a continuous variable to clarify group differences, this may be problematic. There is evidence to suggest that effects of CU traits do not typically emerge as interactions, and suppressor effects can obscure correlational analyses (Frick, 2012). In the past, a median split approach has successfully differentiated groups of children with CP who exhibit different patterns of cognitive and affective processing, but given the nature of these processing patterns, when the groups are pooled together, deficits are far more difficult to detect (Schwenck et al., 2012; Viding et al., 2012). By focusing on groups with CP/HCU and CP/LCU, translational findings can be more easily interpreted and can still be explored via continuous analyses, post-hoc. It is also of note that in the context of bivariate normality, dichotomizing raises concerns about reduced power (Cohen, 1983), but distributions of CP and CU traits do not show bivariate normality, as high levels of CP often exist without high levels of CU traits, but high levels of CU traits are almost always associated with high levels of CP (Fontaine et al., 2011). For these reasons, and to directly compare CP/HCU and CP/LCU groups, we have opted to use a median split approach in the current study, bifurcating the CP sample into those with CP/HCU and those with CP/LCU (See Figure 1).

To date, no study has employed a whole-brain data-driven approach to comparing resting-state functional connectivity across groups of children with CP/HC, CP/LCU, and TD peers. The aim of the current study was to address gaps in the existing literature by exploring baseline brain activity that is specific to children with CP/HCU, compared to those with low CU traits and TD controls. This comparison was meant to clarify the cumulative neurobiological burden of CP/HCU compared to the other two groups, as CP/HCU has been associated with the poorest outcomes. Furthermore, the current study assumes a fully data-driven approach without any a-priori seeds, thereby allowing for any/all robust group

differences to emerge. Because the prior evidence base in this area is so limited we were not able to make strong predictions. Based on the continuous analyses of Werhahn et al (2020), we tentatively predicted that compared to TD peers, children with CP/HCU would show functional connectivity increases within and between limbic/paralimbic areas including the cingulate cortex, medial PFC and insula, and perhaps also in somatomotor areas. We predicted that children with CP/LCU would either not differ from TD peers in the functional connectivity within and between these areas, or that the differences would not be as pronounced as those seen for the CP/HCU group.

5.2 Materials and Methods

5.2.1 *Participants*

Families in and around London, UK were recruited using print advertisements in the newspaper, and by contacting local schools, including those with special education schemes for children who struggle with behavioral problems. Detailed information sheets were provided to Parents/caregivers as well as to the boys participating in the study, and research staff were present to answer questions and provide clarification about their participation. Written informed consent was obtained from all parents/caregivers and all boys also provided written assent to participate. Researchers were trained by an experienced clinician on how to work appropriately and sensitively with boys with CP and their families. Any participants who were using prescription medication for behavioral difficulties, who reported a neurological disorder, who received a formal diagnosis for autism spectrum disorder, or whose cognitive ability was below 70 on a standardized assessment were excluded from the study. All families visited the lab premises at University College London to participate in the

research and received £50 to cover lunch and travel expenses. The current study was part of a larger research protocol, which was approved by the University College London Research Ethics Committee (Project ID number: 0622/001). One hundred and fifty-eight families were screened for participation. Due to scheduling conflicts, noncompliance, or exclusion criteria, sixty-nine families did not participate. Of eighty-nine eligible families who participated in scanning, fifteen were excluded from the study (4 TD, 5 CP/HCU, 6 CP/LCU) due to incomplete data or excessive head motion while inside the scanner, which exceeded a threshold of .3 mm of framewise displacement (e.g. Berman et al., 2016). The final sample for the current study therefore consisted of a total of 73 boys (age 11-17): 38 with CP (20 CP/HCU, 18 CP/LCU, see Figure 1), and 35 TD control participants (See Table 1 for participant demographic information).

5.2.2 *Screening Measures*

Prior to participation, behavioral questionnaires were completed by parents/caregivers and teachers to measure CP and levels of CU traits in the participants. Where both types of informant report was available, final item-level scores were reflective of the highest rating from either informant (Piacentini et al., 1992). The *Child and Adolescent Symptom Inventory* (CASI-4R; Gadow & Sprafkin, 2009), Conduct Disorder scale (CASI-CD), was used to assess CP, as this is a commonly used measure that exhibits good validity and reliability (Sprafkin et al., 2002). Boys were included in the CP group if CASI-CD scores from either parents or teachers met their respective severity thresholds (parent report = 4+ (ages 10–12) and 3+ (ages 13–16) or teacher report = 3+ (ages 10–12), 4+ (ages 13–14), and 6+ (ages 15–16)), as these scores are associated with a clinical diagnosis of conduct disorder (Gadow & Sprafkin, 1998). The current study includes 38 boys who met the research diagnostic criteria for conduct problems.

CU traits were measured using the *Inventory of Callous-Unemotional Traits* (ICU; Essau et al., 2006). Within the CP group, boys were divided into CP/HCU and CP/LCU groups based on a median split of the ICU scores. In the current study, eighteen boys scored less than or equal to 42, which placed them in the LCU group, and twenty boys scored above 42, thereby meeting the criteria for CP/HCU. Median scores ranging from 30-42 have been previously reported in similar studies that have used a median split for the HCU and LCU groups (Jones et al., 2010; Hodsoll, et al., 2014; Martin-Key et al., 2017; O'Nions et al., 2017; Roberts et al., 2018; Schwenck et al., 2012; Sebastian et al., 2016; Sethi,et al., 2018). It has also been suggested that scores exceeding 41 are clinically significant and may serve as an appropriate threshold for HCU (Docherty et al., 2017). This provides further support for the current study's cut-off value of 42 for the median split and underscores that the HCU group shows highly significant scores (estimated to be within the top 5% of the population).

5.2.3 *Image Acquisition*

Structural and functional imaging data were acquired using a Siemens Avanto 1.5T whole body MRI scanner at the Birkbeck-UCL Centre for Neuroimaging. A 32-channel head coil was used during all scans. High-resolution, T1-weighted magnetization prepared rapid gradient echo (MPRAGE) anatomical images were collected for every participant (176 slices, 1 mm slice thickness, 0.5 mm interslice gap, echo time = 2730 ms; repetition time = 3.57 ms; field of view = 256 mm, 256 x 256 acquisition matrix with 1 mm^3 voxels). Next, participants were instructed to lie quietly and fixate on a motionless, greyscale central cross for approximately 8 minutes, while resting-state, T2*-weighted echo-planar images (EPIs) were acquired (170 volumes covering the whole brain, repetition time = 2880 ms, echo time = 45

ms, slice repetition time = 80 ms, 36 slices per volume, FOV: 192 mm; 90° flip angle, 3 x 3 x 3.5 mm voxel size). Surface coil intensity correction was automatically applied by the Siemens Avanto system.

5.2.4 *Image Preprocessing*

EPI data preprocessing was performed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). After the first three volumes were removed from the scan, excessive signal deviations were attenuated with AFNI's 3dDespike. The remaining volumes were then slice-time corrected (to slice-time 0) and co-registered with their corresponding MPRAGE anatomical scans. EPI data was then blurred using a 6 mm isotropic Gaussian kernel (full-width at half-maximum), and rescaled to percent signal change by normalizing to each voxel's mean BOLD signal intensity. Lastly, all scans were resampled to 3.0 mm^3 voxels, and transformed into standard Talairach and Tournoux (1988) space.

Nuisance artifacts were regressed from the BOLD signal using AFNI's ANATICOR protocol (Jo et al. 2010, 2013; see also Gotts et al. 2012; Berman et al. 2016). First, MPRAGEs were segmented using using FreeSurfer (Fischl et al. 2002). Then, white matter and ventricle masks were created, resampled to the EPI's resolution, and eroded by 1 voxel to prevent partial volume effects with the gray matter. Prior to smoothing, localized white matter averages centered on each voxel and averaged within a 40mm-radius sphere were calculated, as was a single average nuisance time series for the ventricles (e.g., Jo et al. 2013). Nuisance variables were then detrended with fourth-order polynomials, followed by least-squares model fitting to every voxel's time series. No physiological data, such as heart

rate or respiration, was collected, so the first 3 principal components of the signal from white matter and ventricles were included as nuisance regressors (e.g. aCompCor; see Behzadi et al. 2007 and Muschelli et al. 2014; Stoddard et al., 2016). The full nuisance regression model, therefore, contained one localized white matter time series, one average ventricle time series, six motion parameters, and the first 3 principal components from white matter/ventricular voxels, along with a 4th-order polynomial baseline model. Residual time series were generated by subtracting the best fit time series of this nuisance model from the full, volume registered time series. All scans met a motion cutoff of less than 0.3 mm/TR of mean framewise displacement.

5.2.5 *Imaging Analysis*

AFNI (Cox, 1996) and MATLAB were used to perform all analyses. A tiered, data driven approach similar to that used by in Smith et al. (2019) was also used for the current study. First, subject-level whole-brain mean "connectedness" maps were created (AFNI's 3dTcorrMaps, e.g. Gotts et al., 2012; Stoddard et al., 2016; Smith, et al., 2019). These maps were computed by correlating each gray matter voxel with every other gray matter (GM) voxel (Pearson's r) within a brain mask comprised of GM voxels with tSNR > 10. A single mean value for all of those correlations was then assigned to each voxel for every subject.

Fisher-z transformed subject-level whole-brain connectedness maps, were then used to perform an analysis of covariance (ANCOVA; AFNI's 3dMVM) across TD, CP/LCU, and CP/HCU groups. Our primary contrast of interest was CP/HCU – TD, as this was the contrast expected to show the largest differences, along with secondary contrasts of CP/LCU – TD and CP/HCU – CP/LCU. A group brain mask was applied, which was comprised of

only those voxels that contained full EPI data in at least 85 percent of the participants in all groups. Whole-brain cluster-size size correction to $P<.05$ (voxelwise $P<.005$.) was performed using AFNI's empirical spatial autocorrelation approach (Cox et al., 2017), and a mask of corrected seed regions was created.

Post-hoc seed tests were then performed to clarify the nature of the initial connectedness analysis, as the regions driving the main effect remain unknown without these follow-up tests. However, given that initial seed detection and seed testing were run within the same sample, noise bias in individual participant data could potentially impact secondary analyses. To control for this potential noise bias, each participant's seed time series was calculated using only those voxels that survived cluster-size correction from the multivariate model *without* that same participant's data included (see Stoddard et al., 2016 and supplementary information from Smith et al., 2019). These individual seed time series were then correlated with all other GM voxels, and a secondary ANCOVA was run for each seed using these seed-based correlation maps. The results from these post-hoc seed tests were corrected for cluster-size within a whole-brain mask (Cox et al., 2017), and for and multiple comparisons (Bonferroni) by dividing $P<.05$ by the number of seed tests.

Finally, pairwise correlations were computed in order to explore all potential relationships between regions with significant effects. To do this, a mask of the original seeds along with the resulting regions was used to pull subject-level time series for each of the 22 regions, and all time series were correlated with one another. A final ANCOVA was run on the resulting correlation matrices, and this model also contained nuisance covariates: motion (AFNI's @1dDiffMag, comparable to mean frame-wise displacement in units of mm/TR), standard deviation of the signal (see Gotts et al., 2020), and IQ. These final

correlation matrices were thresholded below false discovery rate (FDR)-corrected levels ($q < 0.05$).

5.3 Results

Matching across the experimental groups on nuisance variables was evaluated with the Kruskal-Wallis Test. Results indicated a slight difference in head motion between groups (see Table 1), however all three groups met a conservative motion threshold of < .3mm/TR framewise displacement. This variable was also included in the final matrix-level ANCOVA model as a nuisance covariate in order to control for any variance associated with head motion. A similar group difference was observed for IQ (Wechsler Abbreviated Scale of Intelligence score), whereby the CP/HCU group scored lower than the TD group. Lower IQ is often considered to be part of the broader CP phenotype, so this finding is not surprising. However, IQ was also covaried along with head motion (and standard deviation of the signal) to assess whether these differences could be driving functional connectivity effects between any of the region pairs.

Figure 1. Median Split of CU scores in Boys with CP

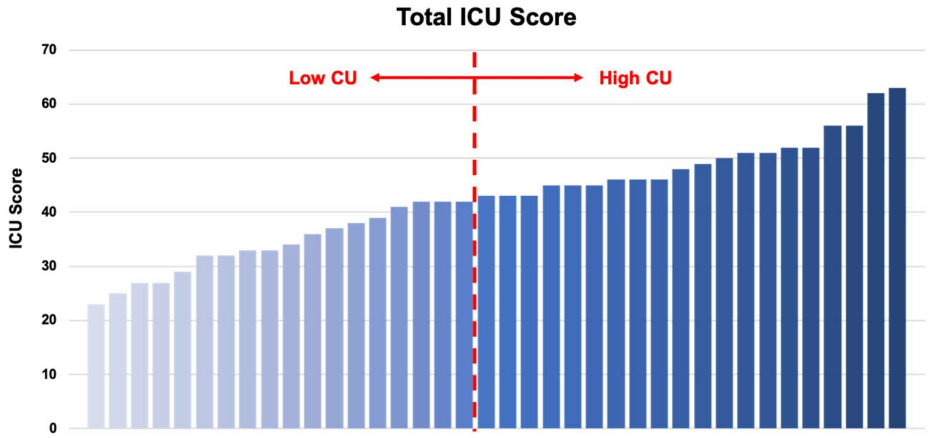

Figure 1. Distribution of CU scores in boys with CP measured by the ICU. Red dashed line demarcates median split. Scores of 43 and higher are indicative of high CU traits in this sample. ICU: Callous Unemotional Traits.

Table 1. Basic Participant Demographics

	TD	**CP/HCU**	**CP/LCU**	***P*-value[b]**
Age (years)	14.92 (1.36)	15.04 (1.14)	15.25 (1.33)	$p = 0.7031$
Head Motion[a]	0.119 (.072)	0.158 (0.064)	0.130 (0.062)	$p = 0.0490$
WASI	98.4 (14.58)	88.1 (9.08)	93.0 (14.27)	$p = 0.0310$

Table 1. WASI: Wechsler Abbreviated Scale of Intelligence. Data are mean(standard deviation). [a]Motion is measured via frame-wise displacement in mm/TR. [b] Kruskal-Wallis Test.

The main contrast of interest for the initial analysis of variance in mean connectedness across groups, was for CP/HCU minus TD controls. Within this contrast, children with CP/HCU displayed significantly increased mean connectedness in 8 clusters, after whole-brain cluster-size correction ($P<.05$, voxelwise $P<.005$), compared to TD boys. These regions included the bilateral posterior insula (extending to the STG/STS), right OFC, right paracentral lobule, medial PFC, left temporal pole, and left cerebellum (see Figure 2 and Table 2). The remaining two contrasts (CP/LCU – TD and CP/HCU – CP/LCU) were then

considered for completeness, however no significant effects were found after whole-brain cluster-size correction.

Table 2. Summary of Seed Regions

Seed #	Location(s)	Peak Coordinates[a]	*T*-statistic (*P*<.05)[b]
1	L. posterior insula / STG / STS	(-37, -19, 20)	3.561
2	R. OFC / IFG	(32, 35, -16)	3.859
3	R. PCC / precuneus	(11, -58, 32)	3.665
4	R. paracentral lobule	(41, -34, 59)	3.827
5	L. inferior temporal pole	(-37, 2, -37)	4.332
6	L/R. medial frontal gyri	(-1, 62, -13)	5.096
7	L. cerebellum (IV / V)	(-13, -31, -28)	4.352
8	R. posterior insula / STG	(50, -25, 17)	3.616

Table 2. Seeds with significant difference in mean connectedness (CP/HCU > TD). STG: superior temporal gyrus, STS: superior temporal sulcus, OFC: orbitofrontal cortex, IFG: inferior frontal gyrus, PCC: posterior cingulate cortex.
[a]Coordinates are (*x, y, z*) in standard, Taliarach-Tournoux space, peaks based on *T*-statistics.
[b]*T*-statistics based on TD – CP/HCU.

Figure 2. Seed regions for CP/HCU - TD contrast

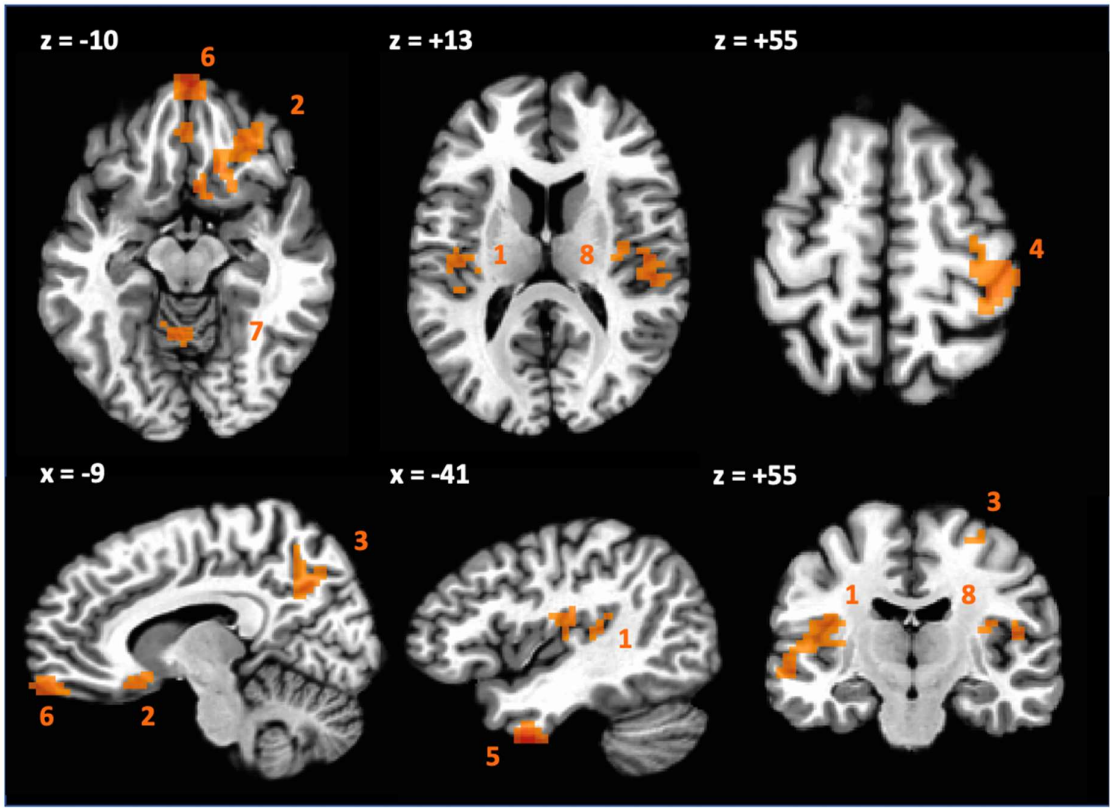

Figure 2. Seed regions detected that exhibited a significant difference in mean connectedness between CP/HCU and TD groups. Orange/red denotes positive *T*-statistics, reflecting CP/HCU > TD mean connectedness values. Numbered regions correspond to those listed in Table 1.

Post-hoc seed-based tests were conducted using each participant's unique seed voxels (determined by an iteration of the ANCOVA that did not contain that participant's data). The regions that survived correction (P<.05 divided by 8 seeds, or *P*<.00625, with a voxelwise *P*<.0001) were then merged with the original seeds in a conjunction map, as some resulting regions overlapped with the seeds. A more stringent voxelwise alpha was used for the seed tests (P<.0001) in order to break apart large clusters so that the remaining clusters are of a more typical size for regions of interest (e.g. < 4,650 mm^3). The final map was comprised of a total of 22 regions, including the original seeds. In addition to the expanded original seeds, 14 unique regions also emerged from the seed tests, including: the bilateral SMA, cuneus,

superior frontal gyri, and anterior insula, as well as the left fusiform, OFC/IFG, paracentral lobule, supramarginal gyrus, and pSTS, and the right temporal pole, and middle occipital gyrus (see Table 3 and Figure 2). In the bilateral insula, the original posterior insula seeds became conjoined with new regions in the bilateral anterior insula (derived from the seed tests). In order to delineate the seeds from resulting regions, and to avoid grouping the anterior and posterior insula into a single large cluster, a small number of voxels were excluded at the site of overlap. This allowed the anterior and posterior insula to be investigated separately at the matrix level.

The final 22 regions were sorted into functional brain networks based on Yeo et al.'s (2011) 7-network parcellation. Network membership was determined using the center of mass of each of the 22 final regions (see Gotts et al., 2012). All 7 networks were represented in these final regions (refer to Table 3 and Figure 3). The cerebellar seed was grouped into its own 'cerebellar' network, as the Yeo et al. (2011) parcellation was not inclusive of subcortical structures.

Table 3. Final 22 Resulting Regions

Region #	Location(s)	Coordinates[a]	Network[b]
1	R. cuneus	(29, -76, 31)	Visual
2	L. cuneus	(-9, -75, 22)	Visual
3	R. middle occipital gyrus	(41, -71, 10)	Visual
4	R. paracentral lobule	(36, -27, 54)	Somatomotor
5	L. paracentral lobule	(-34, -29, 60)	Somatomotor
6	L. posterior insula / STG	(-44, -19, 7)	Somatomotor
7	R. posterior insula	(47, -22, 16)	Somatomotor
8	R. OFC / IFG	(23, 30, -11)	Limbic
9	L. OFC / IFG	(-16, 12, -10)	Limbic
10	R. inferior temporal pole	(53, -3, -30)	Limbic
11	L. inferior temporal pole	(-44, -0, -30)	Limbic
12	R/L. medial frontal gyrus	(-0, 52, -12)	Limbic
13	R/L SMA / cingulate gyrus	(-1, -1, 47)	Ventral attention
14	R. anterior insula	(35, 5, 12)	Ventral attention
15	L. anterior insula	(-36, 10, 15)	Ventral Attention
16	L. IPL / supramarginal gyrus	(-55, -28, 34)	Dorsal Attention
17	L. fusiform gyrus	(-43, -37, -18)	Dorsal Attention
18	L. pSTS / MTG	(-49, -46, 4)	Default Mode
19	R. PCC / precuneus	(8, -57, 37)	Default Mode
20	R. superior frontal gyrus	(37, 41, 33)	Frontoparietal
21	L. superior frontal gyrus	(-41, 33, 35)	Frontoparietal
22	L. cerebellum (IV-V)	(-10, -42, -21)	Cerebellar

Table 3. Numbered list of regions resulting from seed-based tests combined with original seeds. Regions are displayed in Fig. 2, and region numbers correspond to cells in Figure 4A-B. STG: superior temporal gyrus, OFC: orbitofrontal cortex, IFG: inferior frontal gyrus, SMA: supplementary motor area, pSTS: posterior superior temporal sulcus, MTG: middle temporal gyrus, PCC: posterior cingulate cortex.
[a]Coordinates are (x, y, z) in standard Talairach-Tournoux space, peaks based on center of mass from corrected conjunction map of seeds and resulting regions.
[b]Aside from cerebellar, networks refer to those defined by Yeo et al (2011).

Figure 3. **Map of final 22 regions**

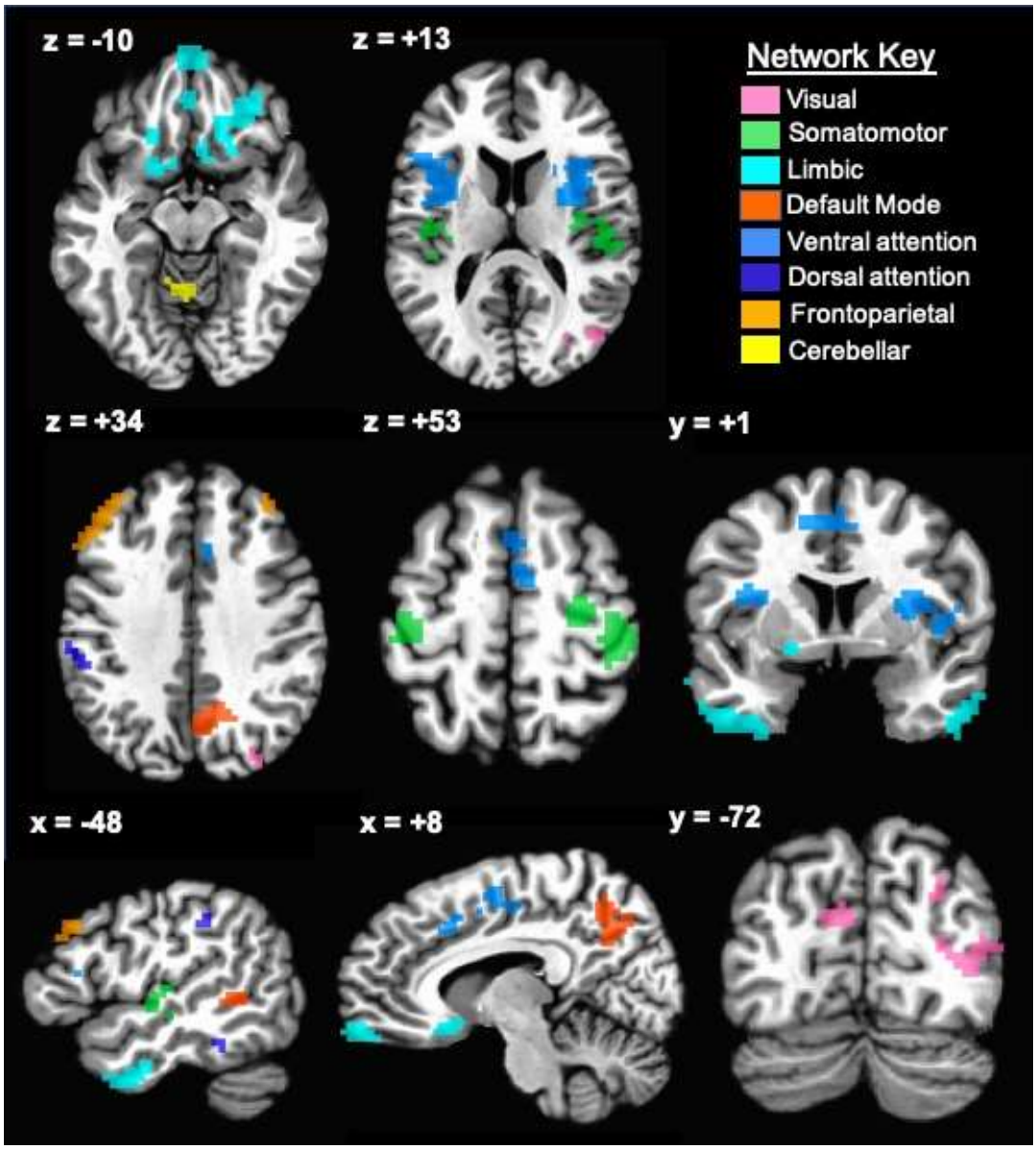

Figure 3. Merged map of all 22 regions with significantly increased functional connectivity in CP/HCU compared to the TD group. Regions are individually listed in Table 3. Colors correspond to network membership (See Key and Table 3).

To investigate all possible inter-region relationships, a final ANCOVA was run on subject-level pairwise correlation matrices between all region pairs. Motion, standard deviation of the signal, and IQ were also covaried within the model to control for any variance that could be explained by these factors. The resulting heatmap of *T*-values revealed a widespread pattern of increased functional connectivity in children and adolescents with CP/HCU, compared to healthy controls. This effect was robust and present across networks, but was most prominent within and between limbic and somatomotor regions, including medial PFC, OFC, temporal poles, posterior insula, and paracentral gryi. After correcting for false discovery rate (FDR; $q<.05$), the *T*-values remained significant in 108 of the possible region-to-region combinations (see Figure 4A-B).

Figure 4A. CP/HCU – TD pairwise correlation matrix

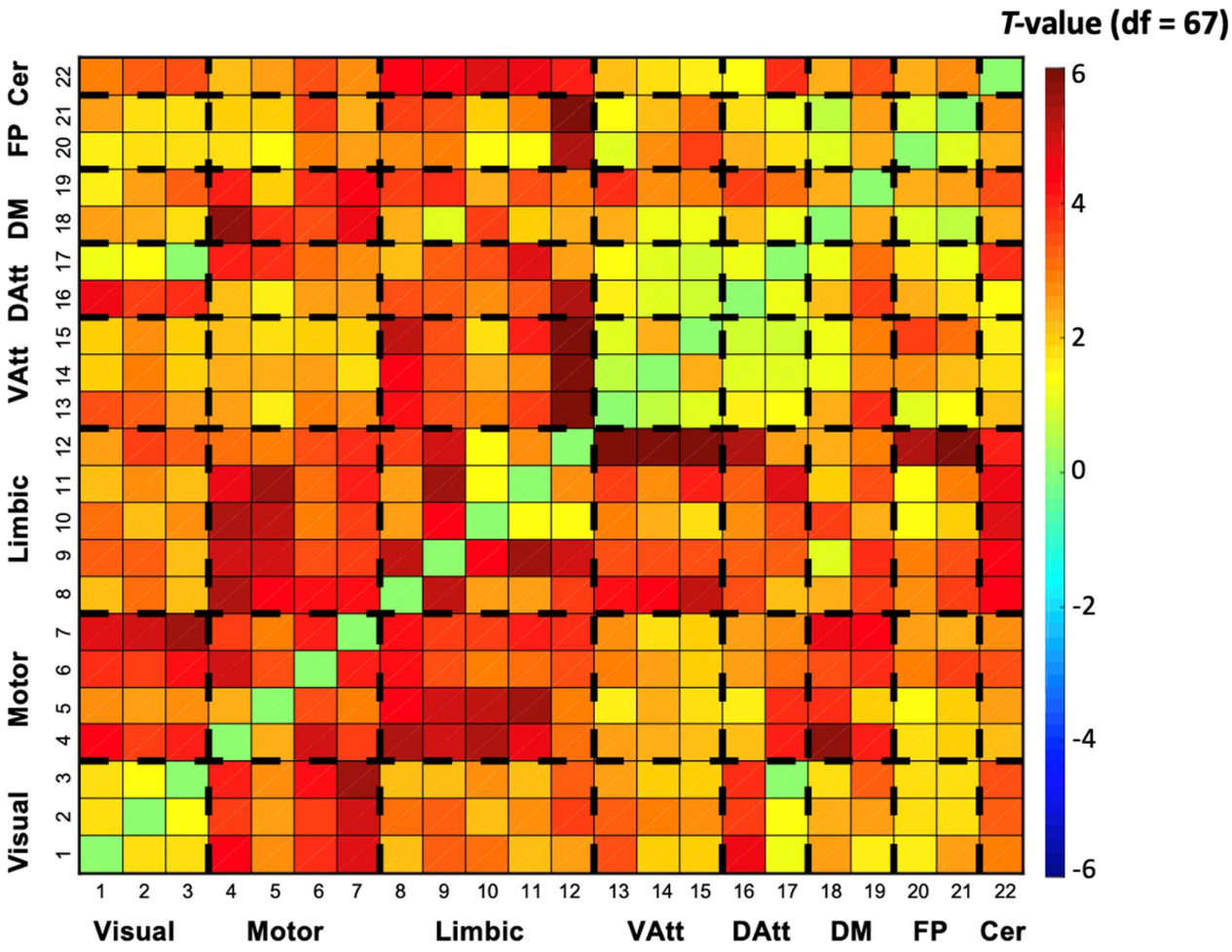

Figure 4A. Pairwise correlation matrix for CP/HCU – TD (with motion, standard deviation, and IQ covaried). Colors correspond to *T*-values and indicate higher connectivity in CP/HCU than in controls. Df: degrees of freedom Dashed lines demarcate networks. VAtt: ventral attention, DAtt: dorsal attention, DM: default mode, FP: frontoparietal, Cer: cerebellar. Axis numbers correspond to each of the final 22 regions listed in Table 3.

Figure 4B. CP/HCU – TD significant *P*-value matrix

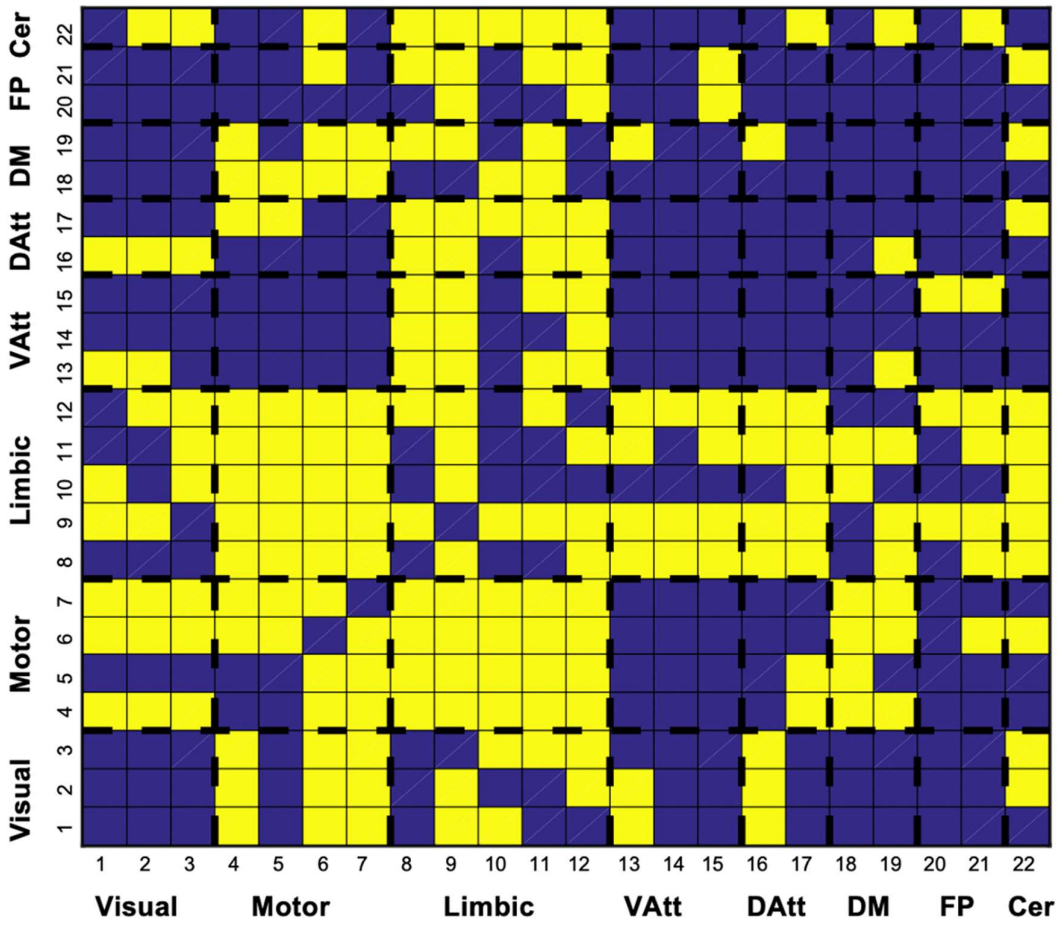

Figure 4B. FDR-corrected *P*-value matrix based on pairwise correlation matrix (Figure 4A). Yellow cells indicate significant region pairs ($p<.0227$). Dashed lines demarcate networks. DM: default mode, VAtt: ventral attention, DAtt: dorsal attention, FP: frontoparietal, Cer: cerebellar. Axis numbers correspond to each of the final 22 regions listed in Table 3.

5.4 Discussion

With its novel, data-driven approach, the current study sought to explore resting-state functional brain differences in children and adolescents with CP/HCU who are at an increased risk of developing psychopathy. To date, only a small handful of studies have used resting-state fMRI to investigate these at-risk children, and no other study has performed direct comparisons of functional connectivity across CP/HCU, CP/LCU, and TD groups in this manner. We predicted that CP/HCU would be related to functional connectivity increases within and between limbic/paralimbic, and somatomotor regions, as was found in a continuous analysis by Werhahn et al. (2020).

The results indicated that CP/HCU was indeed associated with robust and widespread functional connectivity increases within and between networks, but most prominently in limbic and somatomotor regions, as well as the right PCC/precuneus and left cerebellum. A number of limbic/paralimbic regions emerged, including the medial PFC, OFC, IFG, and temporal poles. Effects were also seen in the mid- and posterior cingulate, which belong to somatomotor and default mode networks, respectively (Yeo et al., 2011), but no changes were detected in the ACC, which has been implicated in structural and task-based studies of CP and CU traits. No significant effects were detected for either of the other two contrasts: CP/LCU - TD and CP/HCU - CP/LCU. It is possible that effects in the CP/LCU group were too subtle to be detected, between the relatively small sample size and being subjected to stringent whole-brain correction. Further group difference studies with larger samples or a-priori regions of interest could help to shed light on whether any functional connectivity differences may be related to CP alone (and not co-occurring high levels of CU traits). Given

that CP/HCU is associated with the most severe clinical presentation and outcomes, it is not surprising that effects were only found for this group, when comparison to TD controls.

Overall, the current findings were both directionally and spatially in line with our hypotheses, with a number of additional regions, including those in visual, attention, default mode, and cerebellar networks also exhibiting the same pattern of hyperconnectivity in CP/HCU compared to healthy controls. Furthermore, the fact that the current study's brain findings were so widespread and largely symmetrical supports the broader idea that CP/HCU is associated with a fundamental difference in functional brain organization, which may play a role these children's heightened vulnerability to developing psychopathy later in life. Given that children with CP/HCU display marked deficits in empathy, it is unsurprising that regions previously implicated in empathic processing and socio-emotional cognition such as the anterior insula, vmPFC, temporal poles, supramarginal gyrus, and anterior mid-cingulate (Lamm et al., 2019; Schurz et al., 2020) also emerged in the current study's functional connectivity findings. In addition, researchers believe that sensorimotor regions also play a key role in social and empathic processing, and may help enable individuals form mental representations of others' pain (Riečanský & Lamm, 2019). Our findings, which highlighted the paracentral lobules and posterior insula, support this theory that somatomotor regions as well as those more traditionally associated with affective processing, play an integral role in empathic abilities—or lack thereof as in the case of CP/HCU. Lastly, the SMA/mid cingulate, anterior insula, and IFG, which were implicated in the current study have been identified as key nodes of a network involved in empathy for pain (Decety et al., 2013). In a highly relevant study, incarcerated male adults with high levels of psychopathic traits exhibited aberrant effective connectivity between the anterior insula, OFC, and ventromedial PFC compared to non-psychopathic inmates, while viewing pain stimuli and imagining

others in pain (Decety et al., 2013). It is notable the current study found aberrant resting-state functional connectivity between these exact same regions (anterior insula, OFC, and ventromedial PFC) in boys with high levels of CU traits compared to those with low CU traits and healthy controls. It is likely that these underlying changes in baseline connectivity observed in the current study would play a role in producing atypical patterns of activation and effective connectivity during empathic processing.

With respect to the directionality of the current results, it remains unclear whether general increases in functional connectivity (relative to decreases) relate to any specific functional outcomes, but it is likely that the broad hyperconnectivity or lack of normal network segregation observed in the current study may interfere with efficient socio-emotional computations. The specific mechanism by which this happens, however, remains unknown. If studies converge and implicate hyperconnectivity as a consistent correlate of CP/HCU, there may be new avenues for targeted interventions such as neurofeedback, that aim to decrease aberrant network coupling in order to reduce symptom severity.

The directionality of the current results are also in agreement with findings from Chapter 4, which reported widespread functional connectivity increases associated with psychopathic traits in healthy young adults. This apparent consistency provides evidence for a common neural architectural framework underlying psychopathic or CU traits in different age groups, but additional studies with larger samples and/or longitudinal designs would help to shed further light on this.

5.4.1 *Limitations*

One limitation of the current study is that the sample consisted of solely male children and adolescents. While this was an intentional limitation of the sample, conclusions can therefore only be drawn in the context of males and may not be generalizable to female children with CP and CU traits. Further research is needed in exclusively female samples, as well as work directly comparing males and females with CP/HCU to determine whether any sex differences exist in the neurobiology of CP/HCU. The current study also only provides a limited snapshot of the aberrant functional connectivity associated with CP/HCU in this population and does not shed any light on the developmental stability of these abnormalities. For example, at what age can these brain-organizational changes be detected, and do they persist into adulthood? Do early alterations functional connectivity help to predict longer-term clinical outcomes? Future studies conducted longitudinally would help to address these outstanding questions, but given the similarities between the current study's resting-state findings in children and that seen in adults with psychopathy, it is likely that at least some of the abnormalities remain stable into adulthood.

5.5 Conclusions

The current study adds to the extremely limited literature base on resting-state functional correlates of CP/HCU in children and adolescents at increased risk for developing psychopathy. This novel, data-driven, group comparison found widespread increases in functional connectivity within and between networks in the CP/HCU group, especially in limbic and somatomotor regions including the medial PFC, OFC, anterior and posterior insula, temporal poles, mid-cingulate, and paracentral lobules. These regions overlapped

with areas implicated in earlier structural and task-based studies of CP/HCU. The hyperconnectivity observed in the current study could be suggestive of atypical streams of socio-affective and sensorimotor processing, which underlies core CP/HCU symptomatology. No significant effects were detected in the CP/LCU group, providing support for the idea that CP subgroups may be differentiated endophenotypically based on levels of CU traits. The current study's neurobiological findings may help clinicians, caregivers, and children alike to conceptualize the socio-behavioral abnormalities associated with CP/HCU in a slightly different light, and may also inform alternative interventions (Viding & McCrory, 2019). Additional resting-state research in larger samples of youths is warranted, as is further study of task-based connectivity in order to establish a more complete picture of CP/HCU's neurocognitive profile.

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CHAPTER 6

FORMAL COMPARISON OF RESTING-STATE CORRELATES OF PSYCHOPATHIC TRAITS IN HEALTHY ADULT AND AT-RISK CHILD POPULATIONS

Abstract

Chapters 4 and 5 of this thesis reported converging findings of resting-state hyperconnectivity associated with high levels of psychopathic traits in healthy young adults, and and with high levels of callous unemotional traits in children with conduct problems (CP/HCU) relative to typically developing (TD) peers. There was also apparent overlap in the regions implicated in each chapter's results, particularly in limbic and somatomotor regions. The current follow-up study was designed to directly compare findings from Chapters 4 and 5 from both spatial and quantitative perspectives. Conjunction maps of the fully corrected results from each study revealed 7 common regions exhibiting similar patterns of functional connectivity increases associated with high levels of psychopathic traits in children with CP/HCU relative to TD controls. Permutation tests revealed a statistically significant but modest correlation between the two sets of resting-state findings. These results are suggestive of a partially shared resting-state neural profile in healthy adults with higher psychopathic traits, and in children at risk for developing psychopathy. The modesty of the correlation could be explained by some regions that emerged in the study of children with CP/HCU but not in the community sample, which overlapped with resting state findings in adults with psychopathy (e.g. in medial and orbital frontal regions as well as the anterior insula).

6.1 Introduction

Prior research suggests that psychopathic traits are present to varying degrees in healthy individuals and therefore exist along a continuum with clinically diagnosed psychopathy only at the very extreme end (Hare and Neumann 2005; Levenson et al., 1995). Psychopathic traits can indeed be found at a range of levels in typically developing or community samples, and as Chapter 4 of this thesis has illustrated, these traits may also be linked to individual differences in functional brain organization. More specifically, Chapter 4 found that in a large (n=924) community sample of young adults, psychopathic traits, (as measured by the Self Report Psychopathy Scale [SRP], Neumann & Pardini, 2014; Paulhus et al., 2017), were positively associated with functional connectivity within and between nodes from a range of brain networks, most prominently featuring the default mode, limbic, cerebellar, and somatomotor networks.

These findings showed moderately good spatial agreement with existing clinical literature in criminal offenders, though clinical studies have not been entirely consistent, especially with respect to the directionality of resting-state functional connectivity alterations (e.g. increases versus decreases) (Espinoza et al., 2019; Cohn et al. 2015; Leutgeb et al. 2016; Motzkin et al., 2011; Philippi et al., 2015). Chapter 4 also reported a significant positive relationship between psychopathic traits and functional connectivity in a number of temporal regions, but this part of the brain has received less attention than prefrontal and limbic regions in clinical studies.

In addition to being a continuous trait dimension seen across healthy and clinical adult populations, developmental risk for psychopathy is also detectable in children, with

atypicalities in line with what is seen in adults (Frick & Viding, 2009). Chapter 5 focused on investigating resting-state functional connectivity in children and adolescents with CP and high levels of CU traits (CP/HCU), who are at an increased risk of developing psychopathy later in life (Frick, 2016). Findings from Chapter 5 revealed that these at-risk children and adolescents also exhibit unique patterns of resting-state functional connectivity that differ from typically developing (TD) control participants. More specifically, boys with CP/HCU had widespread increases in functional connectivity between a range of functional networks, most prominently in limbic and somatomotor regions, compared with TD boys. These resting-state findings appear to converge both spatially and directionally with what was found in Chapter 4 in healthy young adults. Some of the most prominent differences between the two studies include the involvement of more ventral portions of the prefrontal cortex (PFC) and orbitofrontal cortex (OFC), and additional clusters in the anterior and posterior insula in the at-risk (CP/HCU) boys compared to what was found in young adults from the community sample.

While longitudinal studies have reported behavioral outcomes in children at risk for developing psychopathy (Lynam et al., 2007; Rivenbark et al., 2018; Wertz et al., 2018), there is a dearth of longitudinal neuroimaging data that charts vulnerable, at-risk children through to adulthood, when some go on to develop the clinical disorder. Such studies would provide greater insight into the developmental pathophysiology of psychopathy. However, until longitudinal neuroimaging data becomes available, it is also valuable to explore the neurocognitive underpinnings of psychopathic traits in different groups representing both sides of the transition from adolescence into early adulthood.

Chapters 4 and 5 of this thesis have independently illustrated the relationships between psychopathic (or CU) traits and functional brain organization in samples of different age groups and degrees of risk, however to date, no studies have made any attempt to directly compare the resting-state correlates of psychopathic traits in adults with those linked to CU traits in at-risk children. The purpose of this final chapter was to follow-up on results from the previous two chapters by spatially and quantitatively comparing the resting-state functional connectivity findings in healthy young adults with those found in children with CP/HCU.

6.2 Methods

Participants for the current analysis consisted of 924 young adults who completed the SRP, and 73 boys from the greater London, UK area (CP/HCU (n = 20), CP/LCU (n = 18), and TD (n = 35). For full details on participant recruitment, screening measures, imaging parameters, and preprocessing steps, please refer to Methods sections in Chapters 4 and 5, respectively.

6.3 Analysis

The direct comparison of Chapters 4 and 5 was approached in two ways: spatially and quantitatively. The purpose of the spatial comparison was to identify and visualize any common voxels across the two studies, using only fully corrected results. Fully corrected masks (of resulting regions plus original seeds) for each dataset were used. However, because the fMRI resolution differed across studies, the mask of the final 22 regions from Chapter 5 was resampled to match the $4mm^3$ voxel resolution of Chapter 4's data. This down

sampling was done with linear interpolation using '3dresample' from the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Next, all significant voxels in Chapter 4's corrected results were assigned a value of 1, and all significant voxels in Chapter 5's corrected mask were assigned a value of 2. The masks were then added to one another, whereby any spatially overlapping voxels would have a new value of 3. In consideration of the larger (4mm3) voxel size, any overlapping regions >2 voxels were considered. Following the logic of conjunction analyses (e.g. Nichols et al., 2005), overlapping regions that are significant and corrected for multiple comparisons in each experiment individually are significant and corrected in both.

The quantitative comparison was performed using permutation testing. To do this, individual whole-brain mean connectedness maps (AFNI's 3dTcorrMaps) from the 924 participants in Chapter 4 were correlated (Spearman's r) with their respective SRP scores. These voxelwise *r*-values were then correlated (again, Spearman's r to avoid distributional assumptions) with *t*-values from the CP/HCU – TD contrast within the CP/HCU, CP/LCU, and TD group analysis of covariance (ANCOVA). However, in order to achieve satisfactory matching for head motion across CP/HCU and TD groups, only a subset of the full TD sample was used in this analysis. More specifically, the top 14 TD boys with the lowest levels of motion were excluded, and this eliminated any significant group differences in head motion. After this exclusion, the group sample sizes for the permutation tests were as follows: CP/HCU (n = 20), CP/LCU (n = 18), and TD (n = 21) (See Table 1). Finally, this same correlation of *r*-values with *t*-values was performed 10,000 times iteratively, with the modification that SRP scores for the n = 924 group were shuffled and assigned imaging datasets at random in order to establish a null distribution of chance correlations between the two sets of corrected results.

Table 1. Motion-Matched Sample from Chapter 5.

	CP/HCU	CP/LCU	TD	*P*-value[b]
Motion[a]	0.158 (0.064)	0.130 (0.062)	0.160 (0.067)	$p = 0.177$

Table 1. Sample used for permutation tests after motion-matching exclusions discussed above. Data are mean(standard deviation) [a]Motion is measured via frame-wise displacement in mm/TR. [b] Kruskal-Wallis Test.

6.4 Results

Findings from the initial spatial overlap analysis identified a total of 7 clusters, each comprised of 2+ 4-mm-isotropic voxels (volume of 128 mm^3 or greater) that were shared among the two studies' fully corrected maps. These regions included the bilateral paracentral gyri, left inferior temporal pole, left superior temporal gyrus/sulcus (STG/STS), right mid-cingulate, and right precuneus (see Table 2 and Figure 1).

In the quantitative comparison analysis, *r* - values and *t* - values were significantly positively correlated with one another ($r = .22$, 2-tailed $p<.0013$), relative to the null distribution of chance correlations after 10,000 permutations. This indicates that there are indeed similarities in the findings across studies and that a significant amount of variance is shared (see Figure 2).

Table 2. Overlapping Regions

Region #	Location(s)	Coordinates[a]
1	R. pre/postcentral gyrus	(39, -24, 49)
2	L. inferior temporal pole	(-52, -4, -30)
3	R. precuneus	(8, -59, 46)
4	L. pre/postcentral gyrus	(-41, -26, 56)
5	L. STG/STS	(-38, -29, 6)
6	R. mid-cingulate	(6, -11, 46)
7	R. precentral gyrus	(24, -21, 54)

Table 2. Numbered list of overlapping regions across fully corrected maps from Chapters 4 and 5. [a]Coordinates are (x, y, z) in standard Talairach-Tournoux (1988) space, peaks based on center of mass from conjunction map of fully corrected regions from Chapters 4 and 5.

Figure 1. Overlapping Regions

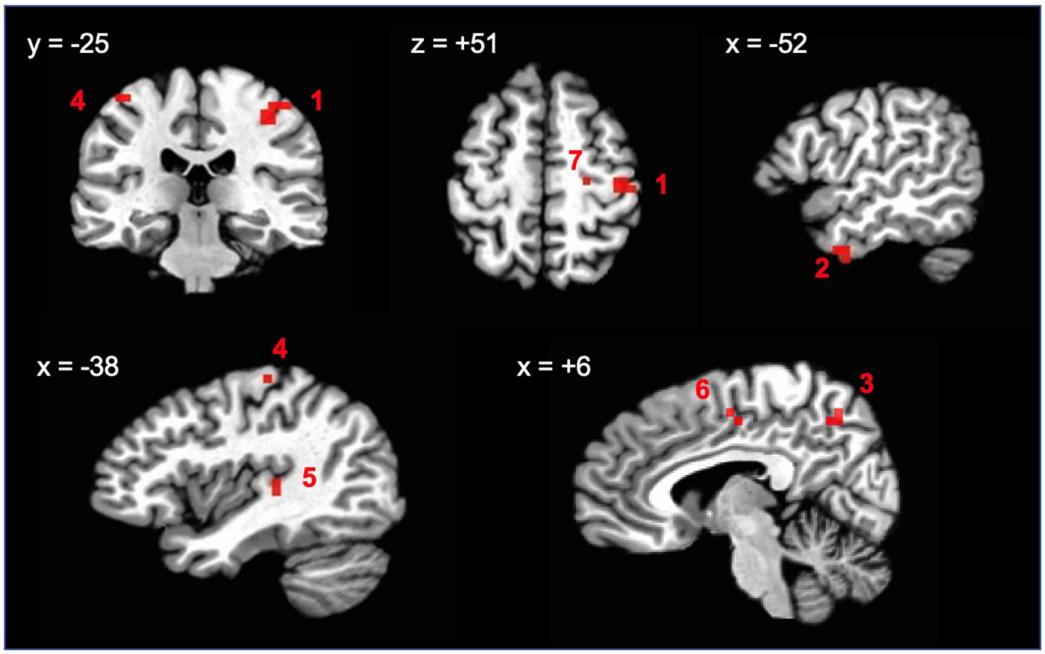

Figure 1. Map of 7 common regions with significantly increased functional connectivity (associated with SRP in Chapter 4, and with CP/HCU in Chapter 5). Regions listed in individually in Table 1.

Figure 2. Similarity of Results

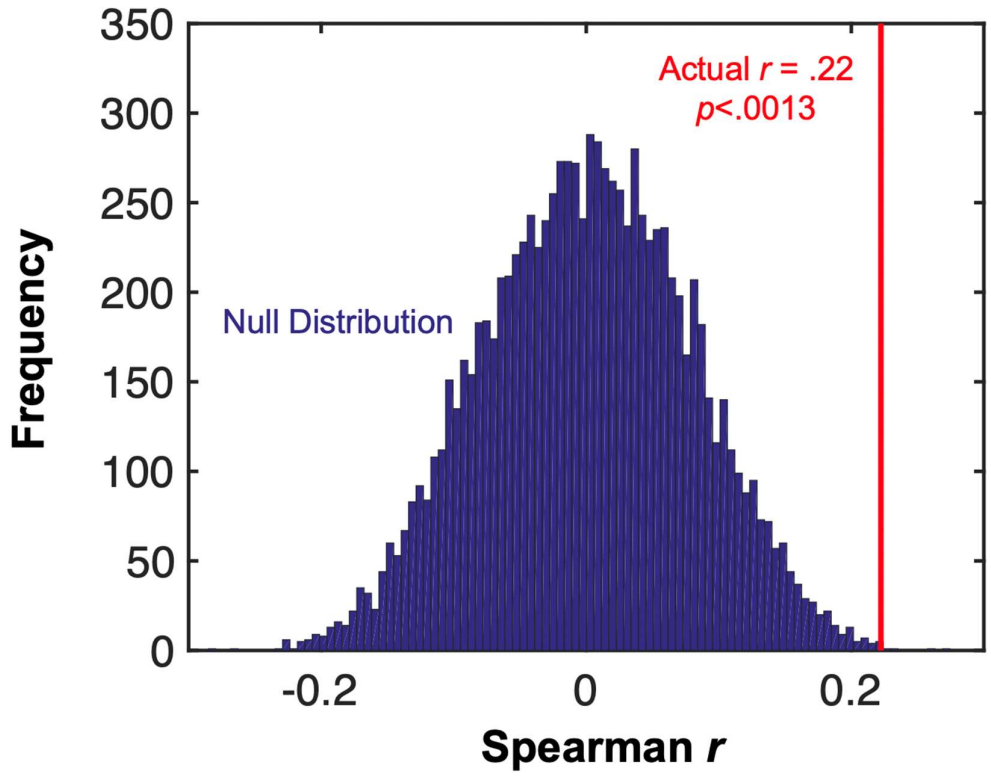

Figure 2. Similarity of Results from Chapters 4 (n=924) and 5 (n = 59), using a motion-matched sub-sample of TD boys). Spearman's *r*, tested by permutation with 10,000 iterations.

6.5 Discussion

Both studies from Chapters 4 and 5, which investigated on psychopathic traits in a community adult sample and group differences in children at risk of developing psychopathy, respectively, reported widespread increases in functional connectivity associated with higher levels of psychopathic or CU traits. Furthermore, similar regions and networks were implicated in these two preceding Chapters, with somatomotor and limbic networks featured prominently across studies. This apparent spatial and directional consistency in brain findings was all the more compelling given that these studies were conducted using different

scanners, in different countries, with different sample sizes, and in different participant age groups. The current Chapter therefore sought to build on the similarities observed in Chapters 4 and 5 by directly comparing the fully corrected results of each study, both spatially and quantitatively (by permutation testing).

The spatial comparison revealed 7 common regions across the two Chapters the bilateral paracentral gyri, left inferior temporal pole, left STG/STS, right mid-cingulate, and right precuneus. There was prominent representation in somatomotor regions, including two clusters along the right pre- and postcentral gyri and one along the left, as well as one in the right mid cingulate cortex. There has often been more emphasis on prefrontal and limbic areas in psychopathy and CU trait literature, but the current findings suggest that motor-related areas should be given equal attention in investigations of these clinical syndromes or trait dimensions. Indeed, a recent review by Riečanský & Lamm (2019) provides extensive evidence for the integral role that sensorimotor regions play in affective processing, especially in mental representations of others in pain or distress. In fact, the region of the mid-cingulate implicated in the current Chapter's spatial results is believed to be a key node within a 'pain matrix' or network of regions that subserve pain processing, both in firsthand experience of pain as well as vicarious pain or empathy (Botvinick et al., 2005; Lamm, et al., 2011; Yesudas & Lee, 2015).

The left inferior temporal pole was another common region that was found to be significant across both Chapter 4 and 5 studies. Not only did the current thesis find temporal pole functional connectivity to be related to psychopathic traits and to high levels of CU traits in children with CP, but Chapter 4 also found this same region to be significantly related to Empathic Concern scores from the Interpersonal Reactivity Index (Davis, 1983). A growing

body of literature supports the idea that the temporal pole subserves both social and emotional computations, and some researchers believe it operates as a relay station for the integration of visceral emotional responses with higher perceptual information (Olson et al., 2007). A recent large lesion study shed further light on the role of this structure in affect sharing and found lesions in the temporal pole to be significantly related to altered sensitivity to others' expressive behavior (Shdo et al., 2018). Taken together, the current Chapter's robust and replicated functional connectivity findings in the temporal pole, combined with existing literature, paint a convincing picture regarding the importance of this structure in socio-affective and socio-cognitive processes.

Lastly, in the current Chapter's spatial comparison, common clusters of voxels were also identified in the posterior STG, extending into the STS, and in the precuneus. The STG and STS have been implicated in a number of studies using theory of mind tasks and in paradigms involving social communication (Schurz et al., 2014). In addition, atypical structure, function, and connectivity of the STG/STS has been linked to a range of psychiatric conditions, especially those that involve social difficulties such as autism spectrum disorder (Patriquin et al., 2016), social anxiety disorder (Bas-Hoogendam et al., 2020), schizophrenia (Bandeira et al., 2020), and problematic hypersexual behavior (Seok & Sohn, 2018). Interestingly, increased activity and functional connectivity in the right precuneus, which was the remaining shared region, has also been linked to risky sexual behavior in adolescents (Eckstrand et al., 2017). The precuneus, along with other regions of the default mode network, is believed to play an integral role in orienting to social stimuli, making self- other-distinctions (Amft et al., 2015) The STG, STS, and precuneus therefore all appear to be highly relevant for social-cognitive functioning.

Permutation tests confirmed that the similarity of results reported in Chapters 4 and 5 was statistically significant and not due to chance, however the level of agreement was relatively modest ($r = .22$). This indicates that while there are significant similarities in these studies' findings, there are also substantive differences. For example, in the sample of boys with CP/HCU, some key regions that have been previously implicated in studies of adult psychopaths emerged, exhibiting increased functional connectivity, compared to TD boys. These regions included the ventromedial PFC, OFC, and anterior/posterior insula. Importantly, they were not found to be significantly associated with psychopathic traits in the larger community sample of young adults. Furthermore, some of the broader similarities were not necessarily in perfect spatial alignment, which could reflect subtle functional subdivisions of brain areas, or could be an artifact of the discrepancy in imaging data resolution. It is also possible that the magnitudes of the functional connectivity effects were not always proportionally consistent, given that Chapter 4's design involved continuous analysis correlating subtle individual differences with imaging data while Chapter 5 compared a clinical, at-risk sample with TD boys. Finally, when thinking about the level of agreement across these two studies, it is important to note that the permutation tests calculated similarity throughout the brain, despite the fact that effects in both studies were only found in a restricted subset brain regions. In other words, because psychopathic traits do not significantly modulate functional connectivity in every voxel of the brain, potential similarities were already limited to a much smaller proportion of the brain, so it is not surprising that the degree of correlation seen in the permutation tests was quite modest.

6.5.1 *Limitations and Future Directions*

Although all preprocessing and analysis parameters were consistent across studies, it should be noted that the neuroimaging data analyzed in Chapters 4 and 5 were collected on different scanners, at different institutions, and with slightly different acquisition parameters, which limits the degree to which a fully integrated analysis could be conducted. However, the fact that the resting state findings associated with psychopathic traits and with CP/HCU still showed statistically significant similarity actually serves to increase confidence in these results and to some degree, offers triangulation across samples, equipment, and scanning parameters. Had the findings been highly dissimilar, this limitation would have been a larger concern as it would make the interpretation of differences more challenging and ambiguous as to whether they were due to these extraneous variables.

Of course, the discrepancy in sample sizes should be noted, and further research aimed at making similar comparisons in larger samples should be conducted. As mentioned in Chapters 4 and 5, longitudinal research spanning the gap between childhood and adulthood would also provide invaluable information about the developmental pathophysiology of psychopathy, and might provide clues about the most sensitive periods for successful intervention.

6.5. Conclusions

The current Chapter sought to assess overlap and clarify the agreement between Chapter 4 and 5's study findings. This was approached in two different ways, based on the spatial overlap and permutation tests. In the spatial analysis, 7 clusters emerged, showing

significant effects after corrections in both studies. These clusters were located in the bilateral paracentral gyri, right mid cingulate, left inferior temporal pole, and left STG. These regions have been implicated in a socio-cognitive and emotional processing, including empathy for pain, sensitivity to others' expressions, and theory of mind (Preckel et al., 2018; Riečanský & Lamm, 2019; Shdo et al., 2018). Results from the permutation tests indicated that there was a modest but statistically significant agreement across these two studies' findings. Overall, these follow-up analyses suggest that there appear to be some consistent functional connectivity correlates of psychopathic traits across development, but that there are also resting-state atypicalities related specifically to the more extreme, clinical end of the psychopathic trait spectrum. Future studies charting the resting-state correlates of psychopathic traits from childhood through to adulthood would provide a more comprehensive picture of the means by which risk may evolve into clinical diagnosis.

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CHAPTER 7: General Discussion

The overarching aim of this thesis was to gain a more comprehensive understanding of the role that functional brain organization plays in disorders of social cognition. This thesis examined the value of resting-state fMRI in understanding psychopathology (Chapter 2), and used this imaging method across studies, with data driven analytic approaches employed in each empirical chapter. First, sex differences in functional brain organization in ASD, a surprisingly neglected area of investigation, were examined (Chapter 3). This thesis also explored whether resting-state FC is associated with individual differences in ASD and psychopathic trait dimensions in an adult community sample (Chapter 4). This enabled assessment of whether unique or overlapping resting-state neural correlates were associated with these distinct trait dimensions. This thesis also sought to identify differences in functional brain organization in children and adolescents who are at increased risk of developing psychopathy in adulthood (Chapter 5), and to then directly compare those differences to functional connectivity profiles associated with psychopathic traits in adults (Chapter 6). The purpose of this comparison was to explore whether psychopathy-related FC differences are observed at different developmental stages, which would add to the evidence base that psychopathy may be seen to some extent as a developmental disorder.

This final chapter provides brief summaries of Chapters 2-6, and then reflects on a number of key limitations and outlines future research that would address the limitations. Findings from each of the empirical chapters are then discussed within the broader context of existing literature, and consideration is given to different conceptual neural frameworks for these disorders. This discussion concludes with a consideration of new or outstanding research questions, broader outlines opportunities for future studies, and translational implications of the findings.

7.1 Summary of Findings

Chapter 2 introduced resting-state fMRI, which is the key methodological approach adopted throughout this thesis. After defining resting-state fMRI and functional connectivity, key limitations of task-based fMRI were considered, thereby highlighting the relative advantage of conducting resting-state studies. These limitations included differences in task performance, questionable ecological validity, biased analytic approaches, and weak reliability (Elliott et al., 2020). Extant resting-state findings in ASD and psychopathy were then summarized, and some outstanding gaps in the literature were identified within these clinical domains. The empirical chapters in this thesis aimed to answer the following research questions: do resting-state functional connectivity profiles differ in males and females with ASD? Can resting-state functional connectivity be related to individual differences in ASD and psychopathic traits outside of clinical populations? If so, how similar or different are the functional connectivity changes associated with each trait domain? Do children and adolescents at risk for developing psychopathy exhibit functional connectivity changes that mirror those seen in adults with psychopathy? How similar are the resting-state features associated with psychopathic traits in at-risk versus community samples?

Chapter 3 presented a novel empirical study that investigated potential sex differences in resting-state functional connectivity in ASD. Although analyses were entirely data-driven, the cerebellum was identified as a key region of interest in this investigation, as it is involved in sensorimotor, cognitive, and socio-affective processes, appears to play both structural and functional roles in ASD, and is developmentally sensitive to sex hormones. Results revealed a significant diagnosis-by-sex interaction whereby females with ASD exhibited increased cortico-cerebellar connectivity and males exhibited reduced cortico-cerebellar connectivity.

Cortical regions whose connectivity with the cerebellum were driving this interaction included the bilateral fusiform, middle occipital, middle frontal, and precentral gyri, cingulate cortex, and precuneus. Interestingly, patterns of cortico-cerebellar functional connectivity in females with ASD more closely resembled that of control males than that of control females. These results point to potentially divergent neurodevelopmental pathways for males versus females with ASD, but potential symptomatic correlate(s) of these brain findings remain unknown.

Chapter 4 shifted gears to examine trait dimensions related to ASD and psychopathy outside of clinical populations. This study was conducted in a very large (n = 924) community sample of young adults, and functional connectivity was related to individual differences in ASD and psychopathic traits as measured by the AQ and SRP, respectively. Higher levels of psychopathic traits were significantly associated with increased functional connectivity within- and between- a number of functional brain networks, however no significant associations were found for ASD traits. Within the regions whose functional connectivity was positively correlated with levels of psychopathic traits, connectivity between the left temporal pole and right MTG/TPJ was specifically related to empathic concern, and when controlling for empathic concern, a number of other regions were no longer significant. This suggests that not only can individual differences in psychopathic traits be directly related to the brain's functional organization, but that subtle differences in this organization can be further explained using a finer grain to explore subcomponents of these larger trait domains.

Chapter 5 presented an empirical study conducted in children and adolescents with CP and high or low levels of CU traits. Groups were created using a median split in CU trait scores, and functional connectivity across CP/HCU, CP/LCU, and TD control groups was

compared. The CP/HCU group showed significant, widespread increases in functional connectivity across functional networks, but primarily within and between a limbic and motor regions, including the ventromedial (vm) PFC, OFC, temporal poles, paracentral gyri, and insula. These findings showed decent agreement with the extremely limited literature base (Cohn et al., 2015; Pu et al., 2017; Werhahn et al., 2020). Given that children/adolescents with CP/HCU exhibit profound empathic deficits, it is unsurprising that regions previously implicated in affective processing and socio- emotional cognition such as the anterior insula, vmPFC, temporal poles, supramarginal gyrus, and anterior mid-cingulate also emerged in Chapter 5's results (Lamm, et al., 2019; Schurz et al., 2020). There were no significant effects were within the CP/LCU group. This is not surprising, as children with CP/HCU exhibit far more severe antisocial behaviors that often persist into adulthood. However, it is also possible that the lack of findings for the CP/LCU group could be due to the relatively small sample size, or indicative of such subtle changes in brain organization that nothing was robust enough to survive whole-brain correction.

Chapter 6 served as a short, follow-up exploration, designed to quantitatively compare results from Chapters 4 and 5. The main purpose of this comparison was to evaluate the similarity in resting-state functional connectivity findings, and determine whether there may be a discernable, replicable resting-state profile associated with psychopathic traits or risk for psychopathy. Results from Chapters 4 and 5 were compared spatially and quantitatively using permutation tests. Based on fully corrected maps, these studies shared a total of 7 regions in common, which exhibited significantly increased functional connectivity (either in relation to psychopathic traits or to CP/HCU compared to TD controls). These regions included the paracentral gyri, left temporal pole, left STG/STS, right mid-cingulate, and right precuneus. Existing literature suggests that activity and connectivity within these regions is

important for a range of social and empathic processes (Amft et al., 2015; Lamm et al., 2011; Olson et al., 2007; Schurz et al., 2014; Shdo et al., 2018). Quantitative comparison via permutation tests revealed modest but statistically significant similarity across results from Chapters 4 and 5, suggesting that there are some key underlying functional connectivity features associated with psychopathic traits across development, but also that some key features are only present in the most severe, at-risk groups.

7.2 Limitations and Future Directions to Address the Limitations

The empirical chapters in this thesis presented novel findings that may address some of the gaps in our knowledge base on the functional neurobiology of psychopathy and ASD. However, there are a number of limitations that should be considered when interpreting these results. One common limitation that applies to all of the studies presented in this thesis is the lack of all-inclusive representation within participant groups. Chapter 3 recruited individuals with ASD who had relatively normal intellectual ability, which is not fully representative of all individuals with ASD, as many have more severe intellectual disability. Therefore, the sex difference reported only pertains to similarly high-functioning individuals with ASD, and this precludes any conclusions from being drawn about people with ASD who suffer from poorer intellectual function. More research is needed in samples representative of the full spectrum of intellectual ability seen in ASD. The relatively wide age range represented in Chapter 3's sample and the cross-sectional nature of the study could also be seen as a limitation, and future work sampling the same individuals throughout development is warranted to establish whether sex differences such as those found in Chapter 3 remain stable over time. In light of the link between cerebellar development and sex hormones, and given that these hormones are produced and released endogenously at different rates/ratios across

the lifespan, it would be particularly interesting to explore whether there is any relationship between age-related changes in reproductive hormone levels and further phenotypic or functional connectivity alterations in ASD.

Chapter 4 was conducted in a large community sample of young adults from around the Duke University campus in Raleigh-Durham, North Carolina. This geographical area and its proximity to a prestigious academic institution would likely have impacted the representative nature of the sample, particularly from an educational standpoint. For example, while the relatively narrow age range represented may also be seen as a strength, research in more diverse age groups is also warranted. One of the largest limitations of chapter 4 was the inability to directly compare the functional brain organization relating to psychopathic and ASD trait domains. We were not able to evaluate whether ASD-trait-related functional connectivity exists along a dimensional spectrum in healthy individuals (as is the case for the behavioral trait domain; e.g. Constantino & Todd, 2003). Although the Autism Quotient was developed for this application, it may not be the most optimal measure for capturing ASD traits in healthy populations. Similar, follow-up studies should be conducted with alternative measures such as the healthy control version of the Social Responsiveness Scale.

Families and children who participated in the study in Chapter 5 may also not have been fully representative, and again, results should be interpreted with this in mind. Most importantly, Chapter 5 only examined male children and adolescents, as conduct problems and CU traits are much more prevalent in males, and females were therefore excluded from the study in order to streamline recruitment and increase statistical power. Consequently, this study only illustrated the functional neural correlates of risk for psychopathy in males, and it

remains unknown whether female children and adolescents at-risk exhibit similar patterns altered functional connectivity. Chapter 5's sample size was also impacted by participant noncompliance and excessive motion while inside the MRI scanner. This resulted in the exclusion of a number of datasets from analysis, where conservative motion thresholds were not met. In Chapters 4 and 5, stringent exclusion criteria and responsible preprocessing pipelines were used to correct for movement in the functional data, but no complementary physiological data (e.g. respiration and heart rate) was collected, which would have allowed for even more precise methods of noise reduction. Collection of this data requires additional equipment and set-up time, which for many is a luxury that cannot be afforded during already limited scanning windows, and with tight research budgets.

A broader interpretive limitation that applies to all chapters in the current thesis is the current lack of clarity on the significance of directionality in functional connectivity alterations (e.g. increases versus decreases). In other words, what do increases and decreases *mean* in the context of information processing? Although studies have been able to link scores on behavioral measures to directional changes in functional connectivity, the mechanistic link between baseline brain organization and behavioral outcome is not yet fully understood. The sex-dependent findings in Chapter 3 are particularly interesting in light of this ongoing quandary. More specifically, both the males and females with ASD were diagnosed using the same clinical standards, with the same validated measures, and based on the data collected, exhibited no glaring behavioral differences, yet from a neurobiological standpoint, group differences between ASD and sex-matched healthy controls were completely divergent with respect to directionality.

The implications of these findings are difficult to disentangle, and it is not evident whether relevant behavioral/phenotypic differences exist but were not properly identified by the standard clinical tools, or whether it is possible that males and females with ASD have developmentally divergent pathophysiology underlying the same clinical outcome. Directional inconsistencies have been noted in the resting-state literature on psychopathy, as well, even within entirely male samples, and this leaves researchers wondering why some studies report functional connectivity increases while others report decreases in the same regions and same clinical populations. Studies utilizing complementary mixed-methods that directly relate resting-state connectivity, effective connectivity, experimental task performance, and behavioral measures would help to illuminate mechanistic links between functional brain organization and these clinical disorders and their respective trait dimensions. However, it is reassuring that functional connectivity findings associated with psychopathic traits in Chapter 4 and with group differences in Chapter 5 show significant spatial and directional overlap.

7.3 Overall Contribution of Thesis Findings to the Broader Evidence Base

The study outlined in Chapter 3 contributes to a growing body of literature highlighting phenotypic and neurobiological differences between males and females with ASD. The current thesis's findings, in particular, support the idea that sex hormones—via their influence on early neural development—may play a key role in the pathophysiology of ASD, and that the coincidence of these factors may also help to explain the male preponderance seen in ASD. It also appears that cortico-cerebellar connectivity may be highly relevant in the neurobiological profile of ASD, especially in the context of sex differences in. Interestingly, the cerebellum has been implicated to at least some extent in

every empirical chapter of the current thesis, across multiple clinical/trait domains, and this suggests that cortico-cerebellar connectivity may be closely related to of higher-order function and a range of psychopathologies.

Chapter 4 provided novel and robust evidence that outside of clinical or forensic populations, individual variation in psychopathic traits can still be related to differences in resting-state functional connectivity. More specifically, the findings suggested that inter- and intra- network hyperconnectivity, mainly in limbic, default mode, somatomotor, and cerebellar regions was directly associated with psychopathic traits in an exceptionally large sample of healthy young adults. In this particular area of research, there is virtually no evidence base to date, so Chapter 4's unique empirical study has helped to lay the groundwork for understanding the functional connectivity correlates of normal variation in psychopathic traits. By also evaluating the contribution of empathic concern to the observed resting-state functional connectivity correlates of psychopathic traits, Chapter 4 also offers a opportunity for further differentiation and clarification of the overall findings.

The evidence base of resting state findings in children at heightened risk for developing psychopathy is also very limited, so the study detailed in Chapter 5 adds valuable data to the literature. In light of the findings reported in healthy young adults, there appears to be consistent, widespread increases in functional connectivity associated with high levels of psychopathic traits. Given the overlap, the current thesis's findings are in line with the idea that to some extent, there may be a common factor underlying continuous variation in psychopathic traits. Although a range of functional brain areas were involved in this common pattern of hyperconnectivity, there were particularly robust findings in limbic and motor-related regions, most of which have been related to empathy for pain (Lamm et al.,

2011). The paracentral gyri, mid-cingulate, anterior and posterior insula, precuneus, temporal pole, and STG/STS are all candidate regions for further, mixed-method/longitudinal exploration.

7.4 Translational Implications

Findings from resting-state studies like those presented in the current thesis have already been applied to clinical-trial-stage treatment approaches such as neurofeedback (Ramot et al. 2017, Gonzalez-Castillo et al., 2020). Neurofeedback can be performed overtly or covertly, and essentially attempts to train brain networks to 'rewire' themselves or alter aberrant functional connectivity between key regions associated with a given disorder. This new experimental intervention has shown promise for children and adolescents with ASD, where post-training scans revealed improvements in functional connectivity changes (Ramot et al., 2017, Gonzalez-Castillo et al., 2020). Additionally, these neurofeedback paradigms are often easy and fun for children who might otherwise struggle to engage or comply with lengthy scan sessions. For example, Ramot et al. (2017) employed a puzzle game whereby participants were instructed to use their minds to turn over puzzle pieces, revealing colorful images. It would be interesting and worthwhile to explore whether similar improvements could be achieved in other clinical and at-risk populations, including in children with CP and high levels of CU traits. If this proves to be helpful, it could reduce the severity of psychiatric outcomes for these children.

Another potential intervention that has shown some promise in the context of modulating social and empathic abilities is transcranial magnetic or direct current stimulation (tMS/tDCS; for review, see Sellaro et al., 2016; Sergiou et al., 2020). In fact, this approach

has already shown some promise in trialed in a range of populations including individuals with ASD and incarcerated violent offenders (Masuda, 2019; Sellaro et al., 2016). One study conducted in a violent prison population used tDCS to modulate activity in the ventromedial PFC and found significant reductions in aggression after 3 sessions (Molero-Chamizo et al., 2019).

In light of the growing body of resting-state literature in a range of disorders, and thanks to the relative ease with which this type of data can be collected, it is possible that pre- and post- intervention scans could provide a mechanistic measure of treatment-related behavioral changes. Of course, a well-replicated knowledge base of base functional connectivity profiles associated with different clinical disorders (and with different sexes) would serve as an empirical point of reference for these measurements, regardless of whether the intervention is physiological (e.g. neurofeedback or tDCS) or behavioral (e.g. psychotherapy or behavior modification). Structural changes have been identified in regions related to empathy and social cognition after specialized meditation protocols (Valk et al., 2017), so it is certainly possible that behavioral interventions like these could also alter atypical patterns of functional connectivity. If resting-state functional (as well as structural) data are collected in concert with behavioral interventions, it would provide even better clues as to the mechanistic link between structure, function, and outcome, as well as the relationship between behavior and neural plasticity.

Developmental studies that employ resting-state fMRI also provide critical information about the brain's organizational plasticity, and longitudinal studies that assume this approach would be invaluable in understanding clinically relevant developmental trajectories. Childhood, adolescence, and early adulthood are key windows for deepening our

understanding of brain network dynamics, as disorders of social cognition such as ASD and psychopathy begin to manifest earlier in life. This added neurobiological information could also help sharpen the clinical formulation of these disorders and provide a new framework for conceptualizing their related symptomatology with patients, families, teachers, and clinicians alike (Viding & McCrory, 2019). In learning that these atypical behaviors are not a choice, but rather arise from differences at the neural level that impact perception and information processing, there may less temptation to place blame or pass judgment, and more motivation to seek effective treatments.

7.5 Conclusions

Disorders such as ASD and psychopathy, which are characterized by socio-affective abnormalities, are often associated with poor interpersonal and professional outcomes, and can be costly burdens on society. The overarching aim of the current thesis was to use resting-state fMRI to help deepen our understanding of the pathophysiology of these disorders of by addressing gaps in the literature and outstanding research questions. More specifically, the studies reported in this thesis sought to explore baseline brain activity in females with ASD, as sex differences in ASD are not clearly understood, and females have been underrepresented in the existing literature. Males and females with ASD were found to have unique, opposing patterns of atypical functional connectivity between the cortex and cerebellum. Taken together with genetic and structural studies of ASD and the cerebellum, this diagnosis-by-sex interaction may hint at sex-specific developmental trajectories for the disorder.

The current thesis also explored normal variation in trait dimensions related to ASD and psychopathy, to determine whether functional brain organization is related to these

individual differences, and whether the correlates mirror that seen in clinical populations. Widespread increases in functional connectivity were associated with higher levels of psychopathic traits in healthy young adults, and these increases were apparent across networks in areas that converged, in large part, with the clinical literature—although resting-state findings in psychopathy have not been entirely consistent.

This thesis also reported a similar pattern of hyperconnectivity in children/adolescents who are at risk of developing psychopathy or persistent antisocial behavior in adulthood. Interestingly, along with likely limbic and default-mode candidates, somatomotor regions were also among the most robustly represented (and overlapping) regions in the studies of psychopathic traits, and of developmental risk for psychopathy. The consistency in these findings highlights the idea that to some extent, there may be a common factor underlying continuous variation in psychopathic traits. Likewise, there may also be resting-state features that are unique to the most severe behavioral phenotypes. Broadly speaking, the current thesis provides novel and substantial evidence that functional neural architecture may help explain atypical social cognition seen in individuals with ASD or with high levels of psychopathic traits. Further studies motivated by this research should combine research modalities to gain more nuanced information about possible pathophysiological mechanisms for these disorders.

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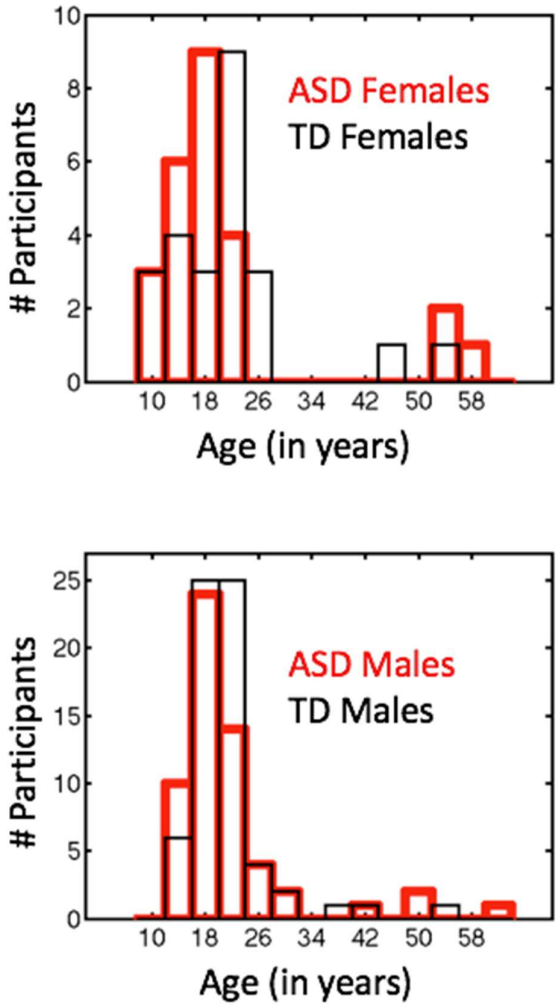
Appendix 1. Age Distribution by Experimental Group



Supplementary Figure 1: Histograms of age distribution by group. X-axis shows age in years, Y-axis shows number of participants Clinical groups shown in red, control groups shown in black.

Appendix 2. Evaluating Noise Bias in Seed Voxel Selection

When performing a two-stage process for the detection of regions using connectedness and follow-up seed testing, noise bias in the individual participant data can potentially affect the regions detected in the post-hoc seed testing (since the same data were used in seed detection and seed testing). This can be evaluated through leave-one-out (LOO) cross validation, defining seeds from connectedness tests for a given participant that excludes their own data. In the current context, 2x2 linear mixed effects models were performed on the whole-brain connectedness maps, leaving each participant out once. The seed locations for each participant corresponded to the peak coordinates within each of the two previously determined cerebellar clusters when not including that participant's data. In this way, the robustness of the previous results using all of the data to noise in the individual participants could be evaluated.

The results for the right cerebellar cluster showed that the peak coordinate was identical when leaving each participant out of the connectedness tests, thereby indicating that the original results for that seed were not strongly affected by noise bias. In contrast, the results for the left cerebellar cluster were modestly affected when leaving each participant out, matching the original peak coordinates 81.6% of the time. This led to a weakening of the seed test results from the left cerebellar seed, with one resulting region surviving correction for 1 test for a voxelwise threshold of $P<.005$ (and exhibiting a trend when correcting for 2 cerebellar seed tests). For comparison, when using all of the data, this same region survived correction for 2 tests at a voxelwise threshold of $P<.0005$. However, when combining the results of the two seed tests with LOO cross validation at $P<.0005$, little was affected overall, since the one resulting region detected from the left cerebellar seed was also detected from the right cerebellar seed. In total, 96.2% of the same voxels were detected at $P<.0005$ when controlling for noise bias compared to the original results, and none of the 13 resulting regions were lost.