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Autistic Traits, Sensory Processing, and Intolerance of Uncertainty:
Neurobiological and Behavioral Correlates

Maggie Buckhannon

A thesis submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of
Master of Science

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ABSTRACT

Autistic Traits, Sensory Processing, and Intolerance of Uncertainty: Neurobiological and Behavioral Correlates

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Master of Science

Sensory processing challenges are common and often difficult for children on the autism spectrum and can affect some neurotypical children. Furthermore, sensory processing atypicalities are associated with autistic traits and other co-occurring behaviors associated with autism, such as intolerance of uncertainty. As such, traits common to autism may vary continuously across diagnostic boundaries (i.e., Broad Autism Phenotype). Working to uncover behavioral and neurophysiologic correlates of sensory differences could positively impact clinical support of children with and without a diagnosis of autism. Therefore, this study examined relationships between sensory processing, intolerance of uncertainty (a possible measure of prediction), autistic traits, and associated resting state brain connectivity, in autistic (n=30) and neurotypical (NT; n=26) children ages 6–11. To this end, we calculated the relationships between behavioral scores on measures related to sensory processing, intolerance of uncertainty, and autistic traits. Also, we carried out independent component network functional connectivity analysis to investigate associations between cortical and cerebellar networks and behavioral results. Autistic participants presented with significant correlations of sensory processing with autistic traits and sensory processing with intolerance of uncertainty. Neurotypical participants presented with significant correlations of autistic traits with sensory processing and autistic traits with intolerance of uncertainty. Between groups correlations demonstrated sensory processing and intolerance of uncertainty scores overlapping and spanning the groups. Brain (rs-fMRI)—behavioral relationships regarding the above were also examined revealing strong associations between sensory and cerebellar networks and behavioral scores. Overall, our findings suggest that sensory differences may be related to altered prediction abilities and, in NT children, autistic traits. Neurophysiologic data pointed to abnormal functional connectivity between sensory cortices and the cerebellum in autistic children. These findings provide evidence for the notion of the BAP and suggest a role of prediction in sensory processing and its behavioral correlates.

Keywords: autism, resting state, sensory processing, intolerance of uncertainty

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DESCRIPTION OF THESIS STRUCTURE AND CONTENT

To adhere to traditional thesis requirements and journal publication formats, this thesis, *Autistic Traits, Sensory Processing, and Intolerance of Uncertainty: Neurobiological and Behavioral Correlates*, is written in a hybrid format. The hybrid format brings together traditional thesis requirements with journal publication formats. The preliminary pages of the thesis adhere to the university requirements. The body of the thesis is presented in a style similar to a journal article and conforms to length and style requirements for submission to journals following American Psychological Association (APA) formatting. Portions of this manuscript may be altered and submitted for publications in a peer-reviewed journal with the primary author listed as a contributing author. The annotated bibliography is included in Appendix A. Appendix B contains information regarding the Institutional Review Board (IRB)-approved template for writing a consent form. Identity-first language (e.g., “autistic participants”) 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., 2016). However, we also acknowledge and respect many people’s preference for person-first language.

Introduction

Autism Spectrum Disorder (ASD) is characterized by social deficits and restricted and repetitive behaviors. A high proportion of autistic individuals can also experience debilitating sensory challenges. Such sensitivities are also experienced by many in the neurotypical (NT) population. Evidence suggests that there is a significant association between sensory processing differences and the prevalence of autistic traits (Boyd et al., 2009; Fugard et al., 2011; Marco et al., 2011; Sinha et al., 2014; Tavassoli et al., 2014; Thye et al., 2017; Wigham et al., 2015). However, the underlying neurobiological mechanisms connecting autistic characteristics and sensory processing are not well understood. Thus, we aim to study the relationship between sensory processing and autistic traits and their neurophysiologic correlates across the broad autism phenotype. Discovering brain function that contributes to sensory processing differences and traits associated with autism could eventually provide targets for treatment leading to gains in areas of social communication, academics, and therapy for many patients.

The following paragraphs will review some fundamentals of autism, sensory processing challenges in this population, and the neurophysiology related to the same. Specifically, we will discuss how sensory differences may be significantly associated with children's difficulties with making adaptive predictions about their environments, as well as autistic characteristics in both those with and without a diagnosis of autism. Then, we will present original data concerning the relationships between sensory processing, prediction, autistic traits, and their neurophysiologic correlates.

Fundamentals of Autism Spectrum Disorder

Autism Spectrum Disorder is a neurodevelopmental disorder characterized by social communication deficits and restrictive and repetitive behaviors (RRBs; American Psychiatric

Association [APA], 2013). Social communication impairments include characteristics such as lack of joint attention, differences in social cognition (i.e., challenges with imitation and theory of mind), and difficulties with social reciprocity (American Speech-Language-Hearing Association [ASHA], 2020). RRBs are a broad behavior defined by invariance, such as intense interests, motor stereotypes, and compulsions (Wolff et al., 2016). Well-known behavioral and emotional challenges like inflexibility to change or insistence on sameness (IoS) are also cited in the literature as being common in autistic individuals (Hurley et al., 2007; Hwang et al., 2020; Lord et al., 2020; Park et al., 2016). Comorbidities such as language impairment, seizure disorders, genetic syndromes, anxiety, cognitive delays, attention-deficit disorders, and sensory processing differences (such as “preference for nonsocial stimuli” and under/over responsivity) are also associated with autism (Lord et al., 2020; Matson & Shoemaker, 2009; Muskens et al., 2017). While it is clear that these comorbidities exist, understanding of their underlying connections to core symptoms of autism is still unfolding.

Autism is labeled as a spectrum disorder due to the substantial heterogeneity in the severity of its traits. The diagnosis of autism is likely overarching and applies to many sub-diagnoses, though efforts to determine the best way to subdivide the population have not been entirely successful (Eisenmajer et al., 1996; Mayes et al., 2009). Individuals without a formal diagnosis of autism often present with similar traits to those with a diagnosis, albeit often in a less prominent form or not in combination with other traits that would yield a full diagnosis (Hurley et al., 2007). This phenomenon is very common in first-degree relatives of autistic individuals but can also manifest in those in the neurotypical population (termed the “Broad Autism Phenotype;” BAP; Baron-Cohen et al., 2001; Broderick et al., 2015; Fugard et al., 2011; Hurley et al., 2007; Ingersoll, 2009; Maxwell et al., 2013). The lack of knowledge regarding the

underlying mechanisms of autistic characteristics, in part, is due to this heterogeneity. In fact, given the variability within and outside of the autistic population, many have argued that it is “fractionable” and have advocated researching and grouping individuals by the individual dimensions of autism, rather than conceptualizing it as a coherent diagnosis (Gershon et al., 2010; Happé & Frith, 2020; Ingersoll, 2009; Leno et al., 2018; Pelphrey et al., 2011; Wright et al., 2013). Yet, the core characteristics of autism frequently occur together, and ASD is still held as a viable diagnostic category in a medical model (American Psychiatric Association, 2013; Wright et al., 2013).

Much of the foundation for clinical and research efforts today was laid by Leo Kanner and Hans Asperger, though the term ‘autism’ was first used by Paul Eugen Bleuler in 1912. Most of the development in diagnostic conceptualization has occurred throughout the 20th and 21st centuries, as in 1980 when autism began to be accepted as a “broader spectrum of social communication deficits,” (Lord et al., 2020, p. 1) and one decade later when it was officially recognized as a disability by U.S. Congress. Finally, in 2013 it was officially classified as a spectrum disorder via the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Studies focusing on finding biomarkers and physiologic differences have also turned up little that is clinically useful (Gaugler et al., 2014; Lord et al., 2020; Wright et al., 2013). Autism remains a behavioral diagnosis. Thus, while autism is considered a viable diagnostic category and original diagnostic elements remain as considerations in autism, its definition has been somewhat fluid historically.

ASD Diagnosis and Etiology: Current Issues

With no valid genetic, physiologic diagnostic assessment in place for autism, diagnosis is reached through obtaining an extensive developmental history, as well as observation of

individual performance on both informal and standardized assessments. That is, the diagnosis is based on behavioral presentations of the core features mentioned previously as listed in the DSM-5. When a decision on the diagnosis was reached in years past, a distinction could be made to classify the individual with either low functioning ASD or high functioning ASD, also known as Asperger's Disorder (DSM-IV; American Psychiatric Association [APA], 1994). In contrast, DSM-5 criteria yield a unitary diagnosis of Autism Spectrum Disorder, which encompasses previous diagnostic categories such as Asperger's and Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS). Though the formal diagnosis of Asperger's meets the new DSM-5 criteria for ASD, the terms "low-functioning" and "high functioning," to describe the spectrum of abilities and behaviors, is falling out of favor. The DSM-5 now advocates for distinguishing three levels of social communication support for autism: Level 1- "requiring support," Level 2- "requiring substantial support," Level 3- "requiring very substantial support" (APA, 2013).

Etiology of ASD is unknown for most patients. However, genetic, neurobiological, and environmental factors can increase the chance of autism development. For instance, genetic studies reveal that younger siblings of autistic children have an increased likelihood of autism. Similarly, a child of a first-degree relative with autism is 20% more likely to be autistic (Broderick et al., 2015; Lord et al., 2020; Wright et al., 2013; Ozonoff et al., 2011). Findings in twin studies report heritability ranging anywhere from 40–90% in monozygotic twins (Broderick et al., 2015; Gaugler et al., 2014; Lord et al., 2020; Wright et al., 2013). Environmental factors commonly associated with high-risk births also seem to be associated with increased incidence of autism. Future studies could add to the body of literature by researching the neurobiological indicators and underpinnings of autism in children.

Signs and Characteristics of Autism

Some propose that early indicators of autism can be detected in the first year of life. Behavioral signs could include fewer vocalizations, less shared smiling, and diminished gazes at faces (ASHA, 2020; Chita-Tegmark, 2016; Murias et al., 2018; Ozonoff et al., 2010). Recent research has considered using eye gaze as a biomarker for autism diagnosis. Eye gaze tracking (EGT) is correlated with behavioral measures, symptom severity, and degree of social impairment (Chita-Tegmark, 2016; W. Jones et al., 2008; W. Jones & Klin, 2013) in autistic children. Chita-Tegmark (2016) suggests that atypicality in sensory modalities, specifically with audio and visual synchronicity, could lead to disengagement from social scenarios later in life, which could explain some of the subsequent core features observed in autistic children. Thus, such physiological phenomena may be useful markers of autism in young children. Some of the literature on using sensory characteristics to diagnose autism early is mixed due to groups of infants with developmental conditions other than autism also experiencing high rates of sensory differences (Green et al., 2020; Rodgers & Ozonoff, 2005). The research regarding the physiologic underpinnings of autism in young children, such as sensory processing, may lead to helpful diagnostic cues (Chita-Tegmark, 2016; Green et al., 2020). Clearly, though, there is a need for additional studies to assess behavioral and physiologic activity together to possibly predict a diagnosis.

Along with early indicators of autism, regression in certain behaviors, following a period of seemingly neurotypical development, can occur sometime between the first and second year. For example, regression in social communication or expressive language has been reported (L. A. Jones & Campbell, 2010; Luyster et al., 2005; Ozonoff et al., 2010). However, due to autism's variable nature, some have reported no regression but an overall developmental delay

and/or plateau throughout the first years of life (Luyster et al., 2005; Siperstein & Volkmar, 2004). Following the first year or 18-month mark, children can continue to present with behavioral signs into their preschool years. For example, continued differences in joint attention and symbolic gesturing can greatly affect language development at the preschool age (Wetherby et al., 2004). Also, some autistic children engage in symbolic and structured play differently than their neurotypical (NT) peers, failing to use toys appropriately during a play scenario (Wetherby et al., 2004). These are some of the most common behavioral markers of autism in the first years of life. The possibility of the behavioral markers stemming from early sensory difficulties continues to be researched today.

The Broad Autism Phenotype

Other autistic characteristics, along with those listed above, occur in individuals without a formal diagnosis, like family members of an autistic child (Hurley et al., 2007) or individuals in the general population (Maxwell et al., 2013). This phenomenon—mild manifestation of autistic traits through genetic liability—is termed the Broad Autism Phenotype (BAP). Studies in the past have used a variety of instruments to characterize the BAP, such as the Autism-Spectrum Quotient (AQ; Baron-Cohen et al., 2001), the Social Responsiveness Scale (SRS-2; Constantino & Gruber, 2012), the Broad Autism Phenotype Symptom Scale (BAPSS; Sung et al., 2005), and Broad Autism Phenotype Questionnaire (BAPQ). All these measures screen for clinical differences in either NT family members or autistic children. Many of the questions on the assessments are appropriate for both populations. For example, the SRS-2 (Constantino & Gruber, 2012) includes a rating for a statement such as, “Thinks or talks about the same thing over and over.” Other BAP measures also exist to evaluate either parents or their children, but the measures are designed differently and include varying subscales or levels of required family

history workups (Bruni, 2014; Sung et al., 2005). Some features that are typically found in autistic individuals through behavioral assessment include social-emotional reciprocity challenges and atypical fixations and reactions to sensory input (APA, 2013). Due to the range of severity levels, there are many other traits associated with autism as a spectrum. Assessments that aim to characterize autism assess both core and accompanying traits such as social cognition, executive functioning challenges, eye contact, and comprehension difficulties regarding verbal and non-verbal communication (ASHA, 2020; Baron-Cohen et al., 2001; Hurley et al., 2007; Tavassoli et al., 2014; Williams et al., 2005).

Common Interventions

A growing number of communities see autism not as a disorder but a diverse way of being. That being said, families of autistic children may seek therapeutic services to facilitate social communication development interpersonally and with institutions. Common interventions for autistic toddlers and school-age children include discrete trial training (DTT; Lovaas, 1977), cognitive behavioral therapy (CBT; Rotheram-Fuller & MacMullen, 2011), the social communication, emotional regulation, and transactional support model or SCERTS (for anxiety and parent coaching; Prizant et al., 2006), augmentative and alternative communication (AAC), Picture Exchange Communication System (PECS; Kravits et al., 2002; Lerna et al., 2014), and social narratives, among others.

While DTT and CBT are commonly used in occupational therapy, the SCERTS model, AAC, and PECS can be helpful resources for autistic children who have minimal expressive communication or are non-verbal. When Prizant and colleagues (2006) developed SCERTS, they suggested that the sensory processing development of autistic children greatly affected later emotion regulation and social communication. Social learning can be full of unpredictability and

be visually and auditorily disorganizing at times for these individuals, which is why the SCERTS model is designed to focus intervention on social communication through researching the relationship between socioemotional development and communication (Prizant et al., 2006). Case-Smith et al. (2015) recognized that sensory therapies like sensory integration therapy (SIT) and sensory-based intervention (SBI) can have positive results in small, randomized controlled trials. However, this systematic review also emphasized that inconsistently defined therapies like SIT and SBI lack evidence and make no attempt to remediate for brain physiology. Future research concerning brain physiology could be cited during evidence-based reasoning for therapy approaches trialed with children with autistic traits.

Sensory Processing in the Autistic Population

Sensory differences were recognized in some of the earliest reports of autistic individuals (Asperger, 1991). More recently, the DSM-5 (2015) has established sensory differences as a core characteristic of autism. In neurotypical children alone, sensory processing disorders can impact anywhere from 5%–16% of children, depending on age (Gouze et al., 2009; Marco et al., 2011; McIntosh et al., 1999; Molinari et al., 2009). For children with a formal ASD diagnosis, some estimate up to 90–95% can be impacted by sensory atypicalities (Ben-Sasson et al., 2009; Chistol et al., 2018; Marco et al., 2011; Robertson & Baron-Cohen, 2017; Sinha et al., 2014; Suarez, 2012; Tomchek & Dunn, 2007; Volkmar et al., 1986). Jean Ayres, a prominent autism researcher in the areas of neuroscience and occupational therapy, describes sensory processing difficulties as an overwhelming fight or flight response in the brain preventing accurate interpretation of inputs (Suarez, 2012). Miller et al. (2007) described it as difficulty with attaining and maintaining appropriate responses to the incoming sensory information. This difficulty can be problematic because sensory processing of the auditory, visual, tactile, olfactory, vestibular,

gustatory, interoception, and proprioception senses is fundamental to all basic and complex processes—from simple perception to action planning, high-level cognition, and social communication (Ayres & Robbins, 2005; Boyd et al., 2009; Dunn et al., 2016; Miller et al., 2007; Robertson & Baron-Cohen, 2017).

Many autistic persons are likely to experience differences in sensory processing marked by either hyposensitivities, hypersensitivities, or both (APA, 2013; Burns et al., 2017; Chistol et al., 2018; Dunn & Brown, 1997; Frith, 2008; South & Rodgers, 2017; Suarez, 2012; Uljarević et al., 2016; Volkmar et al., 1986). Some have used the terms overresponsivity, underresponsivity, and sensory seeking as the manifestations of sensory modulation differences (Suarez, 2012) while others have described the patterns as hyporesponsive, hyperresponsive, and sensory seeking (Miller et al., 2007; Robertson & Baron-Cohen, 2017). In children and adolescents, behavioral manifestations of their responsivity to sensations are likely an attempt to adjust to the sensations surrounding them. Actively seeking or avoiding sensation has the potential to influence some behavioral domains including diet, social communication, academics, and therapy outcomes for both the individual as well as their family and friends (Thye et al., 2017). To cope with the possible anxiety related to sensory processing differences, some resulting behavior includes a variety of RRBs as a way of expressing IoS (Hwang et al., 2020; Joyce et al., 2017). Both higher- and lower-order RRBs can be identified in autistic children. Examples of higher-order RRBs are passionate interests and diets, compulsivity, and difficulty with transitions. Lower-order RRBs like arm flapping, self-injurious actions, rocking, and shouting are behaviors also found in other developmental disabilities related to autism (i.e., intellectual disability, Fragile X Syndrome, or Fetal Alcohol Spectrum; ASHA, 2020; Lam et al., 2008; Suarez, 2012; Van de Cruys et al., 2014; Wright et al., 2013). These behaviors are most often

methods of self-regulation due to an under- or over-responsiveness to lights, sounds, social stimuli, and/or touch, etc. (ASHA, 2020; Van de Cruys et al., 2014). Autistic individuals also often have apparent and heightened behavioral responses to many sensory inputs, like those processed by visual and auditory sensory modalities present when assessed as social stimuli (Hurley et al., 2007; Van de Cruys et al., 2014), though these behaviors are sometimes more observable in older children (Baranek, 1999).

Some have proposed that sensory differences early in life could be a viable cause of later social communication differences or challenges (Schultz, 2005). For example, a difference of sensory processing when attending to faces and suprasegmental processing in the auditory cortex directly affects understanding social cues and stimuli such as an eye roll or exasperated sigh during a conversation (Schultz, 2005). The social communication difficulties that could result from atypical sensory processing like inappropriately entering and exiting a conversation, poor topic maintenance, and misinterpreting humor or sarcasm, influence the family dynamic as well (Ayres & Robbins, 2005; Ooi et al., 2016).

Personal and Family Perspectives Concerning Sensory Processing Difficulties

Most parents and families who have a child with a sensory processing difference make anywhere from minor to significant changes to aspects of their lives. If their child is autistic and demonstrates communication challenges at a young age, early intervention can be a significant consideration since such services can have a positive impact on later academic success, language, performance, reading, etc. (ASHA, 2020; Estes et al., 2015; Lord et al., 2020). Many parents report easily fatiguing in response to the constant adaptations required to care for their children in public spaces with environmental triggers like buzzers at sporting events, fragrant smells, or heavily textured foods in restaurants (Fletcher et al., 2019; Ooi et al., 2016).

Temple Grandin (2009), a prominent author and spokesperson on autism, detailed her experience with sensory processing differences as a child. She described it as an intense fascination with patterns and shapes in sand that was all-consuming for her. Today as an adult, she continues to get distracted by patterns in carpet weavings and wallpapers. Not all individuals with autism share her exact experiences though. For example, some can keenly observe the flicker in florescent lights, which can be an overwhelming visual strain, while others could attend to shapes and colors intently thus creating a passionate interest and talent with the arts (Grandin, 2009). Unfortunately, despite much literature detailing sensory processing difficulties, little is known about the behavioral and neural correlates of it. Thus, attempts to adapt environments for sensory differences are only intermittently successful.

Assessment of Sensory Processing Differences

Different methods have been used to study sensory differences in autistic pediatric and adult populations. A systematic review conducted by Jorquera-Cabrera et al. (2017) found 15 psychometrically rigorous tests measuring sensory processing abilities in children ages 3–11 years. The authors concluded that the most commonly used tests were the Sensory Profile (SP), the Sensory and Integration Praxis Tests (SIPT), and the Short Sensory Profile (SSP) measure (Jorquera-Cabrera et al., 2017). The SSP is a truncated version of the SP designed to assess sensory processing, sensory modulation, and behavioral/emotional responses in children. Both the SP and SSP have strong psychometric properties with over 90% sensitivity and specificity. The assessment process was also coupled with parent reports, questionnaires, and clinical observations. Baranek (1999), Clifford and Dissanayake (2008), and Goldberg et al. (2008) conducted key studies that have used video analysis to document sensory differences in autistic children. The author found trends of subtle sensory-motor and social responsive characteristics in

the videos submitted of their 2-year-old children during the 9–12-month age range. From the video analysis, it was suspected that the visual sense impairment greatly affected joint attention at this age, this being a strong indicator of the child’s future social communication development. Other tasks that measure sensory differences in pediatric and adult populations are standard audiometry and visual assessments (Simmons et al., 2009), the Sensory Challenge Protocol (McIntosh et al., 1999), and Glasgow Sensory Questionnaire (Hwang et al., 2020). While behavioral measures provide much valuable information regarding sensory processing in autistic individuals, they do not describe the underlying mechanisms of such characteristics.

Neural Correlates of Sensory Processing

It is widely held that sensory differences arise from atypical neural processing and/or connectivity. However, consensus is still being sought by researchers on the specifics of such neuronal involvement. Logical areas to investigate these difficulties might be both sensory cortices, supramodal cortical regions, and cerebellar areas of the brain.

Sensory Cortices

Evidence suggests that atypical functioning of the primary sensory cortices (i.e., auditory and visual; Ritvo et al., 1986), the somatosensory cortex, and atypical neural processing outside of primary sensory cortices (i.e., association and supramodal) contribute to aberrant sensory responsivity in autism (Cardon et al., 2017; Robertson & Baron-Cohen, 2017). Literature highlights inconsistent findings in primary and association sensory cortices in autistic individuals. For example, the primary visual cortices of autistic individuals have been shown to process spatial contexts in similar ways as those of their neurotypical peers (Utzerath et al., 2019). Simmons et al. (2009) similarly found that in many autistic individuals, the visual cortices are typical in structure and function (Simmons et al., 2009). In contrast, differences in the

primary visual cortex have been shown in other studies with children and adolescents. For instance, Robertson et al. (2014) studied global visual processing in autistic individuals and found that many had reduced primary visual cortex processing when attending to short lapses of motion. Keehn et al. (2019) completed a study using resting state fMRI, which suggested varying subgroups of autistic adolescents have differing visual responses. That is, some groups presented with hyperconnectivity in the visual cortex (Keehn et al., 2019), while others showed different patterns. The auditory cortices and temporal lobe regions have also been implicated in autism (Gomot et al., 2008; Hitoglou et al., 2010; O'Connor, 2012; Simmons et al., 2009), with evidence suggesting that there are differences in neural connectivity (reports of both hyper and hypo connectivity) as well as structure in autistic children and adolescents. Furthermore, some have suggested delayed and/or limited multisensory stimuli responses in the somatosensory cortex (Marco et al., 2011), and others reported that young autistic boys have stronger connections of areas just outside the somatosensory cortex that relate to autistic trait prominence (Wang et al., 2017). Thus, differences in connectivity of visual and auditory processes could serve as an underlying explanation of common behaviors observed in autistic children and give meaning to a sensory sensitivity's impact. Because abnormalities in unimodal sensory areas can greatly impact a host of other domains (e.g., speech perception, comprehension, and social cognition deficits; Leff et al., 2009) for both autistic and non-autistic populations, but replicability of findings has been elusive, though promising, more studies are required to reach consistent conclusions regarding the utility of this knowledge.

Other networks and locations in the brain are also important for sensory processing, such as the dorsal and ventral attention networks (DAN/VAN) and default mode network (DMN). A study conducted by Farrant and Uddin (2016) found attention network nodes in sensory and

motor regions of autistic children's brains to function with hyper-connectivity. In contrast to an attention network, the DMN is made up of structures such as the precuneus, prefrontal cortex, hippocampus, and parietal lobe regions, and is a network that activates when an individual is at rest. The DMN has under-connectivity with other sensory and social communication networks of the brain in autistic individuals (Assaf et al., 2010; Duan et al., 2017; Hull et al., 2017) and tends to play an important role in executively demanding tasks (Davey et al., 2016). Recently, over-connectivity in the DMN has been proposed to be correlated with autistic traits (Martínez et al., 2020). Thus, it appears that the function of brain regions and networks outside of the canonical sensory cortices may play an important role in atypical sensory processing in autism, and otherwise. As such, it is logical to investigate these areas in order to better understand sensory processing in autistic and neurotypical children.

Supramodality: The Cerebellum

Atypical structure and function of the cerebellum have been implicated in autism (Courchesne et al., 1988; Courchesne, 1991; Courchesne & Allen, 1997; Robertson & Baron-Cohen, 2017). Given its connection with sensory and higher order neural processes, such as language processing (Pierce & Courchesne, 2001; Verly et al., 2014), it is reasonable to believe that the cerebellum may contribute to a number of behavioral manifestations common to autism. Due to the cerebellum's extensive neural connections to other parts of the brain, it is known as one of the most connected structures (Courchesne & Allen, 1997). The structure receives sensory input from each sensory system and then synthesizes the information to make coordinated actions in response (Blakemore & Sirigu, 2003; Glickstein et al., 2009). One of its functions is to prepare neural networks (including memory, motoric, or sensory related systems, etc.) for upcoming events (Courchesne & Allen, 1997). Evidence from Cardon et al. (2017) demonstrated

possible hypo-connectivity of the cerebellum with sensory cortices in autistic children relative to their non-autistic peers. These findings support the notion that the cerebellum is vital to sensory processing. One possible sensory-related cerebellar function might be the use of sensory input to formulate predictions about the environment and then prepare internal conditions for appropriate responses (Courchesne & Allen, 1997). This notion is similarly implicated in discussions of the cerebellum's role in motor functioning. Using instrumentation such as PET and fMRI scans, as well as autopsy, the literature reports that the cerebellum plays a role in detecting sensory mismatch between predicted outcomes and actual consequences, possibly due to abnormal levels of Purkinje cells, which receive and project signals deep in the cerebellum (Blakemore et al., 2001; Kern, 2002). Because of the cerebellum's implications in sensory processing, it would be beneficial to further investigate its relationship with autistic behavioral characteristics, like sensory sensitivities.

The Brain, Sensory Processing, and Prediction

Prediction is one brain process that has been investigated in both autism and sensory processing research (Balsters et al., 2017; Sinha et al., 2014). That is, the brain's ability to predict upcoming sensory events, based on past experience, is central to sensory function (Courchesne, 1995; Neil et al., 2016; Sinha et al., 2014). In fact, prediction is important to overall function in daily life. Humans rely on the expectations developed from long-term memory in order to predict new situations. It is the process that enables humans to read and speak quickly, adjust motor movements to match the environment (e.g., hitting a tennis ball; catching a bus versus walking leisurely), and comprehend facial expressions. In contrast, prediction difficulties could lead to some behavior abnormalities. This notion may be especially true for functions of speech/language, motor control, theory of mind, and sensory processing

(DeLong et al., 2005; Federmeier, 2007, Lopez-Moliner et al., 2019; Richardson & Saxe, 2020). For example, in most sentences, articles and words can be easily predicted. Take, for example, the following sentence: “The day was breezy, so the boy went outside to fly...” (DeLong et al., 2005, p. 1117–1118). Predictive capabilities allow the brain to fill in the blank with “a kite,” or possibly “an airplane.” Both *kite* and *airplane* could fit into the schema, but due to differences in meaning, the brain makes the most appropriate prediction. Difficulties in prediction ability could lead to difficulties in many areas like language, social communication, reading, and emotion management, as well as basic sensory processing.

Long-term predictive difficulties could lead to development of aversions to uncertain situations (i.e., intolerance of uncertainty), which could impact a number of behavioral domains, such as social communication. Van de Cruys and colleagues (2014) wrote that predictive theory suggests autistic individuals have minds that are highly precise, which may hinder their ability to take past sensory experiences and apply them to the future. High precision refers to a context-sensitive measure that estimates predictability (Van de Cruys et al., 2014). This high precision could be due to a categorization difference, in which experiences are grouped into small, hypo-connected semantic networks. With this high precision, each experience in the world would be individually categorized in a very literal manner, with reduced top-down processing (i.e., new events would be less understood, because they would overlap less with previously experienced events). Van de Cruys et al. (2014) continued to argue that with this framework, sensory mismatches in autism can be understood as a higher order prediction difficulty. Carleton et al. (2007) demonstrated this framework with the example of an individual experiencing an excessive heart palpitation, and how having certain knowledge that it was not threatening in the past would decrease present anxiety. Mismatches between predictions and actual sensory inputs

can result in great displeasure, pain, or startling experiences. As such, difficulties in predictive ability could lead to anxiety related to the development of intolerance of sensory filled, but unpredictable, situations.

Intolerance of uncertainty (IU) as a measurable construct is an internal or external reaction to negative perceptions of uncertain situations (Buhr & Dugas, 2002, 2009; Glod et al., 2019; Carleton et al., 2007). It has been documented that autistic individuals often have increased IU levels, which indicates that their perception of everyday uncertainties can be overwhelming and disturbing at times (Glod et al., 2019; Neil et al., 2016; Sinha et al., 2014; South & Rodgers, 2017).

IU has been scrutinized from a psychological standpoint in assessing its correlations with factors like anxiety, fear, and social communication in autistic and neurotypical (NT) persons (Buhr & Dugas, 2009; Glod et al., 2019; Neil et al., 2016; South & Rodgers, 2017; Wigham et al., 2015). For instance, Carleton and colleagues (2007) described the relationship between IU and fear as a probable “hierarchical or mediational relationship” (p. 114). The fear very likely originated from overwhelming sensory experiences. Similarly, Glod et al. (2019) reported that IU had a significant indirect and mediational relationship with IoS and sensory hyposensitiveness from their sample of 4–9-year-old autistic children. Research by Neil et al. (2016) also found that when controlling for anxiety, IU and sensory difficulties showed a significant positive correlation. Most of the aforementioned studies were more concerned with the relationship between IU and sensory processing and not autistic traits. Because of this association between sensory experiences and IU, and the possibility that IU is highly related to prediction difficulties, one could hypothesize that the prediction ability in autistic children may be related to atypical sensory processing. The incorrect predictions could also perpetuate the

cycle of rigidity and anxieties that are common in autistic individuals. Finally, given the relationship between prediction and IU, a possible novel, though indirect, method of measuring degree of prediction deficit could be through the evaluation of intolerance of uncertainty.

Thus, we propose that examining prediction via IU, as it relates to sensory processing and other behavioral domains, could provide a useful perspective in understanding the behavioral and neural correlates of sensory differences in children. Because the cerebellum is highly connected to cortical sensory regions and plays an important role in sensory prediction (Bubic et al., 2010; Courchesne, 1995; Courchesne & Allen, 1997; Kemper & Bauman, 1998), we hypothesize that difficulties with sensory cortical and cerebellar function and connectivity underlie autistic characteristics, differences in sensory processing, and IU. Overall, challenges in the ability to predict occurrence of sensory events could work together with multiple sensory systems to create atypical reactions to sensory stimuli.

Investigation of the association between each of the three behavioral constructs—atypical sensory processing, IU, and autistic traits—with accompanying neural correlates is novel. Studies that have found significant positive correlations between autistic traits and sensory processing atypicalities in adults of the neurotypical population have not included examination of their neural correlates (Horder et al., 2014; Mayer, 2017; Robertson & Simmons, 2013). Similar studies of older autistic persons have most often excluded such variables as well. Studies with child participants tend to omit neurological correlates when they have demonstrated mixed autistic traits and sensory processing correlations that are dependent on the sensations analyzed (Dunn, 1999; Hilton et al., 2010; Tomchek & Dunn, 2007). Only in recent years have other studies examined the association of intolerance of uncertainty challenges with atypical sensory processing with precursory neurobiological underpinning data (Hwang et al., 2020; South &

Rodgers, 2017; Wigham et al., 2015). Focusing on such neural underpinnings could lead to more effective evidence-based supports and give further understanding of autism itself.

Statement of the Purpose

Our study's aim is to examine the relationship between behavioral measures of sensory processing, intolerance of uncertainty, and autistic traits. To this end, we examined correlations between behavioral measures of these constructs and the functional connectivity of sensory/cortical areas and cerebellum. We hypothesize that the experimental and control groups in our study will demonstrate significant positive relationships between sensory processing, intolerance of uncertainty, and autistic traits, although autistic children will show a greater degree of severity in these measures overall. We further hypothesize that these measures will significantly correlate with decreased connectivity between sensory cortices and the cerebellum. Such findings have the potential to increase our understanding of the behavioral and neural correlates of sensory processing in autistic individuals, which could positively influence clinical practice and future research.

Method

Participants

Participants for the current study were 30 school-aged children with a confirmed medical/clinical diagnosis of ASD (27 male and 3 female; mean age = 9.13 years; S.D. = 1.72) and 26 neurotypical (NT) peers (19 male and 7 female; mean age = 9.38; S.D. = 1.54). Autism diagnoses were given according to the DSM-4 or -5 criteria/checklists and assessment via the Autism Diagnostic Observation Scale-2 (ADOS-2) by licensed clinicians in the greater Denver metropolitan area. Inclusion criteria included confirmed clinical diagnosis of Autism Spectrum Disorder (ASD), falling within the age range of 6–11 years at the time of testing, and having no

history of co-occurring developmental disabilities, epilepsy, head injury, neurological disorders, Fragile X Syndrome, or traumatic brain injuries. Table 1 provides descriptive participant information, such as mean ages and overall scores on behavioral tests. Based on observations by our team, all autistic children were highly verbal. Participant recruitment methods included letters sent to families who had participated in previous autism studies at the JFK Partners Autism Center at the University of Colorado Anschutz Medical Campus. Outreach was also made to locations providing autism therapies in the greater Denver, Colorado, area. NT participants were gathered from the greater Denver area by word of mouth and from contacting homeschool and afterschool agencies in Denver. Several participants were also recruited via word of mouth. All recruitment, consent, and testing procedures were compliant with the Colorado Multiple Institutional Review Board (COMIRB; IRB of the University of Colorado Medical School).

Instrumentation

This study implemented the following behavioral measures: the Short Sensory Profile (SSP), Intolerance of Uncertainty Scale-Short Version (IUS-12), and Social Responsiveness Scale-Second Edition (SRS-2).

Short Sensory Profile (SSP)

The SSP (Dunn & Brown, 1997) is a shortened version of the Sensory Profile (SP) that consists of a 38-question caregiver report designed to analyze atypical sensory processing relating to seven categories: “Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Under-responsive/Seeks Sensation, Auditory Filtering, Low Energy/Weak, and Visual/Auditory Sensitivity” (Tomchek & Dunn, 2007, p. 193). Each question uses a 1–5-point Likert Scale. The scores can be used to classify a child with three types of sensory processing: definite difference,

probable difference, and typical. The original 125-item SP included 117 children ages 3–17 for psychometric analysis. The SSP was created by removing 27 items unrelated to sensory modulation and an additional sixty for indistinct differences in the sensory modulation disorder and neurotypical groups (Williams et al., 2018). Immediately following the original SP, the assessment is the second most used in published studies (Burns et al., 2017; Williams et al., 2018). The total scores are most commonly used to indicate atypicality in autistic children and the subscale scores for autistic phenotypic grouping (Lajonchere et al., 2012; Uljarević et al., 2016). The SSP was chosen for our study due its use in the autism literature (Crasta et al., 2020; Glod et al., 2019; Simpson et al., 2019) and its increased discriminatory abilities compared to the SP. Additionally, it has moderate to strong internal consistency ranging from 0.70–0.90 in the different sections (Tomchek & Dunn, 2007), and it has a relatively short administration time of 10 minutes. Of note, higher scores on the SSP indicate less severe sensory processing atypicalities, unlike other measures in which higher scores are suggestive of more severe difficulties (see below).

Intolerance of Uncertainty Scale (IUS-12)

The IUS-12 (Carleton et al., 2007), a 12-item shortened version of the original Intolerance of Uncertainty Scale (IUS) 27-item test, measures levels of aversion to unpredictable situations. Responses to question items can be indicated on a 5-point Likert scale with 1 as “not characteristic of me” and 5 as “entirely characteristic of me.” The correlation with the original IUS is 0.94–0.96, very strong (Carleton et al., 2007). The test divides the scores into two categories in order to obtain a prospective anxiety score (e.g., “I must get away from all uncertain situations”) and an inhibitory anxiety score (e.g., “Uncertainty keeps me from living a full life”) (Carleton et al., 2007, p. 208). Good internal consistency of $\alpha = 0.85$ is present across

the two domains as compared to the internal consistency of the full IUS, $\alpha=0.96$ (Carleton et al., 2007). The IUS-12 was chosen for our study as a proxy measure of behavioral prediction ability. That is, intolerance of uncertainty is related to prediction in that people with intact prediction capabilities likely have more favorable attitudes concerning uncertain situations, and vice versa.

Social Responsiveness Scale (SRS-2)

The Social Responsiveness Scale (SRS-2) is a behavioral screener that assesses varying levels of autistic traits (Constantino & Gruber, 2012). Characteristics examined in the SRS-2 include the following: overall scores, social awareness, social cognition, social communication, social motivation and RRBs. The female and male forms use a 4-point Likert-type scale to score all 65 questions. Total scores of 59 or below are considered within normal limits and are not typically associated with autism. Total scores of 66-75 are considered clinically significant to identify autistic children with moderate social communication challenges and scores of 76 or higher indicate a very strong association with autism (Constantino & Gruber, 2012). The measure has been incorporated in frequent behavioral studies for autistic children and some fMRI studies regarding autism (Assaf et al., 2010; Fishman et al., 2018; Green et al., 2015; Jung et al., 2019). It also has superior reliability and good construct and predictive validity (Armstrong & Iarocci, 2013; Bölte et al., 2008; Bruni, 2014). Due to the option to complete the assessment online and for the factors previously listed, we chose to use the SRS-2 Profile Sheet parent reporting page in our study.

Procedures

All data were collected at the Brain Imaging Center at the University of Colorado Anschutz Medical Campus. Before completing the imaging, participants were screened for any implanted metal and were asked to change their normal clothing to hospital-provided scrubs for

their safety during the MRI scan (i.e., no metal present in the clothing). In all cases, testing sessions lasted no more than 2 hours from consent to finish. During the first hour, participants and their families underwent the consent and assent processes. They were given a chance to become familiarized with the testing facility site, including observation of the MRI scanning facility, the scanner, and associated equipment for as long as they desired. Subjects were allowed to choose a movie to watch during the anatomical scan. During the second hour, all participants underwent a resting-state functional magnetic resonance imaging scan (rs-fMRI) for the duration of 8 minutes followed by a full anatomical MRI. The full anatomical MRI was a T1-weighted anatomical scan (MP-RAGE) gathered for co-registration and normalization to Montreal Neurological Institute (MNI) space for each child. Pillows and weighted blankets were provided for comfort if desired. Subjects were instructed to remain as still as possible and were alerted that the scanner would make some loud noises, but that these were not dangerous in any way. Once they were ready, headphones and goggles were placed over participants' ears and eyes respectively to aid in dampening scanner noise and in the presentation of a fixation cross during the scan (see below).

Participants were asked to stay awake and to keep their eyes open and fixed on a white cross situated on a black field during the fMRI acquisition. A 3T Siemens Skyra MR scanner housed on the University of Colorado Anschutz Medical Campus was used to acquire all structural and functional MRI data. Whole-brain blood oxygen level-dependent (BOLD) datasets were collected for each participant using the following parameters: 40 axial slices, 2.5 mm thick with 0.5 mm gap, 220 mm² fov 64 squared matrix = 3.43 mm³ voxels, repetition time = 2500, echo time = 30 ms.

If children needed breaks, they were instructed to inform the researchers and were allowed out of the MRI. Additionally, while children were in the rs-fMRI scan, their parents were asked to fill out several questionnaires including the Short Sensory Profile (SSP), Intolerance of Uncertainty Scale (IUS-12), Social Responsiveness Scale School-Age Profile Sheet (SRS-2). After completion, the families were compensated for their time and participation.

Data Analysis

All analyses were carried out at Brigham Young University. Scores for the SSP, IUS-12, and SRS-2 were noted and each measure's total scores were calculated according to the authors' instructions. Because the SRS-2 requires some of the test items to be reverse scored, this was accounted for in the analysis.

Mann-Whitney U tests were used to assess between-group and across group differences for each behavioral questionnaire, controlling for age and sex, since data were not normally distributed. Additionally, Spearman rank order correlations were calculated between the total scores of the SSP, IUS-12, and SRS-2 to determine their relationships.

Additionally, following fMRI data download, structural and functional MRI data were imported for analysis into the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), which, in addition to its own analysis sequences, uses many of the routines from the Statistical Parametric Mapping software package (SPM 12; Ashburner et al., 2020).

Overall, functional connectivity analysis of fMRI data between several sensory-related networks and the cerebellum was conducted using the CONN toolbox software package in Matlab (MathWorks, 2019). Within this process, rs-fMRI data were pre-processed and de-noised in order to reduce artifacts such as subject movement. After pre-processing, consisting of motion correction, temporal high pass filtering, spatial Gaussian smoothing (6 mm^3), co-registration, and

motion correction using the ArtRepair toolbox within the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), data were normalized to MNI space. Then, we carried out group independent components analysis (ICA) on rs-fMRI concatenated across the autistic and NT children using Conn (Calhoun et al., 2001). Forty independent components (IC) were initially extracted. Any IC's that were determined to be compromised by noise (e.g., activity in voxels outside of grey matter, motion, etc.) were immediately excluded from future analyses. Following this initial selection, 15 ICs containing areas of activation corresponding to our hypothesis were selected as networks of interest (e.g., primary and association sensory areas, cerebellum, and fronto-parietal and default mode networks). Then, we subjected these 15 networks of interest to a spatial match template within Conn, using the 10 common ICs reported in Smith et al. (2009) and the 14 resting state functional networks reported in Shirer et al. (2012). This step accomplished two goals: 1) to further discriminate between true networks of interest and those containing spurious data and 2) to assign a functional name to each of our networks of interest. Those IC networks that did not match well with the aforementioned network templates were also excluded from analysis. This left 13 of the 15 components with statistically significant results. A full complement of IC networks of interest can be seen in Table 3 and rs-fMRI images of three highlighted IC networks can be seen in Figures 3-5.

Following determination of these networks of interest, a number of distinct functional connectivity analyses were carried out. First, differences in within-network connectivity were tested between the autistic and NT children in each of the retained IC networks via independent samples T-tests within Conn. Multiple comparisons correction (i.e., Bonferroni) was applied in determining significance in the above analysis (corrected $p = 0.003$). Second, the functional connectivity between each IC network and all other voxels in the brain that was associated with

each of our behavioral measures (i.e., SSP, IUS-12, and SRS-2 total scores) was assessed within each participant group in Conn, controlling for age and sex (cluster-based Gaussian random field theory parametric statistics; Worsley et al., 1996). Two-sided false discovery rate (FDR) corrections ($p < 0.05$) were applied to the cluster sizes of connected voxels for each IC network. Final significance of connectivity patterns for each IC-voxel-behavioral measure combination was determined, as above, through Bonferroni correction across IC network results (corrected $p = 0.003$). Connectivity values (z-scores) were extracted for all participants in each of the above comparisons. These values were then imported into SPSS in order to determine the strength of the relationship (Pearson's partial correlation controlling for age and sex) between functional connectivity indices and behavioral performance.

Results

Between Groups Results

Because the data were not normally distributed, comparison of behavioral scores was carried out between the autistic and NT children via Mann-Whitney U non-parametric tests. All behavioral measures were found to differ significantly between groups. Autistic participants presented with significantly lower (i.e., more severe) SSP scores than neurotypical children ($U = 744.50$; $p < 0.001$). Additionally, they exhibited significantly higher IUS-12 scores than their NT peers ($U = 92.50$; $p < 0.001$). The autistic participants had SRS-2 total scores that were significantly higher than the NT group ($U = 11.00$; $p < 0.001$). A total test score over 76 indicates a likely diagnosis of autism while scores 59 and below are considered in the typical range. Despite these statistical differences, overlaps between these groups' scores were readily observed in the SSP and IUS-12. This overlap was less pronounced with SRS-2 scores (detailed results can be seen in Figure 1).

The relationship between the total scores of each of the behavioral questionnaires were examined within groups through nonparametric Spearman correlations. Autistic children demonstrated the following significant correlations in total scores: SSP–SRS-2 ($r = -0.47$; $p = 0.01$) and SSP–IUS-12 ($r = -0.48$; $p = 0.01$). In contrast, the correlation between IUS-12 and SRS-2 did not present as significant in the autistic group.

The NT group demonstrated all significant correlations in total scores: SSP–SRS-2 ($r = -0.68$; $p < 0.001$), IUS–SRS-2 ($r = 0.57$; $p < 0.001$), SSP–IUS-12 ($r = -0.59$; $p < 0.001$) (See Table 2 for all behavioral correlates).

Resting State fMRI Results

Our hypothesis for the rs-fMRI analysis was that we would observe significant correlations between behavioral measures and reduced connectivity between primary and association sensory cortices and the cerebellum. Aligning with the hypothesis, significant correlations were found between the SSP and IUS-12 and areas such as the frontoparietal, temporal lobe, visual/auditory association cortices, and cerebellar region.

Brain Behavior Relationships

After Bonferroni corrections were applied (corrected $p = 0.003$), all significant functional network connectivity in autistic and NT children can be seen in Table 3. Out of the 15 IC-voxel cluster pairings, several networks are highlighted below due to their relation to the hypotheses and overall relevance to the current study. For example, IC9 (cerebellar/vermis network) was positively correlated with a network consisting of the superior/transverse temporal areas (FWE-corrected cluster size $p = 0.0000017$), lingual gyrus regions (FWE-corrected cluster size $p = 0.00003$), and cerebellum (FWE-corrected cluster size $p = 0.00002$; peak voxel-level: 42, -9, 10; $T(26) = 6.49$; $p = 0.000$). Increased connectivity among these brain regions was related to more

favorable SSP total scores ($r = 0.79$; $p = 0.000$; see Figure 3). Additionally, IC4 (cerebellar/brainstem network) exhibited a negative correlation with the left inferior lateral occipital cortices and IUS-12 total scores (FWE-corrected cluster size $p = 0.000003$; peak voxel-level: -47, -76, -12; $T(26) = -5.24$; $p = 0.000018$), such that lower degrees of connectivity were associated with poorer IUS-12 scores ($r = -0.77$; $p = 0.000$; see Figure 4). IC4 (cerebellum/brainstem) was also negatively correlated with the right and left lingual gyrus (peak voxel-level: 0, -80, 1; $T(24) = -5.93$; $p = 0.00004$) and total SRS-2 scores ($r = -0.78$; $p = 0.00$) in the autistic children. IC12 (right dorsal attention network) was implicated in both participant groups. That is, in autistic children, this network was significantly correlated with activity in the precuneus and the IUS-12 (FWE-corrected cluster size $p = 0.0027$; peak voxel-level: -22, -73, 45; $T(26) = 6.14$; $p = 0.000002$; see Figure 5). In the NT group, correlations between IC12 and the left frontal pole lobe and the SSP (L FP; FWE-corrected cluster size: $p = 0.00035$) and left angular gyrus and the SRS-2 (L AG; FWE-corrected cluster size: $p = 0.00026$) were demonstrated. Thus, in general, both groups demonstrated significant brain-behavior relationships that included sensory-related and/or cerebellar, as well as frontal and precuneus, brain regions. These relationships will be further discussed in the following section.

Discussion

Our study's aim was to examine the behavioral and neural correlates of sensory processing, intolerance of uncertainty (IU), and autistic traits within and across groups of autistic and neurotypical children. To this end, we analyzed the differences in and associations between scores on the Short Sensory Profile (SSP), Intolerance of Uncertainty Scale – Short Form (IUS-12), and Social Responsiveness Scale – 2nd Edition (SRS-2), and related resting-state network functional connectivity. We hypothesized that the experimental and control groups in our study

would present with significant differences between scores on the above measures, with some overlap between the groups. Additionally, we predicted that we would observe significant positive relationships between sensory processing, intolerance of uncertainty, and autistic traits both across and within groups, with autistic participants exhibiting stronger correlations overall. We further hypothesized that the aforementioned measures would significantly correlate with decreased connectivity between primary and association sensory cortices and cerebellar areas of the brain. Consistent with these hypotheses, the present study found: (a) While SRS-2 scores suggest that our participants fell into distinct diagnostic groups, overlapping scores on the SSP and IUS-12 support the notion that some behavioral dimensions common to autism vary continuously across the entire population; (b) Each group also had significant SSP–SRS-2 correlations, which points to previous literature that supports links between sensory processing differences and autistic traits (Baron-Cohen et al., 2001; Bayliss & Kritikos, 2001; Hurley et al., 2007, Robertson & Simmons, 2013). We also found that SSP and IUS-12 total scores were significantly correlated in each group, suggesting a link between sensory processing and IU (i.e., possibly prediction) in those with and without a diagnosis of autism; (c) functional network connectivity results revealed significant relationships between sensory-related cortical brain regions and the cerebellum that were also associated with behavioral measures of sensory processing, intolerance of uncertainty, and autistic traits. The following paragraphs will discuss the above in more detail.

The Relationship Between Sensory Processing and Prediction

The current significant results with respect to the SSP and IUS-12 in autistic children support the notion that prediction, as measured indirectly through IU, seems to be related to sensory processing differences (Lidstone et al., 2014; Van de Cruys et al., 2014). That is,

difficulties making accurate predictions about future sensory events could lead to mismatches between predictions and actual sensory inputs, which, over time could result in the development of an aversion to unpredictable situations. This idea has been highlighted in the predictive coding and executive functioning hypotheses of autism, which state that many autistic individuals' perception is less guided by previous experience, because of proposed lack of connection between sensory and higher order areas of the brain (Van Boxtel & Lu, 2013; Van de Cruys et al., 2019; White, 2013). This relationship between SSP and IUS-12 has been previously explained by IU being a determinant for increased anxiety in children with ASD (Boulter et al., 2014). Another model for the relationship that most closely aligns with our results is that of IU possibly leading to increase sensory difficulties (Neil et al., 2016; Wigham et al., 2015). With this model, Neil et al. (2016) were able to explain half the variance of sensory differences with IU in autistic children and one third of the variance in the NT children. Given their unpredictable nature, these relationships may be especially apparent in social scenarios such as social events, work, and classes in school. We take our correlational findings as evidence, albeit indirect, for models that implicate prediction as an important factor in sensory processing in autism.

The correlation between sensory difficulties (SSP) and IUS-12 scores in NT children was significant as well, further suggesting a fundamental link between atypical sensory processing and prediction. Existing literature shows that IUS-12 and SSP are significantly correlated for many clinical populations and the general population (Carleton et al., 2007; Gentes & Ruscio, 2011; Neil et al., 2016; Osmanağaoğlu et al., 2018; Sinha et al., 2014; South & Rodgers, 2017; Wigham et al., 2015), so its presence in our NT group was expected to be represented. As of yet, the effects of IU and atypical sensory processing in NT individuals are not fully understood. We propose that future studies endeavor to further explore the relationship of sensory processing and

IU in NT populations, given its potential implications related to the expression of autistic traits, as well as anxiety, and other concerning trends among those on the spectrum who express increased autistic traits, such as higher rates of death by suicide (Kirby et al., 2019; South et al., 2021).

In addition to within groups significant positive correlations between sensory processing and IU, we demonstrate herein a significant correlation when the autistic and NT children were combined as one group to test our hypothesis concerning the degree of intersection between the two groups (Figure 2). Close inspection of the scatter plot associated with this correlation, reveals a great deal of overlap between children from these different diagnostic categories (see also Figure 1 for an illustration of overlapping scores on the SSP and IUS-12). While the above finding does not address the notion of the Broad Autism Phenotype (BAP; Baron-Cohen et al., 2001; Broderick et al., 2015; Ingersoll, 2009) directly, it is evidence that sensory processing and IU, traits common to autism, vary continuously in a spectrum-like fashion, in both autistic individuals and those not diagnosed with ASD. This information may be useful in considering the various dimensions of autism and how these factors may be related to autism diagnosis—i.e., taking a dimensional, rather than a categorical approach, consistent with the National Institute of Health’s Research Domain Criteria (RDoC; Ibrahim & Sukhodolsky, 2018). Additionally, our combined groups finding may be informative for professionals and families who care for and support individuals without a diagnosis of autism that experience sensory or IU difficulties. Finally, approaching the present issue in a non-categorical manner may help in reducing ableist approaches to autism (Bottema-Beutel et al., 2021).

Several interesting brain-behavior correlations associated with sensory processing and IU were revealed in the current study. For instance, we originally hypothesized that cerebellar-

sensory cortex connectivity would be related to behavioral sensory processing in autistic children. IC9's (cerebellar/vermis) direct correlation with multiple sensory areas of the autistic brain aligned with this prediction. It was expected that higher (i.e., more favorable) SSP scores would be associated with increased connectivity between cerebellar and sensory cortices, and vice versa. This expectation is supported by the literature concerning cerebellar, prediction, and sensory functions in autistic individuals (Fatemi et al., 2012; Kern, 2002). Roles of the cerebellum include using sensory input to formulate predictions about the environment and then prepare internal conditions for appropriate responses (Courchesne & Allen, 1997). Studies like that of Cardon et al. (2017) point to decreased links between the cerebellum and sensory cortices, which they speculated could be related to the cerebellum's role in the sensory processing differences observed in autistic children. The vermis is also implicated in sensory research in that it receives sensory inputs from the visual and auditory systems (Schmahmann & Padya, 1997; Kern, 2002) and has increased activity during attention and sensory processing tasks (Fatemi et al., 2012). Interestingly, additional cerebellar/vermis independent components, such as IC4 and IC15 exhibited significant functional connectivity with higher order visual processing brain regions (i.e., lateral occipital cortices), which was highly correlated with the IUS-12 in autistic children. These findings appear to support the notion that decreased functional connectivity between the cerebellum and sensory cortices contributes to atypical sensory processing in autism, perhaps due to the cerebellum's important role in prediction.

Additionally, IC9 (cerebellum/primary visual cortex) presented with significant functional connectivity with the right superior frontal gyrus in NT children. This activity pattern was also significantly correlated with the IUS-12. Similarly, IC8 (right frontoparietal/ auditory association network) showed strong positive functional connectivity with the left frontal pole in

NT participants, which was correlated with SSP scores. Furthermore, functional connectivity between IC1 (higher order visual) and IC5 (temporal pole), and the left frontal pole, was found to be significantly correlated with the SSP in autistic children. These findings possibly suggest that frontal cortices play an important role in sensory processing and prediction, due to their connections with both the SSP and IUS-12, respectively. Previous studies have shown atypical connectivity between frontal cortices and the cerebellum in autism (Hoffmann et al., 2016; Khan et al., 2015), though these results have not often been connected to sensory processing and intolerance of uncertainty to our knowledge.

The above findings are some of the first to bridge theoretical frameworks and behavioral studies concerning sensory processing and prediction differences in autistic children with neurophysiologic data. Though in only a small sample of subjects, our rs-fMRI results are novel in that they support the hypothesis that sensory differences in autism can be understood as a higher order prediction difficulty stemming from connectivity between the cerebellum and other sensory-related brain regions (Van de Cruys et al., 2014). Additionally, within groups correlations and the correlation in Figure 2 showing a continuous spectrum of sensory processing and IU across both groups is another support for the role IU (i.e., prediction) may play in sensory processing across diagnostic categories. Future studies should directly evaluate the neurophysiologic correlates of prediction, especially as they relate to sensory processing in autism.

Sensory Processing, Prediction, and Autistic Traits

The results of the present study revealed significant correlations between sensory processing and IU and autistic traits in children with autism, which was consistent with our original hypotheses. Though no consensus has been reached regarding the exact role atypical

sensory processing plays with regards to autistic traits and intolerance of uncertainty, numerous studies, cited below, have shown results similar to those reported here. It is clear that sensory processing and these other factors have a complex, but evident, relationship.

We did not observe significant associations between IU and autistic traits in our group of autistic children. This result was unanticipated because there are studies about IU performed with autistic participants (Glod et al., 2019; Joyce et al., 2017; Neil et al., 2016; Wigham et al., 2015) that report indirect or mediational relationships. A few previous studies have shown some relationship between IU and autistic traits. For instance, Joyce et al. (2017) conducted a study about the relationship between autistic traits of RRBs and anxiety measured through assessments such as the Repetitive Behavior Questionnaire-2, IUS-12, anxiety scale, and SRS-2. They found that intolerance of uncertainty levels was significantly and positively correlated with anxiety and RRBs, though the study used a number of measures that were not validated for children. Though previous studies (Glod et al., 2019; Joyce et al., 2017; Neil et al., 2016; Wigham et al., 2015) present data that seem to be in partial contrast to our current results, they did not measure the relationship of IU and autistic traits in the same way as we did. We assessed autistic traits through SRS-2 total scores, while prior studies have used sub scores such as the SRS-2 social communication score or RRB score. Additionally, any discrepancies could be due to the small sample size of autistic children in our study. In this case, each child's results may have had abnormal influence on the overall outcome which could be masking the effect in the group.

In partial contrast to the autistic children in the present study, sensory processing (SSP) and IU (IUS-12) were both significantly correlated with autistic traits (SRS-2) in the NT group. The partial correlation coefficients for these two comparisons were also stronger in the NT group than they were in autistic children. This finding is supportive of our hypothesis and current

literature about the nature of sensory processing and IU in NT individuals (Boulter et al., 2014; Carleton et al., 2010; Comer et al., 2009; Holaway et al., 2006). Specifically, these results point to behavioral dimensions that may contribute to the BAP in NT children. That is, it seems that the degree to which sensory difficulties and/or intolerance of uncertainty are exhibited is associated with the level of autistic trait expression, even in children without an ASD diagnosis.

The current neurophysiologic results give additional insight to the relationship between sensory processing, IU, and autistic traits. For instance, connectivity between IC4 (cerebellum/brainstem) and higher order visual/object recognition and primary visual brain regions was significantly associated with both IU and autistic traits (i.e., IUS-12 and SRS-2 scores), respectively, in autistic children. The lateral occipital cortex is directly involved in higher order visual processing of complex shapes and object recognition (e.g., faces/ facial expressions, body parts, etc.; Grill-Spector et al., 2001; Nagy et al., 2012; Weigelt et al., 2013), indicating that our results continue to be congruent with the idea that higher order processes are different in autistic brain networks (Kourtzi & Kanwisher, 2001; Robertson & Baron-Cohen, 2017; Sinha et al., 2014). Other resting state fMRI studies have findings reflective of ours, that differences in connectivity in the lateral occipital cortices possibly influence SRS-2 communication scores in autistic boys (Jung et al., 2019). Perhaps the decreased connection we found between the cerebellum and these lateral occipital regions could relate to atypical visual motion processing and be associated with difficulties in predicting key parts of social communication (Hubl et al., 2003; Pua et al., 2021; Robertson & Baron-Cohen, 2017).

Another IC network that showed interesting rs-functional connectivity relative to the ideas presented in the current study was IC12 (the right frontoparietal network, related to the dorsal attention network), which was implicated in both autistic and NT children. While we

originally hypothesized that we would see negative correlations only in the rs-fMRI data, autistic children exhibited positive connectivity between the dorsal attention network (DAN) and the precuneus, which was associated with IUS-12 scores. This brain-behavior correlation was such that increased network connectivity was related to higher (i.e., poorer) scores on the IUS-12. The precuneus is instrumental in internally directed thought (Fransson & Marrelec, 2008) and the DAN has been shown to mediate voluntary control of attention (Fox et al., 2006; Ozaki, 2011). Given these functions and these areas' positive connection to IUS-12 scores, it is reasonable to conjecture that enhanced connectivity in this network of brain regions could contribute to atypically increased attention to self, resulting in difficulty processing, attending to, and perhaps making predictions about external events. Additionally, it is known that the DAN plays a role in visuo-spatial perception (Duan et al., 2017) and, along with the precuneus' connectivity with brain locations such as the middle/inferior temporal gyrus, occipital lobe, and amygdala (Fishman et al., 2018; Lynch et al., 2013), it is possible that the current study's IC12 (right frontoparietal) connectivity patterns are more specifically related to sensory prediction abilities. If there are connectivity imbalances in regions responsible for perception, prediction, and anxiety, our result of positive connectivity reasonably points to the prediction challenges in autistic children.

Limitations

The current study represents an attempt to better understand the neural and behavioral correlates for sensory processing, prediction, and autistic traits in children. Limitations to this study include the fact that two parents did not return an SRS-2 parent form for their autistic children. Thus, with fewer assessments there were less data to use for our statistical analyses, which possibly changes the correlations, power, and effect size. Also, compared to the entire

population of children on the autism spectrum, our study had relatively few participants. It would be advantageous for similar future studies to gather more children in order to have a greater statistical power and to reduce the possibility of the effects of heterogeneity among both autistic and NT individuals. It is important to note that this study focused on the cerebellum and other regions of interest (ROIs) related to the current hypotheses. However, there are assuredly multiple other brain regions involved in the behaviors discussed herein. Thus, future studies should endeavor to evaluate additional brain networks' associations with sensory processing, prediction, and autistic traits.

Implications

The implications from this research are complex. To our knowledge, this study is one of the first to correlate the behavioral tests we implemented with rs-fMRI connectivity. Though correlation does not equate to causation, this study can be used to build upon for future research and support the growing literature about the autism community and others who express autistic traits. Knowledge about the interplay of prediction and sensory processing across the BAP could benefit healthcare professionals, therapists, and schoolteachers to know how to adapt environments to reduce sensory ambiguity and possible anxiety in their pediatric clients. In the school and community settings, many NT children with sensory processing differences may be inaccurately labeled as problematic children that act out or distract peers. Because there is no formal diagnosis, NT children may go without formal services unless professionals are aware of data such as ours that indicate NT children may also express differences (regarding sensory processing or prediction) that require accommodations. This is true for the elementary as well as collegiate levels. Ideally in the future, highly individualized interventions could be planned after more studies are conducted taking our data and moving forward with a task-based fMRI study

looking at our implicated brain regions pre- and post- treatment. Our hope is that the current findings could add to evidence-based practices that researchers and therapists in the fields of speech-language pathology, occupational therapy, and psychology use to assist children in their sensory processing and prediction differences.

Conclusion

This is the first study to combine behavioral and neurological findings relating autistic traits, sensory processing, and intolerance of uncertainty. Our observations led us to these main conclusions: there are possible patterns of differences in neural connections of cerebellar, sensory, and cortical networks likely present in a larger population of autistic children that indicate and provide evidence to support our hypotheses. Results from this study add to the growing evidence that children with autism have patterns of behaviors and neural network processing that can be linked to prediction and sensory processing differences. As has been mentioned by other authors, our research highlights the idea that hypo and hyperconnectivity details may not be as important as the ROIs and the networks that continue to be evidenced in research like ours (Burrows et al., 2016; Hahamy et al., 2015). In the future, more research is needed to better understand the brain-behavior relationship in individuals who present with BAP characteristics. A deeper exploration of these topics may assist in evidence-based practices for professionals working with autistic children or children with sensory processing differences and their families.

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Tables

Table 1

Participant Characteristics

	Autistic (n = 30) Mean \square SD (Min – Max)	Neurotypical (NT) (n = 26) Mean \square SD (Min – Max)	Autistic vs. NT	
			U Score	P Value
Age (years)	9.16 \square 1.79 (6.08 – 12.92)	9.44 \square 1.55 (6.50 – 11.92)		
Sex (M/F)	27 / 3	19 / 7		
IUS-12 total	36.33 \square 11.93 (13 – 58)	19.68 \square 6.52 (12 – 36)	92.50	* $<$ 0.001
SSP total	119.70 \square 24.87 (84 – 174)	170.42 \square 15.38 (137 – 190)	744.50	* $<$ 0.001
SRS-2 total	74.64 \square 9.54 (46 – 91)	45.46 \square 5.68 (37 – 59)	11.00	* $<$ 0.001

Note. IUS-12: Intolerance of Uncertainty Scale shortened version 12; SSP: Short Sensory Profile; SRS-2: Social Responsiveness Scale second version.

* $p < 0.05$

Table 2*Within Groups Spearman Rank Order Correlations of Behavioral Total Scores*

	Autistic Group			Neurotypical Group		
	SRS-2	SSP	IUS-12	SRS-2	SSP	IUS-12
SRS-2 r(p)	--	*-0.47(0.01)	0.22(0.26)	--	*-0.68(0.00)	*0.57(0.00)
SSP r(p)	--	--	*-0.48(0.01)	--	--	*-0.59(0.00)

Note. IUS-12: Intolerance of Uncertainty Scale shortened version 12; SSP: Short Sensory Profile; SRS-2: Social Responsiveness Scale second version.

* $p < .05$

Table 3*Functional Network Connectivity and Behavioral Assessment Correlations*

IC	IC Area	Autistic			Neurotypical		
		SSP	IUS-12	SRS-2	SSP	IUS-12	SRS-2
1	Higher Order Visual	L FPole (<0.001)	--	--	--	--	--
2	Sensorimotor	R/L Planum Temp (<0.001)	--	--	--	--	--
3	Ventral DMN	L Ling (0.001)	--	--	--	--	--
4	Cerebellum	--	L LOC (<0.001)	L/R Ling (<0.001)	--	--	--
5	Temporal pole	L FPole (<0.001)	--	--	--	--	--
6	Primary Visual	--	--	--	--	R Sup Front G (0.007)	--
7	Ventral DMN	--	L FP (<0.001)	--	--	--	--
8	Executive Control	--	--	L LOC (<0.001)	--	--	--
9	Cerebellum (vermis)	R Central operculum/Heschels (<0.001); R/L Lingual / Temp Occip Fus (<0.001); L Central operculum / L PoCG (0.001)	--	--	--	--	--
11	Sensorimotor	--	--	--	--	--	--
12	R Fronto-parietal	--	Precuneus (0.003)	--	L FPole (<0.001)	--	L Ang G (<0.001)
13	L Fronto-parietal	--	--	--	--	--	--

IC	IC Area	Autistic			Neurotypical		
		SSP	IUS-12, Intracalcarine/ cuneal/precuneus/ ling (<0.001)	SRS-2	SSP	IUS-12	SRS-2
14	Dorsal Attention (visuospatial) Cerebellum	--		--	--	--	--
15	(vermis)/ brainstem	--	R/L Sup LOC / S Par Lob (<0.001)	--	--	--	--

Note. L/R

= left/right; FPole = frontal pole; poCG = post-central gyrus; Planum Temp = Planum Temporale; mPFC = medial prefrontal cortex; LOC = lateral occipital cortex; S Par Lob = superior parietal lobe; Ling = lingual gyrus; DMN = default mode network; SFG = superior frontal gyrus; Temp Occip Fus = temporo-occipital fusiform SMG = supramarginal gyrus; AG = angular gyrus; DAN = dorsal attention network

* *corr p* < 0.003 (all p-values describe FWE corrected significance for cluster size)

Figures

Figure 1

Histograms of Man-Whitney U Tests Between Groups for All Behavioral Measures

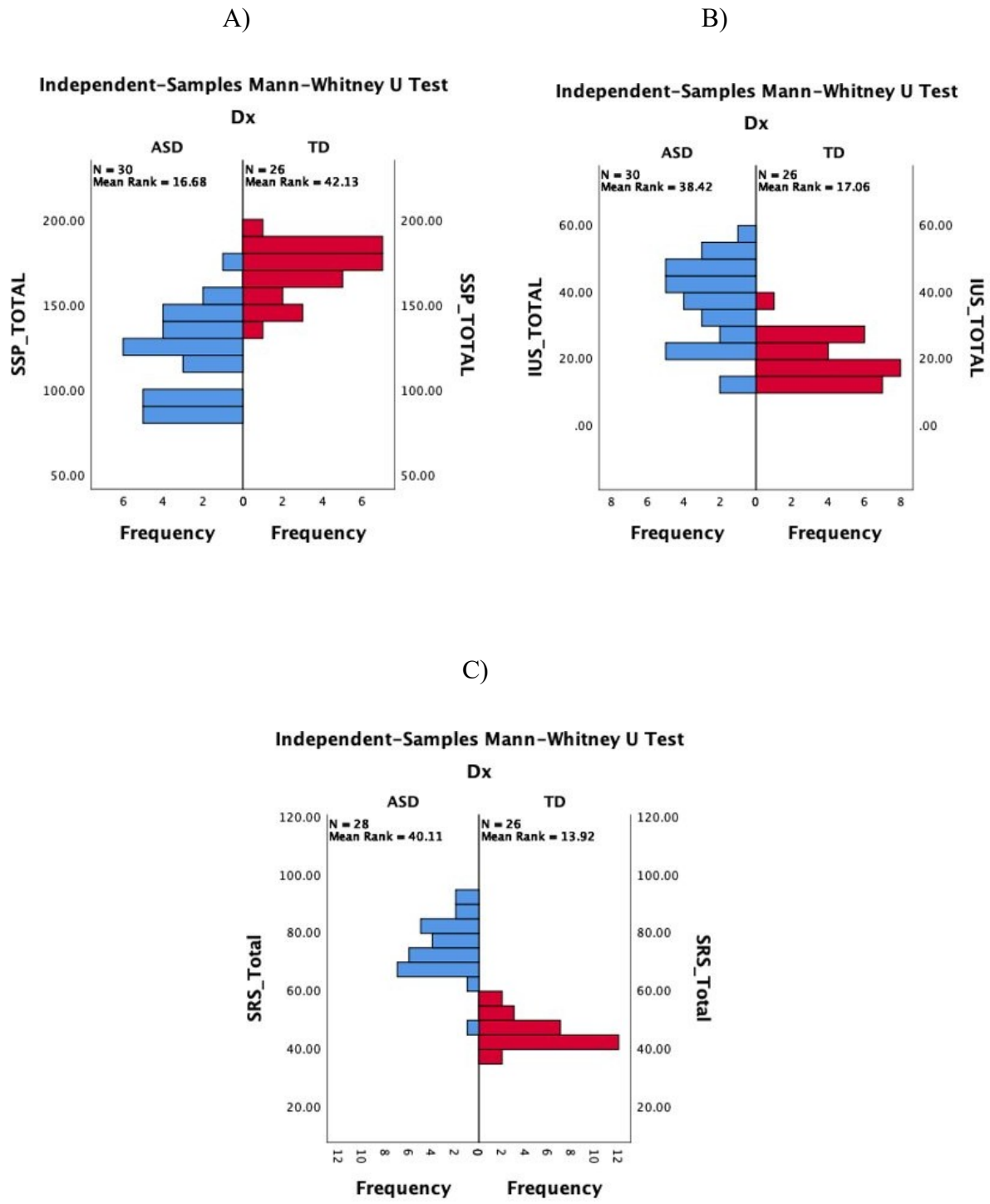
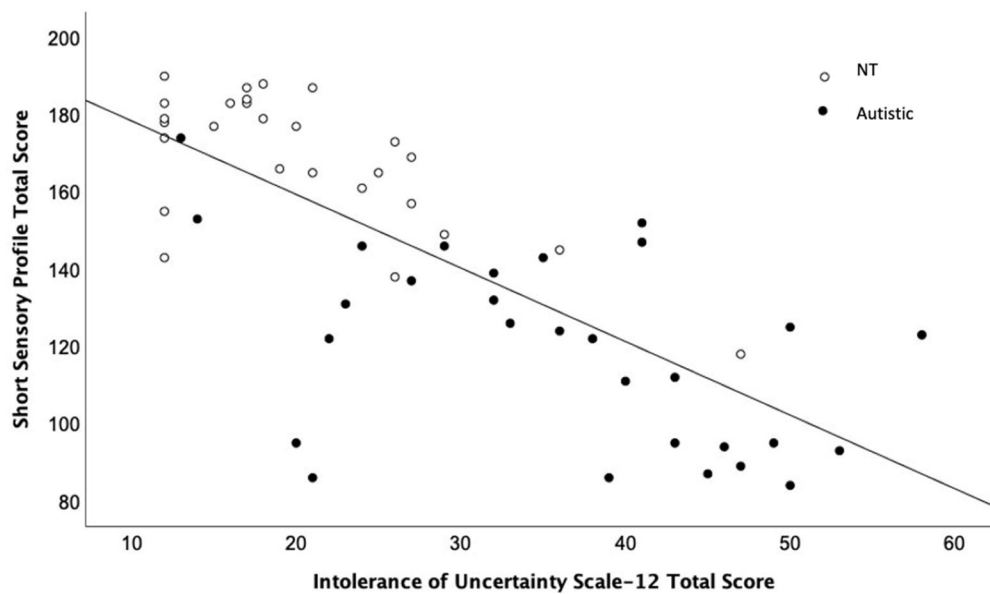
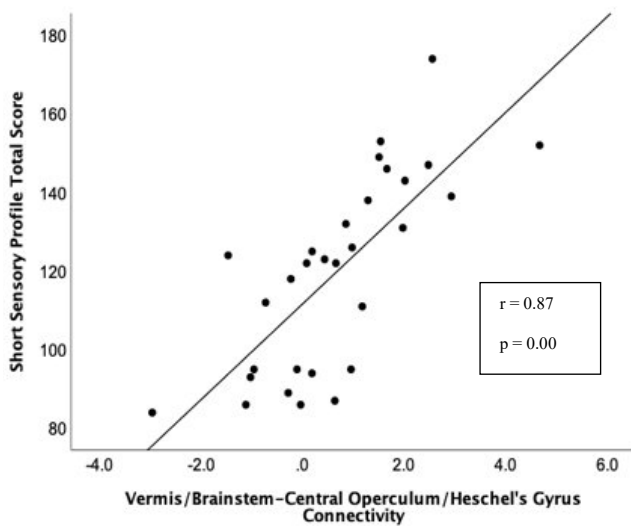
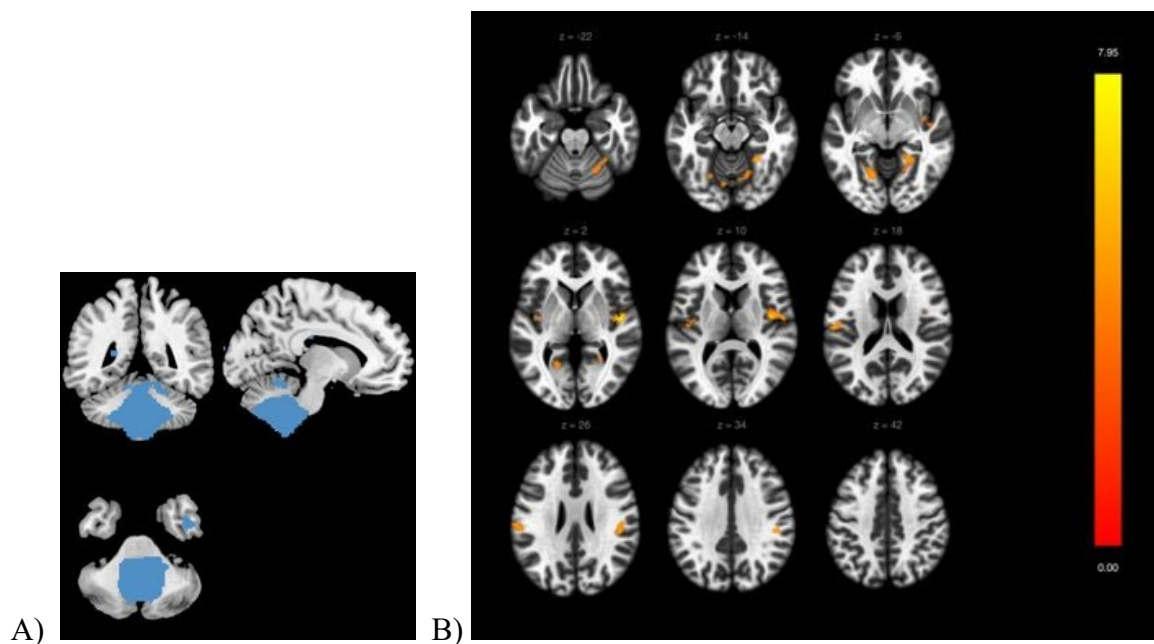


Figure 2

Combined Groups SSP-IUS-12 Correlation Representing the BAP

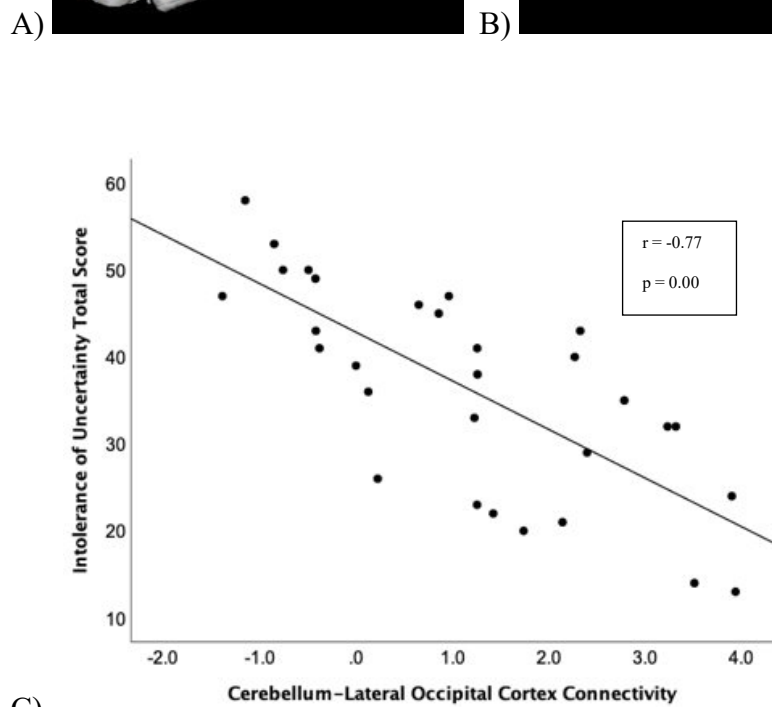
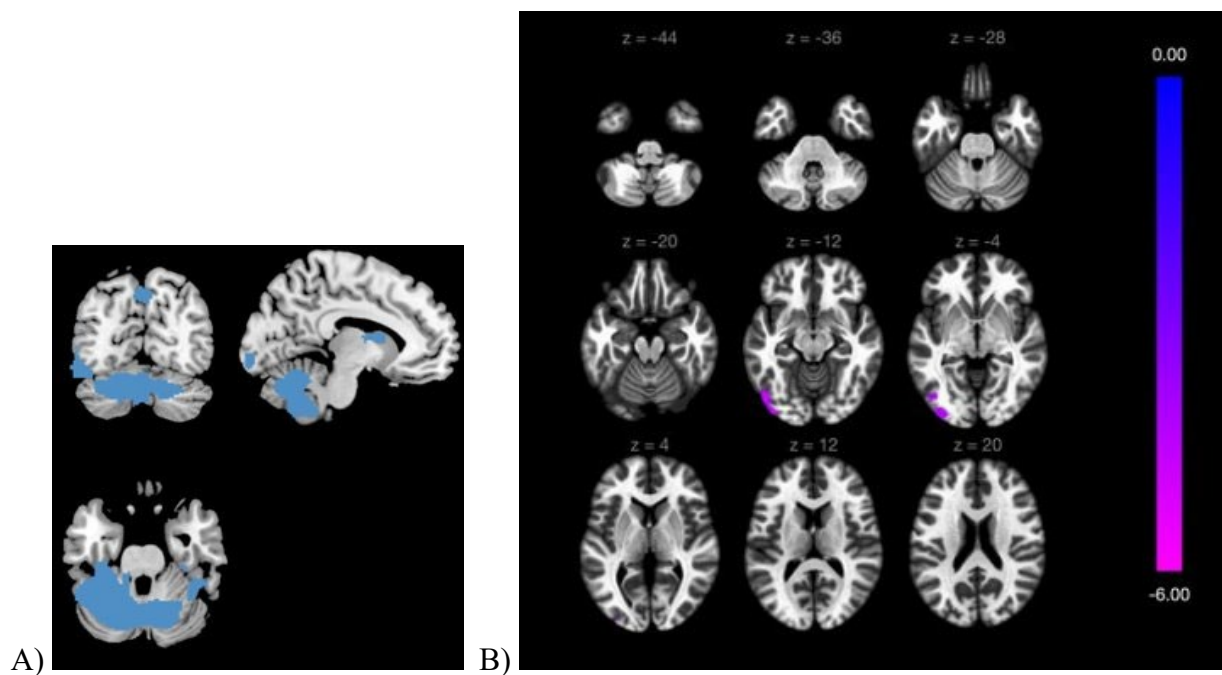


Note. Open circles represent the NT participant scores. Filled circles represent autistic participant scores.

Figure 3*IC9 (Cerebellum/Vermis) Connectivity and Correlations: Autistic Brain*

C)

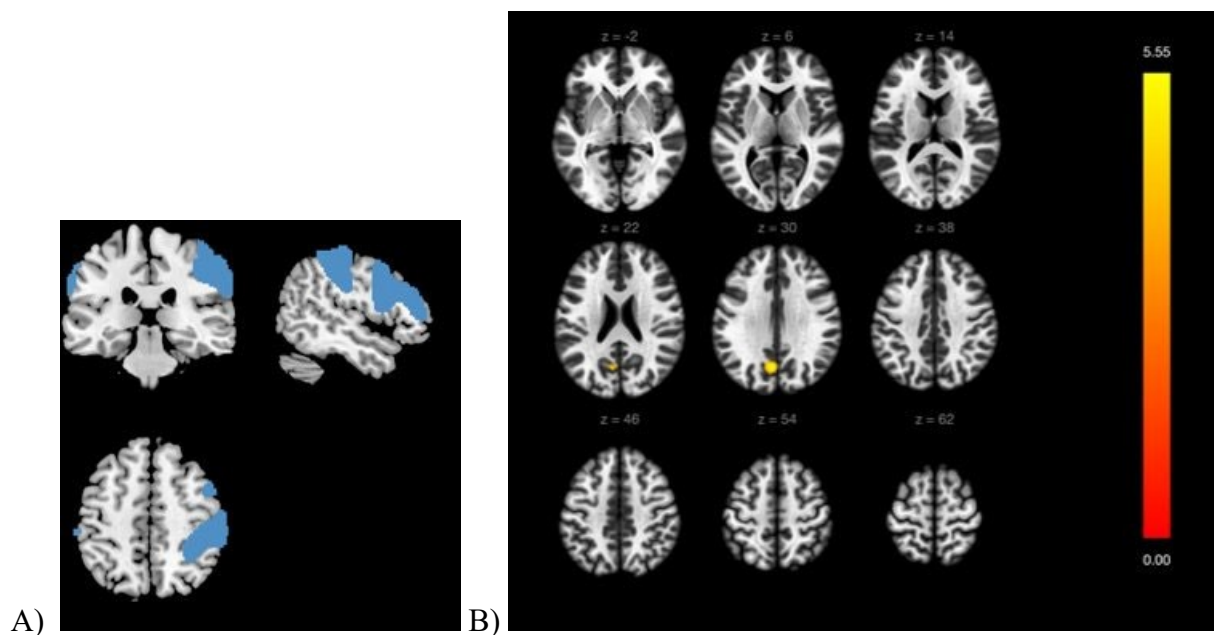
Note. Image A) IC9 (cerebellum/vermis); Image B) Connectivity with lingual gyrus, temporal lobe, and cerebellum (a sensory/prediction network); Image C) Positive correlation of network connectivity on x-axis and SSP scores on the y-axis.

Figure 4*IC4 (Cerebellum) Connectivity and Correlations: Autistic Brain*

C)

Note. Image A) IC4 (cerebellum); Image B) left lateral occipital cortex connectivity; Image C)

Negative correlation of network connectivity on x-axis and IUS-12 scores on the y-axis

Figure 5*IC12 (R Frontoparietal) Connectivity and Correlations: Autistic Brain*

C)

Note. Image A) IC12 (Right frontoparietal); Image B) precuneus connectivity; Image C) Positive correlation of network connectivity on x-axis and IUS-12 scores on the y-axis.

APPENDIX A

Annotated Bibliography

Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. *Journal of Autism and Developmental Disorders*, 29(3), 213–224. <https://doi.org/10.1023/A:1023080005650>

Objective: This was a retrospective video study of children with ASD. The author wanted to see if sensory-motor measures in addition to social behaviors could be used as an early predictor of ASD diagnosis.

Methods: The researchers attempted to gather 1,000 families with children above 2 years who had an ASD or mental retardation diagnosis. They gathered as many video tapes as they could from each family (32 families) and took clips from the 9-12 month range and analyzed them for sensory-motor behaviors. They chose this age because the mass number of videos sent in had the most footage for this age. A large problem with this article is that they changed the criteria for the study halfway through collecting families. Additionally, most of the children were Caucasian.

Results: Early assessments should use sensory processing and or sensory motor functions to predict social responsivity since subtle symptoms of autism were present at 9-12 months. However, this cannot be generalized because the footage could be interpreted differently and there were only 32 babies in this study.

Relevance to thesis: The author discusses how age affects symptomology, making some symptom manifestation in infancy drastically changed in later adolescents or more easily recognized.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The Autism-Spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5–17. <https://doi.org/10.1023/A:1005653411471>

Objective: Baron-Cohen and colleagues wanted to create a quick screener/ test that assessed where typically developing adults were on the autism spectrum.

Methods: Four groups of adults were gathered and given the AQ questionnaire. Group 1 had 58 adults with AS/HFA. Group 2 (control group) consisted of 174 randomly selected adults who lived in the same area as Group 1. Group 3 consisted of 840 students at Cambridge and Group 4 had 16 adult mathletes from the UK. The questionnaire was sent in the mail to participants and asked to be sent back as quickly as possible, so they didn't mull over the questions for too long.

Results: Mean scores and sub score comparisons were calculated using an ANOVA. The control group had overall lower AQ scores than group 1. Baron-Cohen et al. (2001) stated that, “80% scored above a critical minimum of 32+, whereas only 2% of controls did so” (p. 14).

Relevance to thesis: The BAPQ is based on this AQ and the BAP. I should include this information into my literature review. The good thing about the design of the AQ is that it was controlled for false negatives in a person's response by phrasing the questions so that the individual with aspersers and high functioning autism (HFA) would answer about their preference, not necessarily their overall judgment of their behavior.

Buhr, K., & Dugas, M. J. (2002). The intolerance of uncertainty scale: Psychometric properties of the English version. *Behaviour Research and Therapy*, 40(8), 931–945.

[https://doi.org/10.1016/S0005-7967\(01\)00092-4](https://doi.org/10.1016/S0005-7967(01)00092-4)

Objective: The study’s aim was to assess the validity and other psychometric properties of the English IUS.

Methods: There were 276 participants, mostly females, who were asked if they would like to volunteer to take an undergraduate course. In the course, they took multiple exams and were aware of the purpose of completing the IUS.

Results: The study found the IUS is very frustrating for individuals. Also, the study supported the hypothesis that the assessment had adequate to strong psychometric properties. Specifically, the assessment revealed, “excellent internal consistency, good test-retest reliability... and convergent and divergent validity” (p.931).

Relevance to thesis: My thesis uses the IUS as a measure of prediction. Though this study does not support its use to measure prediction, it does support that it is a reliable and valid assessment. Also, I can use this study to reference and describe what the assessment is in my methods section.

Carleton, R. N., Norton M. A., & Asmundson, G. J. G. (2007). Fearing the unknown: A short version of the intolerance of uncertainty scale. *Journal of Anxiety Disorders*, 21(1), 105-117. [https://doi.org/S0887-6185\(06\)00051-X](https://doi.org/S0887-6185(06)00051-X)

Objective: This article discusses the use of 2 studies that were used to create and evaluate a 12-item version of the intolerance of uncertainty scale (IUS). The article’s audience is mainly for those studying anxiety and mental health/ emotional disorders but can be applied to those with ASD. Individuals with autism are characteristically known

for having sensory impairments, some of which stem from anxiety or worry. Those with autism can easily develop fear of those sensations that are uncomfortable and distracting to them. The article discusses that fear often plays on a fight or flight response (Carleton et al., 2007). Along with that, “people who are intolerant of uncertainty are likely to interpret all ambiguous information as threatening, contributing to significant somatic stress reactions” (Carleton et al., 2007, p.106).

Methods: The study used 2 independent data sets. In the first set, there were 254 university students who were collected after a PowerPoint presentation. The participants were primary Caucasian. In the second set, there were 818 undergraduate participants of all levels of university education. The study utilized the BAI to measure anxiety, PSWQ as a measure worry, BDI to measure depression, and the IUS. I think though there were many participants for the study, their homogeneity in race and location could skew the results from the study.

Results: Relating this to the IUS and IUS-12, these tests had significant sensitivity and specificity. The 12-question version had even better internal consistency and was highly correlated with the original version.

Relevance to thesis: I need to reference this article in my thesis to give background on what the questionnaire is, why the IUS-12 was used instead of the 27 item version, and how it applies to the ASD population. I feel I could also discuss how having higher levels of IUS correlates with higher levels on the BAPQ in individuals without ASD.

Courchesne, E., & Allen, G. (1997). Prediction and preparation, fundamental functions of the cerebellum. *Learning & Memory*, 4, 1–35. <https://doi.org/10.1101/lm.4.1.1>

Objective: Courchesne and Allen want to create a theory that states that the cerebellum is crucial to sensory processing/interpretation. Their argument agrees with previous research that implicates the cerebellum predicts internal conditions.

Methods: This article uses a literature review to come to their conclusions. The literature review focuses on studies with fMRI data and PET scans. It also incorporates cerebellar studies using animals.

Results: Because the article is a literature review, the results would be that there is mounting evidence that demonstrates the cerebellum's important role in sensory processing/interpretation.

Relevance to thesis: There are many hypotheses as to how the cerebellum functions with sensory information. This article does a great job tying in sensory information with undertones of prediction research. This supports my thesis that the cerebellum will likely be correlated to sensory processing as well as IU (prediction). This single study brings together many studies to support that “the cerebellum can and does prepare/set a variety of internal conditions in advance of sensory events and neural operations” (p. 29). I would like to cite this study in my sections about areas of the brain I am researching.

Dunn, W. & Brown, C. (1997). Factor analysis on the Sensory Profile from a national sample of children without disabilities. *American Journal of Occupational Therapy*, 51(7), 490–495. <https://doi.org/10.5014/ajot.51.7.490>

Objective: This study was designed to assess what relationships were present between the assessment and the senses.

Methods: There were 115 child participants both with and without disabilities that completed the the SP.

Results: This article found that there were 9 components that indicated sensory impairment.

Relevance to thesis: There are many ways to assess sensory processing. It will be crucial for me to be able to support why we are using the SSP in my study and discuss what senses it assesses. Referencing this article will support the validity the SP has as well as the SSP.

Fletcher, T., Anderson-Seidens, J., Wagner, H., Linyard, M., & Nicolette, E. (2019). Caregivers' perceptions of barriers and supports for children with sensory processing disorders. *Australian Occupational Therapy Journal*, 66(5), 617–626. <https://doi.org/10.1111/1440-1630.12601>

Objective: Their research questions were asking what supports and barriers in community settings do children with sensory processing disorders experience. They also want to know how families manage outings and what exposure to multi-sensory environments does to the children's' behaviors.

Methods: A workshop was created for graduate students and the experimenters which was pitched to four educators. Ultimately, the parents of children with the disorders would be attending the workshop. With some attrition, seven mothers and two grandmothers were collected and they participated in workshops.

Results: Caregivers wanted to know more about sensory processing after attending support groups. They were responsive that the ones with children who had sensory processing difficulties had challenges with specific locations, environmental

triggers, and behavioral challenges. Many of the caregivers reported sensory overload and crowds/ noise were the most challenging for their family member. Going to the bathroom, school, and restaurants can be a particularly challenging experience.

Relevance to thesis: This article does not have much relevance to my thesis besides the emphasis that families are greatly affected by children who have sensory processing disorders. There are gaping holes in their study in that they have a small number of participants and it is all caregiver based.

Hurley, R. S. E., Losh, M., Parlier, M., Reznick, J. S., Piven, J. (2007). The broad autism phenotype questionnaire. *Journal of Autism Developmental Disorder*, 37(9), 1679–1690. <https://doi.org/10.1007/s10803-006-0299-3>

Objective: The study describes the use, reliability, scoring measures, and implications of the questionnaire. Previous to this article, small studies had revealed that some autistic characteristics could be present in non-autistic people. Though in most studies, the milder (but similar) characteristics were observed in relatives through the broad autism phenotype (BAP), they can also be found in anyone that is non-autistic. The article continues to describe the three domains of autism as listed in the DSM-IV and how the BAPQ subscales of rigid personality, aloof personality, and pragmatic language characterize the main domains the best.

Methods: The study recruited 86 parents of children with autism from a research center and previous studies. There were also 64 parents of neurotypical children from the same community.

Results: The study demonstrates “that the subscales of the BAPQ have internal consistency; have high sensitivity and specificity for the direct, clinical assessment

ratings of the BAPQ; and differentiate autism parents with a clinically defined BAP from both autism parents without direct clinical evidence of the BAP and from community control parents” (Hurley et al., 2007, p.1686).

Relevance to Thesis: So long as I use the BAPQ instead of the SRS in my study, this article would be useful to insert portions of it into an abstract as well as the introduction so my readers can become familiar with the BAPQs importance. This article is the original article which states what the BAP and BAPQ are. It describes the use, reliability, scoring measures, and implications of the questionnaire.

Hwang, J., Arnold, S., Srasuebkul, P., & Trollor, J. (2020). Understanding anxiety in adults on the autism spectrum: An investigation of its relationship with intolerance of uncertainty, sensory sensitivities and repetitive behaviours. *Autism, 24*(2), 411–422.

<https://doi.org/10.1177/1362361319868907>

Objective: This article attempts to understand why those with ASD have high anxiety at times. The hypothesis is that Intolerance of Uncertainty should be considered to conceptualize the anxiety in those with ASD and also to understand why those with ASD might have RRBs.

Methods: 176 individuals with autism and 116 individuals without autism qualified for analysis. These individuals were found through the ALSAA Australian Longitudinal Study of Adults with Autism. The IUS-12 was used to assess intolerance of uncertainty. Sensory sensitivity was measured with the Glasgow Sensory Questionnaire. Anxiety was measured with the APA severity index from the year 2013 for Generalized Anxiety Disorder. Authors used a combination on descriptive statistics and linear regressions for analysis.

Results: For those with autism, “IU had the strongest associations with anxiety ($r= 0.55$) and insistence on sameness ($r= 0.53$)” (Hwang et al., 2020, p. 416). This was also the case for non-autistic individuals ($r= 0.65$). For those who are over the age of 25, IU could be a significant mediator between other models and relationships of anxiety and repetitive behaviors. Moreover, “adults on the spectrum had significantly higher IU and anxiety than those not on the spectrum” (Hwang et al., 2020, p. 417).

Relevance to Thesis: This article examines the relationship between IU, sensory sensitivities, repetitive behaviors, and anxiety.

Lord, C., Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., Jones, E. J. H., Jones, R. M., Pickles, A., State, M. W., Taylor, J. L., & Veenstra-VanderWeele, J. (2020). Autism Spectrum Disorder. *Nature Reviews Disease Primers*, 6(5), 1-23.
<https://doi.org/10.1038/s41572-019-0138-4>

Objective: This is a review article of Autism Spectrum Disorder. It is very recent and reviews ASD characteristics.

Methods: Research articles were gathered and assessed collectively.

Results: In 1980 the ASD started to be conceptualized as a “broader spectrum of social communication deficits” (Lord et al., 2020, p. 1) and one decade later it was officially made a disability by U.S. Congress. It wasn’t until 2013 that it was classified as a spectrum via the DSM-V. Though autism studies concerning twins and genetics began in 1977 with Rutter and Folstein, much of the genetic and familial studies continued after 2010 (Lord et al., 2020).

Etiology and environmental factors: Etiology is largely unknown but there are genetic, neurobiological, and environmental factors can increase the risk of ASD

developing. Genetically we know that when an older sibling is diagnosed with ASD, the younger sibling is now at a higher risk. If that same younger sibling has a first-degree relative with ASD, they are 20% more likely to develop it as well (Lord et al., 2020). Similar findings can be located in twin studies as well with heritability ranging anywhere from 40-90% (Gaugler et al., 2014). Environmental factors like increased parental age at the time of conception, maternal obesity, prolonged or premature labor increase risk. With intervention- early intervention is key and is usually drawn upon due to early communication deficits. Additionally, the restrictive behaviors and social opportunities can be challenging for parents to navigate without professional guidance. However, the needs of individuals with ASD will evolve over time and as the child ages, they will require adjustments to therapy to shift into the common social communication and pragmatic domain. Some common interventions for toddlers and school age children with ASD would be discrete trial training (DTT), parent coaching, CBT for anxiety, and the Picture Exchange Communication System (PECS).

Relevance to thesis: This is a great article to reference in my introduction. I can pull much of this information to talk about prevalence, etiology, and some treatments. I think this article with another couple review articles on ASD will provide me with some great insights to ASD as a whole picture.

Park, H. R., Lee, J. M., Moon, H. E., Lee, D. S., Kim, B-N, Kim, J., Kim, D. G., & Paek, S. H. (2016). Review on the current understanding of autism spectrum disorder. *Experimental Neurobiology*, 25(1), 1–13. <http://doi.org/10.5607/en.2016.25.1.1>

Objective: This review article set out to review literature on ASD and dive deeper into literature on brain function, characteristics, and treatment.

Method: A clear method was not explicitly written. However, after reading the article, it seems they broke up their literature by topics and then paraphrased the findings. Much of this paper discusses areas of the brain involved and associated with ASD.

Results: Again, features of ASD are discussed with literature pointing to children being hardly distinguishable during their first year of living but that by 12 month and onward, atypical language trajectories can be mildly seen and by 24 months, severe language delays are present. Research says that clear deficits in social communication and presence of restricted behaviors will be seen by 3 years (Park et al., 2016). History is discussed. Park et al. (2016) suggests that much of the foundation laid for ASD research today was set by Leo Kanner and Hans Asperger though the term ‘Autism’ was first used by Paul Eugen Bleuler in 1912. Both Kanner and Asperger studied boys who were different from their peers in having altered interactions with people. Brain studies were also discussed. They reported many studies agreeing that MRIs should gray matter overgrowth both cortically and subcortically in childhood. Additionally, fMRIs have suggested “global underconnectivity in socioemotional networks” (Park et al., 2016, p. 2). Lastly, etiology is also discussed. Park et al. (2016) terms ASD as a multi-factorial disorder and in regard to genetics, they gathered that chromosomal and genetic etiology accounts for 10-20% of individuals with ASD. Even genes like the ENGRAILED 2, which plays a role in cerebellar development, and ASD diagnosis are now showing correlations as reported by a study with Gharani and colleagues published in 2004 (Park et al., 2016).

Relevance to Thesis: This can be another resource along with the Lord et al. (2020) article to use in my introduction and literature review. I think I should also

mention this article when reviewing fMRI data and what previous literature is saying about ASD and the brain's functioning.

Simpson, K., Adams, D., Alston-Knox, C., Heussler, H. S., & Keen, D. (2019). Exploring the sensory profiles of children on the autism spectrum using the short sensory profile-2 (SSP-2). *Journal of Autism and Developmental Disorders, 49*(5), 2069–2079.
<https://doi.org/10.1007/s10803-019-03889-2>

Objective: The authors were looking to identify sensory subtypes in children with ASD in Australia using the SSP-2.

Methods: The children used for the study were a part of an Australian longitudinal study. “Children in this study were clustered around two mean age points (5 years 3 months and 9 years 9 months) and this age range appears to coincide with highest rates of reported sensory differences in children on the autism spectrum compared with the typical population (6–9 years)” (Simpson et al., 2019, p. 2076).

Results: The group of children with ASD in this study manifested differences in the Avoiding and Sensitivity quadrants of the new SSP-2. However, because there was no control group and because the SSP-2 is still very new, results should be analyzed carefully.

Relevance to thesis: This article reveals many other articles about sensory processing which would be helpful for my thesis. A small portion of it also discusses studies done comparing and correlating ASD traits with sensory profiles of ASD children. This article also might be helpful in discussing the differences between the SSP and the SSP-2. “The four quadrants are Seeking (e.g., “rocks in chair, on floor, or while standing”), Avoiding (e.g., “resists eye contact from me or others”), Sensitivity (e.g., “is

distracted when there is a lot of noise around”), and Registration (e.g., “bumps into things, failing to notice objects or people in the way” (Simpson et al., 2019, p. 2077).

Sinha, P., Kjelgaard, M. M., Gandhi, T. K., Tsourides, K., Cardinaux, A. L., Pantazis, D., Diamond, S. P., & Held, R. M. (2014). Autism as a disorder of prediction. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(42), 15220–15225. <https://doi.org/10.1073/pnas.1416797111>

Objective: Empirical data and theoretical considerations together should characterize the autism as having a specific impairment in predicting abilities.

Methods: Theoretical considerations as well as empirical data were used to support a shared clinical diagnosis in those with autism. Phenotypes such as insistence on sameness, sensory hypersensitivities, difficulty interacting with dynamic objects, difficulties with theory of mind, and islands of proficiency were explored for correlations and evidence.

Results: The hypothesis of prediction as an impairment for those on the autism spectrum, it could be a precursor to using fMRI data in the future to discover what areas of the brain are involved in predictability processing.

Relevance to thesis: Being in a “world” where events happen for no reason and unexpectedly can make interacting with said world very challenging. Knowing this could aid the design of interventions and then monitoring how effective those tools are. We know already that unpredictability in an environment leads to greater anxiety by a positive correlation.

South, M., & Rodgers, J. (2017). Sensory, emotional, and cognitive contributions to anxiety in autism spectrum disorders. *Frontiers in Human Neuroscience, 11*(20), 1–7.

<https://doi.org/10.3389/fnhum.2017.00020>

Doi:10.3389/fnhum.2017.00020

Objective: Not being able to discern emotions correctly can create high levels of confusion and uncertainty. This article is meant to be a mini review of the emerging relationship between atypical sensory processing, IU, and alexithymia (impairment in labeling emotions) in those with ASD. All of these factors are suspected to increase anxiety in those with ASD.

Method: There was no method besides gathering research and reviewing it. The authors report difficulty knowing how to explore this relationship further biologically and behaviorally.

Results: “ASD participants showed more activation than controls in primary sensory areas, amygdala and orbitofrontal cortex in response to auditory stimuli” (South & Rodgers, 2017, p. 2). Another study they looked at reported “that IUS-C and SCAS-P anxiety scores were significant mediators of the relationship between sensory function and core symptoms of repetitive/restricted behaviors in ASD children” (South & Rodgers, 2017, p. 3). South and Rodgers (2017) report that in a study done by Neil et al. in 2016 demonstrated “hierarchical regression analysis indicated that IU significantly predicted sensory sensitivity in both ASD and typical groups but the predictive power of the IU was much greater in the ASD group” (p. 3).

Relevance to thesis: This study supports that more evidence needs to be gathered on this relationship, but that research is already showing that there are correlations. South

and Rodgers (2017) suggest that there are parts of the brain that are associated with this connection like the medial prefrontal cortex, cerebellum, and limbic system. The authors support that some studies have involved children but not on this topic as a whole. For example, they state that Green and colleagues in 2015 conducted “fMRI studies on high-functioning ASD youth during a challenge of mildly aversive sensory stimuli” (South & Rodgers, 2017, p. 2). Figure 1 could be a great reference to explain how IU, prediction, and ASD are all related. I also think the two quotes listed in my results written above indicate that interpreting IU as a prediction impairment could make sense of why it predicts sensory sensitivities so much. The relevance it has for my thesis about brain activity is minimal besides supporting the already known knowledge that those with ASD experience difficulty taking what they are experiencing in the present with prior experiences and information which makes any new experience very overwhelming.

Tomchek, S. D., & Dunn, W. (2007). Sensory processing in children with and without autism: A comparative study using the short sensory profile. *The American Journal of Occupational Therapy, 61*(2), 190–200. <https://doi.org/10.5014/ajot.61.2.190>

Objective: The objective of the study was to complete a descriptive/ comparative study on sensory processing with TD and ASD children ages 3-6. The authors wanted to clearly delineate which domains were significantly different from ASD children and TD children. Because sometimes the sensory responses precede the diagnosis of ASD, many researchers and families are very aware of the abnormalities those with ASD have. Past research suggests the presence of both an over responsivity and unresponsiveness to some stimuli more than others.

Methods: Two groups were gathered with one of children with confirmed ASD and the other group of 1,075 children 3-10 years-old who were not in special education at schools. Then the two groups were age matched and divided into groups of 281 participants. Factors included on the SSP are “tactile sensitivity, taste/smell sensitivity, movement sensitivity, under responsive/ seek sensation, auditory filtering, low energy/weak, and visual/ auditory sensitivity” (Tomchek & Dunn, 2007, p. 193).

Results: All the SSPs for the ASD group were received but only 254-278 of the TD group were considered complete. The children with ASD had consistent higher scores in the abnormal range than the typical group in all section scores. The most prominent differences were in 3 areas: tactile sensitivity, taste and smell sensitivity, auditory filtering, and under responsive/seek attention (Tomchek & Dunn, 2007). Mean scores for SSP in both groups followed a similar trend as seen in Figure 1.

Relevance to thesis: Parents are often the first to notice and report things like strong aversions to certain foods, lack of eye contact, insensitivity to pain, fixations, etc. The SSP is an accurate way to demonstrate increased sensory abnormalities in children with ASD. However, it also shows that the responses are different for many children with ASD. However, a bad thing about this study is that the TD group may not have been as TD as thought since they could have had other impairments.

Uljarević, M., Cooper, M. N., Bebbington, K., Glasson, E. J., Maybery, M. T., Varcin, K., Alvares, G. A., Wray, J., Leekam, S. R., Whitehouse, A. (2020). Deconstructing the repetitive behavior phenotype in autism spectrum disorder through a large population-based analysis. *The Journal of Child Psychology and Psychiatry*, 61(9), 1030–1042. <https://doi.org/10.1111/jcpp.13203>

Objective: This study aimed to research a key autistic characteristic, restrictive and repetitive behavior patterns (RRB), and insistence on sameness. It focuses on “the presence and severity of the following RRB domains: repetitive motor mannerisms (hereafter Repetitive Motor Behaviours), inflexible and rigid adherence to specific routines (hereafter Insistence on Sameness), and stereotyped and restricted patterns of interests (hereafter Circumscribed Interests)” (Uljarević et al., 2020, p.1032). The study was also trying to separate and find independent subdomains of the RRBs.

Methods: The data were taken in Western Australia (WA) and was sourced from an ASD register for Western Australia. Each child that had ASD in the register had to be evaluated by three professionals in order to qualify to be on the register. The mean age for over 3,500 participants was 6 years and 6 months old. Statistical analysis was completed to explore relations of the two primary variables. They used an alpha of 0.5 as their level of significance.

Results: Their results were all over the board. I think the best part of their results was the writing about one of the flaws in their study. They say, “Therefore, some of the inconsistencies, when compared to previous studies, could be related to presenting factors at the age of diagnosis. For example, children tend to be diagnosed earlier due to language delay and social- communication difficulties, rather than specific concerns with regard to RRB, and these issues might override other signs. Therefore, it is possible that, for the children who are diagnosed earlier in life, the relationship between RRB and FSIQ noted at the time of diagnosis will change when they are older” (Uljarević et al., 2020, p. 9). What this long quote means is that age of diagnosis of having ASD is going to contribute to correlations between different restrictive behaviors because children at a

younger age might show more language delay signs than the other children who demonstrate more social/ pragmatic delays.

Relevance to Thesis: This article is relevant to the broad topic of autistic characteristics and how they all relate to each other. Normative fears occur at earlier stages of typical development and, unlike clinical anxiety, are transitory in nature. Therefore, it is not surprising that in their study, the effect changed across groups. Also, this study does well to explain that research of the relationship between RRB subdomains is unclear in previous research done besides knowing the possibility that frequent and more severe problems with social communication can stem from more severe RRBs.

Van de Cruys, S., Evers, K., Hallen, R., Eysenck, L., Boets, B., de-Wit, L., Wagemans, J. (2014).

Precise minds in uncertain worlds: predictive coding in autism. *Psychological Review*, 121(4), 649 - 675. <https://doi.org/10.1037/a0037665>

Objective: Van de Cruys and colleagues (2014) argue that ASD should be thought of as a disorder of prediction. This article is a review of some prediction literature and uses the literature to make inferences about what autism is a disorder in.

Methods: A very comprehensive literature review was completed to create the theory of prediction explained in this article.

Results: There are no set results for this article. However, the authors do informally claim that the results of this article should be that predictive coding provides a framework for conceptualizing ASD as a disorder of prediction. They call this “the core deficit in the high, inflexible precision of prediction errors in autism (HIPPEA)” (Van de Cruys et al., 2014, p. 652).

Relevance to thesis: Two key frameworks for understanding ASD would be the theory of mind framework and nonsocial theories. Neither of these theories describe all sets of symptoms comprehensively. It more describes ASD impacted by differing perception hypothesis just reiterating that the brain plays a role in making predictions based on learned input. This proposed theory has relevance to shape the world in the moment, but to also promote neuroplasticity for future predictions. The authors continue to state that there are neurobehavioral advantages to predictive coding in which the midbrain, hippocampus, amygdala are key structures in this predictive processing.

There's also some relevance to sensory processing in this article and social communication. The authors discuss in pages that there's mixed research on why visual and auditory processing is different from that of TD peers. In speech, acoustic cues often accompany visual ones to integrate meaning, context, and give constraints. Individuals with ASD though have a more difficult time looking at people in the face and can get overwhelmed by speech-in-noise perception which makes maintaining conversations difficult. Someone with ASD might become overwhelmed looking at someone's face also because facial expressions recognition (critical to pragmatic language) has to be obtained in constant variability of lighting, visual clutter of facial features, etc.

APPENDIX B

Consent/Institutional Review Board Approval Letter**Consent and Authorization Form Approval****Valid for Use Through:**

Study Title: Gamma Band Dysfunction as a Local Neuronal Connectivity Endophenotype in Autism

Principal Investigator: Don C. Rojas, Ph.D.

COMIRB No: 07-0675

Version Date: 06/29/2017

(Patient Version)

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

Why is this study being done?

You (meaning you or your child) are being asked to participate in a research study of differences in brain anatomy and function in people with autism spectrum disorders. We believe that individuals with autism spectrum disorders and their first-degree relatives do not process sound the same way people without autism or Asperger's syndrome process sound. 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 have been diagnosed with an autism spectrum disorder, or you are a first-degree relative (parent or sibling) of a child who has been diagnosed with an autism spectrum disorder.

Other people in this study

Up to 500 people from your area will participate in the study over the next 4 years.

What happens if I join this study?

If you join the study, you will do the following things:

1) Be interviewed about your personal and family history of possible psychiatric and/or neurological problems in order to confirm that you or your child has a diagnosis of autism or Asperger's syndrome. You will also answer a questionnaire about your personal history of psychiatric symptoms such as experience with anxiety, depression, and drug use. Sometimes, we need to invite subjects back to clarify answers on the questionnaire. The interviews may be videotaped for the purposes of the research, and will only be viewed by lab personnel. Videotapes will remain strictly confidential and be kept in a locked cabinet when not in use. At the end of the study, the videotapes will be destroyed. Altogether, these interviews will last about 2 hours.

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2) Participate in a series of qualifying interviews in order to confirm a diagnosis of autism or Asperger's syndrome in you or your child. Qualifying interviews will take approximately 1-2 hours.

3) Participate in a magnetoencephalographic (MEG) recording to measure your brain activity in response to sounds, words, movement and touch. During these experiments, you will sit in a chair while the MEG system makes recordings of the magnetic fields of your brain. The MEG machine does not emit any electromagnetic waves or X-rays. It only picks up the natural magnetic fields which the brain produces even when you are not in the MEG scanner. During the MEG scans, you will hear sounds coming through earphones in your ear, touches on your fingertips, and you will see pictures or words on a video screen. The testing session will last approximately 2-3 hours, with breaks provided if necessary for your comfort. We usually break the MEG scans into two separate 1-1.5 hour sessions.

4) Participate in a Magnetic Resonance Image (MRI) of your brain at the Anschutz Medical Center campus of UCHSC. 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 for approximately 60 minutes 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: both MEG and MRI are experimental procedures and therefore, have no clinical interpretation.

5) Complete a series of psychological tests assessing basic functions such as language, memory, attention, motor function and general intellectual ability. This will take approximately 2-3 hours to complete.

6) Be asked to have a blood draw at the Anschutz Medical Campus. We are asking you to have a blood draw so that we may isolate your DNA for genetic testing. We would like to see if there are any connections between certain genetic risk factors for autism and our neuroimaging and behavioral measures.

You may choose not to undergo genetic testing and still participate in the rest of the study. Please check below if you will have a blood draw as part of this study:

D Yes, I will have a blood draw for genetic testing

D No, I will not have a blood draw for genetic testing, but I would like to participate in the rest of this study

Note: Genetic tests will be for known autism genetic risk variants. Identification of risk variants only indicates the potential of an increased susceptibility to autism. This increased susceptibility is thought to also depend on other additional environmental and Combined Biomedical Consent and HIPAA authorization CF-151, Effective 8-31-11

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genetic factors. These tests are not clinically diagnostic. Therefore, these results will not be released. However, we may also be testing for the following autism risk variants that are clinically meaningful:

- 1) 15q11-13 duplications
- 2) the CGG repeat status of *fragile X mental retardation 1 (FMR1)*
- 3) variants of *forkhead box protein P2 (FOXP2)*.

If you would like us to transfer the results of these genetic tests to your health care provider please indicate below:

Yes, I would like you to transfer these results to my health care practitioner and will sign a release indicating this choice

No, I do not want you to transfer the results to my health care practitioner

Summary of Laboratory Visits for Participants

Purpose of Visit:	Estimated duration of visit
Introduction to lab and consent	1 hour
Psychiatric interviews	1.1 hour
Diagnostic interviews	2 hours
Cognitive tests	2.5 hours
MEG scans	2.25 hours
MRI scan	2 hour
Blood draw	1 hour (N/A for all subjects)
Total participation time: 11 hours (10 hrs if no blood draw)	

Note: You may schedule these visits at your convenience over the next 3 months. You will need to schedule approximately 4-7 visits; depending on how much time you have available on any given day. There is no need to hurry to finish all of the studies in a single day or even a week.

What are the possible discomforts or risks?

There are no known significant risks involved in this research study. Some people become claustrophobic during the MEG and MRI procedures. You may become tired during the MEG recordings and will be given rest breaks. 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 can not be guaranteed.

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If you have agreed to have blood taken, we will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about autism and Asperger's syndrome. 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 University of Colorado Anschutz Medical Center.

Will I be paid for being in the study?

You will be paid \$15 per hour (\$10/hour for children < 18 years of age) for participation in this study, paid in cash at the end of each day of the study. This will amount to approximately \$190 total in this research study. If either you or the study doctor decides to withdraw 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 do not take part in the study, your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled.

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 study doctor may decide to stop your participation without your permission, if he or she thinks 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, or

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meeting research criteria for diagnosis of autism or another developmental disability in either you or your child. 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 Don Rojas at (303) 724-4994 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 Don Rojas, Ph.D. You may ask any questions you have now. If you have questions later, you may call Dr. Rojas at (303) 724-4994. 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. Rojas with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

Who will see my research information?

The University of Colorado Denver and the hospital(s) it works with 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:

- University of Colorado Denver

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 and in our Notice of Privacy Practices; however, people outside the University of Colorado Denver and its affiliate hospitals may not be covered by this promise.

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

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further information about you will be collected. Your cancellation would not affect information already collected in this study.

Don Rojas, Ph.D.
University of Colorado School of Medicine
Department of Psychiatry
13001 East 17th Place MS F546, Building 500
Aurora, Colorado 80045

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 Colorado Multiple Institutional Review Board (COMIRB)
- The study investigator and the rest of the study team.
- NIH, who is the organization 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. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

The investigator (or staff acting on behalf of the investigator) will also make *all or some of the following health information about you available to:* Brain Imaging Center, University of Colorado Health Sciences Center, Anschutz Medical Center

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).
- Portions of my previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies (MRI of the brain), procedure results (MRI report one time)
- Research Visit and Research Test records
- Psychological tests
- Alcoholism, Alcohol or Drug abuse
- Genetic test results (N/A for subjects opting not to undergo blood draws)
- Other (please specify): MEG Recordings one time, 3 hours _

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- Other (please specify): Psychiatric Interviews one time, 4 hours

What happens to Data that is collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study 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:

- The data and blood/DNA samples are given by you to the investigators for this research and so no longer belong to you.
- Both the investigators and any sponsor of this research may study your data and blood/DNA samples collected from you.
- If data and blood/DNA samples are in a form that identifies you, UCO or the hospitals involved in this study may use them for future research only with your consent or IRB approval.
- 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.

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: _____

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.

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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 participate in the main study. Please initial next to your choice:

___ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

___ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Consent and Authorization Form Approval**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: