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Neurobiological Underpinnings of Autistic Traits, Sensory Processing, and Mental Health in Young Adult Males and Females

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ABSTRACT

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Females may present with autism more frequently than is diagnosed, due, in part, to autistic trait and sensory processing differences. Unfortunately, recruiting enough autistic female participants is difficult, because of such underdiagnoses. By approaching autism as a continuous variable, neurotypical (NT) individuals can be studied to better understand autistic individuals. Thus, to examine potential neurobiological underpinnings of sex-based behavioral profiles, we recruited 52 NT individuals (22 male; 30 female). Participants underwent resting-state functional magnetic resonance imaging (fMRI) to examine how functional network connectivity (via group independent components analysis) underpinned overall male/female differences in previously measured behavioral autistic trait and sensory processing questionnaire scores. Results showed that males' sensory processing and autistic trait patterns were correlated with sensorimotor and social brain areas while females' intolerance of uncertainty and autistic traits were correlated with areas implicated in sensory processing and anxiety. Additionally, both sexes exhibited a close relationship between sensory processing (e.g., auditory, higher order visual), social functioning (e.g., middle temporal gyrus), and empathizing (e.g., right temporal-parietal junction, fusiform gyrus), though the networks present within these correlations differed somewhat between the sexes. Systemizing was most strongly correlated with executive functioning and language processing areas in both sexes, with different brain networks showing greater significance in males than females. Overall, males and females displayed similar neurophysiological patterns involved in autistic traits, sensory processing, empathizing, and systemizing, though they seemed to activate these networks differently. Understanding these network differences in an autistic population may provide for sex-specific brain-based interventions for sensory processing, anxiety, and autistic trait manifestation.

Keywords: autism, females, autism profiles, atypical sensory processing, neurosciences

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From this experience I have learned the importance of representation in the autism community and the need for more research in every field. By becoming a more empathetic, research-based clinician, I hope to make a positive impact on the field of speech-language pathology—something I could not have done without everyone's support.

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DESCRIPTION OF THESIS STRUCTURE AND CONTENT

This thesis, *Neurobiological Underpinnings of Autistic Traits, Sensory Processing, and Mental Health in Young Adult Males and Females*, is written in a hybrid format. The hybrid format combines thesis formatting with journal-ready publication methods. The preliminary pages of the thesis reflect requirements for submission to the university. However, the thesis itself is presented as a journal article and conforms to style requirements for submitting research reports to scientific journals. Identity-first language (e.g., "autistic individuals") is used throughout the paper due to its growing favor over person-first language in autism communities and published data supporting its use (Kenny et al., 2015). However, we also acknowledge and respect many people's preference for person-first language. The annotated bibliography is included in Appendix A. Appendix B contains the consent/Institutional Review Board approval letter.

Introduction

Autism Spectrum Disorder (hereafter "autism") is a developmental condition characterized by persistent deficits in social communication and restricted, repetitive patterns of behavior, interests, or activities, (American Psychiatric Association [APA], 2013, 2022). Additionally, the 2013 release of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association [APA], 2013) highlighted the occurrence of sensory differences in autism as an essential subcategory of restricted and repetitive behaviors. Such autistic traits manifest differently and with varying intensity among both autistic and neurotypical (NT) individuals (Wheelwright et al., 2010). That is, while autism has traditionally been viewed as a categorical phenomenon, it can also be modeled continuously. In fact, recently, many have advocated for a hybrid of these two perspectives (Elton et al., 2016; H. Kim et al., 2019; Tang et al., 2020).

Roughly one in 36 8-year-old children and one in 45 adults aged 18 and older in the United States are diagnosed with autism (Dietz et al., 2020; Maenner et al., 2023). Though autism has historically been diagnosed more frequently in males (3:1, males to females; Loomes et al., 2017), recent reports argue that more females may be autistic than are currently diagnosed (Dworzynski et al., 2012; Hull et al., 2020; Kreiser & White, 2014; Russell et al., 2011; Tsirgiotis et al., 2021). Possible sex differences in autistic trait profiles may contribute to this discrepancy (Cardon et al., 2023b). Main specific differences include higher internalizing traits, such as mental health, camouflaging, and sensory processing, in females versus males (Kumazaki et al., 2015; Lai et al., 2015; Osorio et al., 2021), though additional research is needed to fully characterize such sex-based differences.

Behavioral differences in autism expression between males and females are likely underpinned by neurobiological factors. For instance, studies utilizing resting state functional connectivity (rs-FC)—which is the measure of connection-strength between structures and networks in the brain regularly used to study brain patterns in autistic individuals—have shown many functional differences regarding autistic traits, sensory processing, intolerance of uncertainty, and mental health in males versus females and autistic versus NT individuals (Assaf et al., 2010; Baron-Cohen et al., 1994; Calton, 2022; Cherkassky et al., 2006; Kennedy et al., 2006; Olivito et al., 2016), though more focal research is needed to analyze sex-based autism profile differences. This study aims to compare differences in functional connectivity (FC) between males and females and to investigate any sex-related correlations between FC, autistic traits, and sensory processing. By further understanding these sex-based neurobiological differences, distinctions between the male and female autism phenotype may be more apparent, allowing for more accurate diagnosis of autistic females and possible management strategies for excess discomfort stemming from phenotypic differences (i.e., different areas of sensory processing and other internalizing traits).

Males Versus Females in Autism Diagnosis

Three predominant theories regarding why males are diagnosed with autism more than females include the female protective effect (Jacquemont et al., 2014; Wigdor et al., 2022; Zhang et al., 2020), the extreme male brain theory of autism (Baron-Cohen, 2002), and differences in the male and female autistic phenotype (Loomes et al., 2017; Rynkiewicz et al., 2016). The female protective effect proposes that females require higher genetic loading than males to exhibit the same degree of autistic traits (Antaki et al., 2022; Deng & Wang, 2021; Jacquemont et al., 2014; Zhang et al., 2020). Several brain-based findings add validity to female protective

factors, such as manifestation of significantly more gray matter asymmetry in autistic females than males with similar trait intensity (Deng & Wang, 2021), greater differences in autistic females' sensorimotor, striatal, and frontal regions of the brain as compared to NT female controls than between autistic males and their controls (Jack et al., 2021), and more pronounced alterations in limbic, somatomotor, and default mode network (DMN) local connectivity in autistic females than males (Kozhemiako et al., 2020). These differences suggest that autistic females have greater brain changes as compared to their male counterparts, and therefore may exhibit greater physiological differences in conjunction with their diagnosis.

The extreme male brain theory of autism is built on the notion that NT females have a tendency toward empathizing (understanding another person's emotions and responding congruently) while NT males have a tendency toward systemizing (effectively creating, following, and analyzing a rule-based system). Baron-Cohen (2009) proposes that both autistic males and females exhibit an extreme version of the male phenotype, expressing extremely low empathizing and extremely high systemizing (Baron-Cohen et al., 2011; Kozhemiako et al., 2018; Ympa et al., 2016). Therefore, if autistic females are not presenting with a high level of systemizing or are camouflaging their systemizing tendencies to appear congruent with the NT female stereotype (Head et al., 2014), they may not be identified as needing to be screened for autism. Ympa et al. (2016) found that autistic males and females share strong and specific reduction in DMN intraconnectivity as compared to NT males and females during resting-state functional magnetic resonance imaging (rs-fMRI), correlating with decreased mentalizing and socializing cognition. This provides initial neurobiological evidence of Baron-Cohen's claim by showing that autistic males and females have brain-based differences resulting in lower empathizing than typically found in NT males and females.

The theory that differences in the male and female autistic phenotype suggest that females are less likely to be diagnosed with autism due to an underrepresentation of the autistic female phenotype in diagnostic criteria. If this is accurate, it may be that females are underrepresented in the autism research that is used to develop and build on current diagnostic checklists (Gould, 2017; Kreiser & White, 2014). And, as mentioned previously, higher levels of social camouflaging (furthermore "camouflaging") in autistic females (Head et al., 2014; Lai et al., 2015, 2017; Schuck et al., 2019; Tubío-Fungueiriño et al., 2020) may also account for fewer females being identified for autism screenings (Allely, 2019; Cage & Troxell-Whitman, 2019; Head et al., 2014; Hull, L. et al., 2017; Tubío-Fungueiriño et al., 2020). These higher levels of camouflaging in autistic females seem to lead to increased internal behaviors, including anxiety, depression, and stress (Bargiela et al., 2016; Cage et al., 2018a; Cage & Troxell-Whitman, 2019; Lai et al., 2017). In their study, Walsh et al. (2021) found evidence of a correlation between camouflaging and a particular pattern of rs-FC in the brains of autistic males and females. Specifically, in autistic females, the strongest predictor of camouflaging was higher FC between the hypothalamus and a limbic reward cluster. Sex-atypical patterns were also found that suggest similar FC and camouflaging patterns between NT males and autistic females as well as NT females and autistic males.

Many studies have been or are currently being conducted to examine possible sex-dependent profile differences related to autistic trait severity in both autistic and NT males and females (Cardon et al., 2023b; Ferreira et al., 2022; Kreiser & White, 2014; Lai et al., 2015; Williams et al., 2021). This trend is due to similar patterns that can be found between autistic and NT populations (Groot & Van Strien, 2017; Hurley et al., 2006; Piven et al., 1997b; Sasson et al., 2013; Wheelwright et al., 2010) and the need to better understand sex differences autism. For

example, some recent findings from our lab showed evidence of differing autistic trait profiles between NT males and females (Cardon et al., 2023b). In this study, males and females presented with similar general degrees of autistic traits, but males exhibited greater aloofness than females. However, there is a need for more research regarding correlations between common autistic traits, including sensory processing difficulties, intolerance of uncertainty, and anxiety. This correlation will be examined in greater depth in the current article.

Atypical Sensory Processing

Sixty to ninety-five percent of autistic individuals experience atypical sensory processing (Crane et al., 2009; Kern et al., 2007). This includes hyposensitivity (slow-to-no response to environmental stimuli, e.g., not responding to one's name or noises that may indicate danger, such as a train horn), hypersensitivity (increased sensitivity to incoming sensations, e.g., experiencing greater sensitivity to light when walking outside than other individuals, or experiencing excessive discomfort due to the feeling of a cotton shirt on one's skin), sensory seeking (behavior leading to increased sensory stimulation, e.g., spinning around in circles or on a swing excessively to experience increased proprioception), or sensory overload (complete overwhelm from incoming sensory input, e.g., rocking back and forth on the floor with hands over one's head in an attempt to block out the incoming stimuli). These behaviors occur in response to stimulation from either one sense (i.e., visual, auditory, olfactory, gustatory, somatosensory, vestibular, and proprioception) or many senses at once (Neil et al., 2016). Many factors that affect the onset and duration of sensory processing differences include context, time of day, and level of fatigue, among other factors (Ben-Sasson et al., 2009; Chistol et al., 2018; Green et al., 2015; Marco et al., 2011; Robertson & Baron-Cohen, 2017; Suarez, 2012; Tomchek & Dunn, 2007). Atypical sensory processing has also been found among the NT population,

though often with less intensity than in autistic individuals (Baron-Cohen et al., 2001; Calton, 2022; Cardon et al., 2023b; Tavassoli et al., 2018).

A number of researchers have found correlations between sensory processing difficulties and other traits commonly seen in autism (Mayer, 2017; Robertson & Simmons, 2012; South & Rodgers, 2017). These include social communication (Bigler et al., 2007; Foss-Feig et al., 2010; Hannant et al., 2016; Hilton et al., 2007; Lincoln et al., 1995; Matsushima & Kato, 2013; Philpott-Robinson et al., 2016; Reynolds et al., 2011; Thye et al., 2017; Watson et al., 2011), restricted and repetitive behaviors (Bishop et al., 2013; Boyd et al., 2010), and anxiety (Gadow et al., 2004; Green & Ben-Sasson, 2010; J.A. Kim et al., 2000; Muris et al., 1998; Sukhodolsky et al., 2008; Weisbrot et al., 2005). Furthermore, intolerance of uncertainty is believed to be a mediator in the correlation between sensory processing abnormalities and anxiety, even in NT individuals (Boulter et al., 2014; Calton, 2022; Hwang et al., 2019; MacLennan et al., 2021; South & Rodgers, 2017; Wigham et al., 2015).

Sex differences in autism can likely be attributed to variations in several traits, including sensory processing. However, few studies have investigated possible sex differences in sensory processing (Cardon et al., 2023b; Kumazaki et al., 2015; Lai et al., 2015; Osorio et al., 2021). For example, Osorio et al. (2021) found that autistic females were more averse to auditory and tactile stimuli and had more postural and movement-coordination problems than autistic males. Similarly, in Kumazaki et al.'s (2015) study, autistic females ages 5 to 9 displayed greater tactile, olfactory, and gustatory sensitivity than autistic males. Findings from our group examining NT young adults initially discovered similar levels of sensory processing difficulties between males and females, as per the Glasgow Sensory Questionnaire (GSQ; Robertson & Simmons, 2012), though a more in-depth analysis found that females displayed significantly greater levels of

hypersensitivity than males, and males displayed significantly greater levels of hyposensitivity than females (Cardon et al., 2023b). Though results are based on data from NT individuals, they can be used as a reference for trait correlations across NT and autistic individuals alike due to the spectrum nature of autism. Taken together, these findings suggest that, though more conclusive evidence is needed, autistic males and females may have similar levels, but different profiles of, atypical sensory processing.

Researchers have sought to uncover the FC underpinnings of atypical sensory processing (Calton, 2022; Green et al., 2015; Hull, J. et al., 2017; Marco et al., 2011; Mayer, 2017; Paaki et al., 2010). While some findings have been variable, or even contradictory, some patterns are starting to emerge. For example, in a recent mega-analysis that analyzed overall resting-state FC patterns in brains of autistic individuals (Ilioska et al., 2022), it was found that hypoconnectivity of the sensory and higher-order attentional networks (specifically the somatomotor network and visual network) were correlated with sensory processing difficulties, as was hyperconnectivity of the default mode network (DMN) and the rest of the brain. These higher-order networks may be implicated in sensory processing due to their involvement in connecting sensory input with the rest of the brain. Because of this, it is logical to examine the DMN, somatomotor, and sensory networks in the brain while investigating sex differences in the FC of atypical sensory processing.

Other researchers have detailed more specific resting-state FC patterns in the brain while examining sensory processing consistent with the above trends. For example, using a measure of FC called Regional Homogeneity, Paaki et al. (2010) found under-connectivity in the right superior temporal sulcus and right insula, which areas have been implicated in atypical sensory processing and multisensory input integration. In their review, Hull, J. et al. (2017) found that

atypical sensory processing may be correlated with over-connectivity between the right posterior temporoparietal junction and the right ventral occipital temporal cortex, and the primary sensory and subcortical networks in the thalamus and basal ganglia. Furthermore, they found that the greater the connectivity between these brain areas, the greater the severity of other autistic traits. Assaf et al. (2010) also discovered that over-connectivity between primary sensory and subcortical regions was correlated with autism trait severity. Taken together, current research points to a few general trends, such as positive correlations between autistic traits and atypical sensory processing and their neurologic underpinnings. However, findings appear to have a great amount of variability, likely due to the heterogeneity of sensory differences in the autistic population. Because of this, more studies are needed that aim to identify general FC trends in atypical sensory processing. Further research is also needed to determine which of these trends may be correlated with biological sex.

Correlates of Sensory Processing: Anxiety and Intolerance of Uncertainty

Atypical sensory processing is correlated with other internalized traits, including intolerance of uncertainty and anxiety (Cardon et al., 2023b; Hwang et al., 2019; MacLennan et al., 2021; South & Rodgers, 2017; Wigham et al., 2015). Intolerance of uncertainty is the difficulty to respond adaptively in situations with an uncertain outcome. This is highly linked to anxiety (MacLennan et al., 2020), which is a constant feeling of tension or dread regarding current or potential upcoming events. While our understanding of the interrelationship between these two constructs is not complete, previous studies have shown that they are related to each other (Boulter et al., 2014; Neil et al., 2016; South & Rodgers, 2017; Wigham et al., 2015). In fact, recent findings from our group showed significantly higher levels of both anxiety and intolerance of uncertainty in females as compared to males (consistent with Cai et al., 2017)

Additionally, we found a significantly higher correlation between autistic traits and anxiety in females, as well as a stronger mediation effect between intolerance of uncertainty and anxiety. This adds evidence to the hypotheses that autistic females experience greater levels of internalizing traits (i.e., anxiety, stress) than their male counterparts, and that males and females, though they show differing levels of the same types of traits, have different autistic profiles in many regards, including mental health (Cardon et al., 2023b).

The Triple Network Model (Menon, 2011) has been proposed as one way to examine FC throughout the brain. The model is composed of three large-scale distributed networks: The DMN, salience network (SN), and frontoparietal network (FPN). The interactions between these three networks have been implicated in autism (Menon, 2011, 2018; Uddin et al., 2013). The SN is the point at which the DMN and FPN connect and interact, and is also where cognitive, emotional, and sensory information are combined (Menon, 2011). The DMN is involved in mentalizing (the ability to understand both one's own and others' minds/mental processes and intentions) and theory of mind, and therefore has a large role in social communication (Padmanabhan et al., 2017). Hogeveen et al. (2018) shows how interactions between the DMN, SN, and FPN may be correlated with internalized characteristics of autism. These investigators found that overconnectivity between areas of the SN (specifically the anterior insula node) and areas of the DMN (specifically the caudal posterior cingulate cortex) was correlated with higher levels of internalizing traits in autistic individuals who underwent resting-state scans.

In NT individuals who show high trait anxiety, Sylvester et al. (2012) showed that there may be decreased connectivity in the FPN during resting-state scans, as well as increased connectivity between FPN and cingulo-opercular networks, and the FPN and supramodel areas such as the amygdala (Basten et al., 2011; Etkin et al., 2009). The DMN was also found to have

decreased FC with the amygdala and decreased interconnectivity overall in individuals with high state anxiety and social anxiety disorder. These networks may similarly be found in autistic individuals, though there are no studies to date examining this possible correlation. Furthermore, better understanding the functioning of the DMN, SN, and FPN, both separately and collectively, may give greater insight into the neurobiological underpinnings of autism, as well as brain pattern differences inherent in autistic males and females.

The Broader Autism Phenotype

Autistic traits are experienced in the general population as well as the autistic population, albeit to a lower degree. As first discovered in relatives of autistic individuals (Bailey et al., 1998; Bolton et al., 1994; Sucksmith et al., 2011), the Broader Autism Phenotype (BAP) refers to this cluster of autism-related characteristics when they are recognizable in NT individuals but are too mild to lead to diagnosis (Groot & Van Strien, 2017; Hurley et al., 2006; Piven et al., 1997b; Sasson et al., 2013; Wheelwright et al., 2010). The BAP supports the theory that autistic traits are continuous rather than categorical, with diagnosed individuals exhibiting the highest degree of autistic traits and related behaviors, and the remainder of the general population expressing varying—though less severe—degrees of the same traits (Wheelwright et al., 2010).

Landry and Chouinard (2016) explore why studying NT individuals may contribute useful information to autism research. Some of these reasons include having increased control for comorbidities in NT individuals, using larger sample sizes to control for variability/heterogeneity and discover smaller effects, utilizing procedures that may be practically difficult to conduct among autistic individuals (i.e., structural and functional MRIs, which can be uncomfortable for someone with intense sensory difficulties), and studying various autistic traits in isolation. In our group's previous study (Cardon et al., 2023b), it was found that

between 5.6% to 16.5% of males and 4.9% to 17.3% of females (using the Autism Quotient [AQ] and Broad Autism Phenotype Questionnaire [BAPQ], respectively) exhibited a significantly high degree of autistic traits, falling above the cutoff which would support further screening for autism (Broadbent et al., 2013). This high degree of autistic traits among an NT sample adds further validity to the use of NT individuals in discovering relevant correlations between autistic traits and other factors.

Though there are many practical reasons for studying NT populations to understand autistic populations, to our knowledge, no studies have yet studied the neurobiological differences between males and females and their associations with autistic traits and sensory processing.

Aim

As shown by the above literature, males and females have both behavioral and neurophysiological differences that are related to autism/autistic traits. Consequently, we posit that the results from our lab's prior study—that NT males and females have similar levels of autistic traits and sensory processing and its correlates, but different overall profiles (higher hyposensitivity in males and higher hypersensitivity in females; more aloofness in males than females; more anxiety and intolerance of uncertainty in females than males, but similar levels of depression)—may be underpinned by sex-based neurobiological differences. Thus, by examining a smaller subset of our group's original study, the present study aims to examine these potential brain-based differences and their correlation with autistic traits, sensory processing, and related behaviors by FC during rs-fMRI. We hypothesize that there will be differences in within- and between-network connectivity in males and females that are associated with autistic traits, sensory processing, and anxiety. Specifically, we project to see differences in the following

networks: large-scale, distributed resting-state networks as found in the DMN, SN, and FPN, supramodel networks (specifically the amygdala and cerebellum), and sensory areas.

Method

Participants

Participants were recruited for this study using advertisements from the university, including fliers, emails, the Brigham Young University psychology research pool (SONA), and social media platforms (e.g., Facebook, Instagram). Approximately 1200 individuals (653 female) took the survey, though only 55 of these 1200 were selected to undergo subsequent resting-state fMRI scans. Three of these participants were excluded from data analysis due to excess artifact in their recordings. Therefore, our final sample was 52 young adult subjects, ages 19–26 (32 females, mean age = 21.34, *SD* = 1.89 and 23 males, mean age = 23.04, *SD* = 1.77), each of whom self-identified as NT. Sex in this survey was determined by participant report of their biological sex assigned at birth. Subjects varied across race/ethnicity, major, GPA, family members with autism, and comorbid diagnoses of autism including ADHD and anxiety. A summary of participant characteristics can be seen in Table 1. All procedures were approved by the Brigham Young University Institutional Review Board and were in accordance with the Declaration of Helsinki.

Procedure and Materials

Behavioral Measures

The initial surveys, compiled and distributed in a previous study (Calton, 2022), were filled out online (Qualtrics XM, 2005) and included basic demographic questions, including age, sex, major, diagnoses, and family members with autism. The options presented for sex were male and female, which may have resulted in some individuals opting out of the survey. Additionally,

the surveys contained the following standardized, self-report questionnaires: the Glasgow Sensory Questionnaire (GSQ), Broad Autism Phenotype Questionnaire (BAPQ), Autism Quotient (AQ), Systemizing Quotient (SQ), Empathizing Quotient (EQ), Depression Anxiety Stress Scale 21 (DASS-21), and the Intolerance of Uncertainty Scale – Short Form (IUS-12). These questionnaires aimed to survey a variety of features found in sensory processing, autistic traits, mental health, and intolerance of uncertainty, respectively.

The GSQ (Robertson & Simmons, 2012) assesses hypo- and hyper-sensitivities and behaviors associated with atypical taste, smell, auditory filtering, and movement (Tomchek & Dunn, 2007). It has been used to assess atypical sensory processing in the general population (Robertson & Simmons, 2012) and to measure hyper- and hyposensitivity (Horder et al., 2014; Robertson & Simmons, 2015; Schaaf & Lane, 2015; Tavassoli et al., 2014). The GSQ has high reliability (Cronbach's Alpha, $r = 0.935$; Guttman's Split-Half technique, $r = 0.929$), with higher scores denoting greater sensory difficulties.

The BAPQ (Hurley et al., 2006) and AQ (Baron-Cohen et al., 2001) both evaluate the existence of autistic traits, though through different subtests and with slightly different intentions. The BAPQ was created as a survey for the general population and focuses on primary components of the BAP, including aloofness, rigid personality, and pragmatic language difficulties. The entire test as well as its subtests have high reliability (overall reliability: $r = 0.95$; aloofness: $r = 0.91$; rigidity: $r = 0.91$; pragmatic language: $r = 0.85$) and high validity for BAP trait measurement. The AQ is regularly used as a preliminary screening for autism, and analyzes social skills, communication, attention to detail, and attention switching and imagination (Baron-Cohen et al., 2001; Robertson & Simmons, 2012). It has a moderate to high reliability in each subcategory (communication: $r = 0.65$; social: $r = 0.77$; imagination: $r = 0.65$;

local details: $r = 0.63$; attention switching: $r = 0.67$) and reasonable construct and face validity. Because of its more conservative nature as a screener, the AQ tends to show fewer individuals with high levels of autistic traits than the BAPQ. Higher scores on both questionnaires suggest greater degrees of autistic traits.

The SQ and EQ are designed to measure, respectively, systemizing and empathizing levels (Baron-Cohen et al., 2003; Baron-Cohen & Wheelwright, 2004). They both have a high degree of internal consistency and reasonable validity and have been used in multiple studies to assess systemizing and empathizing in participants (Baron-Cohen, 2009; Baron-Cohen et al., 2003, 2005; de Vignemont & Singer, 2006; Lamm et al., 2007). It is thought that the AQ and the SQ are positively correlated while the EQ may be inversely correlated with the AQ, revealing potential relationships between empathizing, systemizing, and autistic traits in a NT population (Baron-Cohen & Wheelwright, 2004). Higher scores on both surveys reflect either greater systemizing (SQ) or greater empathizing (EQ).

The DASS-21 is a shortened version of the DASS-42 that has strong reliability ($\alpha = 0.86$ - 0.90; $p = 0.94$) and validity (Antony et al., 1998; Gloster et al., 2008; Henry & Crawford, 2005) and assesses levels of anxiety, stress, and depression (Lovibond & Lovibond, 1995). It has been used to assess anxiety, stress, and depression in NT young adults (Brown et al., 1997), autistic individuals (Nah et al., 2018; S. H. Park et al., 2020) and parents of autistic children (Firth & Dryer, 2013). Higher scores suggest greater levels of anxiety, stress, and depression for each of the subscores, respectively. Though not a diagnostic tool, the DASS-21 was used in this study to gather information regarding correlates of autistic traits and sensory processing and possible profile differences between males and females.

The IUS-12 assesses reactions to unpredictable events (Carleton et al., 2007) and is a short form of the original Intolerance of Uncertainty Scale. It has high internal consistency (α = 0.85) and is a reliable measure of difficulties with behavioral prediction. The IUS-12 measures both prospective anxiety (e.g., "I must get away from all uncertain situations.") and inhibitory anxiety (e.g., "Uncertainty keeps me from living a full life."), revealing correlations between prediction abilities and attitudes toward uncertainty. Higher scores on the IUS-12 denote higher intolerance of uncertainty.

Resting State-fMRI

A 3T Siemens Trio MRI scanner housed on the campus of Brigham Young University was used for all scans. Each subject underwent four MRI scans: field-mapping, localizer, structural MRI, and rs-fMRI, taking approximately 30 minutes per person. During this time, subjects were asked to fix their gaze on a black and white cross and to remain awake and alert. Whole-brain blood oxygen level-dependent measures (BOLD; a measurement of brain activity determined by blood flow to areas of the brain), and MRI scans were taken utilizing the following parameters: 40 axial slices, 2.5 mm thick with 0.5 mm gap, 220 mm 2 fov 64 squared matrix = 3.43 mm 3 voxels, repetition time = 2500 ms, echo time = 30 ms. We also obtained a T1-weighted anatomical scan (MP-RAGE) for co-registration and normalization to Montreal Neurological Institute (MNI) space for each participant. MRI results for three of the participants (two females, one male) were removed from the study due to excess artifact presentation within their scans, making the total number of participants for the remainder of the study 52 (30 females, 22 males).

Data Analysis

Behavioral Measures

Using the SPSS statistical package (IBM, 2021), between- and within-groups effects were analyzed. First, descriptive statistical analysis was performed on each behavioral measure to verify normal score distribution, investigate behavior-related frequencies, and analyze the number of participants who fell above and below previously published autistic trait and sensory processing cutoff scores (Broadbent et al., 2013; Sasson et al., 2013). Nonparametric, Mann-Whitney U tests were used to compute between-groups differences, comparing total and sub-scores for each behavioral measure with mean scores of male versus female participants.

Resting State-fMRI

To eliminate image distortion factors (e.g., motion, small artifacts), all structural and functional scans were preprocessed and denoised using the ArtRepair toolbox within CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012). This included applying temporal high pass filtering, co-registration, Gaussian smoothing (6 mm^3), and motion correction. Independent component analysis—ICA, as contained in the Conn toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), was then conducted on all rs-fMRI data and run through Matlab (MathWorks, 2011).

Independent component (IC) networks correlated with our hypotheses (i.e., sensory, supramodal, and large-scale distributed networks) were then selected from computed ICs. A spatial match to template was used to select and name ICs. Template networks from CONN were utilized in this analysis as well as a list of 14 resting state functional networks detailed in Shirer et al. (2012) and 10 common ICs found in an article by Smith et al. (2009). For the purpose of increasing statistical power, ICs with biological networks that do not correlate with our

hypotheses were not taken into account, nor were networks that contained artefact, such as excessive participants' motion. Next, direct comparison of FC patterns between the chosen IC networks and connected voxels was carried out between male and female groups via independent sample *t*-tests (i.e., between-sex analysis). Then, connectivity patterns corresponding to relevant behavioral measures (e.g., sensory processing, EQ, SQ, and anxiety) were continuously assessed across the male and female participant groups (i.e., across-sex analysis; cluster-based Gaussian random field theory parametric statistics; Worsley et al., 1996). Differences in the brain-behavior correlations were then assessed using a general linear model approach. Two-sided false discovery rate (FDR) corrections ($p < 0.05$) were applied to the connected voxels for each IC network. We ultimately determined significance through Bonferroni correction across IC network results. Connectivity values were calculated for all 52 participants and imported into SPSS to further examine relationships (Pearson correlations) between FC indices and relevant behavioral measures.

Results

Behavior Differences

As compared to our group's previous study containing 1122 participants (556 female), there were fewer, albeit overlapping, significant behavioral results in the current study's 52-person sample (see Table 1). Overall, males and females differed significantly on the BAPQ Aloof Subtest (Mean(SD): Males: 37.39(12.21), Females: 29.21(8.57); $U = 232$; $p = 0.020$), EQ (Males: 38.65(12.64), Females: 47.97(12.65); $U = 526.5$; $p = 0.007$), and SQ (Males: 35.04(8.54), Females: 22.59(10.03); $U = 119.5$; $p < 0.001$). The brain-behavior relationships that follow will primarily focus on the above behavioral differences.

Sex-Based Brain-Behavior Differences

We observed several brain-behavior connectivity patterns that were significantly different between males and females (Table 2). Most of these patterns correlated with EQ/SQ test scores in males and/or females, though a few were related to other test scores, including IUS total score, GSQ total and hypersensitivity scores, and BAPQ total scores. For conciseness, all correlation coefficients and their associated *p*-values for within-groups correlations are presented in Tables 3 and 4. Between-sex and across-sex analyses are outlined below.

Between-Sex Analysis

In each of the following results, direct comparison of male and female patterns of connectivity revealed significant differences. In general, we observed such sex-based differences in patterns of connectivity involving higher order visual areas (IC29). These patterns of functional connectivity correlated with different behavioral measures in males versus females. For instance, males exhibited a significantly greater correlation between higher order visual areas (IC29) and the right precentral gyrus with GSQ total ($t = 0.03$, $p = 0.018$) and hypersensitivity ($t = 2.15$, $p = 0.018$) scores, and BAPQ total scores ($t = 1.98$, $p = 0.027$) than females. Additionally, connectivity between higher order visual areas (IC29) and the right intracalcarine cortex were associated with IUS total scores as well as BAPQ total scores to a significantly greater degree in females than males (IUS: $t = 1.95$, $p = 0.028$; BAPQ: $t = 2.37$, $p = 0.011$).

Across-Sex Analysis

EQ Scores and Patterns of Connectivity

Several connectivity patterns were found to be significantly correlated with EQ total scores in both males and females. A between-sexes *t*-test revealed that all such correlations were also significantly different between the sexes. For example, though males' and females' EQ total

scores were both significantly correlated with connectivity between the left executive control network (IC16) and right temporal fusiform, females exhibited a stronger correlation than males did (t = -5.46, p < 0.001). Conversely, connectivity between the frontal-parietal areas related to language (IC18) and left middle frontal gyrus, (t = 6.36, p < 0.001), the primary motor cortex (IC31) and left frontal pole (t = 5.74, p < 0.001), and the auditory areas (IC6) and right temporal pole (t = -5.69, p < 0.001) showed a stronger correlation in males than females, though both sexes exhibited significant brain-behavior correlations.

In slight contrast to the above, some results were both significantly different between the sexes and significantly more correlated in one sex or the other. Specifically, connectivity with an auditory IC network (IC6) and the pre- and post-central gyrus (t = -4.32, p < 0.001), mid-temporal gyrus (t = -4.99, p < 0.001), and left temporal pole (t = 5.51, p < 0.001) were only significantly associated with the EQ total scores in females and not in males. Males, however, displayed a significantly greater association between EQ scores and connectivity between the primary motor cortex (IC31) and right angular gyrus than females (t = 4.63, p < 0.001).

SQ Scores and Patterns of Connectivity

SQ scores and correlated connectivity patterns displayed similar patterns as EQ scores, in that all SQ total scores which were significantly correlated with both males and females were also significantly different between the sexes. For example, males showed a greater overall correlation in the following areas: the anterior cingulate cortex/medial prefrontal cortex (IC9) and medial prefrontal cortex (t = -5.28, p < 0.001), in which greater connectivity was related to less systemizing, and left executive control network (IC16) and left temporal pole (t = 4.71, p < 0.001), such that greater connectivity was related to higher systemizing levels. Females likewise showed a greater overall correlation between SQ total scores and the left frontal parietal network

(IC22) and putamen/insula/left primary auditory cortex (higher in females; $t = 5.19$, $p < 0.001$) than males, with greater connectivity being correlated with higher levels of systemizing.

Discussion

Males are diagnosed with autism more frequently than females (Loomes et al., 2017). This may be due to differences in each group's expression of specific autism-related characteristics, despite similarities in overall levels of autistic traits (Cardon et al., 2023b; Kumazaki et al., 2015; Lai et al., 2015; Osorio et al., 2021). The current study aimed to examine how sex-based differences in autistic trait profiles might be due to differing underlying neurobiological factors. We hypothesized that there would be sex-based differences in within- and between-network connectivity in males and females that correlated with autistic traits, sensory processing, and anxiety. We expected to see specific differences in large-scale, distributed resting-state networks (DMN, SN, ECN), supramodal networks (specifically the amygdala and cerebellum), and sensory areas. We found various correlations between functional network connectivity and IUS, GSQ, and BAPQ total scores that differed between the sexes, though the most pronounced differences between females and males were observed in brain activity patterns associated with the EQ and SQ.

Research Question 1

How did the connectivity patterns that differed between males and females correlate with behavioral measures of sensory processing and other autism-related traits?

Our between-sex analysis revealed several network connectivity pattern differences between males and females. A number of these differing patterns were also significantly correlated with our behaviors of interest. For example, results in females indicate that both higher IUS-12 and BAPQ scores had a positive correlation with a pattern of connectivity

between higher order visual areas and the right intracalcarine cortex (i.e., part of primary visual cortex). Such a relationship was not seen in males. Intolerance of uncertainty has been heavily implicated in autism (Boulter et al., 2014; Calton, 2022; Cardon et al., 2023a; Jenkinson et al., 2020; Rodgers et al., 2017; Vasa et al., 2018). Additionally, sensory processing—including visual processing—has been shown to impact both intolerance of uncertainty and autistic traits in general (Cardon & Bradley, 2023; Cardon et al., 2023a; Robertson & Simmons, 2012; Wigham et al., 2015), potentially explaining our observation of a connection between IUS-12 and BAPQ scores. FC between higher order visual areas and right intracalcarine cortex may underpin this relationship in the females.

Several studies, including data from our group (Boulter et al., 2014; Calton, 2022; Cardon et al., 2023a, 2023b; Cardon & Bradley, 2023; South & Rodgers, 2017), have noted that prediction mismatches might be highly correlated with sensory processing difficulties. For example, the mismatch of predicting one sensory input (such as a warm bite of soup on the tongue) and receiving another (a cold bite of soup on the tongue) can lead to atypical sensory behaviors—either because of atypical predictions or differences in processing of the actual sensory inputs. Over the long term, mismatches of this sort may lead to intolerance of uncertainty. Thus, we considered the IUS-12 to be an indirect measure of prediction herein. Visual processing may be connected to prediction atypicality. Mismatches between predictions about visual stimuli and the actual visual inputs could give rise to higher levels of intolerance of uncertainty (Boulter et al., 2014; South & Rodgers, 2017; Wigham et al., 2015). Furthermore, our group has found that these interrelationships are fundamental to autistic trait expression in children, regardless of diagnosis, which may have bearing on the present study (Cardon et al., 2023b).

The intracalcarine cortex may also have neurobiological links to depression, anxiety, and obsessive-compulsive disorder (Pannekoek et al., 2015; J. Park et al., 2020), all of which commonly co-occur with autism (DeFilippis, 2018; Ivarrson & Melin, 2008; Mayes et al., 2011; Postorino et al., 2017; Stewart et al., 2006). Several studies have shown a strong relationship between intolerance of uncertainty and anxiety (Carleton, 2014; Carleton et al., 2012; del Valle et al., 2020; Gu et al., 2020; Milne et al., 2019; Osmanagaoglu et al., 2018), suggesting that the correlation between the right intracalcarine cortex and intolerance of uncertainty may be linked to common roots between intolerance of uncertainty and anxiety. In our group's study from which the present participants were recruited, we reported that intolerance of uncertainty mediated the relationship between atypical sensory processing and anxiety in both males and females, though these relationships were stronger in the latter. That is, the relationship between anxiety and atypical sensory processing in both sexes appears to be explained by both factors' additional relationship with intolerance of uncertainty (Cardon et al., 2023b; Hwang et al., 2019; Jenkinson et al., 2020).

It is likely that females displayed the above significant brain-behavior patterns whereas males did not, because of the sexes' different relationships with anxiety. In our prior study, with a larger sample, females displayed significantly higher anxiety than males. Anxiety was also more strongly correlated with autistic traits and sensory differences in females than males (Cardon et al., 2023b). Though this finding was not replicated in our smaller sample, other researchers have found that anxiety tends to be more prevalent in females than males (Bahrami & Yousefi, 2011; Hosseini & Khazali, 2013; Lewinsohn et al., 1998). This is aligned with our findings that females, more than males, may have a stronger underlying brain connections with

areas involved in intolerance of uncertainty and autistic traits, which have a strong connection with both anxiety and sensory processing.

Males' connectivity patterns between higher order visual areas and the right precentral gyrus (i.e., the primary motor cortex) were correlated with GSQ total and hypersensitivity scores as well as BAPQ total scores, such that that greater connectivity was associated with higher reported levels of sensory difficulties and autistic traits. The connection between these areas suggests a fundamental and neurophysiologically mediated connection between sensorimotor function and autistic traits. Sensory activity is linked to motor output (Schneider, 2020), as actions and reactions are only possible through sensorimotor interface (Brooks & Cullen, 2019). Sensorimotor difficulties are highly correlated with autistic individuals' non-social behaviors (e.g., restricted interests) as well as social behaviors (e.g., taking in information from others and responding appropriately both with words and gestures; Hannant, Tavassoli, & Cassidy, 2016; Thye et al., 2017). As the degree to which an individual exhibits difficulty integrating sensation and movement (sensorimotor integration) is directly correlated with their autism severity (Hannant et al., 2016; Hwang et al., 2019; Jenkinson et al., 2020; Thye et al., 2017), perhaps males, and not females, exhibited a correlation between sensory processing and autistic traits because of sex differences in social behaviors. Furthermore, autistic males have been shown to have greater observable social difficulties than females, likely due to females' higher camouflaging levels (Corbett et al., 2021).

Differences in the above brain-behavior correlations between males and females might be evidence that autistic traits are characterized differently between the sexes. However, future studies should aim to discover whether similar patterns are found in autistic females and males.

Research Question 2

How did brain-behavior relationships that were prominent in both males and females differ between the sexes?

Emotional Quotient

NT females have regularly been shown to have higher emotional quotient (EQ) scores than males, suggesting enhanced empathizing tendencies (Baron-Cohen, 2009; Hull, L. et al., 2017; Nettle, 2010). This finding held true in our study, where females had significantly greater overall empathizing levels than males. We, therefore, expected to see sex-based differences in the brain mechanisms associated with empathizing. Though we did see some neurophysiologic differences between males and females, we primarily found similarities that were slightly stronger in one sex than the other, suggesting potential mechanisms for empathy that, though engaged in both sexes, are stronger in either males or females. For instance, *both* sexes showed a strong correlation between EQ scores and connectivity between the left executive control network and right temporal fusiform gyrus, such that less connectivity between these areas reflected higher empathizing scores. However, this trend was stronger in females than in males.

Previous studies have shown that greater connectivity within the left executive control network leads to higher performance of executive tasks in both NT and autistic populations (Schmitz et al., 2006; Seeley et al., 2007). Additionally, systemizing and executive functioning are closely related, such that greater executive functioning leads to higher systemizing, particularly in an autistic population (Cascia & Barr, 2020). The right temporal fusiform area has been implicated in facial recognition and empathy and as well as in social perception (Hudson & Grace, 2000; Lawrence et al., 2006; Nasr & Tootell, 2012; Rossion et al., 2003; Spencer et al., 2011). For example, Besel (2011) demonstrated that individuals who were quicker at identifying

facial expressions were also more likely to exhibit higher EQ scores. However, even though the right temporal fusiform area might contribute to empathizing, it is possible that its connection with the executive control network, and subsequent systemizing, is what led to males' exhibition of lower empathy.

Both sexes' EQ scores were also negatively correlated with connectivity between auditory areas and the right temporal pole, though the strengths of these correlations were found to be significantly different between the sexes. That is, the stronger the connectivity between these two areas, the lower the levels of empathizing were in both males and females, though the pattern was stronger in males. Prior studies have found that activity in the temporal pole underlies emotional responses to strong sensory stimuli, including olfaction, audition, and vision, as well as mentalizing deficits (Frith, 2001; I. R. Olson et al., 2007). As mentalizing and empathy are closely related (Hooker et al., 2008; Swan & Riley, 2015), it is plausible to believe that one's emotional responses to sensory input may affect empathy levels.

Furthermore, atrophy of the right temporal pole has also been shown to lead to empathy deficits and changes in social behaviors, emotion regulation, and personality (I. R. Olson et al., 2007; Rankin et al., 2006). Rankin et al. (2006) hypothesized that right temporal pole atrophy may lead to empathy deficits because of a decreased ability to utilize facial recognition and therefore understand different emotional states. Similarly, Spencer et al. (2011) found that, when viewing pictures of happy faces, siblings of autistic individuals displayed lower activation within the temporal poles than the control group, presenting the possibility that autistic trait levels and facial recognition are related to empathizing levels. In addition to facial recognition, prosodic elements of the voice, which are processed primarily in the right hemisphere (Durfee et al., 2021; Ross & Monnot, 2008), are known to be correlated with a person's ability to empathize (Aziz-

Zadeh et al., 2010; Leigh et al., 2013; Meconi et al., 2018). These findings are consistent with our observation that EQ scores are correlated with activity between auditory areas and the right temporal pole. Males' stronger correlation between the right temporal pole and auditory areas may underlie a greater sensory processing influence on empathy. Future research directions include examining autistic males' relationship with sensory processing and empathy.

Females showed a related connectivity pattern between auditory areas and the pre- and post-central gyrus, as well as the middle temporal gyrus and left temporal pole, relating to empathizing. The pre- and post-central gyri are responsible for motor and somatosensory input, respectively (Banker & Tadi, 2019); together they are responsible for sensorimotor functioning. The connection between auditory areas, sensorimotor functioning, and empathy suggests a direct correlation between sensory input and empathy in females. Esteve-Gibert et al. (2020) determined that an individual's ability to empathize is heavily influenced by their ability to recognize and utilize pragmatics, including voice intonation. The correlation in females between the auditory areas is not aligned with this claim, as we would expect that a stronger correlation between auditory areas and sensorimotor input leads to higher empathy. This discrepancy should be investigated in further studies, as it is possible that either too much or too little connection between these areas in females may create an inability to utilize auditory pragmatic cues in conversation. It is also possible that greater involvement of left-lateralized functions, such as syntax and semantics (Graessner et al., 2021; H. A. Olson et al., 2023), and lower involvement of right-lateralized functions, such as prosody (Li et al., 2023), led to lower levels of empathizing in both sexes. Prior studies have found that higher levels of sensory processing atypicalities are correlated with lower levels of empathizing in an autistic population (Tavassoli et al., 2018), potentially explaining why greater connectivity leads to lower empathizing in our sample. An

exploratory analysis of sex-based differences in the correlations between sensory difficulties (GSQ scores) and empathizing (EQ scores) in the current study showed that the female correlation was both significant (r = -0.41; p = 0.019) and appreciably stronger than that of males (r = -0.13; p = 0.56). Greater involvement of the connectivity between brain regions important to sensory processing and empathizing in females, may be tied to stronger correlations between related behavioral factors.

A second area in the above connectivity pattern, the middle temporal gyrus, has been implicated in facial emotion recognition (Belkhiria et al., 2021), where the left temporal pole's role is to assist in name and noun processing and recall (Carlo, 2011; Tranel, 2008). These two areas' connection with auditory areas and empathy in females suggest two different relationships: one between facial emotion recognition and incoming sensory input, and the other between word processing based on incoming auditory information. However, findings by Van den Brink et al. (2012), who determined a strong connection between social information processing and empathizing ability, may explain the relationship between these two separate correlations. Specifically, they noted that when an individual displayed lower empathizing skills, they were not incorporating socially relevant information (e.g., conversational partner's words or emotional affect) into conversations with others. Therefore, given the observed connectivity pattern between brain regions implicated in auditory, facial, and emotion processing herein, and their link to empathizing, empathy may have roots in the synthesis of these types of processing. In turn, these combined functions may be vital for social processing, especially in conditions such as autism.

Both females and males displayed positive, albeit significantly different, correlations, between the frontal parietal areas related to language and the left middle frontal gyrus, as well as

between the primary motor cortex and left frontal pole. These connectivity patterns were correlated with EQ total scores. That is, higher scores on the EQ corresponded with higher connectivity between these areas, especially in males. The left middle frontal gyrus is heavily involved in word production and inhibitory function within social communication (Martin-Luengo et al., 2023; Wen et al., 2017). As a key facet of empathy is understanding others' emotions and perspectives and responding appropriately (Derntl & Regenbogen, 2014), the connection between the left middle frontal gyrus and language areas is logical.

The correlation between the left frontal pole and primary motor cortex was likewise positively correlated with EQ scores. The left frontal pole has been shown to be related to one's working memory and self-reflection (Raju et al., 2021; Zacharopoulos et al., 2020), suggesting that its connection with the primary motor cortex and empathy is likely due to its role in short-term perceptual and linguistic processing and self-understanding. Self-reflection is fundamental to empathy, as empathy is contingent on one's understanding and application of past experiences and ability to distinguish between self and other (Krol & Bartz, 2022). Additionally, it is possible that males' recruitment of the primary motor cortex in empathy is related to the connection between biological motion processing and empathy. Seeing and interpreting a person's movements (thereby recruiting the help of short-term/working memory) is an integral part of empathy (Gao et al., 2016; Lopez et al., 2013). This function is likely related to the mirror neuron system, which also plays an important role in empathy (Iacoboni, 2009; Iacoboni & Mazziotta, 2007; Lamm & Majdandžić, 2016).

The primary motor cortex is related to motor imagery related to working memory, empathy, and language, possibly due to mental practice (Tomasino & Gremese, 2016), likely overlapping with the function of the left frontal pole. Both above outlined correlations, though

significant in both sexes, were higher in males than females, suggesting that though individuals of both sexes may display higher levels of empathy in conjunction with connectivity between these areas, males' empathizing levels might more accurately be understood through these correlations.

In addition, the primary motor cortex was also significantly associated with the right angular gyrus, but only in males. In their study, De Boer et al. (2020) found a clear connection between the activation of the right angular gyrus and self-identification as it relates to perspective-taking. Additionally, greater activity in the right angular gyrus may also lead to hyperreactivity to incoming sensory stimuli (Wei et al., 2019). This connection between perspective-taking and hyperreactivity suggests a potential correlation between empathy and sensory processing in males. Additional findings suggest that the right temporoparietal junction (rTPJ), which has significant overlap with the right angular gyrus, and which has been implicated in various autism brain studies (Abu-Akel et al., 2016; Donaldson et al., 2017; Lombardo et al., 2011; Murdaugh et al., 2014; Salehinejad et al., 2021), plays a crucial part in theory of mind, social cognitive processing, and empathy (Decety & Lamm, 2007; Krall et al., 2014; Santiesteban et al., 2012). In autistic individuals, lower levels of theory of mind and mentalizing have been correlated with reduced rTPJ connectivity (Abu-Akel et al., 2016; Lombardo et al., 2011; Murdaugh et al., 2014). Taken together, these findings are consistent with our results, as stronger FC within the right angular gyrus, and, by extension, the rTPJ, correlated with higher empathizing scores in our NT population.

It is reasonable to believe that the higher EQ scores among males in our sample are correlated with the FC between the primary motor cortex and right angular gyrus because of the

interaction between sensory processing, perspective-taking, and the recruitment of mirror neurons in theory of mind, mentalizing, and—ultimately—empathizing.

In summary, our results suggest that while males and females likely have more similarities in empathizing brain networks than differences, they display some specific differences in how they empathize. Additionally, while females' empathizing abilities are more heavily influenced by FC between the above areas of the brain, both sexes' empathizing levels seem to be affected by the interaction between empathy, word processing, action observation, semantic cognition, and sensory processing difficulties in general. This is due to males' relationship between empathizing and FC between the auditory network and right temporal pole as well as females' relationship with the auditory areas and pre- and post-central gyri. Taken together, it is plausible that similar overall behavioral interactions lead to higher empathizing levels in both sexes, but that the recruitment of different brain networks subserves the observed differences in empathizing between females and males. This notion adds strength to the claim that males' and females' deviating profiles of autism might be tied in part to different empathizing processes within the brain. Furthermore, since each of the brain areas examined in this study were chosen because of their involvement in sensory processing, the connections found between these areas and EQ total scores emphasize the idea that sensory differences lead to differences in empathizing differently across the sexes.

Systemizing Quotient

Systemizing Quotient (SQ) scores were found to be significantly higher in males than in females. This is consistent with the literature, in which males tend to have higher levels of systemizing than females (Baron-Cohen, 2009; Hull, L. et al., 2017; Nettle, 2010). Overall, brain-behavior results from the SQ suggest that patterns for systemizing are similar between the

sexes, with some brain areas being implicated more strongly in systemizing in males than females.

Males' and females' SQ scores were both negatively and positively correlated with specific brain-connectivity patterns. Stronger connectivity between the anterior cingulate cortex/medial prefrontal cortex and the medial prefrontal cortex in both sexes was indicative of lower SQ scores. This captures both an intra-network connectivity (within the medial prefrontal cortex) as well as inter-region connectivity between the medial prefrontal cortex and anterior cingulate cortex. The anterior cingulate cortex underpins goal-directed behaviors, motivation, and seeing/empathizing with pain in others (Devinsky et al., 1995; Morrison et al., 2004; Morrison et al., 2007; Morrison & Downing, 2007). It is also very frequently studied in autism (Agam et al., 2010; Oblak et al., 2009; Simms et al., 2009; Thakkar et al., 2008; Zhou et al., 2016). Additionally, as part of the limbic system, it is believed to assist in emotion and reward processing (Bush et al., 2000; Kennerley et al., 2006; Rolls et al., 2023). The medial prefrontal cortex (mPFC) has been heavily researched within the context of empathizing and systemizing (Adenzato et al., 2017; Focquaert et al., 2010; E. J. Kim et al., 2020; Takeuchi et al., 2013, 2014). For example, Fan et al. (2014) specifically discovered that higher mPFC activation within an autistic population was related to greater levels of social understanding. This reflects the current trend in literature—that several studies have discovered a correlation between elevated activation within the mPFC and higher empathizing, but no relationship between the mPFC and systemizing (Focquaert et al., 2010; Takeuchi et al., 2014). Adenzato et al. (2017) discovered that when using transcranial direct current stimulation, females' ability to empathize increased when the mPFC was directly stimulated. Though systemizing was not examined in this case, understanding the converse relationship between systemizing and empathizing may suggest that

if greater activation in the mPFC is correlated with higher levels of empathy, it follows that greater activation in the mPFC would also be correlated with lower levels of systemizing, which is what we observed. However, as Adenzato et al.'s sample was exclusively female, these results may need to be replicated in a male population before concluding the validity of this brain-behavior correlation in males. Taken together, it is possible that less connection between the anterior cingulate cortex and mPFC are related to higher systemizing, particularly in males, because of an underlying behavioral connection between emotion, empathy, and reward processing.

Conversely, greater connectivity between the left executive control network and left temporal pole, and the left frontal parietal network and putamen, insula, and left auditory cortex were related to higher systemizing in both sexes. As has been mentioned, connectivity within the left executive control network underlies higher executive task performance, especially in autistic individuals who have a large vocabulary (Cascia & Barr, 2020). Its connection with the left temporal pole and SQ scores suggests that executive task performance and word retrieval are correlated with greater systemizing levels. These findings are directly aligned with the above observation that systemizing is correlated with the brain areas that underlie executive functioning and specific word retrieval.

The left frontal parietal network is involved in both attention and control as well as social cognition (Fischer et al., 2020). The putamen and insula, however, are both part of/connected to the basal ganglia, which helps to control responses to outer and inner stimuli as well as emotion, language, learning, and memory functioning (Pierce & Peron, 2020; Simonyan, 2019). The connection between attention, control, the basal ganglia, and audition does not intuitively seem to be connected to higher systemizing levels. Riekki et al. (2017), for example, found that higher

systemizing was correlated with lower activation within the insula. Though we found the opposite to be true, this may be due to a network connection between the insula and other brain areas. More research needs to be done on this specific network to better understand the implications of how higher systemizing is correlated with greater connection between areas of the basal ganglia, left parietal network, and the left auditory cortex.

Again, though males and females' patterns of connectivity were both related to the above brain-behavior patterns, their significant sex differences suggest that the patterns may more accurately explain males' patterns of systemizing than females' systemizing.

A Theoretical Model for Sex-Based Neurophysiologic Differences Related to Sensory Processing and Autism-Related Traits

Based on our findings, males and females exhibit brain-behavior differences regarding intolerance of uncertainty, sensory processing, and autism-related traits (especially empathizing and systemizing). Females' manifestation of intolerance of uncertainty and autistic traits appears to be correlated with FC between areas implicated in sensory processing and anxiety (higher visual areas the right intracalcarine cortex). Males' sensory processing and autistic trait patterns were correlated with sensorimotor and social brain areas (higher order visual areas and right precentral gyrus).

Our findings also point to the likelihood that the underlying brain mechanisms for empathizing are similar between males and females with some nuanced profile differences. Specifically, both males and females exhibit a close relationship between sensory processing and empathizing. Both negative and positive correlations were present between sensory processing areas (such as the auditory areas, higher-order visual areas, pre-and post-central gyrus) and areas that integrate sensory processing with social functioning (i.e., the right angular gyrus),

suggesting an overall connection between sensory processing, social functioning, and empathy. Social processes (emotion recognition, word production, noun and name recall, prosodic recognition) also appear to have a strong correlation with both males' and females' abilities to empathize. We therefore propose that taking in and processing sensory information may affect an individual's ability to empathize, either by assisting in building a concept of another's mind and creating higher levels of empathy within a social context (Hannant et al., 2016; Thye et al., 2017), or by causing sensory discord that interfere with a person's ability to understand their conversation partner. Though both sexes' empathizing patterns align with this theory, empathizing in females and males was correlated with connections between different sensory and social brain areas. This suggests overall similarities in the manner of empathizing but different underlying mechanisms between the sexes.

As with empathizing, certain brain areas underpinned both higher and lower systemizing in males and females, respectively. The two sexes showed patterns between executive functioning areas (e.g., left executive control network, anterior cingulate cortex, left frontal parietal network), areas involved in language processing (e.g., putamen, insula, and left auditory cortex), and systemizing. The fact that males' patterns of connectivity with these areas were more closely tied to systemizing levels than females' again suggests that, though the brain-behavior patterns are similar, the degree to which systemizing is underpinned by the above FC patterns varies between the sexes. Utilizing executive functioning to understand and respond to language may underlie one's ability to systematically understand individuals and circumstances. Future research should aim to discover what other networks may underlie differences in systemizing between females and males.

Limitations

It should be noted that, though we originally expected to see a reflection of the results from our larger sample in our smaller sample, there were fewer similarities than we anticipated. This is likely due to the vast difference in sample size (1200 participants versus 52), meaning that fewer significant trends could be highlighted. However, we did see similar overall trends in brain activity, but slight differences that may reflect difference in behavior. This is consistent with our former findings.

Because our survey specifically asked for biological sex assigned at birth, it is possible that some individuals opted out of the survey. Furthermore, cultural variables were not heavily considered among our sample size, which may decrease the applicability of our findings to all races, ethnicities, and cultures. The area in which our population was taken from is predominantly white, again highlighting the importance for our methods and results to be replicated in both diverse cultural and gender-identity-based populations to ensure generalizability across the population.

Additionally, because our sample was composed of NT individuals, the hypothesized differences in brain-behavior connectivity patterns are likely less noticeable than if we were to have examined an exclusively autistic population. Because of this, further studies should be conducted to see if the connection between brain-connectivity patterns with empathizing, systemizing, autistic traits, sensory processing, mental health, and intolerance of uncertainty hold in autistic males versus females. It is possible that our small NT sample did not allow for our hypothesized differences between the sexes to be born out in the data.

Conclusion

Overall, our results show that females and males have difference in some autistic traits, sensory processing, and intolerance of uncertainty that, in turn, appear to be underpinned by neurophysiologic differences. These findings support the theory that males and females may have nuanced differences in their autism phenotypes. Additionally, the sexes have similar neurophysiological patterns involved in empathizing and systemizing, with a few specific differences. The differing networks may underlie specific behavioral sex-based variations of empathizing and systemizing, including the integration of sensory processing and cognitive processing into empathizing, and the use of attention and executive functioning in systemizing. Future directions for research include identifying if these brain-behavior correlations are found within the autistic population as well as the NT population. More research into how males' and females' differing empathizing and systemizing brain-behavior patterns may contribute to differences in autistic profiles and diagnosis.

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Tables

Table 1

Participant Demographics and Average Behavioral Scores (n = 52)

	Male (n = 22)		Female (n = 30)			
	Mean	SD	Mean	SD	U	P-Value
Age	23.04	1.77	21.34	1.89		
GSQ T	46.48	20.19	42.31	17.64	332.5	0.544
GSQ Hr	22.48	11.33	21.34	9.99	355.0	0.824
GSQ Ho	24.00	10.54	20.97	8.91	313.5	0.352
BAPQ T	3.11	0.70	2.80	0.52	259.0	0.063
BAPQ A	37.30	12.21	29.21	8.57	232.0	0.020*
BAPQ PL	35.96	7.64	33.47	7.18	288.0	0.171
BAPQ R	38.83	9.85	37.66	7.06	356.0	0.838
AQ	20.00	7.646	17.53	6.97	278.5	0.126
EQ	38.65	12.64	47.97	12.65	526.5	0.007*
SQ	35.04	8.54	22.59	10.03	119.5	< 0.001**
IUS T	32.48	10.18	31.25	9.50	349.0	0.746
DASS T	33.04	26.46	31.53	17.47	400.0	0.584
DASS-Stress	13.04	9.65	12.94	7.00	394.5	0.650
DASS-Anxiety	7.57	7.75	9.06	5.75	457.5	0.123
DASS-Depression	12.43	11.82	9.53	7.68	344.0	0.680

Note. GSQ T = Glasgow Sensory Questionnaire Total; GSQ Hr = Glasgow Sensory Questionnaire Hypersensitivity Subtest; GSQ Ho = Glasgow Sensory Questionnaire Hyposensitivity Subtest; BAPQ T = Broader Autism Phenotype Questionnaire Total; BAPQ A = Broader Autism Phenotype Questionnaire Aloof Subtest; BAPQ PL = Broader Autism Phenotype Questionnaire Pragmatic Language Subtest; BAPQ R = Broader Autism Phenotype Questionnaire Rigidity Subtest; AQ = Autism Quotient; EQ = Empathy Quotient; SQ =

Systemizing Quotient; IUS T = Intolerance of Uncertainty Questionnaire Total; DASS T = Depression Anxiety Stress Scale Total; DASS-Anxiety = Depression Anxiety Stress Scale Anxiety Subtest; DASS-Anxiety = Depression Anxiety Stress Scale Anxiety Subtest; DASS-Depression = Depression Anxiety Stress Scale Depression Subtest

*p < .05; **p < 0.001

Table 2

Independent Components Analysis and Areas of Interest

Cluster	Sig Test	p	Beta	t
LOC/Cer(IC3) – Caud R	GSQ T	0.071	0.017	1.85
	AQ T	0.053*	0.038	1.65
Auditory (IC6) – Temp PR	EQ T	<0.001**	-0.082	-5.69
Auditory (IC6) – P-P CG	EQ T	<0.001**	-0.073	-4.32
Auditory (IC6) – MTG L	EQ T	<0.001**	-0.095	-4.99
Auditory (IC6) – Temp PL	EQ T	<0.001**	-0.077	-5.51
ACC (IC9) – MPFC	SQ T	<0.001**	-0.094	-5.28
L ECN (IC16) – Temp PL	SQ T	<0.001**	0.110	4.71
L ECN (IC16) – Tfus R	EQ T	<0.001**	-0.072	-5.46
FPA (IC18) – MFG L	EQ T	<0.001**	0.12	6.36
L FPN (IC22) – Put, Ins, A1 L	SQ T	<0.001**	0.094	5.19
High Vis (IC29) – ICCR	IUS T	0.056*	0.077	1.95
	BAPQ T	0.022*	0.042	2.37
	AQ T	0.040*	0.110	2.11
	DASS T	0.038*	0.038	2.14
High Vis (IC29) – PCG R	IUS T	0.100	0.043	1.67
	GSQ T	0.035*	0.030	2.16
	GSQ Hr	0.037*	0.052	2.15
	GSQ Ho	0.076	0.049	1.81
	BAPQ T	0.053*	0.023	1.98
	DASS T	0.091	0.020	1.72
Prim MC (IC31) – AG R	EQ T	<0.001**	0.079	4.63
Prim MC (IC31) – FP L	EQ T	<0.001**	0.073	5.74
Sensorimotor (IC38) – sLOC	DASS T	0.121	0.016	1.58
Sensorimotor (IC38) – FO R	IUS T	0.080	0.023	1.43
	GSQ T	0.059*	0.016	1.93
	GSQ Hr	0.040*	0.031	2.10

GSQ Ho	0.162	0.023	1.42
BAPQ T	0.039*	0.015	2.12
AQ T	0.085	0.037	1.76

Note. LOC/Cer = lateral occipital cortex/cerebellum; MFG L = mid-frontal gyrus left; Caud R = caudate right; Auditory = (Auditory Areas related to language); Temp PR = temporal pole right; P-P CG = re-post central gyrus; MTG L = mid-temporal gyrus left; Temp PL = temporal pole left; ACC = anterior cingulate cortex; MPFC = medial prefrontal Cortex; L ECN = left executive control network; Tfus R = temporal fusiform right; sLOC R = superior lateral occipital cortex; FPA = frontal parietal areas related to language; MFG R = mid-frontal gyrus right; L FPN = left frontal parietal network; Put, Ins, A1 L = putamen, insula, primary auditory cortex left; Hig Vis = high visual areas; ICCR = intracalcarine cortex right; PCG R = pre-central gyrus right; Cerb 6 = cerebellum 6; Prim MC = primary motor cortex; AG R = angular gyrus right; FP L = frontal pole left; Sensorimotor = sensorimotor area; sLOC = superior lateral occipital cortex; FO R = frontal operculum cortex right; GSQ T = Glasgow Sensory Questionnaire Total Score; GSQ Ho = Glasgow Sensory Questionnaire Hyposensitivity Subtest; GSQ Hr = Glasgow Sensory Questionnaire Hypersensitivity Subtest; BAPQ T = Broader Autism Phenotype Quotient Total Score; AQ T = Autism Quotient Total Score; DASS = Depression Anxiety and Stress Scale Total Score; IUS T = Intolerance of Uncertainty Scale Total Score; EQ = Empathizing Quotient Total Score; SQ = Systemizing Quotient Total Score

*p < .05; **p < 0.001

Table 3

Correlations Between Patterns of Connectivity and Behavioral Test Scores (Besides EQ/SQ)

Connectivity Pattern	Test	Male		Female		Between-Sex T-Test	
		r	p	r	p	t	p
High Vis (IC29) – PCG R	GSQ T	0.448	0.037*	0.08	0.674	0.03	0.035*
	GSQ Hr	0.448	0.036*	-0.062	0.746	2.15	0.037*
	BAPQ T	0.450	0.036*	-0.032	0.868	1.98	0.053
High Vis (IC29) – ICCR	IUS T	0.158	0.483	0.383*	0.037*	1.95	0.056
	BAPQT	0.303	0.170	0.432*	0.017*	2.37*	0.022*

Note. PCGR = Precentral Gyrus Right; ICCR = Intracalcarine Cortex Right; IUS T = Intolerance of Uncertainty Total Score; GSQ T = Glasgow Sensory Questionnaire Total Score; GSQ Hr = Glasgow Sensory Questionnaire Hypersensitivity Subtest; BAPQ T = Broader Autism Phenotype Quotient Total Score

*p < .05; **p < 0.001

Table 4

Correlations Between ICs and EQ/SQ T-Scores

Connectivity Pattern	Test	Male		Female		Between-Sex T-Test	
		r	p	r	p	t	p
Auditory (IC6) – Temp PR	EQ T	-0.632	0.002*	-0.617	<0.001**	-5.69	<0.001**
Auditory (IC6) – P-P CG	EQ T	-0.257	0.247	-0.718	<0.001**	-4.32	<0.001**
Auditory (IC6) – MTG L	EQ T	-0.367	0.093	-0.567	0.001**	-4.99	<0.001**
Auditory (IC6) – Temp PL	EQ T	-0.381	0.080	-0.665	<0.001**	-5.51	<0.001**
ACC/MPFC (IC9) – MPFC	SQ T	-0.598	0.003*	-0.547	0.002*	-5.28	<0.001**
L ECN (IC16) – Temp PL	SQ T	0.553	0.008*	0.534	0.002*	4.71	<0.001**
L ECN (IC16) – Tfus R	EQ T	-0.436	0.042*	-0.567	0.001*	-5.46	<0.001**
FPA (IC18) – MFG L	EQ T	0.722	<0.001**	0.662	<0.001**	6.36	<0.001**
L FPN (IC22) – Put, Ins, A1 L	SQ T	0.601	0.003*	0.680	<0.001**	5.19	<0.001**
Prim MC (IC31) – AG R	EQ T	0.749	<0.001**	0.346	0.061	4.63	<0.001**
Prim MC (IC31) – FP L	EQ T	0.550	0.008*	0.528	0.003*	5.74	<0.001**

Note. Auditory = Auditory Areas related to language; Temp PR = temporal pole right; P-P CG = pre-post central gyrus; MTG L = mid-temporal gyrus left; Temp PL = temporal pole left; ACC/MPFC = anterior cingulate cortex/medial prefrontal cortex; MPFC = medial prefrontal Cortex; L ECN = left executive control network; Tfus R = temporal fusiform right; FPA = frontal parietal areas related to language; MFG L = mid-frontal gyrus left; L FPN = left parietal network; Put, Ins, A1 L = putamen, insula, primary

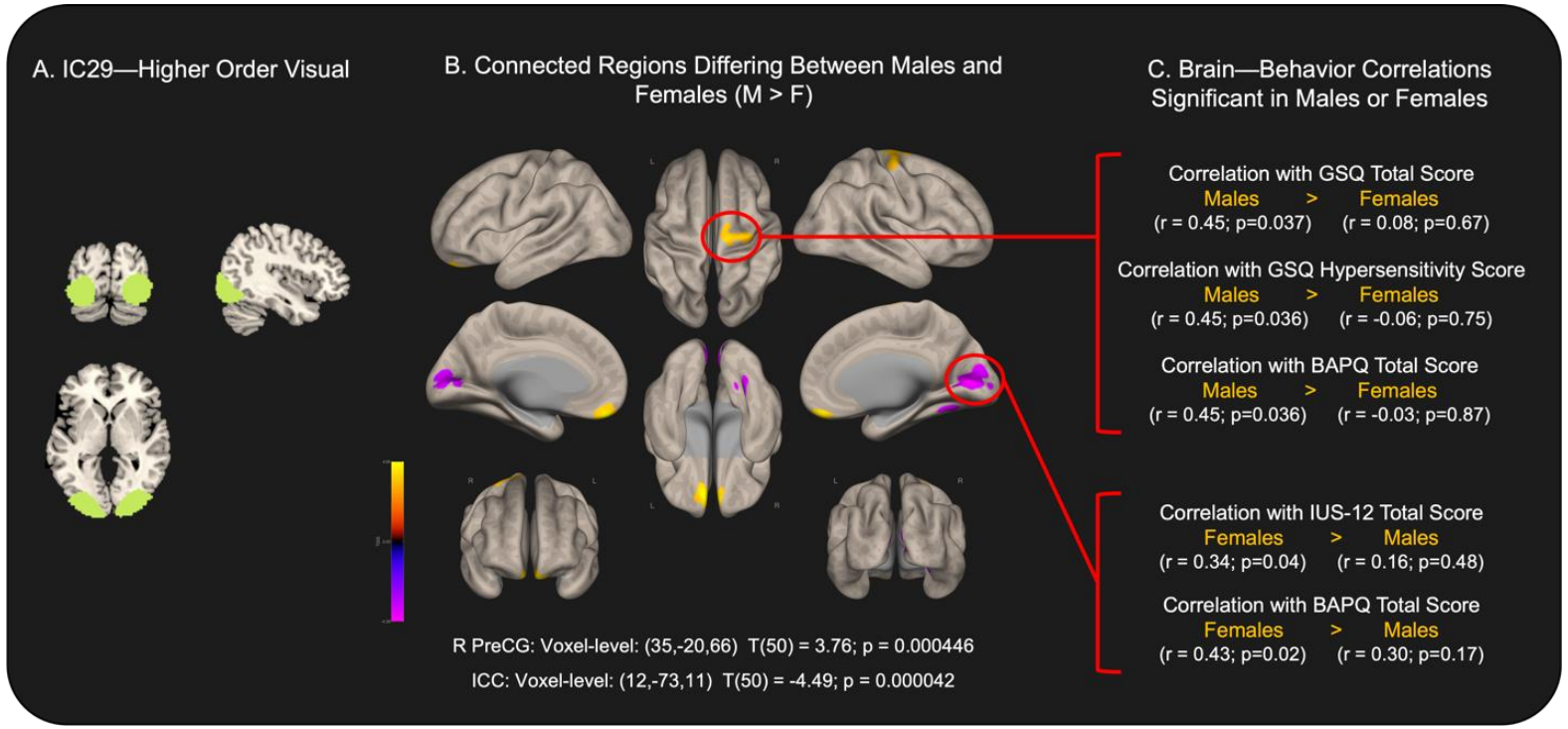
auditory cortex left; Hig Vis = high visual areas; ICCR = intracalcarine cortex right; Prim MC = primary motor cortex; AG R = angular gyrus right; FP L = frontal pole left; SQ T = Systemizing Quotient Total Score; EQ T = Empathizing Quotient Total Score, * = Significant.

*p < .05; **p < 0.001

Figures

Figure 1

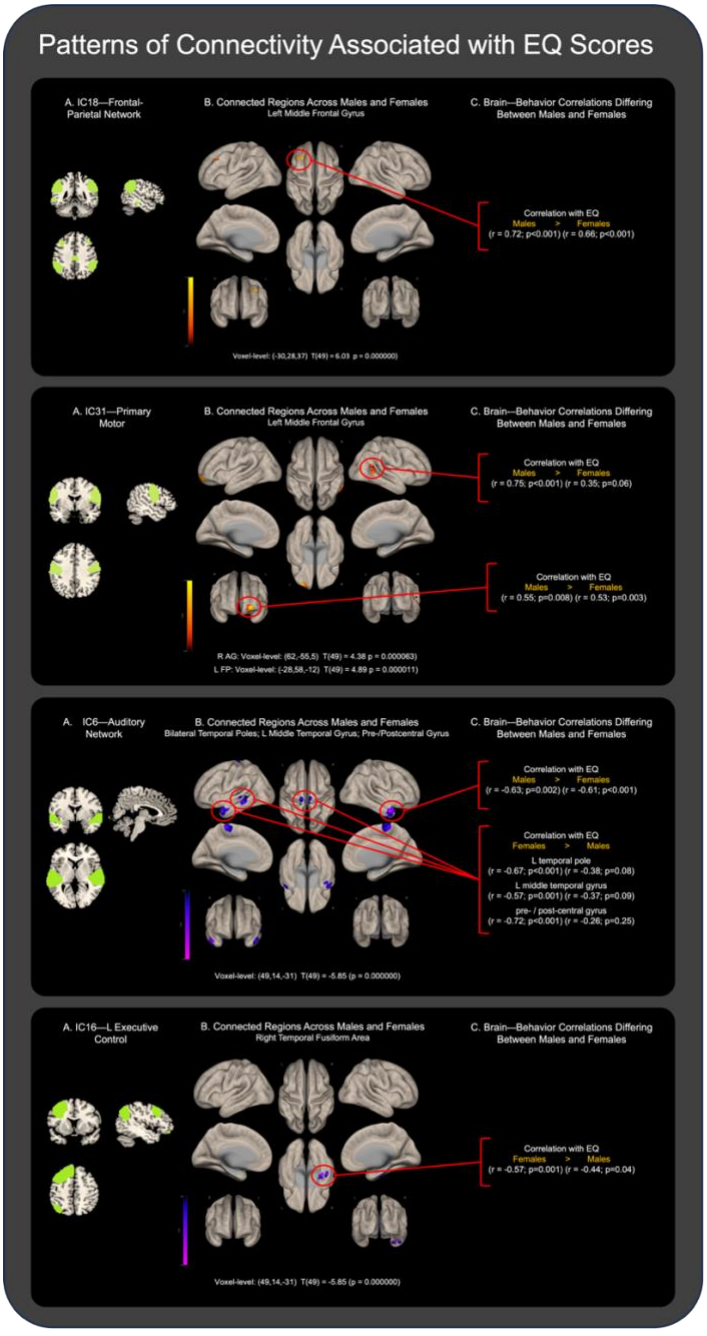
Higher Order Visual Area Connectivity



Note. Resting state functional network connectivity between higher order visual brain regions (A) and the R pre-central gyrus and inferior cingulate and occipital cortices (B), as well as correlations between these connectivity patterns and various behavioral measures in males vs. females (C).

Figure 2

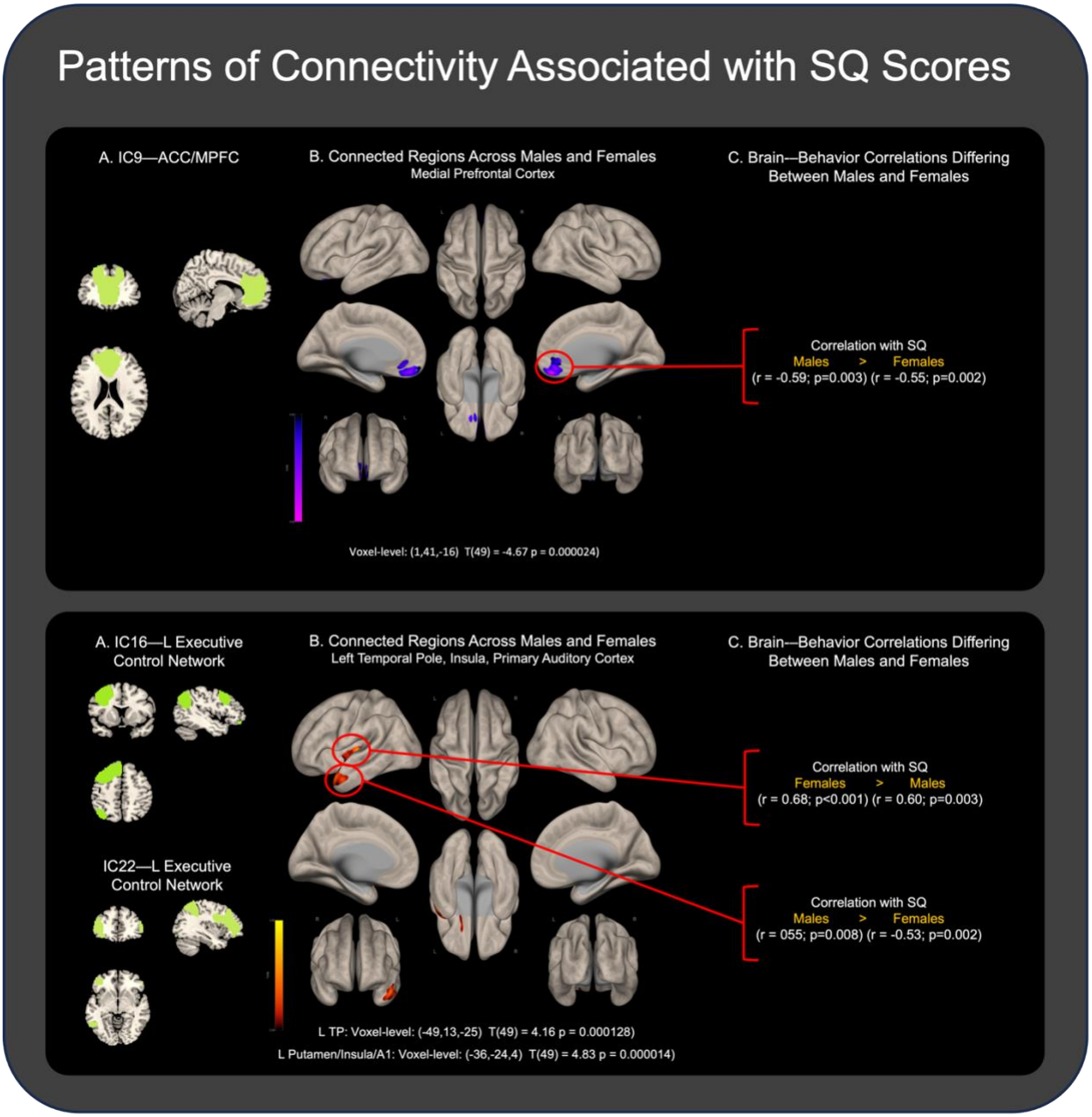
EQ Score Connectivity Patterns



Note. Patterns of functional network connectivity between various independent component networks (A) and voxel clusters (B) across groups that were correlated with the EQ to differing degrees between males and females.

Figure 3

SQ Score Connectivity Patterns



Note. Patterns of functional network connectivity between various independent component networks (A) and voxel clusters (B) across groups that were correlated with the SQ to differing degrees between males and females.

APPENDIX A

Annotated Bibliography

Chaddad, A., Desrosiers, C., Hassan, L., & Tanougast, C. (2017). Hippocampus and amygdala radiomic biomarkers for the study of autism spectrum disorder. *BMC Neuroscience, 18*(52). https://doi.org/10.1186/s12868-017-0373-0

Introduction: This study was created to examine and propose a more thorough way to examine differences in the autistic brain using MRI. In past studies, there have been brain differences in the autistic versus non-autistic putamen, cerebellum, hippocampus, amygdala, and corpus callosum. However, these studies drew results by primarily examining volume and intensity measures in the brain and nothing else. The authors of this study aim to analyze the effectiveness of what's called a region-based radiomics analysis method. This method involves splitting brain images into smaller segments than voxels, and first analyzing the texture of various sections.

Methods: Each MRI was split into 31 key subcortical regions. Several different statistical summaries were found for each region, including the mean, standard deviation, and entropy. After this, a statistical analysis was run to find differences in textures across the different groups (autistic versus neurotypical, autistic males and females versus neurotypical males and females).

Results: In the brains of autistic versus neurotypical individuals, there were differences found in left and right cerebellar white matter, left choroid-plexus, right hippocampus, and posterior of the corpus callosum. They also found unique bilateral asymmetry in the regions of the hippocampus and choroid plexus, and a pronounced symmetry in cerebellar white matter. In neurotypical males versus females, the biggest

texture differences were found to be in the brain stem, left amygdala, and right cerebellar white matter. Overall, the left hemispheres and amygdala between males and females had generally greater differences. There were less significant differences also found in the vessel, accumbens area, hippocampus, and the mid anterior corpus callosum sub-region.

Relevance: This paper has detailed findings regarding both differences in the brains of autistic versus neurotypical individuals, and in males versus females, contributing to the overall comparison between autistic profiles in males versus females.

Kozhemiako, N., Nunes, A., Vakorin, V., Larocci, G., Ribary, U., & Doesburg, S. (2020). Alterations in local connectivity and their development trajectories in autism spectrum disorder: Does being female matter? *Cerebral Cortex, 30*(9), 5166-5179. https://doi.org/10.1093/cercor/bhaa109

Introduction: There haven't been too many studies that have looked at brain connectivity networks in autistic males and females. However, much research has been done that suggests inherent alterations in brain connectivity among the autistic population. These alterations may account for delayed or impaired communication between long-range brain areas. It is predicted that alterations in brain connectivity will look different in autistic females and autistic males.

Methods: The authors analyzed resting state fMRI data for both autistic and neurotypical males and females, as found in the ABIDE database. They then analyzed connectivity relationships in the brain by examining regional homogeneity (which utilizes voxels). ReHo measures synchronization of brain activity within the area outlined by the voxel. Typically, ReHo decreases as age increases, and assists in cognitive control, inhibition, intelligence, and the signaling hierarchy of neural information processing.

Results: The researchers discovered significant differences in regional homogeneity (ReHo) between the autistic and neurotypical groups (some areas had higher ReHo and others had lower ReHo in autistic versus neoryptical groups). The areas where autistic individuals had higher ReHo than their neurotypical counterparts were the right primary motor cortex, left and right supplemental motor areas, left operculum, posterior cerebellum, and bilateral temporal poles. The areas where autistic individuals had lower ReHo than their neurotypical counterparts were the medial prefrontal cortex, middle frontal gyrus, posterior cingulate cortex, precuneus, and right supramarginal area. Ultimately, this means that autistic males and females have significant differences in ReHo in the somatomotor, limbic, and default mode networks compared to their neurotypical counterparts. Interestingly, no significant differences in ReHo were found in autistic males versus females. The findings were slightly more significant in neurotypical males versus females, but they were approaching significance rather than being significant in and of themselves. When comparing both neurotypical and autistic males with both neurotypical and autistic females, it was found that the female groups had significantly lower ReHo than the male groups overall. In the female groups, there were higher ReHo levels in the parieto-occipital sulcus, bilateral inferior temporal cortex, and anterior cerebellum. When testing correlations between an autism diagnostic test (the ADOS) and ReHo results, females were shown to have significant correlations between ReHo results in the limbic system and higher scores on the ADOS. This means that higher connectivity in the limbic system is correlated with higher autism severity in females. Similarly, autistic males had significant correlations between ReHo results in the somatomotor network and ASD severity. Correlations between a social scale (SRS) and

ReHo in the somatomotor network were found to be significant in both neurotypical females and autistic males. There was also a correlation found between neurotypical females' ReHo scores in the limbic network and the subscales in the SRS. Additionally, ReHo in the ventral attention network of both autistic and neurotypical females was significantly correlated with all five of the SRS subscores. This study may add neurological backing to portions of the extreme male brain theory. This is because the findings between autistic males and neurotypical females were more similar than autistic males and autistic females or neurotypical females and neurotypical males. Though, these correlations may be incidental and not indicative of a full EMB. The female protective effect, however, cannot be confirmed through this study because the autistic females observed in this study had already been diagnosed, and so, by the FPE, would have overcome whatever etiological burden was present.

Relevance: In essence, this paper details correlations between autistic traits and social capabilities with various brain areas. It appears that males and females have different areas that correspond with higher autistic traits and social functioning. This supports the hypothesis of males and females having different autistic profiles, not only in their behavior, but also in their brain functioning.

Jack, A., Sullivan, C. A. W., Aylward, E., Bookheimer, S. Y., Dapretto, M., Gaab, N., Van Horn, J. D., Eilbott, J., Jacokes, Z., Torgerson, C. M., Bernier, R. A., Geschwind, D. H., McPartland, J. C., Nelson, C. A., Webb, S. J., Pelphrey, K. A., Gupta, A. R., & GENDAAR Consortium (2021). A neurogenetic analysis of female autism. *Brain: A Journal of Neurology*, *144*(6), 1911–1926. https://doi.org/10.1093/brain/awab064

Introduction: Past research has found that some of the areas of the brain that typically assist in processing human emotion may be impaired in autistic individuals. One of these areas is the posterior superior temporal sulcus, which is used in biological motion perception, and has been shown to be reduced in autistic individuals. There is also an under-response in the amygdala and fusiform gyrus. The FPE would suggest greater structural changes in autistic females than autistic males, due to the hypothesis that females have a higher etiological burden to overcome before manifesting the autism phenotype. However, another possibility of the application of the FPE hypothesis is that females may have decreased manifestation of the autism phenotype, even if they have a higher etiological load. If this is true, autistic male and females may not have significantly different autism profiles.

Methods: A group of equally matched neurotypical and autistic youths, aged 8–17, participated in genotyping, neuroimaging (fMRI), and behavioral phenotyping. The researchers gathered a large group of autistic females in order to gain more accurate data, and therefore more significant results. Next, the researchers compared fMRI data with the genetics of the corresponding participants to gain a clearer picture of the autistic versus neurotypical female profile.

Results: Autistic females were found to have more limited responses in sensorimotor, striatal, and frontal regions, when compared to the neurotypical females. Additionally, neural responses were not significantly different in autistic males and females. Likewise, the differences between autistic females and neurotypical females were not reflective of the differences found between autistic males and neurotypical males. In other words, differences in fMRI results between autistic and neurotypical

females are not the same as their male group counterparts. This may be further evidence for differences in male and female autistic profiles and may add evidence to the Female Protective Effect (FPE).

Relevance: Because we are examining males and females and their potentially differing correlations with both autistic traits and brain connectivity, this information will contribute to our knowledge base regarding females with autism. It may be useful to compare what we find regarding connectivity in our female participants to what Jack et al. found in their female participants.

Hull, J., Jacokes, A., Torgerson, C., Irimia, A., Van Horn, J., Aylward, E., Bernier, R., Bookheimer, S., Dapretto, M., Gaab, N., Geschwind, D., Jack, A., Nelson, C., Pelphrey, K., State, M., Ventola, P., & Webb, S. (2017). Resting-state functional connectivity in autism spectrum disorders: A review. *Frontiers in Psychiatry, 4*(7). https://doi.org/10.3389/fpsyt.2016.00205

Introduction: Brain imaging as a means to research autism is a relatively new concept. Because of this, there have been many cognitive theories developed in the wake of a lack of neuroimaging information. One theory is the Theory of Mind hypothesis, which suggests that autistic individuals do not have as fully developed Theory of Mind as neurotypical individuals. There is also the empathizing-systemizing theory (a.k.a. Extreme male brain hypothesis), suggesting that males tend to be more systemizing and females tend to be more empathizing, except for when it comes to autism. In this category, it is proposed that autistic individuals (both male and females) have a greater systemizing tendency than their neurotypical counterparts. This means that autistic females exhibit systemizing-traits similar to (but far more severe) than those of

neurotypical males. Another theory is called the executive dysfunction hypothesis, which attributes social deficits in autistic individuals to poor executive functioning (working memory, mental flexibility, inhibition, and planning). There is also the weak central coherence theory, which suggests that autistic behaviors are due to an inability to understand parts as a whole, and rather focus on parts. Dysfunction of the mirror neuron system is also being proposed as an explanation for autistic traits. Some theorize that autism is truly due to either over- or under-connectivity in inter-regional neural brain connections. The most common way this is analyzed is by using resting state fMRIs. This article will look at various studies that have focused on both over- and under-connectivity in autistic individuals.

Methods: This review article examined all of the current resting state fMRI studies analyzing brains of autistic individuals. The authors looked for evidence of under-connectivity, over-connectivity, and both under- and over-connectivity.

Results: Many studies support the under-connectivity theory. There are some varying conclusions, but one of the main ones is that the Default Mode Network (DMN; or portions of the DMN) have under-connectivity in certain regions. The DMN is primarily responsible for introspective thought and self-reflection. It is important for socio-emotional behavior, and activity is typically decreased while performing a cognitive task. One study found anterior-posterior under-connectivity and greater connectivity activation in the left, middle, and superior frontal gyrus and supramarginal gyrus in Autistic participants when compared to their controls. However, this was not a completely true resting-state fMRI. One study discovered that, in their autistic participants, the DMN was not deactivated between resting-state and attending to a task.

Another found that autistic individuals had under-connectivity in the DMN, but there were no differences in the TPN (Task-Positive Network = dorsolateral prefrontal cortex + inferior parietal cortex + supplementary motor area; involved in cognitive tasks that require attention to what's happening in the environment). Other studies of the DMN have found under-connectivity throughout the whole DMN in autistic individuals. There have been several studies done examining under-connectivity within the DMN and its correlation to autistic trait severity. One found that under-connectivity has a correlation with symptom severity as scored by the ADOS social subtest. In another study, as compared to their neurotypical counterparts, autistic participants were also found to have both inter- and intra-hemispheric under-connectivity in the posterior cingulate cortex, parahippocampal gyrus, and postcentral gyrus. Specifically, in the DMN, there was global under-connectivity in the medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule, and sensorimotor regions. These findings suggest a possible correlation between social impairments and under-connectivity in the medial prefrontal cortex and posterior cingulate cortex. Multiple studies have discovered a trend of anterior-posterior under-connectivity between the frontal and parietal DMN nodes. There have also been studies conducted that examine connectivity in other areas of the brain. Results among autistic participants include under-connectivity in the insula (one specifically found under-connectivity in the anterior and posterior insula), amygdala, and limbic-related brain regions. These areas of the brain are implicated in self- and others-awareness, social behavior, language, and communication. There are also patterns of under-connectivity in voice perception and language development in autistic individuals. In speech perception, a study found under-connectivity between the left

posterior temporal sulcus and typical dopaminergic areas in autistic subjects. They also found under-connectivity in the right posterior superior temporal sulcus with the orbitofrontal and amygdala regions–these regions process prosody in human speech. These results suggest that autistic individuals experience less of a dopamine hit (and therefore less pleasure) when processing human voices; taken together, it may be that under-connectivity in the superior temporal sulcus may be correlated with the degree of emotional deficits in conjunction with autistic traits. Other studies have reported results of over-connectivity in autistic individuals. Over-connectivity in autistic participants has been found between the striatum and right superior temporal gyrus/insular cortex (areas that have both been implicated in autism), the striatum and the pons, and the pons and insular cortex. The last two results are both very abnormal as compared to neurotypical participants. Researchers have also found over-connectivity of frontostriatal connections as well as a trend in the right hemisphere. Over-connectivity has also been found between subregions of the primary motor cortex. Other areas having over-connectivity in autistic participants include: the right posterior temporoparietal junction with the right ventral occipital temporal cortex and the primary sensory and subcortical networks in the thalamus and basal ganglia (this result suggests that dysfunctional sensory connectivity may be correlated with autistic behaviors). One study discovered a correlation between over-connectivity between primary sensory and subcortical regions and autism symptom severity. This may explain why autistic individuals experience hyper-sensitivity to sensory stimuli. Another study found that autistic individuals, when compared to their controls, had a higher number of connections per node. In terms of the DMN, one group of researchers reported increased connectivity in the DMN in addition to greater inter-

network connectivity/synchrony between neural attention networks and the DMN. Yet more studies have found evidence for both under- and over-connectivity in autistic individuals. This is the type of result most highly reported in research papers studying connectivity in autism. There have been varying findings regarding connectivity in the DMN. One study found under-connectivity of the posterior cingulate cortex (PCC) and the superior frontal gyrus (SFG), and under-connectivity between the PCC and bilateral temporal lobes and the PCC and the right parahippocampal gyrus (PHG) in autistic participants. They also discovered that weaker social functioning (as measured by the social functioning sub score of the ADOS) is correlated with weaker connectivity of the PCC and superior frontal gyrus. Additionally, they saw stronger connectivity between the PCC and right PHG to be correlated with increasingly severe restricted and repetitive behaviors. Paaki et al. conducted their study using ReHo (which is a good measure of functional connectivity, but not global connectivity) in studying their autistic participant's brain connectivity. In their study they found under-connectivity in the right superior temporal sulcus and right insula. These areas have been implicated in atypical sensory processing and multisensory input integration. A common finding has been over-connectivity lateralizing to the right hemisphere of the brain. Maximo et al. and Cardinale et al. found over-connectivity in the right hemisphere and under-connectivity in the left hemisphere in autistic adolescents. It may be that these findings are similar because they both studied adolescents, or because they both used ReHo, which does not explore global connectivity in the same way as resting state fMRI. That being said, it may be a noteworthy finding should there be more research to support it. Other studies that have been conducted that specifically examine global connectivity of the brain and find both

under- and over-connectivity present in autistic subjects. Some suggest that there may be local over-connectivity and long-distance under-connectivity in autism. Specifically with lower inter-hemispheric connectivity in the sensorimotor cortex, anterior insula, fusiform gyrus, superior temporal gyrus, and superior parietal lobule. In this same study, it was reported that the adolescent participants had decreased short- and long-range connectivity within functional systems, and increased connectivity between functional systems. Several other studies have found similar trends, in which autistic subjects have higher connectivity within functional systems, and lower connectivity between functional systems. It's important to note that each autistic individual has different brain patterns and connectivity, though there are some patterns. There were several other studies examining the DMN and over-/under-connectivity. All found different results. One study found over-connectivity in certain parts of the DMN in autistic children, which was positively correlated with severity of social impairment. These findings may suggest that over-connectivity is higher in autistic children than it is in autistic adults. Another study found under-connectivity between DMN nodes but local over-connectivity within different brain regions in the DMN. The older the participants, the greater the connectivity found between the nodes in the DMN. To sum, there have been many different types of studies conducted to try to determine what might be the trends of functional connectivity in the brains of autistic individuals. Though no absolute conclusion has been drawn, it seems that the DMN plays a large part in differences between autistic individuals and their neurotypical counterparts. Connectivity also appears to change as a person ages. Additionally, there is evidence for there being differences within nodes and structures within the DMN as well as longer-range

connectivity between the DMN and other brain structures that may be a trend of people with autism.

Relevance: This paper includes many results regarding connectivity in the brains of autistic individuals. These results may help us in our discovery of the relationship between connectivity and differing severities of autistic traits. The results also raise a few questions: could the under-connectivity in the DMN in males and females be either different overall or in different internal? Could the nodes involved in underconnectivity look different between the sexes?

Deng, Z., & Wang, S. (2021, March 26). Sex differentiation of brain structures in autism: Findings from a gray matter asymmetry study. *Autism Research, 14,* 1115–1126. https://doi.org/10.1002/aur.2506

Introduction: This paper examines how neuroimaging may validate the extreme male brain theory (EMB) or the female protective effect (FPE). There have been a few prior studies that appear to validate the FPE by showing that autistic females may have greater amounts of gray matter than autistic females, and greater white matter compared to their neurotypical controls, where autistic males have similar white matter amounts relative to their neurotypical controls. The same pattern has been found in other studies, where autistic females have a greater difference in brain structures when compared to their controls than autistic males have when compared to their controls. For example, autistic females may have reductions in a distributed network in the white matter of the brain, and global amygdala pattern differences. Results from other studies suggest there may be truth to the Gender Incoherence (GI) theory or EMB as well, due to a pattern of autistic females reflecting results more closely to neurotypical males, and autistic males

reflecting results more closely to neurotypical females. This study is trying to find a neurological basis for any of the above three approaches.

Methods: Using the ABIDE database, the researchers included images from individuals 7–25 years old, and ensured a large number of females in each age group. Using voxelwise asymmetry, differences in gray matter in autistic males versus females were examined.

Results: Autistic females were found to have greater changes in gray matter asymmetry than autistic males. Additionally, autistic females exhibited similar gray matter patterns as neurotypical males. These findings support the FPE.

Relevance: This paper outlines differences in brain structures between autistic males and females. Though we are trying to determine differences in connectivity between males and females, we may expect to see similar patterns. Therefore, this paper informs our hypothesis, in that we may predict greater variability in females with higher degrees of autistic traits when compared to males with similar levels of autistic traits.

Calton, S. (2022). *The behavioral and neurophysiologic relationships between sensory processing and autistic traits in emerging adults* (9547). [Master's thesis, Brigham Young University]. BYUScholarsArchive. https://scholarsarchive.byu.edu/etd/9547/

Introduction: Individuals with autism commonly display sensory processing atypicalities. Many individuals also exhibit anxiety and depression. Atypical sensory processing likely contributes to many difficult experiences of autistic adults. Because of this, finding ways to treat sensory processing differences may help autistic males and females to experience less distress and fewer comorbidities throughout their lives. This

study aims to better understand brain activity in conjunction with sensory processing and autistic traits in young adults.

Methods: Participants filled out a set of questionnaires that surveyed several different behaviors, including sensory processing and autistic traits (among others). Next, 60 neurotypical individuals (35 female, 25 male) to undergo an rs-fMRI (though, five subjects were excluded from the data analysis because of image pre-processing difficulties). Various types of analyses were run in order to discover correlations between brian connectivity and differing levels of autistic traits and sensory processing (as found from the questionnaires).

Results: A common theme among the participants was a network connectivity between the salience network and bilateral pre- and postcentral gyri, which was associated significantly with scores on the autism quotient (AQ), broad autism phenotype questionnaire (BAPQ), and hypersensitivity subtest on the glasgow sensory questionnaire (GSQ), such that greater connectivity was correlated with higher severity. This means that greater connectivity between the salience network and bilateral pre- and postcentral gyri means greater autistic traits and hypersensitivity. In a cluster-analysis, the group of individuals who had higher scores (greater severity) had greater connectivity between a sensorimotor/cerebellar network and bilateral supramarginal gyri, with this connectivity being correlated with autistic traits.

Relevance: The findings from Calton's paper are a starting point for our research regarding males and females with autistic traits. We will be using the same 55 scans (23 male, 32 female) as Calton did, but instead compare males versus females in both brain

connectivity and different traits, including autistic traits, sensory processing, and mental health.

Kreiser, N. L., & White, S. W. (2014). ASD in females: Are we overstating the gender difference in diagnosis? *Clinical Child and Family Psychology Review, 17*(1), 67–84. https://doi/org/10.1007/s10567-013-0148-9

Introduction: Traditionally, more males than females have autism. There are many biological models that attempt to explain why males are diagnosed more often than females. These include the brain differences model (BDM, which includes the EMB), the greater variability model (GVM, which hypothesizes that males develop autism because of genetic variability, where females may develop autism because of some kind of pathology), and liability/threshold model (LTM, which speculates that females and males are both just as likely to develop autism, but females tend to experience more severe cases of autism due to having a higher threshold for impairment. It also insinuates that relatives of autistic females are more likely to have affected relatives). In addition to the biological theories listed above, the researchers of this paper suggest that the reason for females having lower incidence of autism may be due to social underpinnings. Based on findings in various cultures, it is possible that the phenotypic expression is different in males versus females.

Methods: Synthesis of existing literature in order to discover potential social factors regarding autism.

Results: There are several different reasons why females may be diagnosed less frequently than males. One reason is due to an under-representation of autistic females in clinical studies. Specifically, studies examining autistic traits are predominantly done

with a much larger male sample size than females. This may create inaccurate homogeneity in reported symptoms of autism, leading to gender-biased diagnostic criteria for autism. It is also possible that autism manifests differently in males versus females, due to a difference in behavior expectations as driven by society.

Relevance: We are trying to discover if there are neurological differences between autistic males and females. However, we are also considering the information from the prior research paper regarding behavioral and experiential differences between males and females with autism. The two (neurological & behavioral/experiential) are extremely connected and may tell us things about the other. The social underpinnings outlined in this paper bring up potentially important points to consider while synthesizing both types of data.

Ympa, R., Moseley, R., Holt, R., Rughooputh, N., Floris, D., Chura, L., Spencer, M., Baron-Cohen, S., Suckling, J., Bullmore, E., & Rubinov, M. (2016). Default mode hypoconnectivity underlies a sex-related autism spectrum. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 1*(4), 364–371. https://doi.org/10.1016/J.BPSC.2016.04.006

Introduction: There has been little neurobiological research done regarding the EMB theory. This study aims to discover if hypoconnectivity in the DMN is common to autistic females, is more common in neurotypical males than neurotypical females, and is correlated to decreased mentalizing ability.

Methods: Using the CFSA and the ABIDE datasets (one as the primary data, the second as the replication dataset), Ympa et al. segregated the DMN and analyzed its intraconnectivity, comparing males and females, both autistic and neurotypical.

Results: Ympa et al. discovered strong and specific reduction in DMN intraconnectivity in autistic females and female siblings of autistic individuals. In other studies, this same pattern has been discovered in males. They also found that neurotypical females had increased DMN intraconnectivity when compared to neurotypical males, but that overall, autistic male and females, both, tend to have lower DMN intraconnectivity when compared to neurotypical males and females. Finally, they found that DMN intraconnectivity had a correlation with specific mentalizing tasks that are particular to deficits specific to autism. This hypoconnectivity may be related with lower mentalizing and socializing cognition in autistic males and females, shared between both sexes.

Relevance: Because we believe that autistic male and females have different profiles, it may be that examining the differences in DMN connectivity will tell us more about Ympa et al.'s finding that lower DMN connectivity is correlated with lower mentalizing and socializing cognitive abilities. As we also plan to have a control group, this data may inform our hypotheses regarding differences we may see in DMN intraconnectivity between males and females with a higher degree of autistic traits, and males and females with a lower degree of autistic traits.

Jung, M., Mody, M., Saito, D., Tomado, A., Okazawa, H., Wada, Y., & Kosaka, H. (2015). Sex differences in the default mode network with regard to autism spectrum traits: A resting state fMRI study. *PLoS One, 10(*11). https://doi.org/10.1371/journal.pone.0143126

Introduction: There have been prior studies conducted that examine intraconnectivity in the DMN and the neurobiological makeup of male versus female autistic brains. This study used resting fMRI (rs-fMRI) to examine possible DMN connectivity differences in neurotypical males and females, as correlated with AQ scores.

They hypothesized a negative correlation between AQ scores and resting state DMN connectivity in males but not females.

Methods: Forty-two neurotypical females and 45 neurotypical males from Japan underwent rs-fMRIs. The data was analyzed using multiple measurements, including fractional amplitude of low-frequency fluctuation (fALFF), regional homogeneity (ReHo), and seed-based functional connectivity.

Results: Females displayed stronger fALFF in the posterior cingulate cortex (PCC) and precuneus (PreC) than males, though males displayed stronger fALFF in both the inferior frontal gyrus (IFG) and the cerebellum than their female counterparts. Using ReHo, the only sex difference found was in the anterior DMN (specifically the IFG and cerebellum), where the activity was more synchronous in males than in females. Using seed-based functional connectivity, females had stronger connectivity between the angular gyrus and the anterior medial prefrontal cortex (aMPFC) than males, and males had stronger connectivity between the aMPFC and the superior frontal gyrus (SFG), temporal pole (TempP), middle occipital gyrus (MOG), and the superior occipital gyrus (SOG). However, females had stronger connections from the PCC to the medial temporal gyrus (MTG), orbital frontal cortex (OFC), middle cingulate cortex (MCC), and Angular Gyrus (ANG). Jung et al. found significant correlations between DMN intraconnectivity in the aMPFC and MOG and autistic traits in males, but no significant correlations in females. There were also significant negative correlations found between the AQ social scores and connectivity between the aMPFC and TemP in males. These results may indicate, among other things, a large difference in social cognition processing in males

versus females. Additionally, there may be evidence for the EMB theory based on the greater DMN connectivity-Autistic Trait correlation in males than females.

Relevance: This study addresses connectivity in the same areas and with the same population as will be used in our study. As such, we may look for similar findings in our study.

Billeci, L., Calderoni, S., Conti, E., Gesi, C., Carmassi, C., Dell'Osso, L., Cioni, g., Muratori, F., & Guzzetta, A. The broad autism (endo)phenotype: Neurostructural and neurofunctional correlates in parents of individuals with autism spectrum disorders. (2016). *Frontiers in Neuroscience, 10.* https://doi.org/10.3389/fnins.2016.00346

Introduction: The Broader Autism Phenotype (BAP) is a term used to describe a group of lower-severity autistic traits and is commonly found in relatives of those who have autism. This review aims to examine biological data that may explain.

Methods: Using PubMed and ScienceDirect, the researchers found relevant papers regarding their topic. They then analyzed the thirteen qualifying articles and conducted a thorough review.

Results: Though Billeci et al. analyzed studies that used various types of neuroimaging, their fMRI data is particularly of note in regards to the current study. Baron-Cohen et al. (2006) discovered that parents of autistic children (pASD) showed less activity in the visual cortex and reduced activity in the mid-temporal gyrus and inferior frontal gyrus. A difference between the sexes was also found, such that female controls had increased activity in the middle occipital gyrus compared to the male controls, but the mothers and fathers of autistic children were all found to have lower activity than the controls. The mothers and fathers also showed similar brain activity in

the left medial temporal gyrus and left dorsolateral prefrontal cortex to the male controls. Essentially, in the fMRI studies, it was found that relatives of autistic individuals showed brain activity more similar to their autistic relative than to the control group.

Relevance: These findings suggest that the neurotypical population exhibits varying degrees of autistic traits that can be measured similarly to autistic populations. This adds validity to our use of neurotypical individuals to study autistic traits and associated symptoms.

Klaric, K. (2019). The world according to my predictions: Human brains' default mode network in the context of predictive coding. *Research Gate, Preprint.* https://doi.org/10.13140/RG.2.2.19754.67520

Introduction: The predictive coding hypothesis is the idea that the human brain facilitates perception and understanding by generating top-down models at the same time as it receives bottom-up sensory input. The reason for this functionality is to minimize prediction error.

Methods: This paper seminar is an analysis of past data and an explanation of how findings regarding the activation of the DMN during passive perception may support the predictive coding hypothesis.

Results: Unique to the DMN, functional connectivity within the DMN and between the DMN and other parts of the brain is positively correlated. Additionally, both types of connectivity are most active when goal-oriented action stops. Some cognitive scientists believe that the DMN plays a central role in predicting future events based on past sensory input. This would mean that the DMN is less active during goal-oriented activity because there are fewer hypotheses that need to be created during this time.

Unless, that is, there are prediction errors regarding the activity, then the DMN would continue to work to update the inaccurate hypotheses.

Relevance: As discovered in past studies, autistic individuals' DMN is just as active during goal-oriented activity as it is during a lack of activity, which may contribute to an increase of intolerance of uncertainty and anxiety. In our study, where correlations for IUS and anxiety have already been established, there may be more correlations to discover between our quantitative findings and our rs-fMRI data. If there is a difference in DMN connectivity in males versus females as related to autistic traits, there may be neurobiological underpinnings for autistic profile difference in males versus females.

Hogeveen, J., Krug, M., Elliott, M., & Solomon, M. (2018). Insula-retrosplenial cortex overconnectivity increases internalizing via reduced insight in autism. *Biological Psychiatry, 84*(4), 287–294. https://doi.org/10.1016/j.biopsych.2018.01.015

Introduction: There are different internalizing symptoms in autism, including anxiety, depression, and social withdrawal. The researchers tested three different brain networks that may be involved in higher levels of internalizing symptoms: the salience network (SN), frontoparietal network (FPN), and default mode network (DMN).

Methods: Neurotypical and Autistic adolescents/young adults participated in an rs-fMRIs and assessments rating internalizing symptoms. The data from these findings was then analyzed and correlated to find the results.

Results: It was found that in autistic individuals, the anterior insula node of the SN was overconnected to a caudal posterior cingulate cortex node within the DMN. Additionally, there was a positive correlation found between this degree of

overconnectivity and the degree of internalizing symptoms. This same correlation was not found in neurotypical individuals.

Relevance: The above correlation may be of interest when looking at correlations between anxiety and depression in our subjects, though our subjects are neurotypical. Because we have varying degrees of autistic traits in our sample, we may see this correlation or we may not. Additionally, because the females in our sample have higher degrees of internalizing symptoms than males, they may present with this correlation where the males do not.

Mayer J. L. (2017). The relationship between autistic traits and atypical sensory functioning in neurotypical and ASD adults: A spectrum approach. *Journal of Autism Developmental Disorders*, *47*(2), 316–327. https://doi.org/10.1007/s10803-016-2948-5

Introduction: Because autism lies on a spectrum, and atypical sensory processing is correlated with autistic traits, it can be assumed that there is a similar correlation in both autistic and neurotypical populations. This study aims to examine this correlation in both populations. Mayer also compares correlations in a high-level (high AQ) and a low-level-autistic-trait (low AQ) neurotypical population.

Methods: There were 590 neurotypical individuals and 42 autistic individuals who filled out questionnaires targeting autistic traits and atypical sensory processing. Results were then analyzed and correlations drawn.

Results: The neurotypical population was split to compare low AQ groups to low AQ groups. It was found that the low AQ group, high AQ group, and autistic group all scored differently on the sensory profile. The low AQ group had significantly lower sensory scores than the ASD and high AQ groups, though they did report higher

sensation seeking behaviors than both of the other groups. The high AQ group also reported higher sensation seeking scores than the ASD group. This was an outlier finding, though, with the rest of the findings suggesting a very linear relationship between autistic trait severity and atypical sensory processing severity.

Relevance: One of the things we are looking at is sensory processing differences in males versus females. By looking at a higher severity and lower severity group of neurotypical individuals, we will be able to see if the above correlation is accurate in both males and females. Taken one step further, we will be able to see if this correlation leads to another correlation between connectivity in different areas of the brain in males versus females.

Sylvester, C., Corbetta, M., Raichle, M., Rodebaugh, T., Schlaggar, B., Sheline, Y., Zorumski, C., & Lenze, E. (2012). Functional network dysfunction in anxiety and anxiety disorders. *Trends in Neurosciences, 35*(9), 527–535. https://doi.org/10.1016/j.tins.2012.04.012

Introduction: The functional network model, which describes under-, normal, or over-connectivity between different brain regions, may provide a deeper understanding of the underlying neural mechanisms at play in anxiety and anxiety disorders.

Methods: A review was conducted on studies that include traits common in both specific anxiety disorders and high trait anxiety and focus on differences in functional connectivity.

Results: There may be decreased functioning in the fronto-parietal network in individuals with high trait anxiety. There also may be increased connectivity between the frontal-parietal networks and the cingulo-opercular networks, as well as between the frontal-parietal network and the amygdala. In individuals with high state anxiety and

social anxiety disorder, the DMN was found to have decreased functional connectivity with the amygdala, as well as decreased intraconnectivity overall.

Relevance: These findings suggest patterns that we may see in our young adult participants. Additionally, because we found greater anxiety in females than in males, we may find stronger patterns as described above in females when compared to males.

Li, W., Mai, X., & Liu, C. (2014). The default mode network and social understanding of others: What do brain connectivity studies tell us. *Frontiers in Human Neuroscience, 8*(74). https://doi.org/10.3389/fnhum.2014.00074

Introduction: Increasing studies have shown that the DMN is activated in individuals who are working to understand other people's emotions, showing empathy, and inferring information such as the other person's beliefs.

Methods: The authors conducted a thorough review of various brain connectivity studies that describe connectivity and social interaction in neurotypical and neurodivergent individuals.

Results: There were several different trends of connectivity found specifically in studies containing autistic participants. One grouping of studies examining emotion perception found decreased connectivity between the DMN and the fusiform face area when compared to their neurotypical counterparts. Another found that when viewing emotional facial expressions, there was decreased connectivity between the DMN and the ventral medial prefrontal cortex/IFGpo areas compared to the controls. When examining theory of mind, one study found that, during passage reading, there was decreased connectivity both inside the DMN (between the medial prefrontal cortex and the

temporoparietal junction) and between the DMN and the left hemisphere language network as well as the Theory of Mind network as compared to controls.

Relevance: These brain networks, when looked at through the lens of the BAP, may appear in our analysis of connectivity. Though we didn't have specific focuses on theory of mind or face recognition, these are important parts of social functioning, and may be implicated in our social scores (camouflaging, autistic traits).

Liu, D., Sun, J., Ren, Z., Yang, J., Shi, B., & Qiu, J. (2022). The neural basis of acceptance of uncertain situations: Relationship between ambiguity tolerance and the resting-state functional connectivity of the brain: functional connectivity of ambiguity tolerance. *Current Psychology, 42,* 17033–17041. https://doi.org/10.1007/s12144-022-02879-5

Introduction: Ambiguity tolerance (AT, i.e. intolerance of uncertainty, or IU) is made of different parts: a cognitive response, an emotional response (feeling uneasy, anxious, angry, or uncomfortable), and a behavioral response (rejection and avoiding uncertain situations). This study aims to use the relationship between rs-fMRI and self-reported questionnaires to better understand the underlying brain connectivity in AT. As of right now, the areas of the brain best understood to be involved in AT are the inferior parietal lobule (IPL), middle temporal gyrus (MTG), insula, anterior cingulate cortex (ACC), and the orbitofrontal gyrus (OFC).

Methods: There were 315 young adult participants who answered a questionnaire targeting AT as well as an rs-fMRI. Thirty two image slices were taken of the brain and analyzed for functional connectivity.

Results: In the questionnaires, men showed significantly higher tolerance for ambiguity than women (meaning women have a higher IU). From the rs-fMRI, it was

found that AT was positively correlated with functional connectivity between the left IPL and the middle cingulate cortex (MCC), and between the left IPL and the left MTG. An additional negative functional connectivity with AT was observed between the left OFC and ACC.

Relevance: The questionnaire findings are similar to those that we found in our study (Overall, females had higher IU than males). The brain connectivity findings create a helpful template for when we look for patterns of connectivity in IU between males and females.

Tromp, D., Grupe, D., Oathes, D., Mcfarlin, D., Hernandez, P., Kral, T., Jee, B., Lee, E., Adams, M., Alexander, A., & Nitschke, J. B. (2012). Reduced structural connectivity of a major frontolimbic pathway in generalized anxiety disorder. *Archives of General Psychiatry, 69*(9). https://doi.org/10.1001/archgenpsychiatry.2011.2178

Introduction: A common symptom of Generalized Anxiety Disorder (GAD) is uncontrollable worrying. A predominant theory behind the purpose of this worry is that it may be a compensatory strategy to help avoid negative emotional experiences. One of Tromp et al.'s goals in their study was to discover the degree of structural connectivity in the uncinate fasciculus in individuals with GAD (this fasciculus connects the ventral PFC and ACC regions to the amygdala and other areas in the limbic system). They compared these results with results regarding functional connectivity between the amygdala and the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) results. They hypothesized that increased structural integrity of the uncinate fasciculus would be correlated with decreased functional connectivity between the Amygdala and the PFC/ACC. This may

suggest better anxiety regulation in individuals with greater uncinate fasciculus structural connectivity, due to higher regulation of the amygdala.

Methods: Forty-nine patients with GAD and 39 control participants were given a Structured Clinical Interview, completed diffusion-tensor imaging and an fMRI, and gave a genetic sample via the buccal cavity. Structural and functional connectivity were analyzed and correlated with data from the clinical interview.

Results: Patients who had GAD showed lower structural connectivity in fronto-limbic structures. Across both GAD and control patients, it was found that greater structural integrity of the pregenual ACC was correlated with greater negative functional connectivity with the amygdala. Additionally, patients with GAD were observed to have bilaterally reduced structural connectivity in the uncinate fasciculus than their healthy counterparts; their lower connectivity values were correlated with less coupling between the ACC and amygdala. Tromp et al. surmised that this decreased structural connectivity of the uncinate fasciculus may be responsible for decreased emotion regulation in patients with GAD, leading to increased anxiety levels. Furthermore, lower uncinate fasciculus structural integrity may be directly correlated with reduced functional connectivity between the pregenual ACC and the amygdala, suggesting possible structural and functional underpinnings for GAD.

Relevance: Though we are not measuring structural connectivity in our study, the findings regarding functional connectivity are directly related to what we are looking for. Because we are looking at differences in males and females, one question that may be posed is if females will show lower connectivity between the amygdala and ACC than

males. This may also be manifest in individuals with higher intolerance of uncertainty, since the ACC and amygdala coupling is related to anticipating of aversive stimuli.

Yang, B., Wang, M., Zhou, W., Wang, X., Chen, S., Potenza, M., Yuan, L., & Dong, G. (2022). Disrupted network integration and segregation involving the default mode network in autism spectrum disorder. *Journal of Affective Disorder, 323,* 309–319. https://doi.org/10.1016/j.jad.2022.11.083

Introduction: The DMN has been implicated in autobiographical memory retrieval, envisioning the future, and understanding others' perspectives. It has been found to function more homogeneously in autistic individuals than in neurotypical individuals, suggesting a viable difference in autism and a possible way to help diagnosis. As found in different studies, autism-related differences in the DMN may be responsible for poor verbal and nonverbal communication and poorer social functioning/greater social impairment. Yang et al. compared the differences in DMN connectivity between individuals with autism, with Asperger's, and with pervasive developmental disorder not otherwise specified (PDD-NOS). They hypothesized that the autistic group would have DMN connectivity abnormalities, that the degree of DMN abnormality would increase from childhood to adolescence, but then decline from adolescence to adulthood, and that the change in functionality of the DMN might be different between subtypes of autism.

Methods: The imaging findings came from the ABIDE database. In total, fMRIs from 269 autistic individuals and 340 healthy controls were analyzed in this study.

Results: As most relevant to the current study, Yang et al. found significantly more abnormal DMN connectivity in the autistic group than the control group (don't really know if I'm delineating that correctly). Within the DMN, intraconnectivity was

found to be lower in the autistic group than the control group (there were significantly fewer connections in the DMN). Between the DMN and the frontoparietal network (FPN), and the DMN and cingulate-opercular network (CON), the autistic group had significantly greater connectivity than the control group. From this, as well as other results findings included (a) there's an increase in DMN abnormality from childhood to adolescence and a decline from adolescence to adulthood, (b) individuals with Asperger disorder did not show a significant difference in DMN connectivity compared to the control group. The other two groups–PDD-NOS and other autism–did show significant differences compared to controls), Yang et al. concluded that decreased connectivity in the DMN may be a valid biomarker for ASD.

Relevance: In splitting our participants into a higher autistic trait group and a lower autistic trait group, we may expect to see lower internal DMN connectivity in the higher autistic trait group. However, what has not been examined is whether females and the males have similar levels of internal/external DMN connectivity in conjunction with trait severity. This will be a focus of our study.

Walsh, M. J. M., Pagni, B., Monahan, L., Delaney, S., Smith, C. J., Baxter, L., & Braden, B. B. (2021). Sex-related neurocircuitry supporting camouflaging in adults with autism: Female protection insights. *bioRxiv: The Preprint Server for Biology.* https://doi.org/10.1101/2021.11.03.466990

Introduction: This study seeks to highlight possible brain pathways that may be implicated in ASD-F (female autism phenotype) camouflaging.

Methods: Twenty-one male and 24 female autistic participants, and 19 and 21 male and female NT adults answered the CAT-Q and were given an rs-fMRI and DTI.

This is the first study conducted that looks at functional connectivity as it relates to sex and compensatory behavior in autism. Several analyses were run on both the survey responses and brain data to produce results.

Results: The strongest predictor of camouflaging in autistic females was higher functional connectivity between the hypothalamus and a limbic reward cluster. There was also a sex-atypical pattern (meaning that autistic females and NT males had similar patterns, as did the autistic males and NT females) present in the hypothalamus and precuneus that predicted camouflaging.

Relevance: This data shows similar evidence as we may see in our study, as we examine camouflaging in males versus females. In particular, we will examine the FC found between the hypothalamus and limbic reward cluster between the high-autistic-trait group and the low-autistic-trait group.

APPENDIX B

Institutional Review Board Approval Letter and Consent

Memorandum

To: Garrett Cardon
Department: BYU - EDUC - Communications Disorders
From: Sandee Aina, MPA, HRPP Associate Director
Wayne Larsen, MAcc, IRB Administrator
Bob Ridge, Ph.D., IRB Chair
Date: December 01, 2020
IRB#: IRB2020-473
Title: Sensory Abnormalities and Autistic Traits: Behavioral and Neural Correlates

Brigham Young University's IRB has approved the research study referenced in the subject heading as expedited level, categories 4 and 7. The approval period is from 12/01/2020 to 11/30/2021. Please reference your assigned IRB identification number in any correspondence with the IRB. Continued approval is conditional upon your compliance with the following requirements:

1. A copy of the approved informed consent statement and associated recruiting documents (if applicable) can be accessed in iRIS. No other consent statement should be used. Each research subject must be provided with a copy or a way to access the consent statement.
2. Any modifications to the approved protocol must be submitted, reviewed, and approved by the IRB before modifications are incorporated in the study.
3. All recruiting tools must be submitted and approved by the IRB prior to use.
4. In addition, serious adverse events must be reported to the IRB immediately, with a written report by the PI within 24 hours of the PI's becoming aware of the event. Serious adverse events are (1) death of a research participant; or (2) serious injury to a research participant.
5. All other non-serious unanticipated problems should be reported to the IRB within 2 weeks of the first awareness of the problem by the PI. Prompt reporting is important, as unanticipated problems often require some modification of study procedures, protocols, and/or informed consent processes. Such modifications require the review and approval of the IRB.
6. A few months before the expiration date, you will receive a prompt from iRIS to renew this protocol. There will be two reminders. Please complete the form in a timely manner to ensure that there is no lapse in the study approval. Please refer to the IRB website for more information.

Implied Consent

Title of the Research Study: Sensory Processing and Social Interaction in Young Adults
IRB ID#: IRB2020-473

My name is Savanah Calton, I am a graduate student at Brigham Young University and I am conducting this research under the supervision of Professor Garrett Cardon, from the Department of Communication Disorders . You are being invited to participate in this research study about the brain mechanisms involved in social interaction in young adults. I am interested to learn more about the styles of social interaction in young adults between the ages of 18-25. Being in this study is optional.

If you choose to be in the study, you will be asked to complete a survey, that should take approximately 30-60 minutes of your time.

You can skip questions that you do not want to answer or stop the survey at any time. The survey is anonymous, and no one will be able to link your answers back to you. Please do not include your name or other information that could be used to identify you in the survey responses. If you complete the survey you will be entered into a drawing for one of several $50 Visa gift cards.

You will be asked at the end of the survey if you'd like to participate in future phases of the study, at which time you'll be provided a place to enter your contact information. Volunteers who qualify for phase 2 of the study will be asked to undergo a non-invasive brain scan (MRI) and compensated for their participation.

Questions? Please contact Savanah Calton at BYUsocialstudy@gmail.com . If you have questions or concerns about your rights as a research participant, you can call the Human Subjects Protection Program at 801-422-1461 or irb@byu.edu.

If you want to participate in this study, click the *Agree* button to start the survey.

Valid for Use Through:
Study Title: Social Interaction in Young Adults: Neural and Behavioral Correlates
Principal Investigator: Garrett Cardon, Ph.D.
BYUIRB
Version Date:

You are being asked to participate in a research study of differences in brain anatomy and function in young adults, related to their social interaction styles. We believe that social interaction styles are related to sensory processing, anxiety, and peoples' ability to empathize with others. We are trying to discover the mechanisms for this difference by studying the relevant areas of the brain. You have been asked to take part in this research study because you are a young adult between the ages of 18-25. If you join the study, you will undergo a non-invasive MRI scan of your brain. During this scan, you will simply be asked to lie still in the MRI scanner. There are no known significant risks associated with participation in this study. Participation in this study will take approximately 60 minutes and is completely voluntary.

This form provides you with information about the study. A member of the research team will describe this study to you and answer all your questions. Please read the information below and ask questions about anything you don't understand before deciding whether, or not, to take part.

Other people in this study

Up to 100 people from your area will participate in the study.

What happens if I join this study?

If you join the study, you will participate in a Magnetic Resonance Image (MRI) of your brain at the BYU MRI facility. MRI is a technique that uses a magnetic field and radiofrequency energy to obtain pictures of parts of the human body. You will be interviewed before the scan to be certain that you do not have implanted metallic devices such as a pacemaker or metallic clip of a blood vessel in your brain. During the scan, you will lie down on a padded table which will be moved into a large cylinder. You will need to lie very still while the MRI scan is performed. You will not feel anything during the scan but will hear loud noises made by the scanner as the pictures are taken.

Note: In this case, MRI is an experimental procedure and therefore, has no clinical interpretation.

Estimated duration of visit
Introduction to lab and consent: 30 mins
MRI scan: 30-60 mins
Total participation time: 60-90 mins

What are the possible discomforts or risks?

There are no known significant risks involved in this research study. Some people become

claustrophobic during the MRI procedure. You may become tired during the MRI recording and will be given rest breaks, as needed. There are no known risks for exposure to the types of magnetic fields and radio waves which are used in MRI, but there is always a possibility a small, unknown risk may exist to this or any test. Rarely (one in thousands of exams), a sunburn-like skin burn may occur over a small area of the body during the MRI. We take special precautions for this not to occur. However, we believe that we have taken reasonable precautions to ensure your safety. If you have any questions about your safety in this experiment, please feel free to discuss them with us at any time. There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the social interaction styles of young adults. This study is not designed to treat any illness or to improve your health. We will not release any clinically un-interpretable results. Also, there are risks as mentioned in the Discomforts and Risks Section above.

Who is paying for this study?

The sponsor for this study is the National Institute of Health and Brigham Young University.

Will I be paid for being in the study?

You will be paid $10 per hour for participation in this study at the end of each day. If either you or research personnel decide to withdraw yourself/you from the study, you will still receive the hourly rate for all your participation up to the point when you withdraw.

Will I have to pay for anything?

There is no cost to you for participating in this study. There will be no charge for procedures required by the study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The research team may decide to stop your participation without your permission, if they think that being in the study may cause you harm, or for any other reason. We will pay for the hours you have been in the research study up to the time you withdraw from the research study. Some of the other reasons for stopping your participation include having non-removable metallic

implants in your body that are found to be magnetic. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

You should inform your care provider(s) if you decide to participate in this research study. If you have an injury while you are in this study, you should call Garrett Cardon at (303) 241-6666 and/or your private physician. We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Garrett Cardon, Ph.D. You may ask any questions you have now. If you have questions later, you may call Dr. Cardon at (303) 241-6666. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Cardon with questions. You can also call the responsible Institutional Review Board (BYUIRB). You can call them at (801) 422-3841.

Who will see my research information?

Brigham Young University and the research team have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include: Brigham Young University
We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study. We will see, use and disclose your information only as described in this form. We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Primary Investigator, at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Garret Cardon
Brigham Young University
Department of Communication Disorders
1190 N 900 E 130 TLRB
Provo, UT 84604

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information.

- Federal offices such as the Food and Drug Administration (FDA) that protect research subjects like you.
- People at the Brigham Young University Institutional Review Board (BYUIRB)
- The study investigator and the rest of the study team.
- NIH, who is one of the organizations paying for this research study.
- Officials at the institution where the research is being conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. However, in either of these cases, we will always keep the names and other identifying information of the research subjects, like you, private.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.)
- Research Visit and Research Test records
- Diagnoses that have been given to you or your close family members, such as anxiety, Autism Spectrum Disorder (ASD), or Attention Deficit Hyperactivity Disorder (ADHD)

What happens to Data that is collected in this study?

The scientists on the research team work to find the causes and cures of disease. The data collected from you during this study is important to this study and to future research. If you join this study:

- Both the investigators and any sponsor of this research may study your data
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.
These optional procedures involve genetic testing or the use of your genetic information. Your genetic information will be released to your health care practitioner if you so choose.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:

Date:

Print Name:

Consent form explained by:

Date:

Print Name:

PERMISSION TO CONTACT FOR FUTURE RESEARCH STUDIES: Sometimes after a research project is finished, there are new questions that researchers need to ask and new research studies that need to be done. We would like your permission to contact you for participation in future studies that you/your child may qualify for. We will not contact you unless you give us your permission.

_____ I agree to be contacted for future research studies that I/my children might be eligible for.

_____ I do not wish to be contacted in the future for any additional research studies.

If you agree to be contacted, please list an address, phone number, and email address where you can be reached:

Phone:_____

Email:_____