Behavioral and Neural Correlates of Sensory Processing and Anxiety in Autistic Children

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ABSTRACT

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Children diagnosed with Autism Spectrum Disorder (ASD) are known to experience higher levels of sensory processing differences as well as anxiety, compared to the neurotypical population (NT). Both theory and evidence suggest that there is an interrelationship between sensory processing, anxiety and fear, and prediction abilities in autism. However, much more remains to be discovered about their relationship and especially underlying neural mechanisms. Thus, the purpose of the current study was to examine the behavioral relationship between sensory processing, fear and anxiety, prediction, and related brain activity in autistic children. To this end, 30 autistic children (ages 6-11 years) and 25 age-matched peers participated in a resting-state fMRI as well as various behavioral assessments of sensory processing, anxiety, fear, and intolerance of uncertainty (i.e., as an indirect measure of prediction). Between groups comparisons showed higher levels of sensory processing difference, fear/anxiety, sensory processing differences, and intolerance of uncertainty in autistic children when compared to NT controls. Among autistic children, a mediation analysis also revealed that intolerance of uncertainty was a significant mediator between sensory processing differences and both anxiety and fear, supporting past research and suggesting a role of prediction in this relationship. Network connectivity findings showed that cerebellar, higher order sensory, and limbic regions were significantly correlated with anxiety, sensory processing, and intolerance of uncertainty. These results add information concerning the neurophysiologic underpinnings of anxiety/fear, sensory processing, and prediction to prior research focusing on behavioral relationships between these constructs. These results have the potential to inform future clinical practice, demonstrating the need for a predictable clinical environment as well as thorough explanation of expected tasks for autistic children who experience sensory processing differences and resulting anxiety. Finally, these findings may suggest that addressing sensory and prediction difficulties has the potential to lead to improvements in anxiety in children with ASD. Addressing these issues through both neurological and/or therapeutic means may be possible in the future.

Keywords: autism, anxiety, sensory experience, intolerance of uncertainty, prediction
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DESCRIPTION OF THESIS STRUCTURE AND CONTENT

This thesis, *Behavioral and Neural Correlates of Sensory Processing and Anxiety in Autistic Children*, is written in a hybrid format. The hybrid format combines thesis formatting with journal-ready publication methods. The preliminary pages of the thesis reflect requirements for submission to the university. However, the thesis itself is presented as a journal article and conforms to style requirements for submitting research reports to education journals. The annotated bibliography is included in Appendix A. Appendix B contains the study’s instruments, followed by Appendix C, which contains information regarding the research consent form.
Introduction

Up to 90% of autistic children are known to experience some type of atypical sensory processing (Green et al., 2015; Marco et al., 2011; Rajendran & Mitchell, 2007). Additionally, autistic children present with higher rates of anxiety than neurotypical children, with prevalence rates estimated around 42–79%, compared to 7.1% in the neurotypical population (Kent & Simonoff, 2017; van Steensel & Heeman, 2017). Both sensory processing atypicality and anxiety can often lead to intense fears and extreme aversions, which can significantly impact a myriad of behavioral domains, including participation in social interactions, academics, therapy, and everyday living. Numerous studies have connected atypical sensory processing and anxiety in those on the autism spectrum (Green et al., 2015; Marco et al., 2011). However, much more remains to be discovered about their relationship, especially concerning their underlying neural mechanisms. Thus, the purpose of the current study was to examine the relationship between behavioral sensory processing, fear and anxiety, prediction, and the associated brain activity in autistic children. The following paragraphs discuss the relevant background information and the current state of research related to the aforementioned study, our hypotheses, and the methods we propose to use to carry out the study.

Autism Spectrum Disorder (hereafter referred to as Autism or Autism Spectrum Condition) is a developmental disability, estimated by the CDC to be prevalent in 1 in 54 individuals (Maenner et al., 2020) and to affect 4.3 times more males than females. It is characterized by restrictive and repetitive behaviors and interests as well as pervasive difficulties in social communication (American Psychiatric Association [APA], 2013). Autism can affect the way people think, learn, and communicate, both verbally and nonverbally, throughout the lifespan, which can lead to special talents or present difficulties to those on the autism spectrum.
Diagnosable signs of autism generally present around 2 or 3 years of age, with diagnosis possible as early as 18 months. In order for official diagnosis to take place, the DSM-V requires that the person present with “persistent deficits in social communication and social interaction across multiple contexts” and “restricted, repetitive patterns of behavior, interests, or activities,” with these manifestations presenting in the early developmental period and causing a clinically significant impairment in social, occupational, or other important areas of current functioning (APA, 2013).

**Cognitive-Based Theories of Autism**

Many cognitive-based theories have arisen to explain the behaviors prevalent in autism. The weak central coherence theory seeks to provide an explanation for variations in functioning throughout the autism population (Frith, 1989). Weak central coherence theory is a domain-general process that refers to the idea that autistic individuals have difficulty integrating information to create central coherence, or a general understanding of an idea or occurrence. Instead, they process information, especially sensory information, in a detail-focused way. This theory provides explanation for both social and non-social autistic behaviors. It explains that those on the autism spectrum often have difficulty in social situations because they vary in their ability to completely integrate the various signals (such as body language, facial expressions, and intricate cues) found in social interactions. This theory also explains the frequent difficulty with processing sensory information as the process of integrating and creating significance out of sensory information (Rajendran & Mitchell, 2007). Additionally, the weak central coherence theory is supported by neurophysiological findings. fMRI studies have found that autistic individuals have much stronger short-range brain connections than long-range connections, indicating that the difficulty integrating information to create central coherence might be due to a
decreased ability to access long-range connections (Barttfeld et al., 2011; Supekar et al., 2013). Additionally, the hippocampus is a sensory processing hub responsible for integrating sensory information and sending it to appropriate regions (such as the prefrontal cortex) for processing. It also plays a large role in the storing of memories. In children with autism, the hippocampus has consistently been found to be associated with subtle size reduction as well as various abnormalities in structure (Nicolson et al., 2006). The hippocampus plays a significant role in the formation of central coherence as its performance as a sensory processing hub allows for sensory information to be processed in a holistic fashion to form central coherence, so it is reasonable to believe that weak central coherence could be created by hippocampal differences. Though evidence strongly supports this theory, additional replication of such findings is necessary to confirm these correlations.

In recent years, an additional theory to explain the relationship between sensory processing differences and other manifestations of autism including neurocognitive underpinnings has emerged: the predictive coding theory (Friston, 2009). According to this theory, a developing child learns about the world around them by making and testing predictions. When these predictions are proven to be correct, they are solidified in the brain, creating expectations of patterns for future experiences. If an incoming sensory experience does not match a previously established prediction, then an error signal is created and the person has to decide with what degree of flexibility to respond to the error. This process of encoding is important in everything that children do. It allows them to manage expectations; predict what they might see, hear, feel, taste or smell; understand and learn patterns; and create a framework for sensory experiences around them. In autistic children, this skill has been shown to often be atypical (Van de Cruys et al., 2014). It follows then that such prediction errors might also be
associated with difficulties in sensory processing, social interactions, or other experiences that require predicting a pattern of behavior.

**Common Co-Occurring Conditions**

Autism can have a significant impact in various areas of life, including overall health. For instance, the average lifespan for people diagnosed with autism is 36.2 years compared to 72.0 years in the general population (Guan & Li, 2017). Additionally, autistic persons present with a number of co-occurring features that can adversely affect overall health and quality of life, autistic adults more than five times more likely to describes themselves as having “poor health” across the course of their lives (Rydzewska et al., 2019). Epilepsy and chronic gastrointestinal disorders are among the most severe co-occurring conditions, with others such as sleep and feeding disorders common as well (May et al., 2020).

Autistic people also commonly present with a host of mental health difficulties. One of the most common mental health issues for autistic people is anxiety, with clinical anxiety levels present in an estimated 40% of autistic youth (van Steensel & Heeman, 2017), which is more than double the prevalence of clinical anxiety in neurotypical youth. Furthermore, a meta-analysis conducted in 2017 found symptoms of anxiety to be significantly more severe in the autistic youth compared to those with only clinical anxiety disorders (van Steensel & Heeman, 2017).

Anxiety in autistic children and adolescents also presents various qualitative differences when compared to anxiety in those without an autism diagnosis. While neurotypical children with anxiety disorders report and are diagnosed by generalized anxiety symptoms with various somatic effects, often brought on by the anticipation of new or stressful situations (APA, 2013), autistic children describe their anxiety with marked differences. Among the most common of
these differences are anxiety associated with highly specific fears and phobias, a change in the
typical environment, lack of schedule, loud noises, less familiar social situations, or anxieties
related to lack of rigid structure (Kerns et al., 2014). One mother described how even the change
in routine that Christmas provides can be challenging: “He can’t cope with the surprise of it
(Christmas). It’s the not knowing, the routine thing. His Dad had a complete meltdown when he
found out what I had done [shown child his presents in advance]… He said “it’s meant to be a
surprise, he’s not going to enjoy it … No, he’s not enjoying it now because he doesn’t know”
(Ozsivadijan et al., 2012).

Many of the presentations of these anxieties in autistic people were also different than
those in neurotypical persons. For example, while the DSM-V outlines common presentations of
anxiety disorders to be somatic symptoms (such as sleep disturbances or shortness of breath) and
avoidance behaviors, anxiety disorders in autistic people can often present as meltdowns,
generalized arousal, sensory behaviors, or obsessional and repetitive behaviors (Ozsivadijan et
al., 2012). One mother described her daughter’s meltdowns: “She gets very agitated, she wrings
her hands and starts to shout. In the past she was violent, she’s hit us, bitten me…” (Ozsivadijan
et al., 2012). These behaviors compromise the well-being of both the child and his or her close
family members, often making it difficult for families to participate in normal daily routines.

These distinctions in presentation of anxiety demonstrate a difficulty in differential
diagnosis for autistic children and possible co-occurring mental health difficulties. Currently,
anxiety disorders in children are commonly diagnosed using the DSM-V criteria in an interview
fashion, like in the Anxiety Disorders Interview Schedule (ADIS). While this assessment, among
a few others, may also contain an autism addition (Autism Addendum ASA), there is currently
no gold standard for identifying clinical level anxiety disorders in autistic children and youth.
Parents and children report screenings such as the Spence Children's Anxiety Scale (SCAS) or Revised Children's Anxiety and Depression Scale (RCADS) can also be helpful, though results are mixed as to whether these types of parent reports can lead to a false overidentification of symptoms (Ozsivadijan et al., 2012; van Steensel et al., 2012). Until the nature of anxiety in autism is better understood, definitive differential diagnosis will be difficult.

One attempt to understand how anxiety differs in autistic children has been in fMRI research. However, though somewhat informative, results from these studies are not yet conclusive. The main areas of the brain implicated in anxiety processing are the amygdala, the medial prefrontal cortex, and the hippocampus. While the amygdala is mainly responsible for assessing potentially dangerous stimuli and coordinating biological processes for the reaction to the stimuli, the prefrontal cortex is implicit in the top-down regulation of emotional response to stimuli. As mentioned previously, the medial prefrontal cortex has been found to have a hypoactive relationship in autistic patients, which may be connected to anxiety prevalence in autism. Interestingly, the amygdala and medial prefrontal cortex often have an opposite effect from one another. Understanding the exact relationship requires more research (South & Rodgers, 2017). Additionally, the role of the hippocampus in sensory processing and its structural differences in children with autism may be significant in the formation of anxiety symptoms because of its role in creating central coherence and appropriately processing sensory information (Nicolson et al., 2006).

The amygdala has been heavily researched in association with anxiety and autism (Kleinhans et al., 2010; Green et al., 2015; Herrington et al., 2016). However, there are still some relationships between the amygdala and autism that are misunderstood. Hypoactivation of the amygdala has long been associated with social differences in autism (Hamann & Mao, 2002;
Herrington et al., 2016; Kleinhans et al., 2010). However, high levels of anxiety in autism have been connected to hyperactivation of the amygdala (Herrington et al., 2016; Green et al., 2015). Thus, it seems that amygdala abnormalities are associated in some way with common manifestations of autism. Additional research is necessary to explore this issue fully. For instance, one outstanding question is what type of amygdala activity is associated with anxiety in autism. Also, the relationship between sensory differences and anxiety, as well as its neurobiology, needs to be fully elucidated.

**Sensory Processing**

Sensory processing may play a role in the high prevalence of anxiety in autism. One of the many characteristics of autism listed in the DSM-V is sensory processing abnormality, which refers to increased or decreased reactivity to sensory input. It is estimated that approximately 90% of individuals diagnosed with autism experience sensory processing differences (Green et al., 2015; Marco et al., 2011; Rajendran & Mitchell, 2007). These sensory processing difficulties can affect any and all sensory modalities, including visual, auditory, somatosensory, olfactory, gustatory, vestibular, and proprioceptive senses (Green & et al., 2015). One commonly cited type of sensory processing difference in autism is hyper- or hypo-reactivity (Posar & Visconti, 2018; South & Rodgers, 2017; Green et al., 2015; Kern et al., 2016). Hypo-reactivity often presents as sensory-seeking behaviors, or “stimming,” where the person engages in repetitive behavior, engaging with sensory stimuli to fulfill a sensory need. On the other hand, hyper-reactivity might result in avoidance of sensory stimuli, such as taste aversion, refusal to engage with objects that are known to make a loud noise, or dislike and avoidance of physical contact (Ozsivadjian et al., 2012; Kerns et al., 2014). However, these opposing responses are not mutually exclusive. They can occur simultaneously in the same individuals in reaction to different sensory stimuli (Balasco
et al., 2020). Such reactions to sensory input can be severe and have a dramatic impact on an autistic person’s quality of life. Specifically, they have been found to cause negative impacts on an individual’s level of independence, social relationships, self-esteem, and participation, even in preferred activities (van Heijst & Geurts, 2015). In younger children and those who need more support overall, these sensory processing differences can even lead to self-directed aggression or other harmful behaviors (Ozsivadjian et al., 2012).

fMRI data related to sensory processing difficulties in children with autism suggests that sensory processing disorders may play a role in the high prevalence of anxiety in the population. Similar to anxiety, more severe sensory processing difficulties are associated with both amygdala hyperreactivity and hippocampal structural abnormalities (Green et al., 2015). The hippocampus has been shown to play a significant role in sensory processing, especially in integrating multiple sensory stimuli and sending the sensory information to various brain locations for appropriate processing. Because interpreting sensory input is essential for making sense of interactions in the surrounding environment, it is reasonable to believe that a difficulty with processing sensory input could lead to greater likelihood of developing anxiety. Because amygdala hyperreactivity is associated with both sensory processing differences and anxiety in autism, researchers have begun to investigate if sensory processing could play a significant role in mediating anxiety. While it appears that those with sensory processing difficulties do experience a higher level of anxiety, the exact nature of this correlation has not been conclusive across the research base (Green et al., 2015).

The Role of Prediction

One possible clue for the relationship between anxiety and atypical sensory processing is found in predictive coding. People on the autism spectrum have been shown to experience
differences in the initial process of coding sensory experiences into predictions (Sinha et al., 2014; Van de Cruys et al., 2014). As the weak central coherence theory points out, children diagnosed with autism tend to process sensory information in a detail-oriented way, often with difficulties in conceptualizing the greater meaning of this information (Rajendran & Mitchell, 2007). As prediction requires the recognition of greater patterns, it follows that autistic children may be more likely to have difficulty with predictive coding.

One structure that plays a significant role in this process of predictive coding is the cerebellum (Hull, 2020; Popa & Ebner, 2019). Most classically implicated in the process of motor learning, the cerebellum processes incoming sensory information in order to coordinate proper motor reactions. However, more recent research has found the cerebellum to be involved in cognition, social processing, and emotion and aggression, with strong connections between the cerebellum and cerebral cortex (McDougle et al., 2016; Van Overwalle et al., 2015;). These connections make it clear that the cerebellum plays a prominent role both in processing sensory information as well as making and testing predictions about movement, reward, and other motor and non-motor operations through a constant feedback loop. The fact that differences in cerebellar structure and function have been correlated with autism may point to a possible irregularity in prediction processing in some on the autism spectrum (Hull, 2020; Popa & Ebner, 2019; Wang et al., 2018).

Another difference in the predictive coding process is the flexibility with which children with autism process error messages (Van de Cruys et al., 2014). When a sensory signal does not match an already established pattern, neurotypical children are more often able to cope with the difference than those diagnosed with autism. For autistic children, the reconciliation of these
unexpected signals often result in repetitive behaviors or other insistence on sameness. This type of behavior can be highly disruptive to the person’s daily activities and quality of life.

Prediction difficulties over an extended period of time could lead to an aversion to unpredictable situations (i.e., intolerance of uncertainty), due to the unpleasant nature of prediction errors. For this reason, the construct of intolerance of uncertainty has been included in recent research about anxiety in autistic children (Boulter et al., 2014; Wigham et al., 2015; Jensen et al., 2016; South & Rogers, 2017). Intolerance of uncertainty was originally researched as an explanation for anxiety symptoms in neurotypical individuals. It refers to the “tendency to react negatively on an emotional, cognitive, and behavioral level to uncertain situations and events” (Boulter et al., 2014). People who show signs of intolerance of uncertainty may have difficulty adjusting to changes in routine and may interpret ambiguous information as threatening in some way, as is true with prediction difficulties. This can contribute to anxiety significantly, especially in many autistic children, as they often report symptoms of anxiety to be related to these types of changes. Children and adolescents on the autism spectrum have consistently been found to have higher levels of intolerance of uncertainty (Boulter et al., 2014; Chamberlain et al., 2013; Jensen et al., 2016).

A study conducted by Boulter et al. in 2014 with 224 children ages 8–18, 114 diagnosed with autism and 110 neurotypical controls, found that the autistic group had markedly higher anxiety levels and higher intolerance of uncertainty. However, when intolerance of uncertainty was looked at as a mediating factor for anxiety levels, there was almost no perceptible difference between the anxiety levels of the autistic children and the control group. This indicates that intolerance of uncertainty may play a significant, possibly mediating, role in the high levels of anxiety in autistic individuals. Similar notions were reported in a review by South and Rodgers
in 2017, confirming the mediating role of intolerance of uncertainty in the relationship between sensory processing and anxiety in autistic children.

Overall, there is still much to be learned about the interactions between sensory processing abnormalities, intolerance of uncertainty, and anxiety in autism, especially with respect to their neurobiology. Thus, the purpose of the current study was to examine the behavioral relationship between sensory processing, fear and anxiety, prediction, and brain activity related to these behavioral interactions in autistic children.

**Research Hypotheses**

We hypothesized first that we would observe more severe behavioral differences in sensory processing, intolerance of uncertainty, and anxiety in children with an autism diagnosis than in neurotypical children. We also hypothesized that intolerance of uncertainty would be a mediating factor between behavioral sensory processing scores and measures of anxiety. Finally, we projected observing underconnectivity between sensory cortices, the medial prefrontal cortex, hippocampus, and cerebellum and overconnectivity between these areas and the amygdala, as well as significant relationships between these patterns of connectivity and behavioral scores.

**Methods**

In this section, the participants, instrumentation, and procedures for the current study will be discussed. Additionally, the planned methods for data analysis will be elucidated. Ethical practices in obtaining human subjects institutional review board approval and participants’ consent/assent were utilized.

**Participants**

30 school-aged children with a confirmed clinical diagnosis of Autism Spectrum Disorder (27 males) and 26 neurotypical (NT) peers (19 males) participated in the current study.
The mean age was 9.13 years (SD = 1.72 years) for the autistic children and 9.38 (SD = 1.54 years) for the NT peers. Autistic children were diagnosed according to the Autism Diagnostic Observation Scale-2 (ADOS-2), following criteria from the DSM-V. Participants were mainly recruited via previous participation in autism studies at the University of Colorado Anschutz Medical Campus. Additional participants were gathered via word of mouth and outreach to childcare agencies throughout the Denver, CO, area. The Colorado Institutional Review Board (COMIRB) approved all recruitment, consent, and testing procedures.

**Instrumentation**

This study implemented the following behavioral measures: the Short Sensory Profile (SSP), Intolerance of Uncertainty (IUS-12), the Screen for Child Related Anxiety Disorders (SCARED), and Revised Fear Survey Schedule for Children (FSSC-R). The Short Sensory Profile (SSP) is a truncated version of the Sensory Profile (SP). It is a 38-item caregiver questionnaire that is meant to assess areas of sensory processing, modulation, and behavioral and emotional responses in children ages 3–10. The SSP is split into seven subscales: tactile sensitivity, taste/smell sensitivity, movement sensitivity, under-responsive/seeks sensation, auditory filtering, low energy/weak, and visual/auditory sensitivity (Tomchek & Dunn, 2007). Each question utilizes a Likert Scale of 1–5 to assess if a child’s sensory experience is “different” or typical. The original 125-item SP used 117 children ages 3–17 for psychometric analysis. The SSP removes 27 items that are less related to sensory modulation and 60 others that, in the SP, proved to not be as effective in discriminating the TD population from those with sensory differences (Williams et al., 2018). The SSP was indicated for our study due to its widespread use in assessing children in the Autism community (Crasta et al., 2020; Glod et al., 2020; Simpson et al., 2019). Ease of administration was also a factor. Additionally, it has
moderate to strong internal consistency ranging from 0.70–0.90 in the different sections (Tomchek & Dunn, 2007).

The IUS-12 measures tolerance to different types of unpredictable scenarios, such as the future, ambiguity, and uncertainty as a whole. It consists of 12 items, taken from the 27-item original Intolerance of Uncertainty Scale, that can be responded to using a 5-point Likert scale. The test has two factors: prospective intolerance of uncertainty (IU), which refers to the desire for predictability, and inhibitory IU, which refers to the difficulty acting in the face of uncertainty. Good internal consistency of $\alpha = 0.85$ is present across the two domains as compared to the internal consistency of the full IUS-12, $\alpha = 0.96$ (Carleton et al., 2007). For our study, the IUS-12 functions as a proxy of behavioral prediction due to the likelihood of developing IU secondary to a prediction deficit.

The Screen for Child Related Anxiety Disorders (SCARED) is a 41-item questionnaire to be filled out by child (ages 8–18) or parent, rating common anxiety-inducing situations on a 3-point Likert scale (Birmaher et al., 1999). The questions include items such as “I feel nervous with people I don’t know” or “I have nightmares about something bad happening to me” and require the child or parent to respond from 0–2, with 0 indicating “not true or hardly ever true” and 2 indicating “very true or often true.” The questionnaire screens for anxiety disorders in four domains: panic/somatic, separation anxiety, generalized anxiety, and school phobia. The SCARED has been shown to have generally high internal consistency ($\alpha=.91$) as well as moderate sensitivity (.71) and specificity (.67) (Hale et al., 2011). This screener was chosen not just for its overall validity in identifying anxiety disorders, but also for its accuracy in identifying these disorders in autistic children. Stern et al. (2014) found moderate to strong psychometric
properties in the SCARED for identifying anxiety disorders in autistic children, with Chronbach’s alpha .92 for child report.

The Revised Fear Survey Schedule for Children (FSSC-R) (Ollendick, 1983) is a self-report for children ages 7–16 which consists of 80 items related to common fears and phobias in the areas of fear of the unknown, fear of minor injury and small animals, fear of danger and death, medical fear, and fear of failure and criticism. The FSSC-R identifies common fears such as “giving an oral report” or “snakes” and asks the children to rate the amount of fear the phenomenon creates for them, as either “none,” “some,” or “a lot.” The FSSC-R also has good internal consistency at $\alpha = 0.932$ (Gullone et al. 2000). Reliability for children in the U.S. was also calculated to be significant at .91 (Muris et al., 2014). These measures make it a reliable and appropriate test for the sample of school-aged autistic children from Colorado in our study.

**Procedures**

All data were collected at the Brain Imaging Center at the University of Colorado. Upon arrival at the Imaging Center, participants completed an MRI screening questionnaire for metal safety, were briefed on the procedures, and were asked to change into hospital scrubs to wear during the MRI scan. In all, research appointments lasted two hours. During the first hour, participants were allowed to tour the MRI facility as well as the scanner for as long as they desired and ask any questions they had. Participants also gave assent during this time. During the second hour, MRI testing took place. Participants were allowed to pick out a show to watch during the fMRI structural scan. They also were given a weighted blanket, pillows for their legs, and goggles and headphones for their comfort during the movie and duration of the scan. All participants underwent a resting-state functional magnetic resonance imaging scan (rs-fMRI) for the duration of 8 minutes as well as a shorter full anatomical MRI. Participants were asked to lie
as still as possible despite any loud sounds the machine may make. The goggles and headphones aided in dampening the noise and allowing subjects to focus on the fixation cross. While the fMRI scan was performed, parents were asked to fill out the aforementioned behavioral questionnaires.

During the fMRI scan, patients were instructed to lay flat and stay still while keeping their eyes fixed on a white cross situated on a black field. 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 mm 2 fov 64 squared matrix = 3.43 mm 3 voxels, repetition time = 2500 ms, echo time = 30 ms. Additionally, a T1-weighted anatomical scan (MP-RAGE) was obtained for co-registration and normalization to Montreal Neurological Institute (MNI) space for each child. The 3T Siemens Skyra MR scanner at the University of Colorado Anschutz Medical Campus was used to collect structural and functional fMRI data.

Data Analysis

First, differences in connectivity between autistic and NT children on the SSP, IUS-12, SCARED, and FSSC-R were calculated using between groups Mann-Whitney U tests. Additionally, Spearman rank order correlations were employed to investigate the correlations between all pairings of behavioral measures. Non-parametric statistics were used in behavioral analyses because our data were not distributed normally.

For neurophysiologic analysis, structural MRI and fMRI data were first imported to CONN toolbox (Whitfield-Gabrieli et al., 2012) associated with MATLAB (MathWorks, 2011) to perform both preprocessing and functional connectivity analyses in addition to other routines from the Statistical Parametric Mapping software package (SPM 12). 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 mm³), 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 on rs-fMRI concatenated
(ICA) across the autistic and NT children using Conn (Calhoun et al., 2001). 40 independent
components (IC) were initially extracted. Any IC’s that were determined to be comprised of
noise (i.e., activity in voxels outside of grey matter, motion, etc) were immediately excluded
from future analyses. Following this initial selection, 18 ICs containing areas of activation
corresponding to our hypotheses were selected as networks of interest (i.e., primary and
association sensory areas, cerebellum, as well as fronto-parietal, attention, and default mode
networks). Then, we subjected these 18 networks of interest to a spatial match to 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 (2011). 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. Thus,
the final number of ICs that were included in our final analysis was 15.

Following determination of IC 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. Second, the functional connectivity between each IC network and
all other voxels in the brain that were associated with SSP, IUS-12, SCARED, and FSSC-R 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. Significance of between groups comparisons and connectivity patterns for
each IC-voxel-behavioral measure combination was determined through final Bonferroni
multiple comparisons corrections for each of the above tests (corrected p=0.0034). 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

The present study was designed to examine the behavioral and neurobiological
relationships between measures of sensory processing, intolerance of uncertainty, and
anxiety/fear in autistic individuals. Thus, first, we calculated total scores on the SSP, IUS-12,
SCARED, and FSSC-R. These scores were used in both between and within group statistical
comparisons. Following these calculations, differences in rs-functional connectivity between the
ASD and TD groups were computed. Finally, we performed rs-functional connectivity analysis
to determine the brain activity patterns that were associated with scores on the above measures.

Between Group Behavioral Comparisons

Between groups comparison of behavioral scores revealed that autistic and neurotypical
participants differed significantly in their scores on all behavioral measures included in the
current study, such that the former group presented with more severe sensory processing
difficulties, intolerance of uncertainty, anxiety and fear. For instance, on the SSP, autistic
participants had significantly lower (more severe) scores (mean = 119.7; SD = 24.87; U =
than the NT group (mean = 170.4; SD = 15.38). A similar pattern was also found in the IUS-12, with the ASD group receiving significantly higher (more severe) scores when compared to the NT group (ASD mean = 36.24, ASD SD = 11.93; NT mean = 19.38, NT SD = 6.57; U = 92.50; p = 0.000). Similarly, autistic individuals had significantly higher (more severe) scores than neurotypical peers on the SCARED (ASD mean = 31.23, ASD SD = 20.77; NT mean = 13.3, NT SD = 8.8; U = 185; p = 0.001). Finally, the ASD group had significantly more severe (higher) scores on the FSSC-R compared to the NT group (ASD mean = 137.83, ASD SD = 29.54; NT mean = 114.54, NT SD = 16.13; U = 199.50; p = 0.003. Thus, Mann-Whitney U tests revealed that the ASD group differed significantly from the TD group on all four measures, such that autistic children presented with more severe scores on all measures (See Table 1).

**Within Group Behavioral Correlations**

Results of the SSP, IUS-12, SCARED, and FSSC-R were compared within the groups of autistic and NT children via non-parametric Spearman rank order correlation analyses to determine the degree of association between the behavioral measures, since behavioral data were not normally distributed. All correlations for both groups can be seen in Table 2.

Within our group of autistic children, several significant correlations were found. For instance, the IUS-12 and SSP had a moderate significant negative correlation (r = -0.48; p = 0.007). Such a correlation was hypothesized, because higher scores on the SSP indicate fewer sensory difficulties, while increased scores on the IUS-12 point to greater difficulty with IU. The IUS-12 also showed a moderate significant correlation with the SCARED (r = 0.52, p = 0.003) and the FSSC-R (r = 0.51, p = 0.005). The SSP also was negatively significantly correlated with
the SCARED ($r = -0.45$, $p = 0.013$) and the FSSC-R ($r = .41; p = 0.025$). Finally, the FSSC-R and the SCARED exhibited a strong significant positive correlation ($r = 0.82$, $p = 0.000$).

In the NT group, while some similar patterns of correlation were observed, others differed. For instance, The SSP and IUS-12 showed a significant negative correlation ($r = -0.059$, $p = 0.002$). On the other hand, neither the SSP nor the IUS-12 were significantly correlated with scores on the SCARED or FSSC-R in this group.

Two parallel mediation analyses were performed to investigate the possible mediational role of intolerance of uncertainty in the relationship between sensory processing and both anxiety (SCARED) and fear (FSSC-R). Results revealed that both the relationships between sensory processing and anxiety and sensory processing and fear were mediated by intolerance of uncertainty (see Figures 1 and 2). That is, the standardized regression coefficient between the SSP and IUS-12 was significant ($\beta = -0.24; p = 0.006$) in both analyses. A similar pattern was also seen between IUS-12 and scores on the SCARED ($\beta = 0.84; p = 0.012$) and FSSC-R ($\beta = 0.98, p = 0.045$). The direct effect of SSP on SCARED was not significant ($\beta = -0.14; p = 0.36$). This pattern was also true for the direct effect between SSP and FSSC-R ($\beta = -0.23; p = 0.32$). Indirect effects of both models were tested using bootstrapping procedures (5,000 samples). The bootstrapped unstandardized indirect effect in the SCARED model was -0.198, while in the FSSC-R model, this effect was -0.23. Both of these values fell within 95% confidence intervals, suggesting that IU was a mediator of the relationship between sensory processing and anxiety/fear. Similar relationships were not seen in TD individuals.

**fMRI Calculations**

Independent t-tests were performed for 15 Independent component networks that were hypothesized to be relevant to sensory processing, intolerance of uncertainty, and anxiety/fear.
This analysis revealed no significant differences between groups in within network functional connectivity.

Following the above, the connectivity between IC networks’ activation patterns and all other voxels in the brain and its association with each behavioral measure was calculated via separate regressions to determine the extent to which these patterns could predict behavioral scores. Details concerning all connectivity results can be seen in Table 3. Based on our hypotheses, several of these network connectivity—behavioral data connections were of note. For example, the network represented in IC9 (cerebellum vermis), comprised of cerebellar vermis and brainstem regions, exhibited positive connectivity with central opercular (primary somatosensory cortex), superior/transverse temporal (primary and association auditory cortices), lingual gyrus (primary and higher order visual cortices), and cerebellar hemisphere regions (see Figure 3). This connectivity was significantly related to SSP total scores, such that lower degrees of connectivity were associated with lower (more severe) SSP scores in the ASD group. Also, IC4 (cerebellum), another network comprised of cerebellar vermis regions, was found to have negative connectivity with left inferior lateral occipital (i.e., higher order visual and object recognition) cortices (see Figure 4). This connectivity pattern was also significantly related to IUS-12 total scores, where lower connectivity was associated with higher (more severe) IUS-12 scores in the ASD group. Additionally, IC14 (cerebellum vermis/brainstem), made up of cerebellar vermis and brainstem regions, exhibited positive connectivity with superior lateral occipital/superior parietal lobule (i.e., higher order visual, dorsal attention, and multisensory integration) regions bilaterally (see Figure 5). The region demonstrated lower degrees of connectivity with more favorable IUS-12 scores in the ASD group. IC14 (cerebellum vermis/brainstem) was similarly related to SCARED scores, with lower connectivity associated
with less severe SCARED scores (see Figure 6). IC10 (sensorimotor), somatosensory and primary motor cortical areas, is another area that demonstrated connectivity with the SCARED. The region exhibited negative connectivity with the left basal ganglia and amygdala (see Figure 7). Lower degrees of connectivity among these areas were also associated with more severe SCARED scores.

Discussion

This study examined the relationships between sensory processing, intolerance of uncertainty (as an indirect measure of prediction), and fear/anxiety in autistic individuals. To assess this, participants completed 4 behavioral assessments (SSP, IUS-12, FSSC-R, SCARED) and underwent a resting-state fMRI. The behavioral data were compared between autistic and NT children, and within groups behavioral correlations were calculated. Then, these results were combined with fMRI data to determine brain-behavior associations. Overall, we found the following: i) significant differences between the ASD and NT behavioral groups, such that the ASD group presented with more severe scores on all measures; ii) In autistic children, IU was found to have a mediating relationship between sensory processing and anxiety. A similar mediational relationship was found for our behavioral measure of fear; iii) sensory, cerebellar, and limbic brain regions were significantly associated with behavioral sensory processing, intolerance of uncertainty, and anxiety scores.

Behavioral Differences Between ASD and NT Groups

The increased severity and incidence of sensory processing differences demonstrated in this study follows previous research demonstrating almost double prevalence of sensory processing difference in autistic individuals when compared to their neurotypical peers (e.g., Green et al., 2015; Marco et al., 2011; Rajendran & Mitchell, 2007). Increased severity of scores
on the IUS-12 is supported by research from Boulter et al (2014), Chamberlain et al (2013) and Jensen et al. (2016), showing that children and adolescents on the autism spectrum have consistently been found to have higher levels of intolerance of uncertainty. Significant between group differences for the SCARED and FSSC-R also aligns with current research demonstrating higher prevalence and severity of anxiety in autistic individuals compared with their neurotypical peers (van Steensel & Heeman, 2017).

Interestingly, some of the correlations and functional connectivity found in this study were only seen in the ASD group. The correlations were not found in the NT group. This adds evidence to the significant differences between autistic and neurotypical individuals, while also giving ground to the notion that even fairly common childhood conditions can have atypical presentations when comorbid with ASD. While neurotypical children with anxiety disorders report and are diagnosed by generalized anxiety symptoms with various somatic effects, often brought on by the anticipation of new or stressful situations (APA, 2013), autistic children describe their anxiety with marked differences, such as anxiety associated with: highly specific fears and phobias, a change in the typical environment, lack of schedule, loud noises, less familiar social situations, or lack of rigid structure (Kerns et al., 2014). A similar distinction is found in autistic sensory processing differences, with different presentations often reported as hyper- or hypo-reactivity (Green et al., 2015; Kern et al., 2016; Posar & Visconti, 2018; South & Rodgers, 2017), which present very differently from one another but are not mutually exclusive. Rather, they can occur simultaneously in the same individuals in reaction to different sensory stimuli (Balasco et al., 2020).

Similarly, Hahamy et al. (2015) demonstrated conflicting patterns of increased and decreased activity in fMRI scans of autistic individuals compared to the control group. Namely,
autistic individuals often demonstrate idiosyncratic distortions of the functional connectivity pattern relative to the typical. The focus therefore should not necessarily be on the specific connectivity pattern but the presence of simply atypical connectivity. These distinctions between autistic and neurotypical presentations of common childhood conditions, as well as the diversity amongst overall behavioral and neurological presentations of autism is an important consideration in the interpretation of these results.

**The Mediating Relationship of Prediction on Sensory Processing and Fear/Anxiety**

The correlations and mediation results revealed in the present study strongly suggest a relationship between sensory processing, intolerance of uncertainty, and anxiety/fear in autistic children, though similar relationships were not observed in NT children. That is, in the present study, mediation analyses were performed to investigate the possible mediatory role of intolerance of uncertainty in the relationship between sensory processing and fear/anxiety. The analysis revealed that intolerance of uncertainty mediated both the relationship between sensory processing and anxiety as well as sensory processing and fear, with IU explaining at least a third of the variance in sensory processing. This is consistent with previous research demonstrating similar results – that anxiety and sensory processing are more strongly related when intolerance of uncertainty is considered as the mediator (Boulter et al., 2014; Neil et al., 2016; South & Rodgers, 2017; Wigham et al., 2015). For instance, Wigham et al. (2015) suggested that there was a moderate positive correlation between scores on the intolerance of uncertainty scale to sensory over-responsiveness which was measured using the short sensory profile in autistic children. Subsequently, both Neil et al. (2016) and South and Rogers (2017) reported that intolerance of uncertainty explained at least half of the variance in sensory sensitivity scores on the short sensory profile for autistic children, though this relationship does not seem to be
significant in NT children. When anxiety was controlled for, sensory sensitivities and intolerance of uncertainty remained closely related for children on the autism spectrum. Interestingly, South and Rodgers presented a model in which intolerance of uncertainty mediated the relationship between sensory processing and anxiety (among other factors). This model is consistent with the findings of the present study. Additional work is needed to fully characterize all of the constructs that play important roles in the complex relationship between sensory processing, IU, and fear/anxiety.

One prominent cognitive theory to explain autism is the predictive coding theory, which suggests that many autistic traits may be related to autistic individuals’ ability to typically process incoming sensory signals in order to make predictions about future events. There are many brain regions that are involved in such a process (Bubić et al., 2010). One of these key areas is the cerebellum, which has also been implicated repeatedly in autism (e.g., Courchesne, 2003; Fatemi et al., 2002; Olivito et al., 2016). Since the cerebellum receives inputs from all sensory systems and is instrumental in integrating this information for the purpose of making predictions about future events and preparing the body to respond, cerebellar function may underlie the relationship between sensory processing and prediction, though it is likely not the only such brain area (Bubić et al., 2010). Over time, difficulties in prediction ability might cause an individual to become aversive to uncertain stimuli, which might, in turn lead to intolerance of uncertainty (IU). IU appears to contribute significantly to anxiety in autistic children (e.g., South & Rodgers, 2017). This notion is borne out in the present study, given the mediatory role of IU in the relationship between anxiety and sensory processing that we present here. This finding suggests that anxiety may worsen in response to sensory stimuli when the individual has difficulty predicting/has become intolerant of the uncertain things that follow.
The present study also presents resting-state functional network connectivity findings to support the above notions and behavioral results. Unfortunately, since we did not employ a direct measure of prediction and fMRI data were collected in the resting state, we cannot conclusively say at this time whether this cerebellar-sensory cortex relationship is due to prediction. However, in the current study, we reasoned that IU could serve as an indirect measure of prediction. Interestingly, IC4 (cerebellum) showed connectivity between the cerebellum and left inferior lateral occipital (i.e., higher order visual) brain regions that was significantly negatively related to scores on the IUS-12. That is, as connectivity was increased, IUS-12 scores also improved across autistic children. Similar patterns of connectivity were found with the network represented in IC1 (higher order visual), comprised of bilateral lateral and inferior occipital cortical regions. IC1 (higher order visual) was found to have negative connectivity with left frontal polar regions in the ASD group which was significantly related to SSP scores. Studies by Barttfeld et al. (2011) and Supekar et al. (2013) demonstrate decreased ability to access long-range connections in autistic individuals which may correlate to weak central coherence, or the difficulty processing sensory information cohesively. Bubić et al. (2010) also propose a role for frontal cortices in prediction. Taken together, these findings are consistent with our hypotheses and the notion that the connection between the cerebellum and sensory brain areas seem to be important to the processes of sensory processing and prediction (Bubić et al., 2010).

In conjunction with the above brain-behavior relationships associated with sensory processing and prediction, IC14 (cerebellum vermis/brainstem) was shown to be implicated in both intolerance of uncertainty and anxiety. The network represented in IC14 (cerebellum vermis/brainstem), comprised of cerebellar vermis and brainstem regions, exhibited positive connectivity with lateral occipital and inferior temporal cortices. Lower degrees of connectivity
were associated with more favorable SCARED scores. This correlation was also found with the FSSC-R, though the correlation did not survive multiple comparisons correction. Behaviorally, the FSSC-R and SCARED were found to be highly correlated, suggesting a strong link between anxiety and fear in autistic individuals especially when sensory processing differences are also present (e.g., Green et al., 2015). Overall, the connectivity of the lateral occipital cortices to the cerebellar vermis suggests that in the ASD group, lower sensitivity to visual stimuli may contribute to decreased anxiety in autistic children. This connectivity pattern suggests that atypical cerebellum-sensory connectivity (i.e., sensory prediction) could be linked to anxiety in autistic children. These areas offer excellent evidence of the relationship between sensory processing, prediction, and anxiety/fear.

**Neurobiological Underpinnings of Sensory Processing, Prediction, and Fear/Anxiety**

In addition to fMRI results supporting the mediating relationship of prediction in fear/anxiety and sensory processing, functional connectivity analyses revealed more detail about the specific neurobiological underpinnings of these constructs. For instance, the amygdala is one area that we hypothesized would be highly correlated with anxiety/fear in autistic individuals. Amygdala hyperreactivity has previously been associated with both anxiety and sensory processing (Green et al., 2015). The amygdala also plays a significant role in processing emotional reactions to sensory stimuli, especially fear and anxiety and is highly connected to cortical sensory regions alongside the cerebellum (Belmonte & Allen, 2004; McHugo et al., 2013). In the present study, IC10 (sensorimotor), comprised of somatosensory and primary motor cortical regions, exhibited negative connectivity with the left basal ganglia and amygdala. This connectivity was significantly related to SCARED total scores, such that lower degrees of connectivity were associated with poorer SCARED scores. These findings in IC10
(sensorimotor) suggest that abnormal connectivity between a sensorimotor network and limbic regions may underlie increases in anxiety in autistic children. The findings in the present study in IC10 (sensorimotor) demonstrate the role that the amygdala plays in anxiety as well as the potential role it may have in sensory processing differences in autistic children.

As mentioned above, IC4, 9 & 14 (cerebellum; cerebellum vermis; cerebellum vermis/brainstem, respectively) exhibit connectivity between the cerebellum and sensory cortices that varied significantly with scores on the SSP and IUS-12. IC9, a cerebellar/vermis IC, presented with functional network connectivity with areas of the brain known to be involved in auditory, visual and somatosensory processing that was positively correlated with SSP Total scores in autistic children. This correlation indicated that decreased connectivity between the cerebellum and sensory areas was related to increased sensory difficulties in this group. This finding may support the notion that typical function of the cerebellum, and its connection to sensory brain regions, is important for typical sensory processing. Dunn’s model of sensory processing (2007) supports this pattern of connectivity, suggesting that those with a low neurological threshold have increased responses to sensory stimuli. The cerebellum plays a prominent role both in processing sensory information as well as making and testing predictions about movement, reward, and other motor and non-motor operations through a constant feedback loop. This pattern of abnormal connectivity alludes to the possible irregularity in prediction processing in some autistic individuals, which may have a significant impact on sensory processing (Hull, 2020; Popa & Ebner, 2019; Wang et al., 2018).

While functional connectivity analyses revealed significance in connectivity patterns in the cerebellum, sensory cortices, and the amygdala, our results did not support our hypothesis of abnormal connectivity patterns in the hippocampus and medial prefrontal cortex. South and
Rodgers (2017) demonstrated that the amygdala and the medial prefrontal cortex often have an opposite effect of one another; whereas one is significantly connected, the other may not be. Additionally, the hippocampus and medial prefrontal cortex are extremely important in the top-down regulation of emotional response to stimuli, specifically in regulating fear processing and theory of mind (Wang et al., 2018). Their lack of abnormal connectivity in autistic individuals may allude to the importance of prediction in the processing of such sensory stimuli, in that they are not significantly connected to anxiety without the mediating effect of prediction. It is possible that we did not see significant connectivity of these areas that was connected to our behavioral results in the present study because our participants underwent resting-state fMRI, rather than task-based recordings. Targeting these brain areas via well-designed tasks or stimuli in future MRI studies may reveal different results.

**Clinical Implications**

These neural and behavioral results could have significant implications for clinical practice. First, the brain regions implicated in this study provide a framework for future research in both neurological and/or therapeutic treatments of anxiety disorders in autistic individuals. These findings may suggest that addressing sensory and prediction difficulties has the potential to lead to improvements in anxiety in children with ASD. Addressing these issues may be possible in the future.

Additionally, our results have the potential to inform future clinical practice, demonstrating the importance of a carefully controlled clinical environment in successful treatment. They indicate that a predictable clinical environment as well as thorough explanation of expected tasks for autistic children who experience sensory processing differences and resulting anxiety may help to mitigate negative responses and allow for more effective and
focused treatment. Additionally, as consensus regarding the brain structures and functions related to sensory processing, prediction, and anxiety in autistic individuals is established, it may become possible to lessen these difficulties prior to or during therapy, educational, and other support sessions, and thereby improve outcomes.

Limitations and Future Directions

One of the main limitations of our study is the relatively small sample size with which we calculated our results. Though we were able to draw strongly significant results from our 60-person sample size, the limited number of participants limits the ability of these results to be generalized across the ASD population. Additionally, the impact of these results is somewhat limited due to the spectrum nature of ASD. The notable variation of autistic individuals in manifestation as well as severity of symptoms indicates a limited likelihood that this particular sample is perfectly representative of the autism population as a whole.

Therefore, future studies may attempt to replicate these results with a larger sample size, with the intention of improved representation of autistic individuals. They may draw on individuals of more varied demographics, such as different regions of the United States, gender, and ethnic group. Additionally, future studies may attempt to further investigate the importance of medial prefrontal cortex and hippocampal regions in the process of sensory processing and prediction.

Conclusion

Anxiety is the single most prevalent co-occurring mental health disorder with autism, with prevalence rates 5 to 10 times higher in autistic children than in neurotypical children. Additionally, up to 90% of autistic children are known to experience some type of atypical sensory processing. Both sensory processing atypicality and anxiety can lead to fears and
aversions which can significantly limit desire and ability to participate in social, academic, and even everyday living situations. The ability or inability of an individual to make predictions regarding sensory stimuli is likely to play a significant role in this relationship and in mitigating these challenging responses.

For this reason, the purpose of the current study was to examine the behavioral relationship between sensory processing, fear and anxiety, prediction, and brain activity related to these behavioral interactions in autistic children. We hypothesized 1) more severe behavioral scores in sensory processing, intolerance of uncertainty, and anxiety in the ASD group, 2) We intolerance of uncertainty (as a proxy for prediction) would be a mediating factor between sensory processing and anxiety, and 3) abnormal connectivity in sensory cortices, medial prefrontal cortex, hippocampus, amygdala and cerebellum, as well as significant relationships between these patterns of connectivity and behavioral scores.

Consistent with our hypotheses, results indicated that autistic children presented with significantly more anxiety, fears, prediction difficulties and sensory abnormalities than their typically developing peers. Furthermore, intolerance of uncertainty (i.e., prediction abilities) plays a mediating role between sensory processing differences and anxiety in autistic children. Finally, while our results did not reveal abnormal patterns of connectivity in the hippocampus, or medial prefrontal cortex, abnormal connectivity was found in sensory cortices, the amygdala, and the cerebellum, such that they were significantly correlated with behavioral measures. Our results are consistent with recent literature that points to the notion that prediction difficulties may trigger abnormal fear responses in individuals with ASD. These data have the potential to guide future treatment in various therapeutic areas, especially in mitigating debilitating anxiety responses in autistic individuals.
References


Tables

Table 1

Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASD group (n = 30)</th>
<th>NT group (n = 26)</th>
<th>ASD vs NT</th>
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<td>Mean ± SD (Min - Max)</td>
<td>Mean ± SD (Min - Max)</td>
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<td>P value</td>
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<td>Age (years)</td>
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<td>9.44 ± 1.55 (6.50 – 11.92)</td>
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<td>19 / 7</td>
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<tr>
<td>SSP total</td>
<td>119.70 ± 24.87 (84 – 174)</td>
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<tr>
<td>IUS-12 total</td>
<td>36.33 ± 11.93 (13 – 58)</td>
<td>19.68 ± 6.52 (12 – 36)</td>
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<td>SCARED total</td>
<td>31.23 ± 20.77 (0.00 – 74.00)</td>
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<td>FSSC-R total</td>
<td>137.83 ± 29.54 (92.00 – 191.00)</td>
<td>114.54 ± 16.13 (86.00 – 146.00)</td>
<td>199.50</td>
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Table 2

*Within Group Correlations of Total Behavioral Scores*

<table>
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<tr>
<th></th>
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<th>NT Group</th>
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<td>SCARED</td>
<td>FSSC-R</td>
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<td>SCARED</td>
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<td>-0.48(0.007)</td>
<td>-0.47(0.012)</td>
<td>-0.41(0.025)</td>
<td>-</td>
<td>-0.59(0.002)</td>
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<tr>
<td>IUS r(ρ)</td>
<td>-</td>
<td>-</td>
<td>0.52(0.003)</td>
<td>0.51(0.005)</td>
<td>-</td>
<td>-</td>
<td>0.11(0.592)</td>
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<tr>
<td>SCARED</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.82(0.000)</td>
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### Table 3

**Functional Connectivity in Independent Components**

<table>
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<tr>
<th>IC</th>
<th>IC Functional Name</th>
<th>Autistic</th>
<th>NT</th>
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<tr>
<td></td>
<td></td>
<td>SSP</td>
<td>IUS-12</td>
</tr>
<tr>
<td>1</td>
<td>Higher Order Visual</td>
<td>L FPole (0.000)</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>Sensorimotor</td>
<td>R/L Planum Temp (0.000)</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Ventral DMN</td>
<td>L Ling (0.001)</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>Cerebellum</td>
<td>--</td>
<td>L LOC (0.000)</td>
</tr>
<tr>
<td>5</td>
<td>Temporal pole</td>
<td>L FPole (0.000)</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Primary Visual</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Ventral DMN</td>
<td>--</td>
<td>L FP (0.000)</td>
</tr>
<tr>
<td>8</td>
<td>Executive Control</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>Cerebellum (vermis)</td>
<td>R Central operculum/ Heschels (0.000); R/L Lingual / Temp Occip Fus (0.000); L Central operculum / L PoCG (0.001)</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>Sensorimotor</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>11</td>
<td>R Frontoparietal</td>
<td>--</td>
<td>Precuneus (0.003)</td>
</tr>
<tr>
<td>12</td>
<td>L Frontoparietal</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>13</td>
<td>Dorsal Attention</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>IC</td>
<td>IC Functional Name</td>
<td>Autistic</td>
<td>NT</td>
</tr>
<tr>
<td>----</td>
<td>------------------------------------</td>
<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SSP</td>
<td>IUS-12</td>
</tr>
<tr>
<td>14</td>
<td>Cerebellum (vermis)/brainstem</td>
<td>--</td>
<td>R/L Sup LOC / S Par Lob (0.000)</td>
</tr>
<tr>
<td>15</td>
<td>Sensorimotor</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

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

**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
Figures

Figure 1

Results of the Analysis of the Relationship Between Sensory Processing (SSP) and Fear (FSSC-R) as Mediated by Intolerance of Uncertainty (IUS-12)
Figure 2

Results of the Analysis of the Relationship Between Sensory Processing (SSP) and Anxiety (SCARED) as Mediated by Intolerance of Uncertainty (IUS-12)
Figure 3

IC9 Network Connectivity in the ASD Brain

Note. The network represented in IC9 (figure 3A), comprised of cerebellar vermis and brainstem regions, exhibited positive connectivity with central opercular, superior/transverse temporal, lingual gyrus, and cerebellar hemisphere regions (figure 3B). This connectivity was significantly related to SSP total scores, such that lower degrees of connectivity were associated with more favorable SSP scores (figure 3C).
**Figure 4**

*IC4 Network Connectivity in the ASD Brain*

*Note.* The network represented in IC4 (figure 4A), comprised of cerebellar vermis regions, exhibited negative connectivity with left lateral occipital cortices (figure 4B). This connectivity was significantly related to IUS-12 total scores, such that lower degrees of connectivity were associated with poorer IUS-12 scores (figure 4C).
**Figure 5**

*IC14 Network Connectivity in the ASD Brain (IUS-12)*

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**Note.** The network represented in IC14 (figure 5A), comprised of cerebellar vermis and brainstem regions, exhibited positive connectivity with superior lateral occipital regions bilaterally (figure 5B). This connectivity was significantly related to IUS-12 total scores, such that lower degrees of connectivity were associated with more favorable IUS-12 scores (figure 5C).
Note. The network represented in IC14 (figure 6A), comprised of cerebellar vermis and brainstem regions, exhibited positive connectivity with lateral occipital and inferior temporal cortices (figure 6B). This connectivity was significantly related to SCARED total scores, such that lower degrees of connectivity were associated with more favorable SCARED scores (figure 6C).
**Figure 7**

*IC10 Network Connectivity in the ASD Brain*

Note. The network represented in IC10 (figure 7A), comprised of somatosensory and primary motor cortical regions, exhibited negative connectivity with the left basal ganglia and amygdala (figure 7B). This connectivity was significantly related to SCARED total scores, such that lower degrees of connectivity were associated with poorer SCARED scores (figure 7C).
APPENDIX A

Annotated Bibliography


Objective: To assess dynamic brain connectivity in ASD using low-frequency EEG

Methods: 10 adults with high-functioning ASD, 10 in control group. They participated in EEG recorded with active electrodes. They were recorded in a resting state for 7-minutes.

Results and Analysis: There were reliable and consistent differences in the connectivity patterns of both groups. ASD subjects lacked long-range connections, with largest deficit in fronto-occipital connections. They also have extra short-range connections in lateral-frontal areas. This increased with ASD severity.

Conclusions: Those with ASD may favor more parallel processing, with minimal long-range connections and more short range connections.

Relevance to the current work: In fMRI data, we may see hypoactivity of the frontal areas. We also should look for more short-range connections.


Objective: Model the relationship between anxiety and IU in ASD
*Methods:* 114 ASD, 110 TD, ages 8-18; IUS-C, SCAS and SRS completed by child or parent

*Results and Analysis:* Children with ASD had higher anxiety and IU levels than TD children. After IU taken into account, no difference in anxiety between the diagnostic groups was noted.

*Conclusions:* IU is a dispositional risk factor for the development of anxiety in ASD.

*Relevance to the current work:* IU should be investigated as a mediating factor for our behavioral measures. There is not yet fMRI data to back up this correlation.


*Objective:* To describe mechanisms responsible for predictive coding in those with ASD

*Methods:* 59 8-15-year-old children with ASD and ADHD or TD were monitored via high-density electroencephalography.

*Results and Analysis:* Children with ASD and ADHD share neural-marker abnormalities of atypical top-down processing. Those with ASD have a tendency to inhibit bottom-up processing. The flexible adjustment of precision is lacking in ASD, leading to nongeneralizable predictions.

*Conclusions:* Children with ASD are strongly influenced by explicit task instructions and less affected by novel/unexpected stimuli.
Relevance to the current work: We may look for evidences of top-down being stronger than bottom-up processing in fMRI results.


**Objective:** To determine differences in brain responses, habituation and connectivity during exposure to mildly aversive sensory stimuli in youth with ASD

**Methods:** 19 high-functioning ASD and 19 age and IQ matched youth were examined using fMRI. Functional connectivity was examined and compared for the amygdala and orbitofrontal cortex for both groups.

**Results and Analysis:** ASD participants displayed stronger activation in primary sensory cortices and the amygdala. This was correlated with sensory overresponsivity. Those with sensory overresponsivity also had decreased neural habilitation to stimuli in these areas. Those without sensory overresponsivity showed amygdala downregulation with negative connectivity between the amygdala and orbitofrontal cortex.

**Conclusions:** Youth with ASD and SORs have hyperresponsivity to mildly aversive tactile and auditory stimuli due to failure to habituate.

Relevance to the current work: Amygdala and primary sensory cortices hyperresponsivity may play a part in sensory processing abnormalities.

Objective: To examine epidemiological patterns of injury fatalities in individuals with a diagnosis of ASD.

Methods: Causes of death for individuals with ASD between 1999 and 2014 were screened and compared to the mortality rates in general US population.

Results and Analysis: Age at death was 36.2 years compared with 72.0 years for the general population. Injury mortality was high, especially in suffocation and asphyxiation.

Conclusions: Individuals with ASD have a shorter life expectancy and higher risk for injury mortality.

Relevance to the current work: Discovering the realities of these correlations in our study is not just of importance for the data, but across the lifespan of those with ASD.


https://doi.org/10.1093/scan/nsw015

Objective: To prove that fMRI amygdala activity is a signal of opposing social functions and anxiety symptoms.

Methods: 81 youth with ASD and 67 non-ASD controls completed a face recognition paradigm that elicits robust amygdala activation.

Results and Analysis: Those with ASD or low anxiety levels showed decreased amygdala activation. Anxiety in ASD was positively correlated with amygdala activity, but core symptoms were negatively correlated.
Conclusions: Hypoactivation of the amygdala in ASD may be masked by comorbid anxiety.

Relevance to the current work: The reactivity of the amygdala may be impacted by anxiety symptoms in our study.


Objective: To evaluate how distinct presentations of anxiety influence the measurement and estimated rate of anxiety in ASD.

Methods: 75 children with ASD and 52 TD controls participated. Parents filled out the ADIS-P, which has a series of prompts for ASD children as well. They also filled out the CBCL, MASC-P, and SCARED.

Results and Analysis: Anxiety was present in 69% of those with ASD, with 8% in TD population. Very specific phobias were also very common.

Conclusions: ASD is associated with more frequent and varied presentations of anxiety.

Relevance to the current work: Anxiety in ASD does not necessarily follow typical patterns, so it may not be able to be assessed in the typical way.

Objective: To report on the nature and impact of anxiety in children with ASD from parent report

Methods: 5 focus groups of 17 parents of children and adolescents with ASD and anxiety. They met for 2 hours, facilitated by two of the authors. A topic guide was used to generate discussion. Those discussions were analyzed for themes.

Results and Analysis: Children have great difficulty expressing their worries verbally. Most showed their anxiety through changes in behavior. The anxiety was more impactful than the ASD itself. Common anxiety triggers were related to changes in routine, language, specific fears, sensory triggers, triggers related to obsessions or social situations.

Conclusions: Across the spectrum, anxiety had a large impact on children with ASD. There are noticeable patterns for manifestations of anxiety.

Relevance to the current work: The fact that anxiety has a distinctive presentation in those with ASD demonstrates that it may need to be assessed differently.


Objective: To understand the main features of sensory abnormalities and the respective implications for the signs of ASD

Methods: Search was performed in PubMed related to sensory abnormalities in children with ASD.

Results and Analysis: Sensory symptoms are not specific to ASD, but prevalent in ID as well. Main sensory patterns included: hypo-responsiveness, hyper-responsiveness,
sensory seeking, and enhanced perception. The impairment includes multisensory integration along with unsensory modalities.

Conclusions: Atypical sensory reactivity may be a key in understanding other symptoms/behaviors in children with ASD.

Relevance to the current work: We may expect a positive relationship between sensory abnormalities and increased ASD behaviors.

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

Objective: to explore factors impacting the relationship between ASD and anxiety

Methods: Mini-systematic review

Results and Analysis: Greater sensory dysfunction is correlated to higher stress in children with ASD. IU had a causal mediational model where IU almost completely mediated the relationship between diagnostic group and anxiety scores. Research is lacking on the effectivity of established questionnaires for the ASD population. Alexithymia is a symptom that has correlation with anxiety in ASD

Conclusions: Atypical sensory function, alexithymia, and IU appear to be closely correlated and strongly predict anxiety in ASD.

Relevance to the current work: IU may be a factor to research while understanding the relationship between sensory abnormalities and anxiety in ASD.

https://doi.org/10.1016/j.rasd.2014.06.006
Objective: To describe patterns of sensory processing found in 400 children with ASD

Methods: 400 ASD patients of a wide age range and a gender ratio that matches that of actual prevalence statistics participated. All completed the SSP. Then an exploratory factor analysis was completed to identify patterns of sensory processing in those with ASD.

Results and Analysis: A six factor structure was found: low energy/weak, tactile and movement, smell/taste and auditory and visual sensitivity along with sensory seeking and hypo-responsivity factors.

Conclusions: These elements are most important in sensory processing in those with ASD. Targeting these areas will allow for more proper assessment and diagnosis.

Relevance to the current work: The SSP can be a valid measure for determining sensory processing symptoms in those with ASD, especially when this factor structure is considered.


Objective: To perform a meta-analysis of resting-state brain activity in patients with ASD

Methods: They drew data from 15 resting-state functional neural activity datasets.

Results and Analysis: Patients with ASD showed hyperactivity in the right supplementary motor area, middle frontal gyrus, inferior frontal gyrus, left precentral gyrus, and bilateral cerebellum hemispheric lobule. Hypoactivity was also found in the
right middle temporal gyrus, superior temporal gyrus, left precuneus, posterior and median cingulate cortex and bilateral cerebellum.

Conclusions: Those with ASD have significant alterations in the language comprehension areas as well as the DMN and cerebellar crus I.

Relevance to the current work: These brain regions may serve as particular interest for functional connectivity analyses.
APPENDIX B

Instruments

The Short Sensory Profile (SSP) is a truncated version of the Sensory Profile (SP). It is a 38-item caregiver questionnaire that is meant to assess areas of sensory processing, modulation, and behavioral and emotional responses in children ages 3–10. The SSP is split into seven subscales: tactile sensitivity, taste/smell sensitivity, movement sensitivity, under-responsive/seeks sensation, auditory filtering, low energy/weak, and visual/auditory sensitivity. Each question utilizes a Likert Scale of 1–5 to assess if a child’s sensory experience is “different” or typical, asking questions such as “fears falling or heights” and “avoids going barefoot”.

The Revised Fear Survey Schedule for Children (FSSC-R) is a self-report for children ages 7–16 which consists of 80 items related to common fears and phobias in the areas of fear of the unknown, fear of minor injury and small animals, fear of danger and death, medical fear, and fear of failure and criticism. The FSSC-R identifies common fears such as “giving an oral report” or “snakes” and asks the children to rate the amount of fear the phenomenon creates for them, as either “none,” “some,” or “a lot.”

The SCARED and IUS-12 are included on the following pages.
Screen for Child Anxiety Related Disorders (SCARED)

**CHILD Version**—Page 1 of 2 (to be filled out by the CHILD)

Developed by Boris Birmaher, M.D., Sumantha Khetarpal, M.D., Marlene Gill, M.Ed., David Brent, M.D., and Sandra McKenney, Ph.D.,
Western Psychiatric Institute and Clinic, University of Pittsburgh (October, 1995). E-mail: birmaherb@upmc.edu


Name: ___________________________ Date: ___________________________

**Directions:**
Below is a list of sentences that describe how people feel. Read each phrase and decide if it is "Not True or Hardly Ever True" or "Somewhat True or Sometimes True" or "Very True or Often True" for you. Then, for each sentence, fill in one circle that corresponds to the response that seems to describe you for the last 3 months.

<table>
<thead>
<tr>
<th></th>
<th>0 Not True or Hardly Ever True</th>
<th>1 Somewhat True or Sometimes True</th>
<th>2 Very True or Often True</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. When I feel frightened, it is hard to breathe</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>2. I get headaches when I am at school.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>3. I don’t like to be with people I don’t know well.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>4. I get scared if I sleep away from home.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>5. I worry about other people liking me.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>6. When I get frightened, I feel like passing out.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>7. I am nervous.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>8. I follow my mother or father wherever they go.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>9. People tell me that I look nervous.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>10. I feel nervous with people I don’t know well.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>11. I get stomachaches at school.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>12. When I get frightened, I feel like I am going crazy.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>13. I worry about sleeping alone.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>14. I worry about being as good as other kids.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>15. When I get frightened, I feel like things are not real.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>16. I have nightmares about something bad happening to my parents.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>17. I worry about going to school.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>18. When I get frightened, my heart beats fast.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>19. I get shaky.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>20. I have nightmares about something bad happening to me.</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>
Screen for Child Anxiety Related Disorders (SCARED)
CHILD Version—Page 2 of 2 (to be filled out by the CHILD)

<table>
<thead>
<tr>
<th></th>
<th>0 Not True or Hardly Ever True</th>
<th>1 Somewhat True or Sometimes True</th>
<th>2 Very True or Often True</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.</td>
<td>I worry about things working out for me.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>22.</td>
<td>When I get frightened, I sweat a lot.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>23.</td>
<td>I am a worrier.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>24.</td>
<td>I feel really frightened for no reason at all.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>25.</td>
<td>I am afraid to be alone in the house.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>26.</td>
<td>It is hard for me to talk with people I don’t know well.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>27.</td>
<td>When I get frightened, I feel like I am choking.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>28.</td>
<td>People tell me that I worry too much.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>29.</td>
<td>I don’t like to be away from my family.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>30.</td>
<td>I am afraid of having anxiety (or panic) attacks.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>31.</td>
<td>I worry that something bad might happen to my parents.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>32.</td>
<td>I feel shy with people I don’t know well.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>33.</td>
<td>I worry about what is going to happen in the future.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>34.</td>
<td>When I get frightened, I feel like throwing up.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>35.</td>
<td>I worry about how well I do things.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>36.</td>
<td>I am scared to go to school.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>37.</td>
<td>I worry about things that have already happened.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>38.</td>
<td>When I get frightened, I feel dizzy.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>39.</td>
<td>I feel nervous when I am with other children or adults and I have to do something while they watch me (for example, read aloud, speak, play a game, play a sport).</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>40.</td>
<td>I feel nervous when I am going to parties, dances, or any place where there will be people that I don’t know well.</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>41.</td>
<td>I am shy.</td>
<td>O</td>
<td>O</td>
</tr>
</tbody>
</table>

**SCORING:**
A total score of ≥ 25 may indicate the presence of an Anxiety Disorder. Scores higher than 30 are more specific. TOTAL = [sum of scores]

A score of 7 for items 1, 6, 9, 12, 15, 18, 19, 22, 24, 27, 30, 34, 38 may indicate Panic Disorder or Significant Somatic Symptoms. PN = [sum of scores for these items]

A score of 9 for items 5, 7, 14, 21, 23, 28, 33, 35, 37 may indicate Generalized Anxiety Disorder. GD = [sum of scores for these items]

A score of 5 for items 4, 8, 13, 16, 20, 25, 29, 31 may indicate Separation Anxiety. SP = [sum of scores for these items]

A score of 8 for items 3, 10, 26, 32, 39, 40, 41 may indicate Social Anxiety Disorder. SC = [sum of scores for these items]

A score of 3 for items 2, 11, 17, 36 may indicate Significant School Avoidance. SH = [sum of scores for these items]

For children ages 5 to 11, it is recommended that the clinician elicits all questions, or have the child answer the questionnaire sitting with an adult in case they have any questions.

The SCARED is available at no cost at [www.spc.pitt.edu/research/under tools and assessments], or at [www.pediatric bipolar pitt.edu under instruments].

March 27, 2012
Intolerance of Uncertainty Scale - Short Form
(Carleton, Norton, & Asmundson, 2007)

Please circle the number that best corresponds to how much you agree with each item.

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all characteristic of me</th>
<th>A little characteristic of me</th>
<th>Somewhat characteristic of me</th>
<th>Very characteristic of me</th>
<th>Entirely characteristic of me</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unforeseen events upset me greatly.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. It frustrates me not having all the information I need.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Uncertainty keeps me from living a full life.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. One should always look ahead so as to avoid surprises.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. A small unforeseen event can spoil everything, even with the best of planning.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. When it’s time to act, uncertainty paralyses me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. When I am uncertain I can’t function very well.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. I always want to know what the future has in store for me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. I can’t stand being taken by surprise.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. The smallest doubt can stop me from acting.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. I should be able to organize everything in advance.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. I must get away from all uncertain situations.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Score:______
APPENDIX C

Consent Form

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:

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

<table>
<thead>
<tr>
<th>Purpose of Visit</th>
<th>Estimated duration of visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction to lab and consent</td>
<td>1 hour</td>
</tr>
<tr>
<td>Psychiatric interviews</td>
<td>1.1 hour</td>
</tr>
<tr>
<td>Diagnostic interviews</td>
<td>2 hours</td>
</tr>
<tr>
<td>Cognitive tests</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>MEG scans</td>
<td>2.25 hours</td>
</tr>
<tr>
<td>MRI scan</td>
<td>2 hours</td>
</tr>
<tr>
<td>Blood draw</td>
<td>1 hour (N/A for all subjects)</td>
</tr>
</tbody>
</table>

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, UCD 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.

Permissions 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.
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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:

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