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# A fMRI of Fear Conditioning and Auditory Looming in Autism Spectrum Disorder

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# An fMRI Examination of Fear Conditioning and Auditory Looming in Autistic Adults

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A dissertation submitted to the faculty of
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Doctor of Philosophy

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## ABSTRACT

### An fMRI Examination of Fear Conditioning and Auditory Looming in Autistic Adults

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Many autistic adults experience debilitating anxiety that interferes with their daily functioning. Atypical sensory processing and intolerance of uncertainty are cognitive processes linked to atypical limbic system functioning and impaired fear conditioning as potential mediators of anxiety in autism. A previous fear conditioning study using fMRI found atypical amygdala functioning in autism when the threat stimulus was only partially reinforced. The first aim of this dissertation is a multimethod examination of brain and psychophysiological response in autistic and in neurotypical adults during a fear conditioning/extinction task with the threat stimulus reinforced 100% percent of the time. We were also interested in the responses of autistic and neurotypical adults during an auditory looming task that requires no learning contingencies. We used fMRI, pupillometry, and skin conductance response as the dependent measures. Results demonstrated a significant main effect for insula activation, but not amygdala activation, during the 100%-reinforcement fear conditioning task with no between-group differences or group x condition interactions. There were likewise no condition differences (Safe vs Threat) for amygdala in the auditory looming task. However, the autism group demonstrated increased insula response to both Threat and Safe auditory conditions of the looming task, suggesting the autism group utilized alternative cognitive resources than the neurotypical group. Results indicate intact fear conditioning and extinction in autism for *more certain* conditions and suggests that behavioral (exposure) anxiety treatments for phobias could be useful under certain conditions. Results of this study are inconsistent with the atypical/hyperactive amygdala

hypotheses of anxiety with autism and inconsistent with the portion of the South & Rodgers (2017) anxiety model regarding the importance of intolerance of uncertainty in autism samples.

Keywords: autism, anxiety, fear conditioning, looming, fMRI, pupillometry

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# An fMRI Examination of Fear Conditioning and Auditory Looming in Autistic Adults

Autism spectrum disorder (AUT) is a neurodevelopmental condition characterized by atypical social communication and social interactions, and a preference for restricted/repetitive behaviors and interests that may impair everyday functioning (American Psychiatric Association, 2013). Current prevalence estimates are 1 in 160 persons worldwide, with the prevalence rate in the US being 1 in 68 (Christensen et al., 2016; World Health Organization, 2018). Many autistic individuals also meet criteria for one or more anxiety disorders (Buck et al., 2014; Kerns et al., 2014; South & Rodgers, 2017). Indeed, anxiety disorders have the highest lifetime prevalence rates of any associated mental health condition in autism, with 27.5-52.7% of individuals with autism meeting criteria for an anxiety disorder at some point in their life (Buck et al., 2014; van Steensel, Bögels, & de Bruin, 2013; van Steensel, Bögels, & Perrin, 2011). Although some individuals with autism are not diagnosed with a categorical anxiety disorder according to formal diagnostic criteria, up to 85% of children with autism have some degree of impairing anxiety (White, Oswald, Ollendick, & Scahill, 2009). A study by Kerns et al., (2014) found that many individuals with autism show atypical expressions of anxiety including social discomfort without a fear of negative evaluation, compulsive behavior that does not seem motivated by distress relief, and strange phobias. Because of the unique expression of anxiety in autism, it is likely that the rates of anxiety are higher than those previously estimated according to the DSM-IV-TR criteria, though measures to disentangle these overlapping symptoms are lacking (Vasa, Keefer, Reaven, South, & White, 2018).

Researchers investigating impairments related to anxiety, beyond core autism symptoms, have found that autistic children with anxiety have increased rates of problematic behaviors

including irritation, aggression, attention problems, and repetitive behaviors (Gotham et al., 2013; Rodgers, Glod, Connolly, & McConachie, 2012). Current studies have also shown that adolescents with autism and anxiety experience greater social difficulties than adolescents with autism alone (McVey et al., 2018) and have more frequent thoughts pertaining to personal failure (Keefer et al., 2018). Heightened anxiety in autism has also been associated with difficulty making decisions (Luke, Clare, Ring, Redley, & Watson, 2012). Additionally, higher anxiety in autism has been shown to be associated with higher parental anxiety (Conner, Maddox, & White, 2013) and increased stress on family systems (Palilla, 2015). The additional impairment that anxiety places on autistic individuals and their families makes it imperative to develop targeted anxiety treatments for this population.

Basic etiological research investigating the underlying mechanisms that account for the similar and dissimilar manifestations of anxiety in autism is an important first step towards developing such interventions (Kerns et al., 2014; Rodgers et al., 2012; White et al., 2014). Moreover, recent data suggests that standard behavioral and pharmacological mental health interventions will benefit from understanding and targeting these highly-specific underlying mechanisms in autism (Keefer et al., 2016; Walsh et al., 2017). A recent review article by South and Rodgers (2017) highlights several potential mechanisms that may lead to anxiety in autism including atypical sensory functioning and intolerance of uncertainty.

**Atypical Sensory Processing and Autism**

Atypical sensory processing (e.g., sensory sensitivity, sensory seeking, sensory avoidance) is classified as part of the restricted/repetitive behaviors cluster of autistic traits. Previous research has found that atypical sensory processing is an important factor contributing to the general development and maintenance of affective disorders (Ahadi & Basharpoor, 2010;

Aron & Aron, 1997; Benham, 2006; Goldsmith, Van Hulle, Arneson, Schreiber, & Gernsbacher, 2006; Neal, Edelmann, & Glachan, 2002). Liss, Mailloux, and Erchull (2008) found that multiple sensory processes (e.g., ease of excitation, and low sensory threshold) were related to self-reported autism spectrum traits and anxiety in a large population sample. Research using questionnaire-based methods have shown significant associations between atypical sensory processing, autism, and anxiety (Ben-Sasson et al., 2008; Green & Ben-Sasson, 2010; Lidstone et al., 2014; Neil, Olsson, & Pellicano, 2016; Top Jr, Luke, Stephenson, & South, 2019; Uljarević, Carrington, & Leekam, 2016; Wigham, Rodgers, South, McConachie, & Freeston, 2015). In autism samples, the severity of anxiety appears to be higher in individuals with more severe sensory dysfunction (Gillott & Standen, 2007; Uljarević et al., 2016). A landmark study investigating the relationship between sensory processing, autism, and anxiety found that sensory over-responsivity emerges earlier than anxiety in autism and significantly predicts anxiety symptoms (Green, Ben-Sasson, Soto, & Carter, 2012). Many other studies have found an association between the three constructs, although the type of sensory process that predicts anxiety in autism differs. For example, Lidstone and colleagues (2014) found that sensory avoidance and sensory sensitivity are related to anxiety and autism symptoms in children diagnosed with autism, while Neil et al. (2016) and Wigham & McConachie (2015) reported significant relationships between sensory under-responsiveness and sensory sensitivity, levels of anxiety, and autistic symptoms. Additionally, a recent study found that worry and autistic traits were only significantly correlated with the construct of sensory sensitivity (Top Jr et al., 2019).

Using functional magnetic resonance imaging (fMRI), Green et al. (2013) reported that youth with high-functioning autism showed more activation than controls in primary sensory cortical areas as well as the amygdala, hippocampus, and orbital-frontal cortex when presented

with mildly aversive sensory stimuli. Additionally, the atypical activation was correlated with parent-reported anxiety and sensory over-responsiveness (SOR). A follow-up fMRI study (Green et al., 2015) using multi-modal sensory stimuli, comparing youth with autism with SOR to youth with autism without SOR, yielded similar results. Specifically, autistic youth with SOR showed sensory cortical and amygdala hyper-responsivity to the mildly aversive tactile and auditory stimuli, particularly when multiple modalities were presented simultaneously. They were also able to show that this hyperresponsivity in the autism+SOR group was due to failure to habituate to the stimuli. These findings suggest that a subset of autistic youth can regulate their responses through prefrontal downregulation of amygdala activity. However, a recent study examining auditory habituation using pupillometry did not find differences between adults with autism, typically developing adults, and typically developing adults with high levels of anxiety, nor did it show a significant relationship between auditory habituation, anxiety, and autistic symptoms (Top Jr et al., 2019), suggesting that difficulties with sensory habituation is not the only sensory process that could lead to anxiety in autism.

In 2012, Pellicano and Burr (2012) theorized that the abnormal sensory processing difficulties found in autism are due to reduced utilization of "Bayesian priors" related to the processing and interpretation of sensory experience—that is, previously experienced information does not exert the same amount of bias on current perception and interpretation. Pellicano and Burr argued that individuals with autism have difficulty utilizing prior experience when processing inherently ambiguous sensory information, which gives rise to a greater reliance on bottom-up sensory signals and, subsequently, creates differences in the way that autistic individuals interpret sensory information. This Bayesian hypo-prior theory suggests that although people with autism may be exposed to specific sensory stimuli repeatedly, they

continue to interpret the ambiguous stimuli as “new,” creating a sense of uncertainty. Thus, individuals with autism are in a continuous state of uncertainty regarding their processing of sensory stimuli, suggesting that the anxiety in autism may also be due to the intolerance of uncertainty many people with autism report having.

**Intolerance of Uncertainty and Autism**

Intolerance of Uncertainty (IU) is a transdiagnostic psychological construct that refers to decreased thresholds for ambiguity and enhanced discomfort with ambiguity (Dugas, Gagnon, Ladouceur, & Freeston, 1998). Although typically a factor associated with generalized anxiety disorder, IU has shown to negatively affect transdiagnostic constructs including depression as well as other anxiety disorders (Einstein, 2014; McEvoy & Mahoney, 2012). The characteristics of IU appear to share some common features with aspects of the insistence on sameness seen in autism (Boulter, Freeston, South, & Rodgers, 2014) as manifest by the preference for autistic people for predictable situations (Chamberlain et al., 2013). Multiple studies have now established the link between IU, anxiety, and autistic traits (Boulter et al., 2014; Chamberlain et al., 2013; Maisel et al., 2016; Neil et al., 2016). A study by Boulter et al. (2014) reported a ‘‘causal mediational model’’ in which IU almost completely mediated the relationship between the diagnostic group and anxiety scores. Another study, using an autism only sample, found a link between sensory over-responsiveness, IU, and anxiety in which IU mediated the relationship between sensory processing and anxiety (Wigham et al., 2015). Neil et al. (2016), replicating the Wigham et al. (2015) study with a larger sample that includes typically developing individuals, found that IU had a direct effect on sensory sensitivity and anxiety.

**Fear Conditioning/Extinction in Autism**

Although there is evidence suggesting that atypical sensory processing and IU are related to anxiety in autism, it is still unclear how these concepts interact with each other in the brain. It has been suggested that classical fear conditioning and extinction paradigms could be particularly helpful in understanding the maladaptive anxiety in humans generally, as well as in autistic samples (Baron-Cohen et al., 2000; Duvarci & Pare, 2014; Gilmartin, Balderston, & Helmstetter, 2014; VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014). Classical fear conditioning refers to the phenomena in which organisms learn to fear previously non-feared (typically, neutral valence) stimuli (Fullana et al., 2016). Fear conditioning takes place when a neutral stimulus (e.g., a black square) becomes associated with a naturally aversive stimulus (e.g., loud noise or burst of air) and the individual shows a fear response to the non-threatening stimuli (e.g., they are now afraid of the black square). Fear extinction refers to the phenomena in which the fear conditioning is reversed through multiple exposures of the feared non-threatening stimulus that is not reinforced by the naturally aversive stimulus. Behavioral models of psychology assume this is the process by which organisms effectively learn to distinguish between what is "safe" and what is "dangerous," and is one mechanism through which anxiety disorders develop and are treated (Fullana et al., 2016).

Previous neuroimaging studies of classical fear conditioning in typically developing and healthy samples indicate that a healthy regulation of an initial fear response relies on activation of amygdala, insula, middle frontal gyrus, and dorsal anterior cingulate cortex (Carter, O'Doherty, Seymour, Koch, & Dolan, 2006; Feng, Feng, Chen, & Lei, 2014; Fullana et al., 2016; Milad, Rosenbaum, & Simon, 2014; Sehlmeyer et al., 2009). Successful extinction requires an inhibition of previously learned responses that involves the network of hippocampus,

amygdala, and medial prefrontal cortex (Schiller, Levy, Niv, LeDoux, & Phelps, 2008). In humans, orbitofrontal cortex (OFC) activation is associated with updating information about fear context and sustained anticipatory anxiety involves disruption in amygdala-OFC feedback systems (Finger, Mitchell, Jones, & Blair, 2008; Fullana et al., 2016; Schiller et al., 2008). Fear conditioning and extinction fMRI studies indicate that individuals with anxiety disorders, and healthy controls with elevated levels of anxiety, exhibit atypical activation of the aforementioned neural networks (Etkin, 2012; Shechner, Hong, Britton, Pine, & Fox, 2014). For example, adults with panic disorder showed amygdala hyperreactivity to the safe cues compared with typically developing adults (Lueken et al., 2014), while patients with post-traumatic stress disorder showed amygdala hyporeactivity to threatening stimuli (Diener et al., 2016). Healthy controls with high levels of trait anxiety showed lower activation in the anterior cingulate in response to threatening stimuli (Britton et al., 2013). High levels of trait anxiety are also associated with increased amygdala activation and reduced dorsal anterior cingulate recruitment during fear extinction, suggesting that healthy individuals with elevated levels of anxiety show increased resistance to extinction and are thus more likely to develop anxiety disorders (Sehlmeye et al., 2011). Is has also been found that stronger physiological reactions to the fear conditioning in healthy adults are associated with increased amygdala and dorsal anterior cingulate activation (van Well, Visser, Scholte, & Kindt, 2012).

To date, there have been few fear conditioning studies in autism, with all but one examining psychophysiological measures of fear, and yielding mixed results. The first fear conditioning in autism study was reported by Bernier, Dawson, Panagiotides, and Webb (2005) who used potentiated startle measures – which measures emotion-related modulation of the blink response to very short bursts of white noise played through headphones – and a 100%

reinforcement rate for the unconditioned stimulus (a burst of air to the base of the larynx). They found no difference between autistic adults and typically developing adults. Another study using skin conductance responses (SCR) as the dependent variable and a partial reinforcement schedule of the unconditioned stimulus (a loud auditory stimulus) found impaired fear conditioning in autistic adults (Gaigg & Bowler, 2007). A later study using an aversive noise as the unconditioned stimulus with a 100% reinforcement schedule and SCR as the dependent variable found intact fear conditioning in a sample of autistic children and adolescents (South, Larson, White, Dana, & Crowley, 2011). Although there was no difference between groups, South et al. (2011) reported that the better fear conditioning was associated with reduced social anxiety and social functioning in the autistic group. A reversal learning study—a fear conditioning study in which the conditioned threat and safe cues are switched half-way through the experiment—using SCR as the dependent variable and a partial reinforcement schedule of the unconditioned stimulus (an airburst to the base of the larynx) found intact fear conditioning, but delayed reversal learning in the autistic group (South, Newton, & Chamberlain, 2012). The results of the South et al. (2012) study suggests the anxiety in autism may be due to 1) a failure to extinguish previous learning, 2) a failure to learn the new association, or 3) perhaps deficits in both learning and extinction. A study published by Powell et. al (2016) using SCR as the dependent variable, with multi-modal unconditioned stimuli (sound and visual stimuli), and a partial reinforcement schedule showed that individuals with autism had impaired fear conditioning, an effect which was more pronounced as the task becomes more complex. Additionally, participants with autism who showed greater explicit awareness of the contingencies showed conditioned responses more similar to participants with typical development (Powell et al., 2016).

Given the mixed findings of the fear conditioning studies using psychophysiological measures, Marin and Milad (2016) propose that neuroimaging studies will provide helpful information that may account for these mixed results and point to particularities of the fear network in individuals with autism. They likewise argue that future fear conditioning studies can learn more about the potential mechanisms of anxiety in autism by combining neuroimaging techniques with other psychophysiological and behavioral measurements.

To date, the only fMRI fear conditioning study in autism found atypical neural responses in adults with autism compared to typically developing controls (Top Jr et al., 2016). Using an airburst to the neck as the unconditioned stimulus and a partial (42%) reinforcement schedule, Top and colleagues found that the neurotypical control group had a more pronounced right amygdala response in the threat versus safe contrast than the autism group. During the extinction phase, autistic individuals showed greater left amygdala activation in response to the threat versus safe contrast. On the next day, during the extinction recall phase, the healthy controls showed higher left amygdala activation for the threat cues relative to the safety cues than the autistic group.

Although results of the Top et al. study shed some light on the neural mechanisms of fear conditioning and extinction in autism, it is unclear whether the atypical fear conditioning responses are due to a hyperactive response to the safety cue or a hypoactive response to the threat cues. As set forth by White et al. (2014), possible atypical hyperactivation of the amygdala makes it difficult for autistic persons to distinguish between the threat and safety cues, and thus they perceive both cues as threatening. White et al. (2014) also suggested that the atypical insula activation often found in autism may interfere with emotional regulation and fear learning. On the other hand, hypoactivation of the amygdala to the threat cues suggests that people with

autism have a reduced fear response or enhanced habituation to startling stimuli (Top Jr et al., 2016). Additionally, partial reinforcement of the unconditioned stimulus may have accounted for the between-group differences in the Top et al. study since only the fear conditioning studies that used partial reinforcement schedules showed differences between autism and healthy controls (Gaigg & Bowler, 2007; Powell et al., 2016). This suggests that the atypical responses in autism may be due to the uncertainty of the reinforcing stimulus, rather than problematic fear learning or extinction mechanisms on their own.

A recent fear conditioning study utilizing fMRI and pupillometry simultaneously in a neurotypical population found that pupil responses to the threat and safe cues were not associated with amygdala response but were associated dorsal anterior cingulate cortex and insula responses (Leuchs, Schneider, Czisch, & Spoormaker, 2017). This suggests that suggests that previous fear conditioning in autism studies using skin conductance or pupillometry to infer amygdala responses may not hold when measuring psychophysiology and fMRI simultaneously. To date, there has only been one fear conditioning and extinction study in autism research utilizing fMRI, and none that have used fMRI and psychophysiology measures simultaneously. Our study hopes to fill this gap in the literature by conducting one of the first fear conditioning/extinction in autism study to utilize fMRI, skin conductance response, and pupillometry measures simultaneously as separate dependent variables.

**Non-Learning Fear Responses in Autism**

One question raised by the previous literature is how much impaired learning affects the response to threats in autism. Fear conditioning in autism seems more impaired by partial reinforcement schedules, which add an element of uncertainty to the threatening stimulus. Thus,

we cannot be sure whether amygdala response to non-learned threat stimulus is impaired or if atypical amygdala activation to a learned threat stimulus is impaired.

Auditory looming is a sensory process that functions as a warning system to increase the chances of survival in potentially dangerous situations (Guski, 1992; Rosenblum, Carello, & Pastore, 1987; Rosenblum, Wuestefeld, & Saldaña, 1993). Looming sounds—auditory stimuli that get progressively louder—initiate a series of protective physiological, cognitive, emotional, and behavioral responses that do not occur in response to sounds that move in any other direction (Bach, Furl, Barnes, & Dolan, 2015; Bach, Neuhoff, Perrig, & Seifritz, 2009; Bach et al., 2008; Neuhoff, 2016; Seifritz et al., 2002). Studies of auditory looming in humans found that people rate dynamically approaching sounds as closer, louder, faster; and more unpleasant, alerting and threatening than withdrawing sounds (Bach et al., 2009, 2008; Cappe, Thut, Romei, & Murray, 2009; Ellermeier, 1996; Neuhoff, 1998; Stecker & Hafter, 2000). Besides evoking greater behavioral responses, looming sounds are also more physiologically arousing, producing greater autonomic responses as indexed by changes in skin conductance response and pupillometry than receding sounds (Bach et al., 2009, 2008; Fletcher et al., 2015). An fMRI study of auditory looming found that looming sound increased activation the right amygdala compared to receding sounds in healthy adults, suggesting that auditory looming protocols can serve can a non-learning alternative to examine the neural mechanisms of fear and anxiety (Bach et al., 2008). Riskind et al. (2014) found that anxiety symptoms were associated with a stronger auditory looming response in healthy controls, indicating that auditory looming may be an effective way to explore the relationship between sensory processing and anxiety in autism. Auditory looming protocols have been used in other clinical samples (e.g., schizophrenia, dementia) to examine the sensory and emotional processing of sounds in these populations (Bach, Buxtorf, Strik, Neuhoff, &

Seifritz, 2011; Fletcher et al., 2015). To date, there have been no published auditory looming studies performed with an autistic sample.

**Study Aims**

The purpose of this dissertation is to characterize possible relationships between amygdala and related brain activity and exacerbated anxiety commonly found in autism. More specifically, we will determine if the atypical amygdala function in autism is related to atypical sensory processing of naturally threatening stimuli (non-learned fear responses) or atypical fear conditioning (learned fear responses). We will accomplish this by comparing the fMRI, SCR, and pupillometry responses of healthy and autistic adults during 1) a fear conditioning/extinction task in which we will decrease the uncertainty of the reinforcing stimulus by having a 100% reinforcement schedule and 2) an auditory looming task. Additionally, we are interested in examining the relationship between amygdala and insula activation to each of the tasks and reported anxiety symptoms. For this purposes of this study, we will be testing two separate models of anxiety in autism and will be using them for the basis of our hypotheses: 1) an atypical emotional regulation theory of anxiety in autism (White et al., 2014) and 2) the South and Rodgers (2017) model of anxiety that emphasizes the role of intolerance of uncertainty.

**Atypical Emotional Regulation Model of Anxiety in Autism**

White et al. (2014) proposed specific atypical input from amygdala, insula, vmPFC, and orbital frontal cortex that lead to impaired emotional regulation and subsequent anxiety in autism (See Figure 1). One of their specific hypotheses related to fear conditioning is a prediction of hyperactive amygdala and insula activation to both threat and safe cues. This inability to differentiate between safe and threat leads to impaired emotional regulation, and this impaired emotional regulation leads to anxiety in autism. Our previous study (Top Jr et al., 2016), using a

partial reinforcement of the threat cues, supports the idea that threat and safe cues are not adequately discriminated in autism.

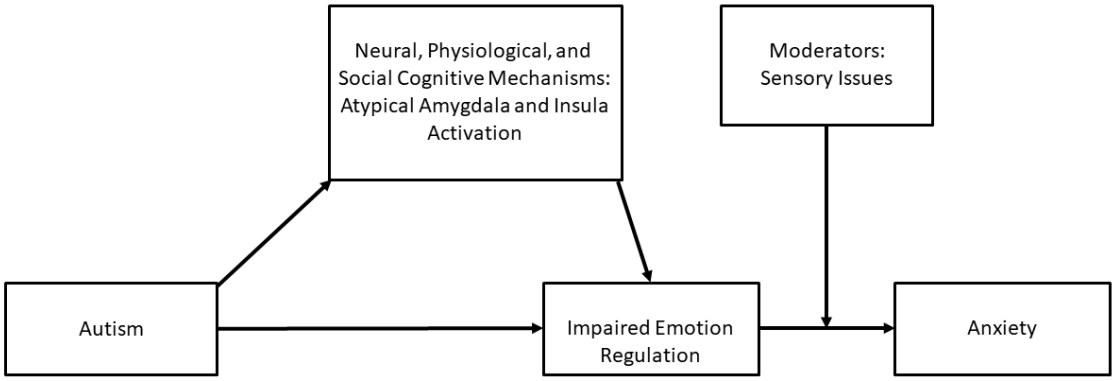


*Figure 1.* Summary of the atypical emotional regulation model of anxiety proposed by White et al. (2014)

The specific hypotheses utilizing the atypical emotional regulation model as the basis are as followed:

***Study 1.1 Aim: Fear Conditioning and Extinction – Compare Brain Activity and Physiological Response Between the Autism (AUT) Group and the Neurotypical (NT) Group, when Controlling for Uncertainty of the Reinforcing Stimulus***

- Fear Conditioning Hypotheses– We hypothesized a significant group-by-condition interaction effect in the amygdala and insula during the fear conditioning phase. Specifically, we hypothesized that the NT group would have greater activation in the amygdala and insula to the threat cues compared to the safe cues, whereas the AUT group would show diminished distinction in amygdala response to safe and threat cues. This pattern of activation would be replicated in the SCR and pupillometry data

- Extinction Hypotheses – Consistent with the disrupted emotional regulation model, we hypothesized that there would be a significant group-by-condition interaction effect in the fear extinction phase. We hypothesized that the AUT group would show greater amygdala responses to the threat cues compared to the safe cues during extinction, while the NT group would have similar amygdala activations to both cues. We also hypothesized that there would be a significant main effect of group with the AUT group having greater amygdala activation than the NT group to both the safe and threat cues during the fear extinction phase. This pattern of activation would also be seen in the SCR and pupillometry data.
- We hypothesized that anxiety would be predicted by sensory sensitivity and the amygdala and insula responses to the fear conditioning/extinction protocols.

***Study 2.1 Aim: Auditory Looming – Compare Brain Activity and Physiological Response Between the Autism (AUT) Group and the Neurotypical (NT) Group in Auditory Looming***

- Given the White (2014) emotional regulation theory, we hypothesize that there will be an interaction effect between the looming (threat) and receding (safe) stimuli with the AUT group having greater BOLD response in the amygdala and insula activation to both stimuli, whereas the NT group will greater BOLD response in the amygdala and to the looming but not the receding stimulus. We hypothesized a similar response pattern would be found in the SCR and pupil measures.
- Supposing the White (2014) emotional regulation theory, we hypothesized that there would be positive correlations between sensory sensitivity, anxiety, and the amygdala and insula responses to the auditory looming protocol. More specifically, we

hypothesized that anxiety will be predicted by sensory sensitivity, and the amygdala and insula responses to the auditory looming protocol.

**South and Rodgers (2017) Model of Anxiety in Autism**

The anxiety in autism model proposed by South and Rodgers (2017; See Figure 2) which highlights the role of sensory dysregulation or atypical sensory processing, alongside atypical emotion awareness (alexithymia), and rigidity of thoughts which are common features of autism. These separately contribute to increased intolerance of uncertainty, which can lead to increased anxiety seen in autism. In this model, the anxiety experienced in autism is driven, at least in part, by intolerance of uncertainty. This is congruent with the alternative explanation in the Top Jr. et al. (2016) paper which suggested that the uncertainty engendered by the partial reinforcement fear conditioning paradigm may disrupt learning in autism for the fear conditioning and extinction tasks. Since that study was published, several studies of emotion response have suggested that these emotional dimensions serve to predict outcome variables including anxiety (Herrington, Miller, Pandey, & Schultz, 2016) and depression (Gotham et al., 2018) better than core autism traits,. This model lead to a second set of study aims and hypotheses in which we wanted to evaluate the role of these core brain regions in predicting intolerance of uncertainty rather than autism per se.

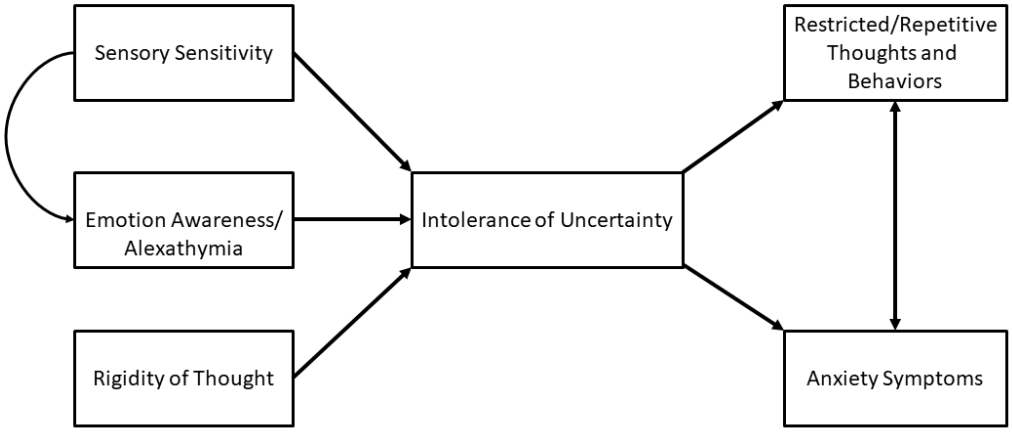


*Figure 2.* South and Rodgers (2017) model of anxiety in autism.

***Study 1.2 Aim: Fear Conditioning and Extinction – Compare Brain Activity and Physiological Response Between the High Intolerance of Uncertainty (High IU) Group and the Low Intolerance of Uncertainty (Low IU) Group, when Controlling for Uncertainty of the Reinforcing Stimulus***

- Fear conditioning hypothesis – We hypothesized that there would be an interaction effect of group (divided by scores on the Intolerance of Uncertainty Scale, High IU vs Low UI) and experimental condition (Safe vs Threat) during the fear conditioning phase. Specifically, participants in the High IU will have greater activation in the amygdala, insula, and other areas in the "uncertainty network" (Tanovic et al., 2018) to both the safe and threat cues, whereas the low intolerance of uncertainty group will have greater activation in amygdala, insula, or other "uncertainty" areas only to the threat stimuli compared to the safe stimuli. We hypothesized a similar pattern in the SCR and pupillometry data.

- Extinction hypothesis – According to the South and Rodgers (2017) model, we hypothesized that there would be an interaction effect of group (High IU vs Low IU) and condition (Safe vs Threat) during the extinction phase. Specifically, participants in the High IU group will have greater BOLD response in the amygdala, insula, and other areas in the "uncertainty network" (Tanovic et al., 2018) to both the safe and threat cues, whereas the Low IU group will have greater BOLD response in amygdala, insula, or other "uncertainty" areas to the threat stimuli only compared to the safe stimuli. We hypothesized a similar pattern in the SCR and pupillometry data as well.

- We hypothesized that anxiety would be predicted by intolerance of uncertainty, sensory sensitivity and the amygdala and insula responses to the fear conditioning/extinction protocols.

***Study 2.2 Aim: Auditory Looming – Compare Brain Activity and Physiological Response Between the Autism (AUT) Group and the Neurotypical (NT) Group in Auditory Looming***

- Given the South & Rodger (2017) model, we predicted there would be an interaction effect between the looming (threat) and receding (safe) stimuli with the High IU group having greater BOLD response in the amygdala and insula activation to both stimuli, whereas the Low IU group will greater BOLD response in the amygdala and to the looming but not the receding stimulus. We hypothesized a similar response pattern would be found in the SCR and pupil measures.
- We hypothesized that anxiety will be predicted by intolerance of uncertainty sensory sensitivity, and the amygdala and insula responses to the auditory looming protocol.

- Given the South and Rodger (2017) model, we also hypothesized that intolerance of uncertainty could be predicted by sensory sensitivity, and amygdala and insula responses auditory looming protocol.

## General Methods and Materials

### Participants

We recruited sixty-four adults ages 17 to 40 to participate in this study. Participants signed an informed consent form approved by the university's Institutional Review Board and in accord with the Declaration of Helsinki. The autism group (AUT; *n* = 29; mean (SD) age = 25.48 (5.07); see Table 1) had a clinical diagnosis of autism and scores above autism cut-offs on the Autism Diagnostic Observation Schedule, 2nd Edition, Module 4 (Lord et al., 2000) administered by a licensed psychologist trained to research reliability standards. The neurotypical group (NT; *n* = 35; mean (SD) age = 20.14 (2.32)) consisted of typically developing adults with no reported history of head injury or diagnosis of any neurological or psychiatric condition. There were no differences in verbal comprehension or perceptual reasoning composite scores between the AUT and NT groups as measured by the Weschler Adult Intelligence Scales, Fourth Edition (Wechsler, Psychological Corporation, & Pearson Education, 2008; see Table 1). Although the AUT group working memory and processing speed scores we in the average range, the AUT group scores were had significantly lower scores on working memory and processing speed composites compared to the NT group.

Table 1
*Descriptive Statistics of Participants*

| Measure | AUT (n = 29) | | NT (n = 35) | | z-* or t-value | *p*-value | Effect |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | | |
| Male *n* | 20 | - | 22 | - | - | - | - |
| Female *n* | 9 | - | 13 | - | - | - | - |
| Age | 25.48 | 5.07 | 20.14 | 2.32 | 4.68* | <.001 | AUT > NT |
| ASQ | 28.65 | 8.10 | 16.02 | 4.85 | 5.74* | <.001 | AUT > NT |
| DASS Depression | 12.48 | 9.33 | 5.25 | 5.86 | 3.73* | <.001 | AUT > NT |
| DASS Anxiety | 11.83 | 8.00 | 5.43 | 3.99 | 3.41* | <.001 | AUT > NT |
| DASS Stress | 15.83 | 9.53 | 8.66 | 5.74 | 3.05* | .002 | AUT > NT |
| DASS Total | 40.14 | 21.21 | 19.34 | 12.58 | 4.06* | <.001 | AUT > NT |
| SP Low Registration | 40.48 | 8.37 | 31.17 | 6.75 | 4.93 | <.001 | AUT > NT |
| SP Sensory Seeking | 42.62 | 8.02 | 50.23 | 6.75 | -4.09 | <.001 | NT > AUT |
| SP Sensory Sensitivity | 42.83 | 10.44 | 35.37 | 6.41 | 3.51 | <.001 | AUT > NT |
| SP Sensory Avoidance | 44.96 | 8.18 | 36.65 | 6.35 | 4.57 | <.001 | AUT > NT |
| IUS | 38.82 | 9.90 | 30.43 | 6.62 | 4.04 | <.001 | AUT > NT |
| PSWQ | 56.58 | 13.86 | 44.86 | 15.64 | 3.14 | <.001 | AUT > NT |
| WAIS-IV Full Scale | 110.34 | 16.44 | 116.56 | 9.39 | -1.87 | .033 | NT > AUT |
| WAIS-IV VCI | 118.34 | 19.10 | 118.74 | 11.67 | -0.10 | .541 | - |
| WAIS-IV PRI | 111.59 | 18.63 | 112.12 | 9.37 | -0.14 | .568 | - |
| WAIS-IV WMI | 103.00 | 18.41 | 111.62 | 13.09 | -2.16 | .017 | NT > AUT |
| WAIS-IV PSI | 99.07 | 24.22 | 111.29 | 9.64 | -4.09* | <.001 | NT > AUT |

Note: *Signifies use of the Mann-Whitney U Test instead of t-test. ASQ = Autism Spectrum Quotient. DASS = Depression, Anxiety, and Stress Scale. SP = Adult/Adolescent Sensory Profile. IUS = Intolerance of Uncertainty Scale. WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition. VCI = Verbal Comprehension Index. PRI = Perceptual Reasoning Index. WMI = Working Memory Index. PSI = Processing Speed Index. AUT = autism group. NT = typically developing group.

**Imaging Parameters**

All MRI scans were performed using a Siemens Trio 3T MRI scanner, equipped with a 12-channel head coil. Scanning parameters included a standard T1-weighted structural imaging (TR = 1900ms; TE = 2.26ms; flip angle = 9°; matrix size = 224 x 256; field of view = 250 x 250 mm; 176 slices; slice thickness = 1mm; voxel size = 1 x 1 x 1 mm; scan duration = 3:59) and functional T2*-weighted echoplanar images (TR = 2000 ms; TE = 25ms; flip angle = 75°; matrix size = 64 x 64; field of view= 192 x 192mm; 40 slices; slice thickness = 3mm (no skip); voxel

size = 3 x 3 x 3 mm) that were coregistered with structural images for each participant and corrected for head motion using SPM's ArtRepair function, similar to the Top Jr et al. (2016) study. Functional scan duration for the fear conditioning and extinction tasks were two scans that were 520 seconds each (1040 seconds total), while the auditory looming task was 580 seconds. The baseline scan lasted 60 seconds.

**Behavioral Measures**

***Adolescent/Adult Sensory Profile***

The *Adolescent/Adult Sensory Profile* (AASP; (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001) is a 60-item questionnaire measuring four sensory processing categories: low registration, sensation seeking, sensory sensitivity, and sensation avoiding according to Dunn's model of sensory processing (Dunn, 1997). The AASP has been used in previous studies examining the relationship between atypical sensory processing, anxiety, and autism traits (Milosavljevic et al., 2016; Top Jr et al., 2019).

***Autism Spectrum Quotient***

The *Autism Spectrum Quotient* (ASQ; (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) is a 50-item questionnaire that asks participants to indicate the extent to which they can identify with statements describing behaviors and attitudes that reflect core facets of the AUT phenotype. The ASQ has been used as a dimensional measure of autism traits in clinical populations and in the general public and has also been demonstrated to be sensitive to subclinical autism traits (Bishop et al., 2004).

***Depression Anxiety Stress Scales-21***

The *Depression Anxiety Stress Scales-21* (DASS-21; (Lovibond & Lovibond, 1995) is a 21-item rating scale in which respondents are asked to rate on a 4-point Likert scale about a

range of possible events that may have occurred during the past week. The scales of the DASS-21 (depression, anxiety, and stress) have been shown to have high internal consistency ($\alpha = .97$) and yield meaningful discriminations in a variety of settings (Antony, Bieling, Cox, Enns, & Swinson, 1998).

***Intolerance of Uncertainty Scale-12***

The *Intolerance of Uncertainty Scale-12* (IUS-12; (Carleton, Norton, & Asmundson, 2007) is a 12-item measure that includes questions about the unknown regarding one's prospective anxiety (e.g., "Unforeseen events upset me greatly") and inhibitory anxiety (e.g., "Uncertainty keeps me from living a full life"). While these two subdomains can be scored separately, only the total score will be used in the current study to investigate the total contribution of this construct on anxiety in autism. The IUS-12 has been successfully used to show an association between IU and anxiety in autistic individuals (Boulter et al., 2014; Chamberlain et al., 2013; Maisel et al., 2016; Top Jr et al., 2019).

***Penn State Worry Questionnaire***

The *Penn State Worry Questionnaire* (PSWQ) is a 16-item questionnaire that measures the severity of worry thoughts in both clinical and nonclinical populations (Meyer, Miller, Metzger, & Borkovec, 1990). The PSWQ has been shown to have good discriminant validity and convergent validity; to be unrelated to other measures of depression (measured by the Beck Depression Inventory) and general anxiety (measured by the State Trait Anxiety Inventory); and to be sensitive to cognitive oriented treatment (Dear et al., 2011; Meyer et al., 1990).

***Wechsler Adult Intelligence Scale – 4th Edition***

All participants completed the Wechsler Adult Intelligence Scale – 4$^{th}$ Edition (Wechsler et al., 2008) to control for possible cognitive ability differences in our sample.

**fMRI Preprocessing**

fMRI preprocessing and analysis was completed using SPM8 and SPM12. All images were preprocessed using SPM12's slice timing, realign, coregister, normalizing and smoothing functions. SPM8's ArtRepair function was used before preprocessing to correct for any physical motion outliers. SPM8's ArtRepair processing motion adjustment and de-spiking algorithms were used after the realign processing to filter excess motion and noise associated with motion during scanning. Motion parameters and regressors were automatically estimated during the second realign function (post-ArtRepair) for the three translation (X, Y, Z) and three rotation (pitch, yaw, roll) motions. Preprocessing took place in the following order: 1) DICOMimport, 2) SPM8 ArtRepair's art_slice function, 3) SPM12 slice timing, 4) SPM12 realignment (unrepaired images), 5) SPM8 ArtRepair art_global function, 6) SPM12 realignment (ArtRepaired images), 7) SPM12 coregistration, 8) SPM12 Normalize, and 9) SPM12 Smoothing function. As recommended by the developers, individuals needing more than 20% of TRs to be repaired in a run were excluded from analyses (Mazaika, 2007, 2009; Mazaika, Glover, & Reiss, 2011).

**Eye-Tracking Apparatus and Measurement**

Pupils were recorded via an SR Research Eyelink 1000 plus MRI compatible eye tracker (spatial resolution of 0.01°) sampling at 1000 Hz. Participants were positioned in the MRI in a supine position looking at a 60.1 cm LCD screen they saw through a mirror attached to the head coil. The distance from the eye tracker camera and the mirror was approximately 90 cm. Head movements were minimized by the head coil and head cushions. Although viewing was binocular, recordings were taken from the right eye only. Prior to recording, the eye tracker was calibrated using a nine-point calibration routine. The experiment was controlled with E-Prime experiment software.

**Pupillometry Data Preparation**

Data was cleaned as recommended by Sirois & Brisson (2014), with samples that occurred during blinks and saccades removed, and then smoothed using a loess filter with a span of 0.25. The mean pupil size for the 100ms before the onset of the trial served as the baseline for a given trial, and delta pupil size for a given event was computed by subtracting this baseline value from the mean pupil size during the last 100 ms of the trial. Outlier samples greater than or less than 3 interquartile ranges from the participant's median response were fenced to the value median pupil size ±3 interquartile ranges so that we could still include the participants data in analysis while attempting to minimize possible over-estimation of the models (Kwak & Kim, 2017).

**Skin Conductance Response Collection and Data Preparation**

Skin conductance response (SCR) were collected using disposable, pre-gelled, MRI compatible electrodes placed on the palmar surface of the middle and ring fingers of the left hand centered around the top joint on each finger. MRI compatible measurement leads were snapped onto the electrodes to acquire the SCR data at 1000 Hz using the Biopac MP150 EDA-100C MRI module (Biopac Systems, Inc., Goleta, CA, USA). These data were recorded and extracted using AcqKnowledge software (Biopac Systems, Inc.) As reported by Bechara, Damasio, Damasio, and Lee (1999), we used the AcqKnowledge software's built-in Difference mathematical transformation to attenuate drift in the SCR data across the course of the experiment. We extracted the SCR delta value (SCR at the end of the trial - SCR at start of trial) within the four second presentation of the stimulus for each trial for analysis. We used the time range of +.5 to 4.5 second to control for a potentially delayed SCR response to the stimulus. This

data was then subjected to normality testing. Like the pupillometry data, SCR outliers were fenced to ±3 interquartile ranges as recommended by Kwak and Kim (2017).

### Data Collection Event Order

The data for all the studies for each participant were collected during a single visit that lasted between 1 to 2 hours. After completing the informed consent and MRI safety forms, all participants entered the MRI scanner in a supine position with the 12-channel head coil and placed in the center of the scanner. Once participants were in the scanner, the researcher setup and calibrated the eye tracking equipment and SCR equipment. Once all the equipment was properly calibrated, there was a 10 second localizing scan followed by a 60-second functional scan that was used to help the participants become acquainted with the MRI environment. Participants then complete the structural T1 scan. After the structural scan, participants completed either the fear conditioning and extinction tasks (Study 1) or the auditory looming task (Study 2) in a randomized counterbalanced order. Participants were removed from the scanner after they had completed all three tasks, unless they requested or withdrew their consent for participation in which they were removed from the scanner soon after withdrawing their consent. Two from the AUT group and one from the NT group voluntarily withdrew from the study after completing the baseline task. The number of participants reported in the Table 1 do not include the number of participants who voluntarily withdrew.

## Study 1 – Fear Conditioning and Extinction

### Study 1 Methods and Materials

#### *Fear Conditioning and Extinction Protocol*

The fear conditioning and extinction tasks are adapted from the previous Phelps et al. (2004) and Top Jr et al. (2016) fear conditioning studies (See Figure 3). The unconditioned

stimulus (UCS) was a short (300ms) burst of air delivered to the base of the neck near the larynx, similar to that used in other studies of vulnerable samples (Monk et al., 2003; South et al., 2011; Top Jr et al., 2016). The conditioned stimulus (CS) consisted of a black, horizontally-oriented rectangle or black vertically-oriented rectangle that was displayed for 4300 ms on an LCD monitor one at a time during the scan session. The CS+ trials (also referred as *threat* trials) consisted of one of the oriented rectangles (i.e., the vertical rectangle) being paired with the 300 ms UCS (airburst). Each burst of air was triggered electronically during the last 300ms of the CS+ presentation so that the CS+ and UCS co-terminated. The other stimulus orientation (i.e. the horizontal rectangle) never was associated with the airburst and served as the CS- trials (also referred to the *safe* trials). Assignment of threat or safe signal orientation was randomly assigned to each participant. Participants were instructed at the beginning of the early acquisition fMRI run that, "you may or may not receive a puff of air against your neck at the end of the picture of a black rectangle." Trials were presented in a pseudorandom order such that no more than two stimuli of the same type occurred consecutively. The fixation cross was black and contained the same number of pixels as the CS- and CS- stimuli to minimize pupil dilation changes due to changes in the visual luminance of the stimuli. Each CS trial occurred for 4000 ms + 300 ms airburst/no airburst with a jittered inter-trial interval (ITI) consisting of a central fixation cross, ranging from 11700 ms – 15700 ms. Each trial was 16000 ms to 20000 ms long.

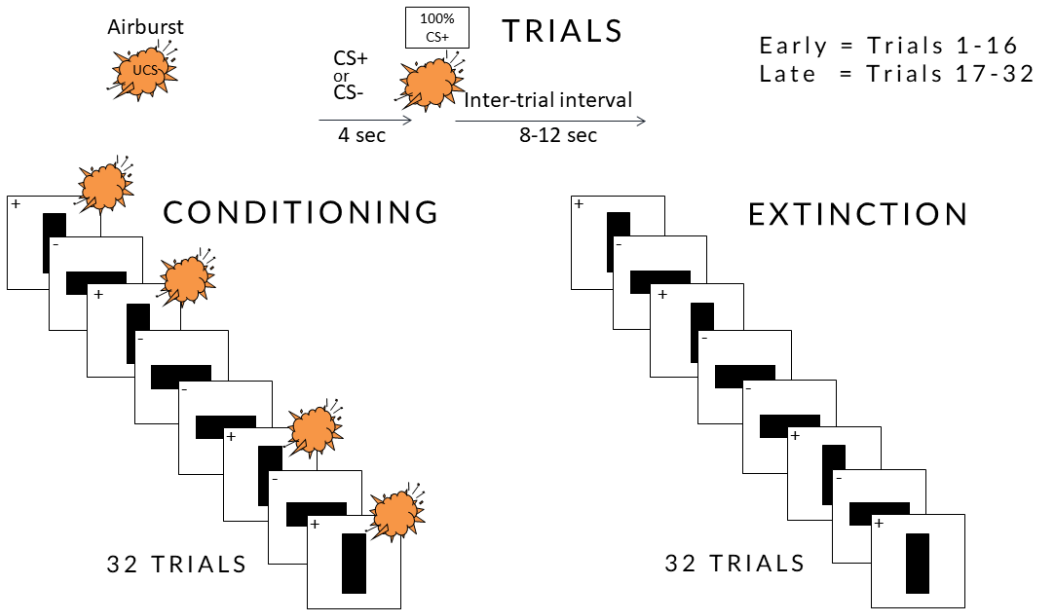


*Figure 3*. Diagram of fear conditioning task.

The task consisted of two functional runs: 1) *fear conditioning* and 2) *fear extinction*. The *fear conditioning* run included 34 trials that consisted of two learning trials (the first presentation of CS+ and CS-), 16 CS+ trials, and 16 CS- trials. The CS+ reinforcement schedule during the fear acquisition phase was set at 100%, meaning that the airburst was presented at the end of all CS+ trials. The f*ear extinction* run consisted of a total of 34 trials consisting of two learning trials, 16 unreinforced CS+ and 16 unreinforced CS- trials. The fear acquisition and fear extinction runs were divided into early (trials 3-18) and late (trial 19-34) trials similar to Phelps et al. (2004) and Top Jr et al. (2016) studies.

***Airburst Apparatus***

The airburst used during the fear conditioning task was delivered by means of a vest that closed with Velcro straps and had a ½ inch firm-yet-flexible hose threaded up through the vest and adjusted to point towards the junction of the neck and chin. The vest was connected to a tank

of compressed air secured outside the scanner room with a medical-grade valve and regulator set to 75 psi. The tank was electronically signaled via Experiment Builder software to deliver each burst of air, which was delivered during the last 300 ms of the of the CS+ presentation. Participants were exposed to a practice air burst before entering the scanner to ensure proper fit of the vest and then were placed in a supine position in the MRI scanner. Once the participant was lying down, the vest was adjusted as needed so that the airburst was directed towards the larynx.

### *Pupillometry and SCR Analysis*

A measure of delta (SCR or pupil measure at the end of the trial minus the measure at the start of the trial) for pupil and SCR responses to the CS+ and CS- was our dependent variable. To test the White et al. (2014) model we predicted delta pupil response and delta SCR response using an HLM with fixed effects of group (NT, AUT), condition (CS-, CS+), and a group-by-condition interaction each phase of the protocol. Random effects for this model consisted of the individual by-participant intercepts and random by-participant slopes for condition. To test the South and Rodger Model, a separate analysis predicting delta pupil response and SCR using an HLM with fixed effect of group (High IU, Low IU), condition (CS-, CS+), and a group-by-condition interaction each phase of the protocol. Random effects for this model consisted of the individual by-participant intercepts and random by-participant slopes for condition.

### *Fear Conditioning/Extinction fMRI Analysis*

First-level analysis regression parameters included the presentation of the CS+, CS-, airburst, ITI, and the motion regressors. We used a Canonical Hemodynamic Response Function with no derivatives to adjust for the time difference between presentation of the stimulus and expected neural blood flow. The extracted values/images of the CS+ and CS- trials were in the

second-level analyses. Second-level analyses were conducted using SPM's 2 (AUT, NT) x 2 (CS+, CS-) repeated-measure ANOVA summary statistic approach to test the White et al (2014) model. We used a family-wise corrected *p*-value of 0.05. Significant clusters of activation were labeled and defined using the xjView plugin for SPM (http://www.alivelearn.net/xjview8/). *A priori* Regions of Interest (ROIs) from previous literature were evaluated and corrected for multiple comparisons using the SPM small volume correction analysis function. A separate 2 (High IU, Low IU) x 2 (CS+, CS-) repeated-measure ANOVA using the same ROIs was used to test the South & Rodgers (2017) model.

***Regions of Interest Selection***

*A priori* Regions of Interest (ROIs) were identified from existing fear conditioning and uncertainty literature included the amygdala, medial prefrontal cortex (MPC), insula, hippocampus, dorsolateral prefrontal cortex (PFC), medial frontal gyrus, PFC, middle frontal gyrus (MFG), superior temporal pole, locus coeruleus, rostral cingulate cortex, posterior cingulate and anterior cingulate cortex (ACC) literature (Adams et al., 2011; Bach et al., 2008; Cohn et al., 2013; Mechias, Etkin, & Kalisch, 2010; Ponz et al., 2010; Top Jr et al., 2016). We created a single mask which included all of the aforementioned ROIs using the Wake Forest PickAtlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002). We used the Wake Forest PickAtlas integrated automated anatomical labeling atlas to define an ROI for each hemisphere. Because the locus coeruleus we not an identified structure in the PickAtlas, we created a 10 mm sphere around the coordinates provided by de Haan et al. (2018) and Keren et al. (2009). (x = 2, y = -38, z = -25) The estimated BOLD responses for the insula and amygdala were extracted for each run using the MarsBaR SPM toolbox.

### *Exploratory Whole-Brain Analysis*

An exploratory whole brain analysis was performed to identify significant clusters of voxels that were not captured by the ROI analysis. We used the same 2 x 2 repeated measures ANOVAs described above. Significant clusters were reported if they were 10 or more clustered voxels that were significant at family-wise corrected *p*-value of .05.

### *Predicting Anxiety*

We first wanted to determine if any of the physiological measures were associated with our anxiety measures and intolerance of uncertainty measure. The results of this analysis were used to determine the appropriateness of using the physiological variables in in future regression analyses. We used a Spearman's correlation with a Sidak correction due to the non-normal distribution of some of the variables.

We used a step-wise logistic regression to examine how sensory sensitivity, intolerance of uncertainty, level of autism characteristic, and any of the physiological measures identified in the preceding spearman correlations predict anxiety, following the method outlined by Meyer et al. (2017). The dependent variable of anxiety status was defined using a median split of the DASS-21 Anxiety score, with those below the median classified as the Low Anxiety (LA) group and those above the median classified as the High Anxiety (HA) group. We used the following steps in our analysis:

1) Linear Regression: We will first use linear regression to have the AQ to predict IUS, and AQ to predict AASP to confirm the variables are correlated with each other for proper use in a mediation analysis according to the White et al. (2014) and South and Rogers (2017) models.

2) Logistic Regression: We used the physiological measures identified in the spearman correlation above predict High Anxiety or Low Anxiety groups.
3) Logistic Regression: We used the Autism Questionnaire (AQ) to predict anxiety group.
4) Logistic Regression: We used Adolescent/Adult Sensory Profile Sensory Sensitively score (AASP) to predict anxiety group.
5) Logistic Regression: We used the Intolerance of Uncertainty Scale (IUS) to predict anxiety group.
6) Logistic Regression: We used the AQ, AASP, and IUS to predict anxiety group.
7) Logistic Regression: (If physiology measures in step 2 were predictive of anxiety measures) We used AQ, AASP, IUS, and the physiological measures from step 1 to predict anxiety group.

The steps above were repeated using the PSWQ median split to determine High and Low Anxiety groups. We used a Sidak Correction with a *p*-value of .026, as we used two separate anxiety measures.

**Study 1 Results**

***Early Fear Conditioning***

One participant from the AUT group and one participant from the NT were excluded from the fear conditioning and fear extinction analyses due to excessive motion. Analysis of the SCR data for the first 16 trials (early phase) of the fear conditioning paradigm show a main effect for condition (z = -3.73, $p$ = <.001; see Table 2 & Figure 4), with the threat cue having more SCR response than the safe cue. There were no significant main effects for group (z = .02, $p$ = .986) or for the interaction effect (z = -.06, $p$ = .554). When using the Low IU vs High IU

comparison (See Table 3), there was a significant main effect for condition (z = -3.18, *p* = <.001), but not no significant main effect for group (z = -.21, *p* = .835) nor an interaction effect (z = -.64, *p* = .522).

The pupillometry data also showed a main effect for condition (z = -2.77, *p* = .006; Threat > Safe; see Table 4 & Figure 5) but no main effect for group (z = -0.62, *p* = .535) or interaction effects (z = 1.12, *p* = .264). When splitting the participants by High IUS and Low IUS, the main effect of condition was marginally significant (z = -1.87, *p* = .062; Threat > Safe; see Table 5). The group main effect (z = 0.50, *p* = .614) and the interaction effect (z = -0.06, *p* = .554) were not significant.

Table 2
*AUT vs NT: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Fear Conditioning. AUT n = 26 NT n = 28*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.222 | .059 | -3.73 | <.001 | [-.339, -.106] | Threat > Safe |
| Group | .001 | .071 | 0.02 | .986 | [-.138, .140] | |
| Condition x Group | -.111 | .188 | -0.06 | .554 | [-.480, .257] | |
| Constant | -.126 | .049 | -2.55 | .011 | [-.222, -.029] | |

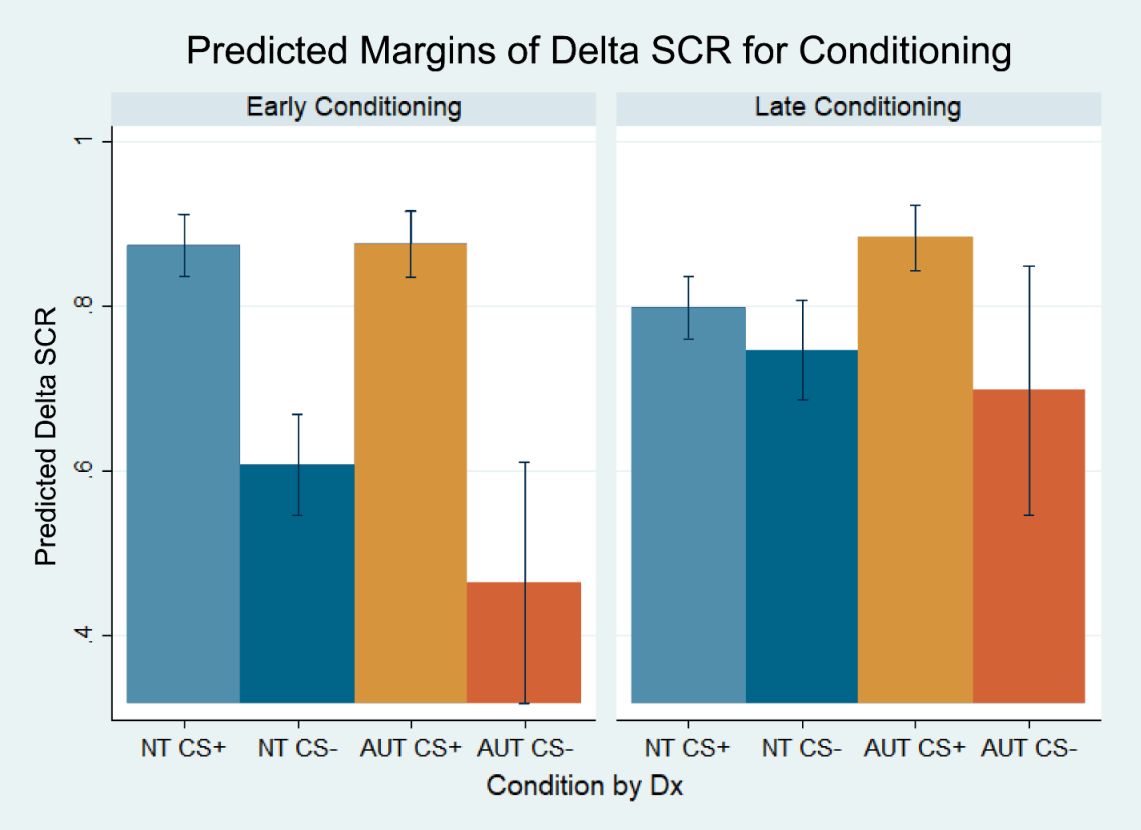


*Figure 4.* AUT vs NT: HLM of delta SCR for fearing conditioning task. NT = neurotypical group. AUT = autism group. CS+ = threat trials. CS- = safe trials.

Table 3

*Low IU vs High IU: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Fear Conditioning. High IU n = 26 (AUT n = 10) Low IU n = 28 (AUT n = 16)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.212 | .067 | -3.18 | <.001 | [-.343, -.106] | Threat > Safe |
| Group | -.014 | .071 | -0.21 | .835 | [-.153, .124] | |
| Condition x Group | -.078 | .122 | -0.64 | .522 | [-.316, .161] | |
| Constant | -.118 | .049 | -2.40 | .016 | [-.214, -.022] | |

Table 4

*AUT vs NT: HLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Fear Conditioning. AUT n = 21 NT n = 23*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -37.78 | 13.64 | -2.77 | .006 | [-64.51, -11.04] | Threat > Safe |
| Group | -11.35 | 18.31 | -0.62 | .535 | [-47.24, 24.54] | |
| Condition x Group | 22.07 | 19.78 | 1.12 | .264 | [-16.69, 60.83] | |
| Constant | 24.51 | 12.63 | 1.95 | .051 | [-0.23, 49.25] | |

Table 5

*Low IU vs High IU: HLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Fear Conditioning. High IU n = 21(AUT n = 14) Low IU n = 23 (AUT n = 7)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -25.63 | 13.71 | -1.87 | .062 | [-52.51, 1.24] | Threat > Safe |
| Group | 9.24 | 18.31 | 0.50 | .614 | [-26.63, 45.11] | |
| Condition x Group | -3.47 | 19.78 | -0.18 | .861 | [-42.26, 35.31] | |
| Constant | 14.72 | 12.64 | 1.16 | .244 | [-10.05, 39.50] | |

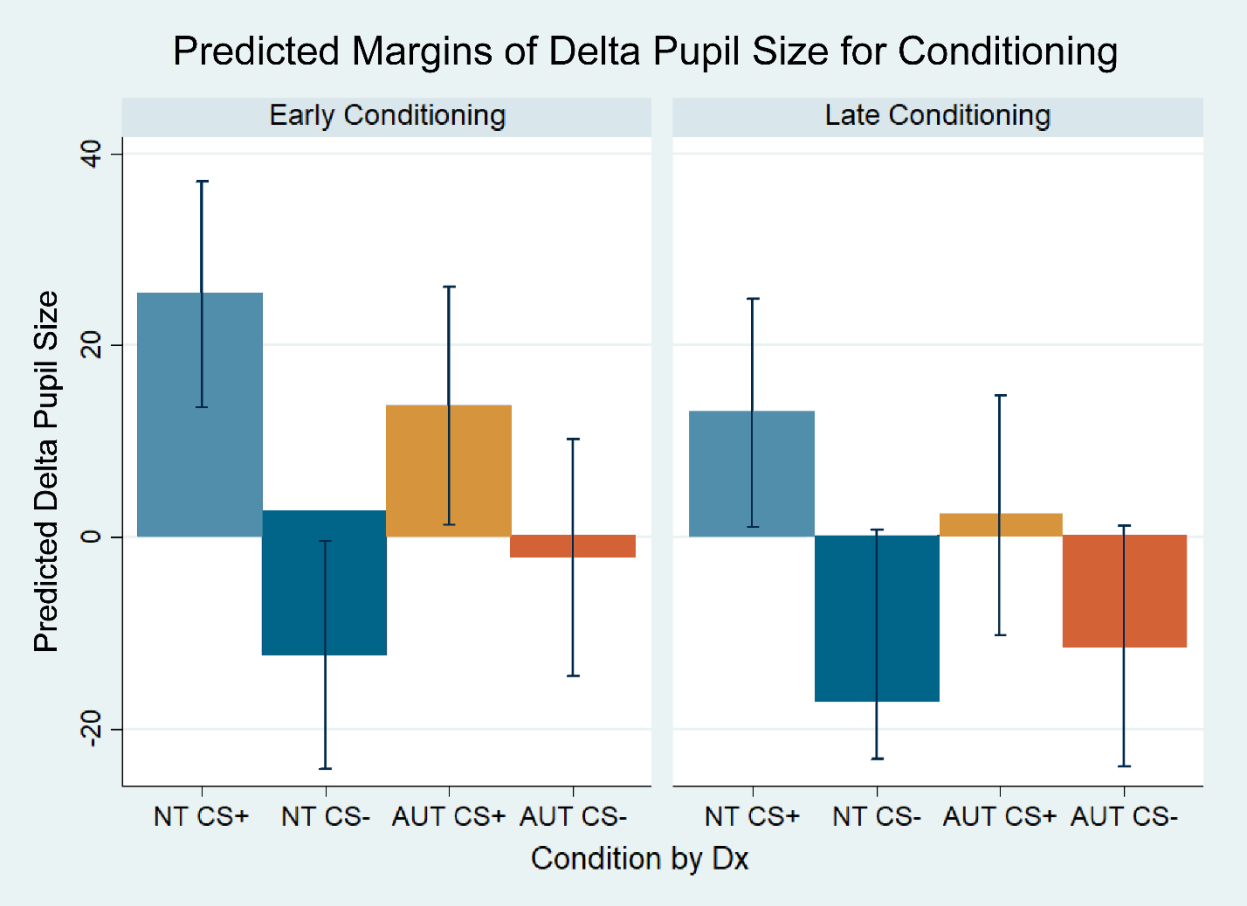


*Figure 5.* AUT vs NT: HLM of delta pupil size for fearing conditioning task. NT = neurotypical group. AUT = autism group. CS+ = threat trials. CS- = safe trials.

ROI analysis of the early fear conditioning trial showed a main effect for condition with greater activity to the threat cues than and safe cues in a number of critical brain regions as shown in Table 6 & Figure 6. The significant clusters include the right and left insula, right and left posterior cingulate, right and left medial frontal gyrus, and the Brodmann area 30. There were no significant main effects for diagnostic group nor were there significant interaction effects. When using High IUS and Low IUS groups (See Table 7), there were significant main effects for condition in the right and left insula, right and left superior temporal gyrus, right middle frontal gyrus, right inferior frontal gyrus, right middle temporal gyrus, and right temporal pole, and there were no group or interaction effects.

Table 6

*AUT vs NT: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Early Fear Conditioning Using a Small Volume Correction with the a priori Regions of Interest. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Insula | R | 34, -24, 14 | 33.53 | <.001 | Threat > Safe |
| | | 36, -16, 10 | 24.52 | .026 | Threat > Safe |
| Insula | L | -34, 20, 8 | 28.08 | .007 | Threat > Safe |
| Posterior Cingulate | R | 22, -60, 10 | 27.29 | .009 | Threat > Safe |
| Posterior Cingulate | L | -22, -62, 4 | 34.59 | .001 | Threat > Safe |
| Medial Frontal Gyrus | R | 6, 4, 56 | 31.91 | .002 | Threat > Safe |
| Medial Frontal Gyrus | L | -8, 8, 40 | 28.34 | .006 | Threat > Safe |
| Brodmann Area 30 | L | -16, -68, 8 | 23.45 | .040 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| Null | | | | | |

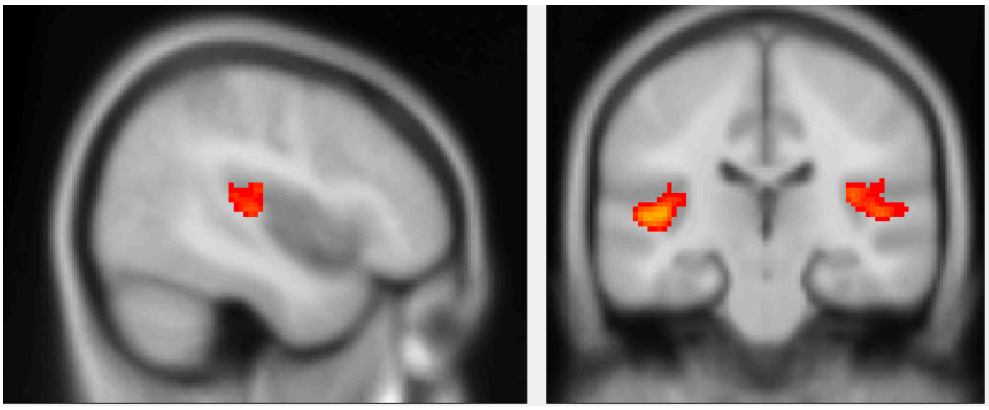

*Figure 6.* AUT vs NT: Significant insula activation clusters of activation during early fear conditioning task threat (CS+) > Safe (CS-).

Table 7

*Low IU vs High IU: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Early Fear Conditioning using a Small Volume Correction with the a priori Regions of Interest using High IU and Low IU Group. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Insula | R | 36, -22, 12 | 86.29 | <.001 | Threat > Safe |
| | | 34, -14, 16 | 42.47 | <.001 | Threat > Safe |
| | | 32, 24, 2 | 53.05 | <.001 | Threat > Safe |
| | | 36, 12, 14 | 29.62 | .003 | Threat > Safe |
| Superior Temporal Gyrus | L | -44, -24, 0 | 66.76 | <.001 | Threat > Safe |
| | | -52, -32, 8 | 58.53 | <.001 | Threat > Safe |
| | | -52, -40, 10 | 35.94 | <.001 | Threat > Safe |
| Superior Temporal Gyrus | R | 58, -40, 10 | 50.63 | <.001 | Threat > Safe |
| Insula | L | -34, 20, 8 | 58.32 | <.001 | Threat > Safe |
| | | -32, 22, 0 | 55.01 | <.001 | Threat > Safe |
| | | -38, -20, 8 | 56.30 | <.001 | Threat > Safe |
| | | -32, -24, 12 | 50.86 | <.001 | Threat > Safe |
| | | -34, -30, 20 | 44.44 | <.001 | Threat > Safe |
| Middle Frontal Gyrus | R | 38, -10, 48 | 53.53 | <.001 | Threat > Safe |
| | | 32, -6, 54 | 25.56 | .015 | Threat > Safe |
| | | 56, 0, 42 | 35.77 | <.001 | Threat > Safe |
| | | 18, -14, 66 | 26.49 | .011 | Threat > Safe |
| Inferior Frontal Gyrus | R | 38, 24, -6 | 39.59 | <.001 | Threat > Safe |
| Middle Temporal Gyrus | R | 44, -62, 8 | 29.06 | .004 | Threat > Safe |
| | | 54, -20, -8 | 31.72 | .002 | Threat > Safe |
| Temporal Pole | R | 50, -56, 8 | 23.96 | .028 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| Null | | | | | |

Whole Brain exploratory analysis is presented in Table 8. There were multiple areas of the brain that showed greater activation for the threat cues compared to the safe cues. There was significantly greater activation for the AUT group in the left inferior temporal gyrus. The interaction effects were not significant. Whole brain exploratory analysis when using the High IUS and Low IUS group is shown in Table 9 and indicate multiple areas of activation when comparing threat to safe cues. There were no main effects for group nor an interaction effect.

Table 8
*AUT vs NT: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Fear Conditioning. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Lingual Gyrus | R | 16, -88, 0 | 85.27 | <.001 | Threat > Safe |
| | | 12, -64, 0 | 30.33 | <.001 | Threat > Safe |
| Lingual Gyrus | L | -12, -88, -4 | 62.60 | <.001 | Threat > Safe |
| | | -20, -54, -2 | 29.10 | .013 | Threat > Safe |
| Superior Temporal Gyrus | R | 54, -16, 2 | 40.06 | <.001 | Threat > Safe |
| Superior Temporal Gyrus | L | -42, -28, 8 | 53.20 | <.001 | Threat > Safe |
| Brodmann Area 13 | R | 36, -24, 14 | 40.45 | <.001 | Threat > Safe |
| Precentral Gyrus | L | -38, -18, 38 | 33.19 | .003 | Threat > Safe |
| | | -46, -16, 36 | 30.23 | .009 | Threat > Safe |
| Putamen | R | 22, 4, -6 | 32.60 | .004 | Threat > Safe |
| Medial Frontal Gyrus | R | 6, 4, 56 | 31.91 | .005 | Threat > Safe |
| Claustrum | R | 30, 18, 0 | 29.59 | .011 | Threat > Safe |
| Brodmann Area 24 | L | -6, 6, 38 | 28.65 | .016 | Threat > Safe |
| Brodmann Area 4 | R | 22, -28, 62 | 28.36 | .018 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Inferior Temporal Gyrus | L | -40, -72, -4 | 42.41 | <.001 | AUT > NT |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

Table 9

*Low IU vs High IU: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Fear Conditioning using High IU and Low IU group. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Lingual Gyrus | R | 16, -88, 0 | 201.70 | <.001 | Threat > Safe |
| | | 12, -64, 0 | 30.33 | <.001 | Threat > Safe |
| Lingual Gyrus | L | -12, -88, -4 | 139.83 | <.001 | Threat > Safe |
| | | -20, -54, -2 | 29.10 | .013 | Threat > Safe |
| Superior Temporal Gyrus | R | -44, -26, 6 | 120.46 | <.001 | Threat > Safe |
| Precentral Cyrus | L | -38, -18, 38 | 79.26 | <.001 | Threat > Safe |
| | | -56, -4, 16 | 62.00 | <.001 | Threat > Safe |
| | | -16, -30, 64 | 47.10 | <.001 | Threat > Safe |
| Precentral Gyrus | R | 36, -16, 42 | 66.66 | <.001 | Threat > Safe |
| | | -16, -30, 64 | 47.10 | <.001 | Threat > Safe |
| Insula | R | 36, -24, 8 | 96.59 | <.001 | Threat > Safe |
| Superior Frontal Gyrus | R | 6, 2, 58 | 72.24 | <.001 | Threat > Safe |
| Putamen | R | 22, 2, -6 | 65.59 | <.001 | Threat > Safe |
| | L | -24, -2, 0 | 44.71 | <.001 | Threat > Safe |
| Thalamus | R | 6, -12, 2 | 52.02 | <.001 | Threat > Safe |
| Brodmann Area 18 | R | 8, -96, 12 | 37.70 | .001 | Threat > Safe |
| Declive | R | 12, -66, -20 | 31.44 | .006 | Threat > Safe |
| | L | -8, -68, -24 | 29.38 | .014 | Threat > Safe |
| Extra-Nuclear | R | 34, 12, 16 | 29.63 | .012 | Threat > Safe |
| Precuneus | L | -14, -68, 36 | 28.98 | .016 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | | | | |
| **Interaction: Condition x Group** | | | | | |
| Null | | | | | |

### *Late Fear Conditioning*

Analysis of the last 16 trials of the fear conditioning task (late phase) show a significant main effect for learning condition for the SCR measures (z = -2.45 *p* = .014; Threat > Safe; see

Table 10 & Figure 4). There was also a significant main effect for group (z = 1.97, *p* = .050) with AUT group showing a greater SCR response than the NT group. There was no significant interaction effect for SCR (z = -0.91, *p* = .361). When using the High IU vs Low IU group comparison, the main effects of group (z = -0.18, *p* = .858) and condition (z = -1.61, *p* = .108) were not significant (See Table 11).

Analysis of the pupillometry data did not show any significant main effect for condition (z = -1.65, *p* = .099; see Table 12 & Figure 5), main effect for group (z = -0.65, *p* = .513), nor a significant interaction effect (z = 0.51, *p* = .609). There were no significant main effects for condition (z = -057, *p* = .571; See Table 13), for group (z = 1.06, *p* = .290), nor a interaction effect (z = -1.05, *p* = .292) when splitting the group by High IUS and Low IUS.

Table 10
*AUT vs NT: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Fear Conditioning. AUT n = 26 NT n = 28*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.112 | .046 | -2.45 | .014 | [-.202, -.023] | Threat > Safe |
| Group | .086 | .044 | 1.97 | .050 | [.000, .171] | AUT > NT |
| Condition x Group | -.135 | .148 | -0.91 | .361 | [-.425, .155] | |
| Constant | -.201 | .030 | -6.64 | <.001 | [-.260, -.142] | |

Table 11
*Low IU vs High IU: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Fear Conditioning. High IU n = 26 (AUT n = 10) Low IU n = 28 (AUT n = 16)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.082 | .051 | -1.61 | .108 | [-.183, -.018] | |
| Group | .007 | .044 | -0.18 | .858 | [-.094, .079] | |
| Condition x Group | -.134 | .09 | -1.43 | .153 | [-.317, .050] | |
| Constant | -.156 | .030 | -5.11 | <.001 | [-.217, -.096] | |

Table 12
*AUT vs NT: HLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Fear Conditioning. AUT n = 21 NT n = 23*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -24.11 | 14.62 | -1.65 | .099 | [-52.76, 4.54] | |
| Group | -11.36 | 17.39 | -0.65 | .513 | [-45.45, 22.71] | |
| Condition x Group | 10.77 | 21.08 | 0.51 | .609 | [-30.55, 52.08] | |
| Constant | 13.34 | 12.03 | 1.11 | .268 | [-10.26, 36.93] | |

Table 13
*Low IU vs High IU: HLM analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Fear Conditioning. High IU n = 21(AUT n = 14) Low IU n = 23 (AUT n = 7)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -8.27 | 14.58 | -0.57 | .571 | [-36.86, 20.32] | |
| Group | 18.39 | 17.36 | 1.06 | .290 | [-15.65, 52.43] | |
| Condition x Group | .22.18 | 21.06 | -1.05 | .292 | [-63.47, 19.11] | |
| Constant | -1.00 | 12.07 | -0.08 | .934 | [-24.66, 22.65] | |

ROI analysis of the late fear condition task showed a significant main effect for condition with threat cues having greater activation than safe cues in the following brain structures (see Table 14 & and Figure 7): right medial orbital frontal cortex, right and left insula, and right and left ACC. The main effect group and the interaction effect were not significant. ROI analysis using the High IUS and Low IUS group showed significant activations in the left and right insula, right inferior frontal gyrus, and right middle orbital frontal cortex (see Table 15). There were no significant group or interaction effects.

The exploratory analysis showed significant activation difference between safe and threat cues in several clusters listed in Table 16. The exploratory analysis did not reveal any significant clusters for the group main effect or the interaction effect. Exploratory analysis using the High IUS and Low IUS groups showed multiple clusters of activations when comparing safe to threat cues, but no group effects or interactions effects (see Table 22).

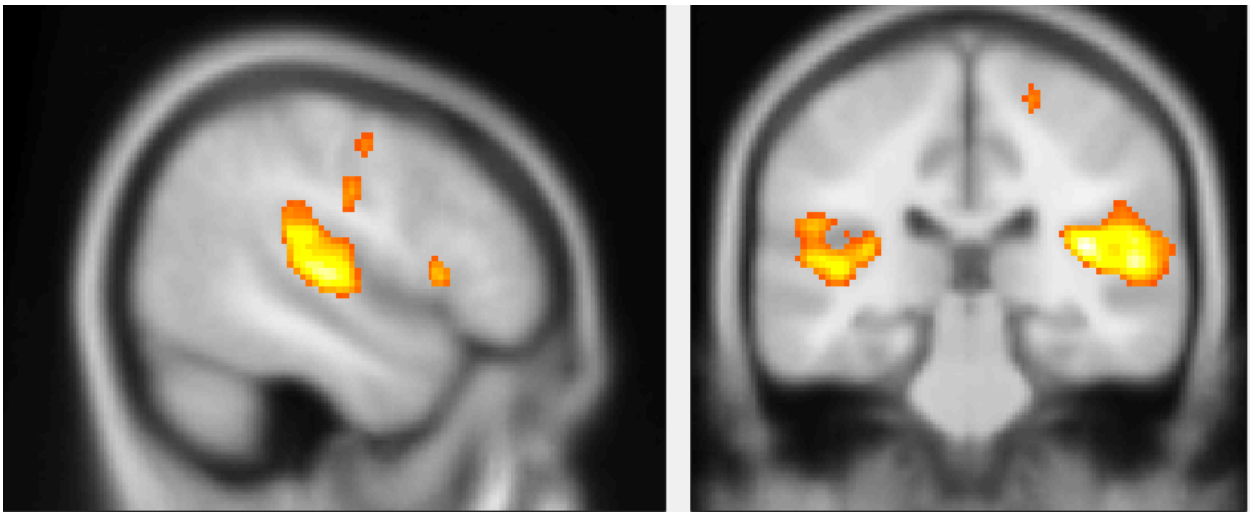

*Figure 7.* Significant clusters of activation during late fear conditioning task threat > safe.

Table 14
*AUT vs NT: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Late Fear Conditioning using a Small Volume Correction with the a priori Regions of Interest. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Medial OFC | R | 0, 4, 50 | 48.04 | <.001 | Threat > Safe |
| Anterior Cingulate Cortex | R | 8, 14, 36 | 32.04 | .002 | Threat > Safe |
| Anterior Cingulate Cortex | L | -8, 10, 38 | 45.56 | <.001 | Threat > Safe |
| Insula | R | 38, -28, 18 | 47.70 | <.001 | Threat > Safe |
| | | 36, 22, 8 | 37.94 | <.001 | Threat > Safe |
| | | 34, 16, 0 | 34.08 | .001 | Threat > Safe |
| Insula | L | -34, -22, 8 | 45.42 | <.001 | Threat > Safe |
| | | -32, 18, 0 | 32.21 | .002 | Threat > Safe |
| | | -44, 4, 0 | 27.14 | .010 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| Null | | | | | |

Table 15

*Low IU vs High IU: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Late Fear Conditioning using a Small Volume Correction with the a priori Regions of Interest. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Insula | R | 34, -24, 14 | 50.24 | <.001 | Threat > Safe |
| | | 36, -14, 16 | 25.11 | .017 | Threat > Safe |
| | | 32, 22, 6 | 36.98 | <.001 | Threat > Safe |
| | | 34, 16, 0 | 27.61 | .001 | Threat > Safe |
| Insula | L | -34, 22, 8 | 46.92 | <.001 | Threat > Safe |
| | | -32, 20, 0 | 33.41 | .001 | Threat > Safe |
| | | -44, 4, 0 | 27.61 | .007 | Threat > Safe |
| Inferior Frontal Gyrus | R | 42, 18, -6 | 26.72 | .014 | Threat > Safe |
| Middle Orbital Frontal Cortex | R | 44, 18, 2 | 24.08 | .026 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| Null | | | | | |

Table 16

*AUT vs NT: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Fear Conditioning. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Brodmann Area 13 | R | 38, .28, 14 | 66.38 | <.001 | Threat > Safe |
| | | 44, -22, 8 | 62.91 | <.001 | Threat > Safe |
| | | 36, 22, 8 | 37.94 | .001 | Threat > Safe |
| Brodmann Area 13 | L | -36, 20, 8 | 46.85 | <.001 | Threat > Safe |
| Superior Temporal Gyrus | R | 54, -26, 8 | 59.75 | <.001 | Threat > Safe |
| Cuneus | R | 18, -88, 2 | 66.01 | <.001 | Safe > Threat |
| Ceneus | L | -14, -70, 6 | 28.70 | .017 | Threat > Safe |

| | | | | | |
|---|---|---|---|---|---|
| Lingual Gyrus | L | -12, -90, 0 | 50.37 | <.001 | Threat > Safe |
| Middle Temporal Gyrus | L | -44, -26, 6 | 49.10 | <.001 | Threat > Safe |
| Precentral Gyrus | L | -40, -18, 36 | 46.60 | <.001 | Threat > Safe |
| Precentral Gyrus | R | 46, -10, 48 | 33.92 | .003 | Threat > Safe |
| | | 60, 0, 14 | 31.74 | .006 | Threat > Safe |
| PostCentral Gyrus | L | -48, -18, 26 | 45.55 | <.001 | Threat > Safe |
| PostCentral Gyrus | R | 20, -30, 62 | 31.84 | .005 | Threat > Safe |
| Medial Frontal Gyrus | L + R | 0, 4, 50 | 48.04 | <.001 | Threat > Safe |
| Cingulate Gyrus | L | -10, 8, 36 | 47.58 | <.001 | Threat > Safe |
| Brodmann Area 24 | R | 8, 12, 34 | 32.95 | <.001 | Threat > Safe |
| Brodmann Area 47 | L | -32, 18, 0 | 32.21 | .005 | Threat > Safe |
| Red Nucleus | R | 6, -20, -2 | 42.98 | .006 | Threat > Safe |
| Midbrain | L | -4, -22, -2 | 31.35 | .006 | Threat > Safe |
| Brodmann Area 6 | R | 46, -12, 32 | 41.02 | <.001 | Threat > Safe |
| Brodmann Area 45 | R | 50, 18, 4 | 37.38 | .001 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | NS | NS | NS | |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

Table 17

*Low IU vs High IU: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Fear Conditioning. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Cuneus | R | 18, -88, 2 | 80.32 | <.001 | Safe > Threat |
| Cuneus | L | -14, -70, 6 | 29.42 | .013 | |
| Superior Temporal Gyrus | R | 46, -22, 8 | 68.54 | <.001 | |
| Brodmann Area 17 | L | -12, -90, 0 | 57.65 | <.001 | |
| Brodmann Area 6 | L | -4, 2, 52 | 50.70 | <.001 | |
| Precentral Gyrus | L | -40, -18, 36 | 49.32 | <.001 | |
| Insula | L | -36, 22, 8 | 48.48 | <.001 | |
| Red Nucleus | R | 6, -20, -2 | 44.67 | <.001 | |
| Brodmann Area 6 | R | 46, -12, 32 | 42.21 | <.001 | |

| | | | | |
|---|---|---|---|---|
| Brodmann Area 18 | R | 10, -96, 18 | 40.50 | <.001 |
| Brodmann Area 45 | R | 50, 18, 4 | 40.14 | <.001 |
| Extra-Nuclear | R | 32, 18, 0 | 37.25 | .001 |
| Lingual Gyrus | R | 2, -84, -10 | 36.62 | .001 |
| Precentral Gyrus | R | 46, -10, 48 | 35.41 | .002 |
| | | 60, 0, 14 | 31.63 | .006 |
| | | 38, -16, 42 | 31.30 | .007 |
| Post Central Gyrus | R | 20, -30, 62 | 34.10 | .002 |
| Post Central Gyrus | L | -20, -30, 60 | 27.42 | .027 |
| Cingulate Gyrus | L | -10, -16, 40 | 27.94 | .022 |
| **Main Effect: Group** | | | | |
| Null | | NS | NS | NS |
| **Interaction: Condition x Group** | | | | |
| Null | | NS | NS | NS |

***Early Extinction***

Analysis of the SCR data for the first 16 trials of the Extinction paradigm did not reveal a main effect for condition for groups divided according to autism diagnosis status (z = -.046, *p* = .647; see Table 18 & Figure 8). There was a significant main effect for group (z = 1.97, *p* = .049) with the AUT group having greater SCR responses during the task compared to the NT group. The interaction effect of early extinction was not significant (z = -.06, *p* = .554). When using the High IU vs Low IU grouping (See Table 19), there were not significant main effect for group (z = -0.21, *p* = .831), main effect for condition (z = -0.04, *p* = .972), nor interaction effects z = -0.15, *p* = .879).

The pupillometry data did not reveal any significant effects for the main effect of condition (z = 1.65, *p* = .099; see Table 20 & Figure 9), the main effect for group (z = -0.65, *p* = .513), and the interaction effect (z = 0.51, *p* = .609). The analysis spitting the group by High IUS and Low IUS yielded null results (See Table 21).

Table 18

*AUT vs NT: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for Early Extinction. AUT n = 26 NT n = 28*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.004 | .008 | -0.46 | .647 | [-.020, .012] | |
| Group | .039 | .020 | 1.97 | .049 | [0, .0778] | AUT > NT |
| Condition x Group | .007 | .012 | 0.56 | .575 | [-.017, .030] | |
| Constant | -.104 | .014 | -7.50 | <.001 | [-.131, -.077] | |

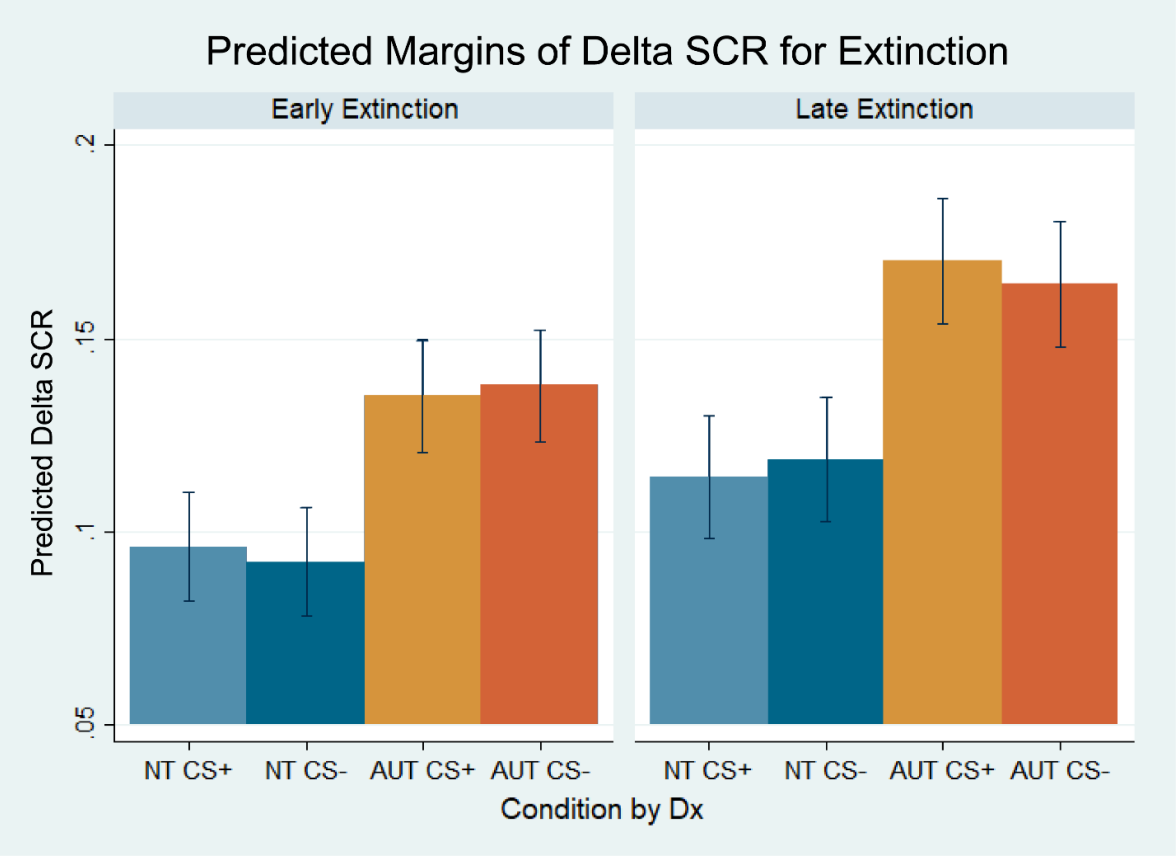


*Figure 8.* AUT vs NT: HLM of delta SCR for fear extinction task. NT = neurotypical group. AUT = autism group. CS+ = threat trials. CS- = safe trials.

Table 19

*Low IU vs High IU: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for Early Extinction. (Group = Low IU vs High IU). High IU n = 26 (AUT n = 10) Low IU n = 28 (AUT n = 16)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.001 | .008 | -0.04 | .972 | [-.015, .016] | |
| Group | .004 | .021 | -0.21 | .831 | [-.044, .036] | |
| Condition x Group | -.002 | .012 | -0.15 | .879 | [-.025, .021] | |
| Constant | -.083 | .014 | -5.95 | <.001 | [-.110, -.056] | |

Table 20

*AUT vs NT: HLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Extinction. AUT n = 21 NT n = 23*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | 1.41 | 13.71 | 0.10 | .918 | [25.45, 28.28] | |
| Group | 15.73 | 14.31 | 1.10 | .272 | [-12.33, 43.79] | |
| Condition x Group | 1.85 | 19.11 | 0.10 | .923 | [-35.61, 39.31] | |
| Constant | 1.86 | 10.26 | 0.18 | .856 | [-18.25, 21.97] | |

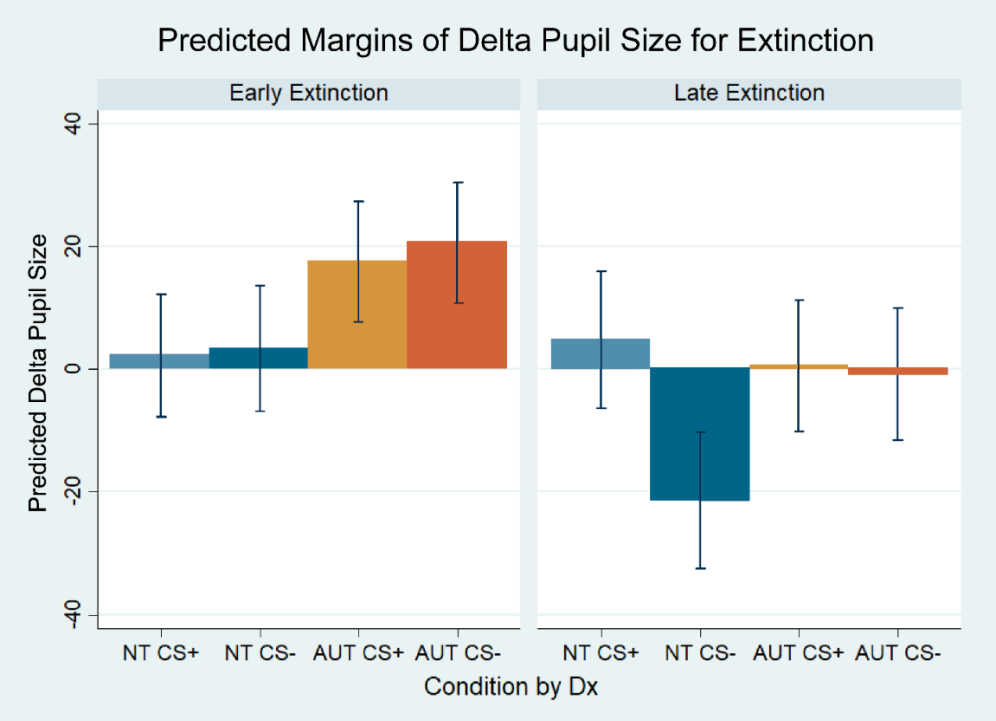


*Figure 9.* AUT vs NT: HLM of delta pupil size for fear extinction task. NT = neurotypical group. AUT = autism group. CS+ = threat trials. CS- = safe trials.

Table 21
*Low IU vs High IUHLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Extinction (Group = Low IU vs High IU). High IU n = 21(AUT n = 14) Low IU n = 23 (AUT n = 7)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -4.75 | 12.88 | -0.37 | .712 | [-29.99, 20.48] | |
| Group | 1.92 | 14.52 | 0.13 | .895 | [-26.53, 30.37] | |
| Condition x Group | 15.73 | 19.20 | 0.82 | .413 | [-21.91, 53.36] | |
| Constant | 9.07 | 9.69 | 0.94 | .349 | [-9.92, 28.05] | |

The ROI analyses were all null (See Tables 27 for AUT vs NT; See Table 23 for Low IU vs High IU). Exploratory analysis using the AUT vs NT comparison (see Table 24 & Figure 10) of the early extinction phase showed greater activation to CS+ (threat) cues than CS- (safe) cues in the following areas: left lingual gyrus, right lingual gyrus, and left Brodmann area 18. The right Brodmann area 17 showed greater activation for CS- compared to the CS+. There was no significant main effect for group nor an interaction effect. The analysis using High IUS and Low IUS groups showed a similar pattern (see Table 25)

Table 22
*AUT vs NT: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Early Fear Extinction using a Small Volume Correction with the a priori Regions of Interest. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| | Null | | | | |
| **Main Effect: Group** | | | | | |
| | Null | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| | Null | | | | |

Table 23

*Low IU vs High IU: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Early Fear Extinction using a Small Volume Correction with the a priori Regions of Interest. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| | Null | | | | |
| **Main Effect: Group** | | | | | |
| | Null | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| | Null | | | | |

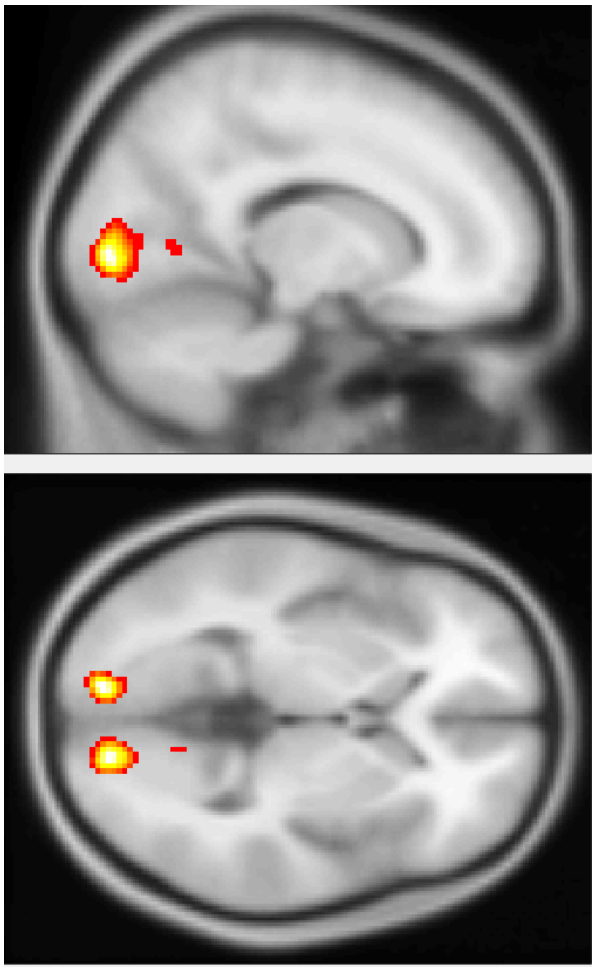

*Figure 10.* Significant clusters of activation during early extinction task.

Table 24
*AUT vs NT: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Extinction. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Lingual Gyrus | L | -11, -88, 0 | 126.54 | <.001 | Threat > Safe |
| Lingual Gyrus | R | 16, -85, 0 | 124.33 | <.001 | Threat > Safe |
| | | 12, -62, 2 | 56.27 | .004 | Threat > Safe |
| Brodmann Area 18 | L | -14, -84, 14 | 27.79 | .032 | Threat > Safe |
| Brodmann Area 17 | R | 2, -82, -10 | 56.27 | <.001 | Safe > Threat |
| **Main Effect: Group** | | | | | |
| Null | | NS | NS | NS | |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

Table 25
*Low IU vs High IU: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Early Extinction. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Brodmann Area 17 | R | 14, -88, 2 | 130.83 | <.001 | |
| Brodmann Area 17 | L | -12, -90, 0 | 130.23 | <.001 | |
| Brodmann Area 18 | L | -14, -86, 14 | 28.63 | .023 | |
| Lingual Gyrus | L | -2, -82, -10 | 55.47 | <.001 | |
| Lingual Gyrus | R | 12, -62, 2 | 34.99 | .002 | |
| Ceneus | R | 12, -98, 14 | 31.82 | .007 | |
| **Main Effect: Group** | | | | | |
| Null | | NS | NS | NS | |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

### *Late Extinction*

Analysis of the SCR data for the last 16 trials of the Extinction paradigm did not reveal a main effect for condition (z = 0.58, *p* = .651; see Table 26 & Figure 8). There was a significant main effect for group with the AUT group showing greater SCR response than the NT group (z = 3.56, *p* = <.001). No significant interaction effects were found (z = -0.95, *p* = .343). When splitting the group by High IU and Low IU, no effects were significant (See Table 27).

The pupillometry data did not reveal any significant effects for the main effect of condition (z = -1.84, *p* = .066; see Table 28 & Figure 9), the main effect for group (z = -0.28, *p* = .778), and the interaction effect (z = 1.26, *p* = .208). A similar pattern of pupil activity was found when splitting the group by High IU and Low IU (See Table 29).

Table 26
*AUT vs NT: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for Late Extinction. AUT n = 26 NT n = 28*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | .005 | .008 | 0.58 | .651 | [-.011, .019] | |
| Group | .056 | .016 | 3.56 | <.001 | [.025, .087] | ASD > NT |
| Condition x Group | -.011 | .011 | -0.95 | .343 | [-.032, .011] | |
| Constant | -.086 | .011 | -7.80 | <.001 | [-.107, -.064] | |

Table 27
*Low IU vs High IU: HLM Analysis of SCR Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for Late Extinction. High IU n = 26 (AUT n = 10) Low IU n = 28 (AUT n = 16)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -.003 | .007 | 0.48 | .630 | [-.018, .011] | |
| Group | .009 | .017 | 0.53 | .593 | [-.024, .043] | |
| Condition x Group | .007 | .011 | 0.59 | .556 | [-.015, .028] | |
| Constant | -.062 | .012 | -5.41 | <.001 | [-.085, -.040] | |

Table 28
*AUT vs NT: HLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Extinction. AUT n = 21 NT n = 23*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -26.47 | 14.39 | -1.84 | .066 | [-54.68, 1.73] | |
| Group | -4.48 | 15.87 | -0.28 | .778 | [-35.59, 26.64] | |
| Condition x Group | 25.14 | 19.95 | 1.26 | .208 | [-13.96, 64.24] | |
| Constant | 4.98 | 11.49 | 0.43 | .665 | [-17.54, 27.49] | |

Table 29
*Low IU vs High IU: HLM Analysis of Pupil Data for the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Extinction. High IU n = 21(AUT n = 14) Low IU n = 23 (AUT n = 7)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition | -5.58 | 13.48 | -0.41 | .679 | [-32.01, 20.84] | |
| Group | -6.67 | 16.00 | 0.42 | .677 | [-24.69, 38.04] | |
| Condition x Group | -17.42 | 20.03 | -0.87 | .384 | [-56.69, 21.84] | |
| Constant | -0.46 | 10.80 | -0.04 | .966 | [-21.63, 20.72] | |

The ROI analysis did not yield any significant main effects for condition or group (see Table 30). Interaction effects were not significant. Splitting the participants by High IUS and Low IUS did not change the results (see Table 31)

The exploratory whole brain analysis showed a significant main effect for condition (CS- > CS+) in left lingual gyrus, and right lingual gyrus. No significant main effects for group or interaction effects were found (see Table 32). A similar pattern was found when using High IUS and Low IUS as the group variable (see Table 33).

Table 30

*AUT vs NT: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Late Fear Extinction using a Small Volume Correction with the a priori Regions of Interest. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| | Null | | | | |
| **Main Effect: Group** | | | | | |
| | Null | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| | Null | | | | |

Table 31

*Low IU vs High IU: Contrast of Threat (CS+) and Safe (CS-) Stimuli in for the Late Fear Extinction using a Small Volume Correction with the a priori Regions of Interest using High IU and Low IU group. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| | Null | | | | |
| **Main Effect: Group** | | | | | |
| | Null | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| | Null | | | | |

Table 32
*AUT vs NT: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Extinction. AUT n = 28 NT n = 34*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Lingual Gyrus | L | -12, -90, -2 | 123.47 | <.001 | Safe > Threat |
| Lingual Gyrus | R | 17, -85, -2 | 109.82 | <.001 | Safe > Threat |
| **Main Effect: Group** | | | | | |
| Null | | NS | NS | NS | |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

Table 33
*Low IU vs High IU: Exploratory Whole Brain Analysis of the Contrast of Threat (CS+) and Safe (CS-) Stimuli for the Late Extinction using High IU and Low IU group. High IU n =27 (AUT = 18) Low IU n = 35 (AUT n = 10).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Lingual Gyrus | L | -12, -90, -2 | 119.48 | <.001 | Safe > Threat |
| Lingual Gyrus | R | 16, -88, 2 | 112.61 | <.001 | Safe > Threat |
| **Main Effect: Group** | | | | | |
| Null | | NS | NS | NS | |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

### *Predicting Anxiety Status*

Results from the Spearman correlation between the anxiety/intolerance of uncertainty measures and the physiological measures are listed in Table 34. None of the brain activation or psychophysiological measures were significantly correlated to the anxiety or intolerance of

uncertainty measures, and we did not use any of the psychophysiological measures in the subsequent analyses.

Table 34
*Spearman Correlation Analysis for Fear Conditioning and Extinction Tasks with Sidak's Correction.*

| Physiological Measure | DASS | PSWQ | IUS |
|---|---|---|---|
| Early Fear Conditioning Threat Amygdala | .11 | .07 | -.04 |
| Early Fear Conditioning Safe Amygdala | .09 | -.05 | .00 |
| Early Fear Conditioning Threat Insula | .15 | .00 | -.09 |
| Early Fear Conditioning Safe Insula | .31 | .03 | .12 |
| Late Fear Conditioning Threat Amygdala | .16 | .07 | .12 |
| Late Fear Conditioning Safe Amygdala | -.09 | .03 | -.20 |
| Late Fear Conditioning Threat Insula Late | -.09 | .04 | -.17 |
| Late Fear Conditioning Safe Insula | .24 | .02 | .04 |
| Early Extinction Threat Amygdala | -.05 | -.17 | .04 |
| Early Extinction Safe Amygdala | .04 | -.01 | .13 |
| Early Extinction Threat Insula | .02 | -17 | .07 |
| Early Extinction Safe Insula | .02 | -.08 | .11 |
| Late Extinction Threat Amygdala | -.01 | -.11 | .02 |
| Late Extinction Safe Amygdala | .08 | -.07 | .14 |
| Late Extinction Threat Insula | -.11 | -.20 | .01 |
| Late Extinction Safe Insula | -.12 | -.16 | .08 |
| Pupil Early Fear Conditioning Safe | -.14 | -.05 | .07 |
| Pupil Early Fear Conditioning Threat | -.01 | .06 | .00 |
| Pupil Late Fear Conditioning Safe | -.11 | -.14 | -.11 |
| Pupil Late Fear Conditioning Threat | -.07 | -.09 | .07 |
| Pupil Early Extinction Safe | .18 | .07 | .15 |
| Pupil Early Extinction Threat | .02 | .09 | .12 |
| Pupil Late Extinction Safe | -.04 | -.09 | -.07 |
| Pupil Late Extinction Threat | -.00 | -.11 | -.04 |
| SCR Early Fear Conditioning Threat | .14 | .17 | .09 |
| SCR Early Fear Conditioning Safe | .21 | .07 | .02 |
| SCR Late Fear Conditioning Threat | .09 | .18 | .12 |
| SCR Late Fear Conditioning Safe | .15 | .18 | .10 |
| SCR Early Extinction Threat | -.03 | -.04 | -.06 |
| SCR Early Extinction Safe | .10 | .25 | -.06 |
| SCR Late Extinction Threat | .09 | .10 | .04 |
| SCR Late Extinction Safe | .12 | .23 | .16 |

Note: * indicates p-value <.05 after Sidak's correction for multiple comparisons. ** indicates uncorrected p-value of <.05.

Linear regression of autism symptoms predicting sensory sensitivity and intolerance of uncertainty are show in Tables 40 and 41. Analyses showed that the AQ significantly predicted AASP sensory sensitivity scores (β =.637, $t$ = 7.00, $p$ = <.001) and accounts for 41.9% of the variance. Additionally, AQ significantly predicted IUS (β =.611, $t$ = 6.16, $p$ = <.001) and accounted for 38.5% of the variance.

Table 35
*Linear Regression of AQ Predicting AASP Sensory Sensitivity*

| Predictors | Coefficient | Standard Error | $t$ | $p$-value | Confidence Intervals |
|---|---|---|---|---|---|
| AQ | .637 | 0.09 | 7.00 | <.001 | [0.46, .081] |
| Constant | 25.00 | 2.15 | 11.65 | <.001 | [20.72, 29.29] |

$R^2$ = .419

Table 36
*Linear Regression of AQ Predicting IUS*

| Predictors | Coefficient | Standard Error | $t$ | $p$-value | Confidence Intervals |
|---|---|---|---|---|---|
| AQ | .611 | 0.10 | 6.16 | <.001 | [0.41, 0.81] |
| Constant | 20.88 | 2.34 | 8.92 | <.001 | [16.21, 25.55] |

$R^2$ = .358

Logistic regression analyses are presented in Table 37. None of the brain activation of psychophysiological measures were used as predictors in the logistic regression because none of them were significantly related to the anxiety or intolerance of uncertainty measures (see Table 34). AQ significantly predicted DASS-A (OR = 1.11, z = 3.18, $p$ = .001, $R^2$ = .134) and PSWQ (OR = 1.12, z = 3.35, $p$ = .001, $R^2$ = .156). The AASP sensory sensitivity subscale also predicted DASS-A (OR = 1.15, z = 3.41, $p$ = .001, $R^2$ = .180) and the PSWQ (OR = 1.18, z = 3.70, $p$ = <.001, $R^2$ = .237). Additionally, IUS significantly predicted DASS-A (OR = 1.21, z = 3.32, $p$ = .001, $R^2$ = .148) and PSWQ (OR = 1.11, z = 3.17, $p$ = .001, $R^2$ = .131). When utilizing all the predictors in the same model ($R^2$ = .244), the AQ (OR = 1.02, z = 0.54, $p$ = .558) and IUS (OR =

1.08, z = 2.01, $p$ = .04) do not significantly predict DASS-A, while the AASP sensory sensitivity scale was a significant predictor (OR = 1.13, z = 2.23, $p$ = .026). This same pattern was found for the PSWQ ($R^2$ = .284). These analyses suggest that the AASP sensory sensitivity scale mediates the relationships between AQ and the anxiety measures.

Table 37
*Logistic Regression Predicting Anxiety Status from Behavioral Measures Responses. Low Anxiety n = 32; High Anxiety n = 30*

| Model: DV $R^2$ | Predictor | Odds Ratio | Standard Error | z | $p$-value | Confidence Intervals |
|---|---|---|---|---|---|---|
| Model 1: | | | | | | |
| DASS-A | AQ | 1.11 | 0.04 | 3.18 | .001 | [1.04, 1.19] |
| $R^2$ = .134 | Constant | 0.95 | 0.07 | -3.13 | .002 | [0.02, 0.42] |
| PSWQ | AQ | 1.12 | 0.04 | 3.35 | .001 | [1.05, 1.20] |
| $R^2$ = .156 | Constant | 0.08 | 0.06 | -3.30 | .001 | [0.02, 0.35] |
| Model 2: | | | | | | |
| DASS-A | AASP | 1.15 | 0.05 | 3.41 | .001 | [1.06, 1.24] |
| $R^2$ = .180 | Constant | 0.01 | 0.01 | -3.44 | .001 | [0.00, 0.10] |
| PSWQ | AASP | 1.18 | 0.06 | 3.70 | <.001 | [1.08, 1.30] |
| $R^2$ = .237 | Constant | 0.00 | 0.00 | -3.73 | <.001 | [0.00, 0.04] |
| Model 3: | | | | | | |
| DASS-A | IUSS | 1.12 | 0.04 | 3.32 | .001 | [1.05, 1.19] |
| $R^2$ = .148 | Constant | 0.02 | 0.02 | -3.30 | .001 | [0.00, 0.21] |
| PSWQ | IUSS | 1.11 | 0.04 | 3.17 | .002 | [1.04, 1.18] |
| $R^2$ = .131 | Constant | 0.03 | 0.03 | -3.15 | .002 | [0.00, 0.26] |
| Model 4: | | | | | | |
| DASS-A | AQ | 1.02 | 0.04 | 0.54 | .558 | [0.94, 1.11] |
| $R^2$ = .244 | AASP | 1.13 | 0.06 | 2.23 | .026 | [1.01, 1.23] |
| | IUS | 1.08 | 0.04 | 2.01 | .044 | [1.00, 1.17] |
| | Constant | 0.00 | 0.00 | -3.48 | <.001 | [0.00, 0.04] |
| PSWQ | AQ | 1.02 | 0.04 | 0.63 | .526 | [0.94, 1.12] |
| $R^2$ = .284 | AASP | 1.16 | 0.06 | 2.71 | .007 | [1.04, 1.29] |
| | IUS | 1.07 | 0.04 | 1.63 | .102 | [0.98, 1.16] |
| | Constant | 0.00 | 0.00 | -3.48 | <.001 | [0.00, 0.04] |

*Note: DASS-A = DASS-21 anxiety subscale; PSWQ = Penn State Worry Questionnaire; AQ = Autism Questionnaire; AASP = Adult/Adolescent Sensory Profile Sensory Sensitivity Subscale; IUS = Intolerance of Uncertainty Scale

## Study 1 Conclusions

### *Fear Conditioning Task*

One of the aims of this study was to identify the brain and physiological response differences in fear conditioning and extinction between adults with autism and neurotypical adults (NT) when controlling for the uncertainty of the reinforcing stimulus. In line with the atypical/hyperactive amygdala theory (e.g., White et al., 2014) and previous fMRI findings (Top Jr et al., 2016), we first hypothesized that there would be a group-by-condition interaction effect in the amygdala and insula during the fear conditioning phase, and that this pattern would be replicated in the SCR and pupillometry data. We rejected this first hypothesis, as there were no interaction effects found in the fMRI, SCR, and pupillometry measures for the fear conditioning task. While we did not directly compare uncertain versus certain reinforcement schedules within the same study, differences between studies where the only major difference was reinforcement schedule support the suggestion from Top Jr. et (2016) that fear conditioning in autism may be especially affected by reinforcement rates.

Our second hypothesis, consistent with the South & Rodger (2017) model of anxiety in autism, stated that there would be an interaction effect between group and condition when we split the group between High IUS and Low IUS groups during the fear conditioning phase. This hypothesis was also rejected, as there were no significant interaction effects nor group effects for any of the depend measures during the fear conditioning task. These results suggest that difference in intolerance of uncertainty between participants did not affect how members from either group responded to the fear conditioning. While this finding is not congruent with the South and Rodgers (2017) model, it is likely a result of the protocol design attempting to minimize the uncertainty of the task.

Although the experimental protocol was designed to evoke difference in amygdala activation when comparing safe and threat cues (Phelps et al., 2004; Top Jr et al., 2016), there were not significant clusters of activation in the amygdala while producing significant clusters of activation in the insula. However, SCR and Pupillometry measures suggest that fear conditioning took place. This is consistent with the meta-analysis of Fullana et al. (2016) that concluded that human fMRI fear conditioning experiment do not consistently evoke the amygdala defense/threat detection circuity, while fear conditioning experiments do induce robust bilateral insula activation. While the findings of Fullana et al. (2016) suggest the fear conditioning protocol use in this study replicates their meta-analysis, it is unclear if we were able to effectively test the White et al (2014) model that made specific predictions that there would be differences in amygdala activation between the neurotypical and autism groups. It will be important for future studies testing components of the Emotional Regulation Model of anxiety in autism to use protocols that reliably evoke amygdala response in human populations.

***Fear Extinction Task***

For the fear extinction task, the White et al (2014) model hypothesized that there would be a significant group-by-condition interaction effect in the amygdala, replicating the findings of Top Jr et al. (2016). Additionally, we hypothesized there would be a group main effect with the AUT having greater amygdala and insula activation than the NT group to both the threat and safety cues during the extinction protocol. This hypothesis was also rejected, as there were no significant group, condition, or interactions effect in the amygdala or insula during the extinction phase. However, a significant main effect for group when examining the SCR data, with the AUT group having greater SCR reaction to the safe and threat cues compared to the NT group.

When testing the South and Rodgers (2017) model, we hypothesized that there would be a significant interaction effect in the amygdala and insula, as well as in the SCR and pupillometry data when we split the sample into High IUS and Low IUS groups. We also hypothesized that there would be a group effect with the AUT group having greater activation than the NT group for all of our measures. These hypotheses were also rejected by our data, as there were no significant group nor interaction effects in this analysis. As mentioned earlier, this finding may be attributed to the protocol design of the fear conditioning task that attempted to minimize the uncertainty of the fear conditioning task. In other words, if there was nothing to be uncertain about in the task, it is unlikely we will see differences between High IUS and Low IUS groups. Further information could be gained by using a fear conditioning/extinction protocol manipulates the level of uncertainty within the task.

Lastly, we hypothesized that anxiety status would be predicted by amygdala and insula responses to the safety and threat cues, as well as behavioral measures of sensory sensitivity and intolerance of uncertainty. The results indicted amygdala and insula activation is not significantly related to anxiety or intolerance of uncertainty. Additionally, the significant relationship between autism traits and anxiety status is mediated by sensory sensitivity, but not intolerance of uncertainty (after comparing for multiple comparisons). This suggests that amygdala and insula activation during this task are not statistically related to anxiety status in autism, as suggested by the hyperactive amygdala theory (e.g., White et al., 2014). Additionally, it seems that sensory sensitivity has a stronger mediation effect on anxiety than intolerance of uncertainty; thus, only partially supporting the South and Rodgers (2017) model of anxiety in autism. While several studies have proposed links between sensory function, intolerance of

uncertainty, and anxiety but these findings suggest that there may not be straightforward links to brain activity.

Taken together, the results of this study indicate that there do not seem to be meaningful differences in fear conditioning and extinction between the AUT and NT groups or High IUS and Low IUS groups in the context of a regular, predictable reinforcement rate of the threatening stimulus. These data suggest that the atypical amygdala functioning during fear conditioning/extinction found in the Top Jr et al. (2016) study is likely due, at least in part, to the uncertainty elicited by that protocol's partial reinforcement of the threatening stimulus. This is in line with emerging theories that some of the anxiety commonly seen in autism is more likely to be due to uncertainty of expectations more than deficits in learning abilities or inherently atypical amygdala functioning. As mentioned by South and Rodgers (2017), an autistic individual may experience greater anxiety if they do not have enough information to reliably predict the outcome of a situation. Because this task was reinforced at a 100% rate, it seems that the AUT and High IUS groups had enough information to predict the results of each conditioned stimulus, and thus did not experience a higher level of arousal than the NT and Low IUS groups. As later mentioned in the general discussion section, these finding offer promising evidence for the clinical utility of behavioral (exposure) therapies for the treatment of phobias in autism.

## Study 2 – Auditory Looming

### Methods and Materials

#### *Audio Looming Protocol*

We adapted the audio looming protocol from Bach et al. (2008) who reported amygdala response to audio looming stimuli (see Figure 11). The auditory looming task consisted of 16 trials each (48 total) of three categories (rising, falling, and constant) presented in an event-

related design. We acquired the Bach et al. (2008) stimuli directly from the original authors, and pilot testing revealed no significant difference in pupil dilation or galvanic skin response from the receding and looming stimuli as expected. Because of this, we contacted the authors of the Bach et al. (2008) study to request auditory looming stimuli that were from more recent studies. We received the auditory stimuli from the author of the Neuhoff (2016) auditory looming study. The stimuli can be acquired at the website http://www.jneuhoff.com/links.html. The stimuli were of a moving three-dimensional (3D) virtual sound source that were presented over headphones that traveled on a path parallel to the listener's interaural axis. The virtual listening point was situated 2 m from the straight-line trajectory of the source. The stimuli receded and approached along a path between 2 m and 47 m from the median plane of the listener that traveled at 15 mps (33.5 mph). A square wave with a fundamental frequency of 400 Hz and a sampling rate of 44.1 kHz was used as the sound source with a virtual source height of 0.5 m. The simulation produced realistic 3D auditory motion that included Doppler shift, atmospheric filtering, gain attenuation due to atmospheric spreading, ground reflection attenuation, and head-related transfer function (HRTF) from the MIT KEMAR dataset (Gardner & Martin, 1995; see Neuhoff et al., (2009) for simulation details). We used a bypass trajectory to maximize interaural cues to the source's approach. Stimuli were presented bilaterally through OptoActive Active Noise Canceling headphones (Optoacoustics, Israel).

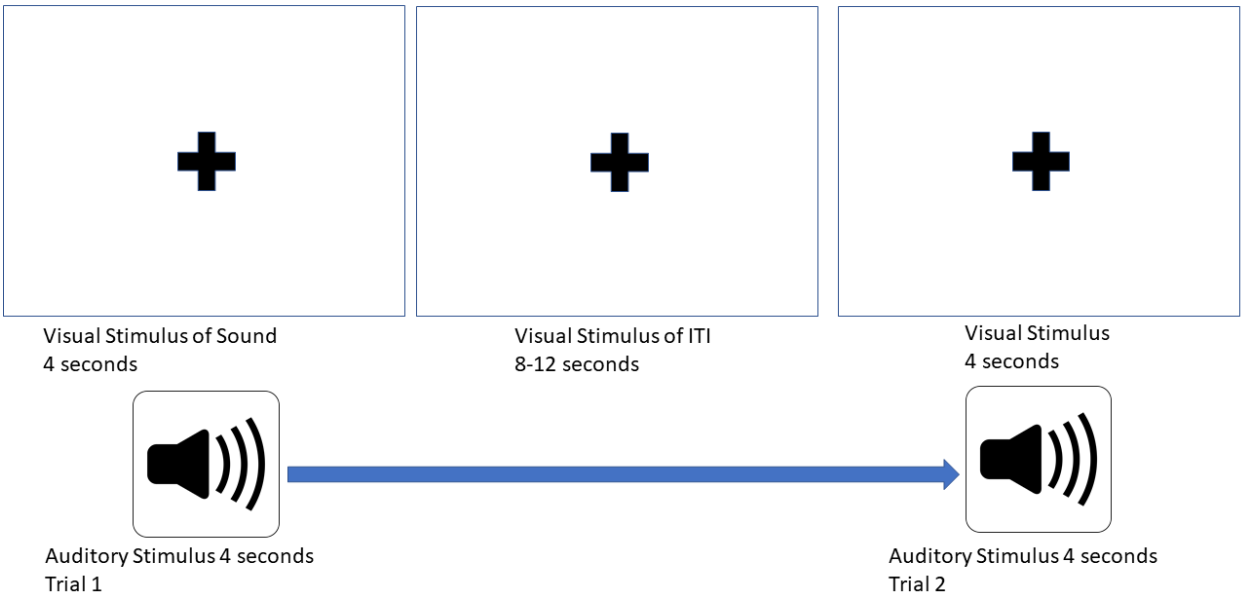


*Figure 11.* Auditory looming task design.

Each sound stimulus was presented for 4000 ms with an average ITI of 18000 ms ranging from 16000 ms and 20000 ms. Acquisition of fMRI data produced a background noise peaking at 100 dB; however, noise reduction by OptoActive Active Noise Canceling Headphones (Optoacoustics, Israel) reduced that to approximately 60 dB, making the difference between scanner noise and presented sounds great enough to allow for the clear perception of stimuli.

At the beginning of the auditory looming run, all participants were instructed to concentrate on the changes in the auditory signals and to fixate on a fixation cross to avoid eye movements. Like the Bach et al. (2008) study, we chose this passive listening task because it was more likely to resemble a real-life situation, where an immediate reaction to warning cues is not normally provided.

### *Looming Pupillometry and SCR Analysis*

Similar to the fear conditioning and extinction analyses, we used the delta pupil and SCR reaction for a given trial as our dependent variables. An HLM was then used to model the delta pupil or SCR response with fixed effects of group (NT, AUT), condition (Constant, Receding, Looming), and a group-by-condition interaction. Random effects from this model consisted of the individual by-participant intercepts and random by-participant slopes for condition. A separate HLM was then used to model the delta pupil or SCR response with fixed effects of group (High IU, Low IU), condition (Constant, Receding, Looming), and a group-by-condition interaction to assess the hypotheses set by the South and Rodgers (2017) model. Random effects from this second set of models consisted of the individual by-participant intercepts and random by-participant slopes for condition.

### *Looming fMRI Analysis*

First level analysis regression parameters included the presentation of the looming stimuli, receding stimuli, stable stimuli, baseline, ITI, and the motion regressors. We used a Canonical Hemodynamic Response Function with no derivatives to adjust for the time difference between presentation of the stimulus and expected neural blood flow. The extracted values/images of the Looming and Receding trials were in the second level analyses. Second level analyses were conducted using SPM's repeated-measure ANOVA summary statistics approach with a 2 (AUT, NT) x 2 (Looming, Receding) comparison as done in the Bach et al. (2008) study. We used a family-wise corrected *p*-value of 0.05. Significant clusters of activation were labeled and defined using the xjView plugin for SPM (http://www.alivelearn.net/xjview8/). *A priori* ROIs from previous literature were evaluated and corrected for multiple comparisons using the SPM small volume correction analysis function. A separate 2 (High IU, Low IU) x 2

(Looming, Receding) repeated-measures ANOVA was completed to evaluate the South and Rodger (2017) model.

### *Regions of Interest Selection*

*A priori* Regions of Interest (ROIs) were identified from existing auditory looming literature included the amygdala, insula, intraparietal sulcus (IPS), superior temporal sulcus, and the temporal plane (Bach et al., 2008; Krumbholz et al., 2005). We created a single mask which included all of the aforementioned ROIs using the Wake Forest PickAtlas (Maldjian et al., 2004, 2003; Tzourio-Mazoyer et al., 2002). We used the Wake Forest PickAtlas integrated automated anatomical labeling atlas to define an ROI for each hemisphere. Because the IPS was not an identified structure in the PickAtlas, we created a sphere with a 20 mm radius centered around the IPS based on the anatomical data given by the atlas of Ono, Kubik, and Abernathey (1990) and were used by the Bach et al. (2008) study of auditory looming ($x = \pm32$, $y = -50$, $z = 28$). We also used a 15 mm sphere around the coordinates ($x = \pm54$, $y = -28$, $z = 12$) as the definition of the temporal plan as described by (Krumbholz et al., 2005). The estimated BOLD responses for the insula and amygdala were extracted for each run using the MarsBaR SPM toolbox.

### *Exploratory Whole-Brain Analysis*

An exploratory whole brain analysis was performed to identify significant clusters of voxels that were not captured by the ROI analysis. We used the same 2 x 2 repeated measures ANOVAs described above. Significant clusters were reported if they were 10 or more clustered voxels that were significant at a family-wise corrected *p*-value of .05.

### *Predicting Anxiety*

Replicating the methods completed in Study 1, we used a Spearman's correlation with a Sidak's correction to examine the relationships between the brain/psychophysiological measures

and the anxiety and intolerance of uncertainty measures. Significant correlations between brain/psychophysiological measures and anxiety were used in a logistic regression predicting anxiety status. Anxiety status was determined by using a median split of the DASS-21 anxiety subscale (DASS-A) and the (PSWQ). We used a Sidak's corrected p-value of .026 because we were running the analyses with two difference dependent variables. Logistic regressions using the behavioral measures are presented in Study 1, and thus will not be presented in this section.

**Looming Results**

Three participants from the AUT group and two from the NT group were excluded from the Auditory Looming task due to excessive movement or falling asleep in the scanner during the task. The HLM of the SCR data showed a significant main effect for condition with Receding stimuli having a larger response than the Looming stimuli ($z = 4.79$, $p = <.001$; see Table 38 & Figure 12). The differences between Stable stimuli and Looming stimuli ($z = 1.39$, $p = .163$) and Stable stimuli and Receding stimuli ($z = 1.59$, $p = .111$) were not significant. The main effect for group was significant ($z = 2.78$, $p = .005$) with the AUT group having greater SCR responses compared to the NT group. The interaction effects were not significant (AUT & Recede: $z = -0.95$, $p = .344$; AUT & Stable: $z = -0.49$, $p = .628$). When separating the groups based on High IU vs Low IU (See Table 39), there was a significant effect of condition with the Receding stimuli evoked greater activity than the looming stimuli group ($z = .44$, $p = .659$). There was not a significant main effect of group ($z = 3.94$, $p = <.001$) nor an interaction effect when comparing High IU to Low IU (AUT & Recede: $z = 0.51$, $p = .607$; AUT & Stable: $z = -0.16$, $p = .872$).

Table 38
*AUT vs NT: HLM Analysis of SCR Data for the Contrast of Looming and Receding Stimuli for Auditory Looming Task. AUT n = 26 NT n = 28*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition: | | | | | | |
| Vs. Recede | .037 | .008 | 4.79 | <.001 | [.022, .052] | Recede > Loom |
| Vs. Stable | .012 | .008 | 1.39 | .163 | [-.005, .028] | |
| Group | .045 | .016 | 2.78 | .005 | [.013, .077] | AUT > NT |
| Condition x Group: | | | | | | |
| Vs. AUT & Recede | -.011 | .011 | -0.95 | .344 | [-.32, .011] | |
| Vs. AUT & Stable | -.005 | .012 | -0.49 | .628 | [-.109, -.065] | |
| Constant | -.087 | .011 | -7.70 | <.001 | [-.109, -.065] | |

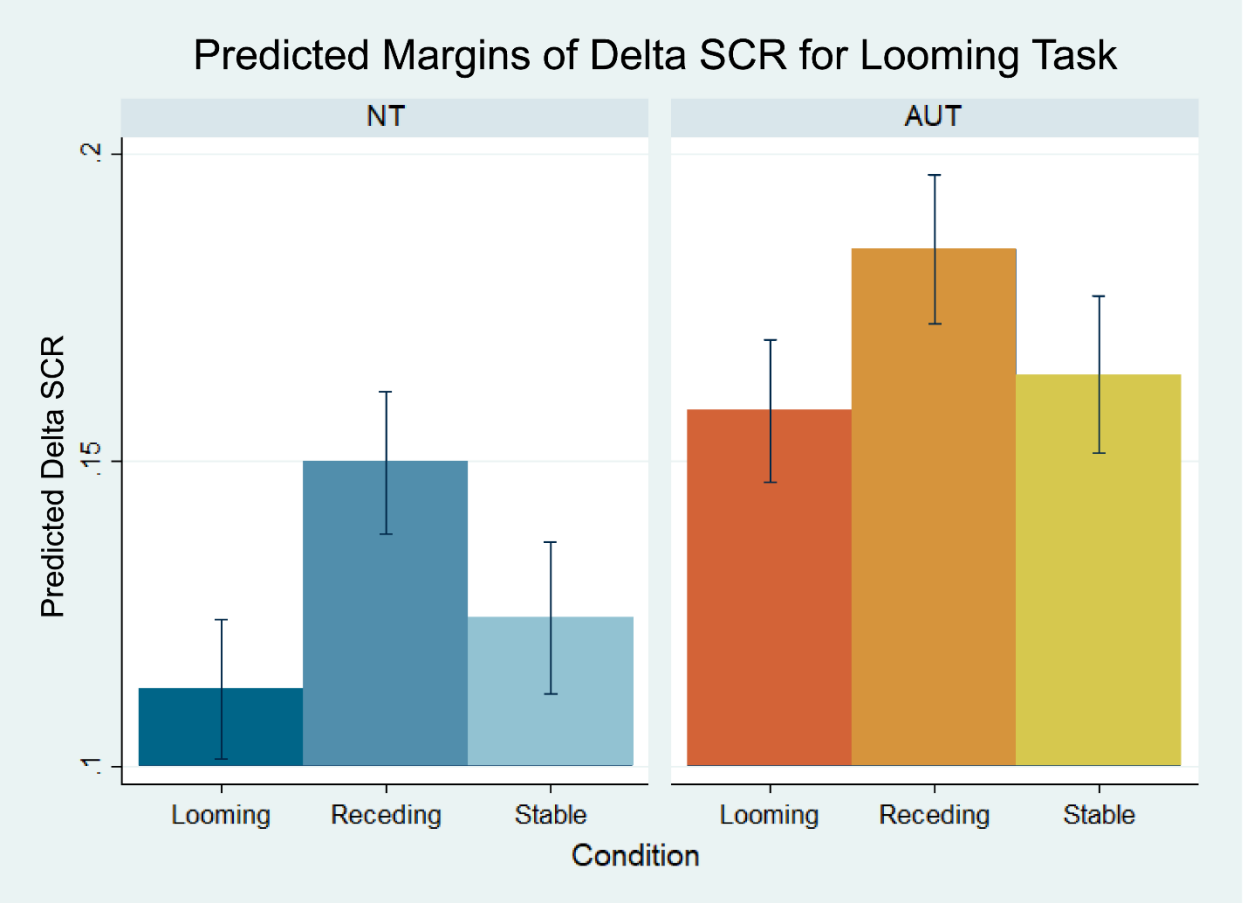


*Figure 12.* AUT vs NT: HLM of delta SCR for auditory looming task. NT = neurotypical group. AUT= autism group.

Table 39
*Low IU vs High IU: HLM Analysis of SCR Data for the Contrast of Looming and Receding Stimuli for Auditory Looming Task. High IU n = 19 (AUT n = 13) Low IU n = 23 (AUT n = 6)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition: | | | | | | |
| Vs. Recede | .029 | .007 | 3.94 | <.001 | [.015, .044] | Recede > Loom |
| Vs. Stable | .008 | .008 | 0.99 | .321 | [-.008, .024] | |
| Group | .008 | .018 | .44 | .659 | [-.026, .042] | |
| Condition x Group: | | | | | | |
| Vs. AUT & Recede | .006 | .011 | 0.51 | .607 | [-.016, .028] | |
| Vs. AUT & Stable | .002 | .012 | 0.16 | .872 | [-.021, -.025] | |
| Constant | -.069 | .012 | -5.95 | <.001 | [-.091, -.046] | |

Analysis of the pupil data showed a significant main effect for condition with Receding stimuli eliciting larger pupil responses than the Looming stimuli (z = 2.56, $p$ = .010; see Table 40 & Figure 13). Similar to the SCR data, there were no differences between Looming and Stable stimuli (z = 1.39, $p$ = <.163) or the Stable and Receding stimuli (z = 1.25, $p$ = .212). Unlike the SCR data, there was not a main effect for group (z = -1.52, $p$ = .129). No interaction effects were significant for the pupil data (AUT & Recede: z = 0.41, $p$ = .683; AUT & Stable: z = 0.18, $p$ = .856). The analysis splitting the participants into High IUS and Low IUS group showed a similar pattern (See Table 41).

Table 40

*AUT vs NT: HLM Analysis of Pupil Data for the Contrast of Looming and Receding Stimuli for Auditory Looming Task. AUT n = 21 NT n = 23*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition: | | | | | | |
| Vs. Recede | 24.27 | 9.47 | 2.56 | .010 | [5.71, 42.83] | Recede > Loom |
| Vs. Stable | .012 | .008 | 1.39 | .163 | [-.005, .028] | |
| Group | -15.83 | 10.44 | -1.52 | .129 | [-36.28, 4.63] | |
| Condition x Group: | | | | | | |
| Vs. AUT & Recede | 5.62 | 13.77 | 0.41 | .683 | [-21.37, 32.62] | |
| Vs. AUT & Stable | 2.52 | 13.87 | 0.18 | .856 | [-24.66, 29.71] | |
| Constant | 23.87 | 7.15 | 3.34 | .001 | [9.85, 37.88] | |

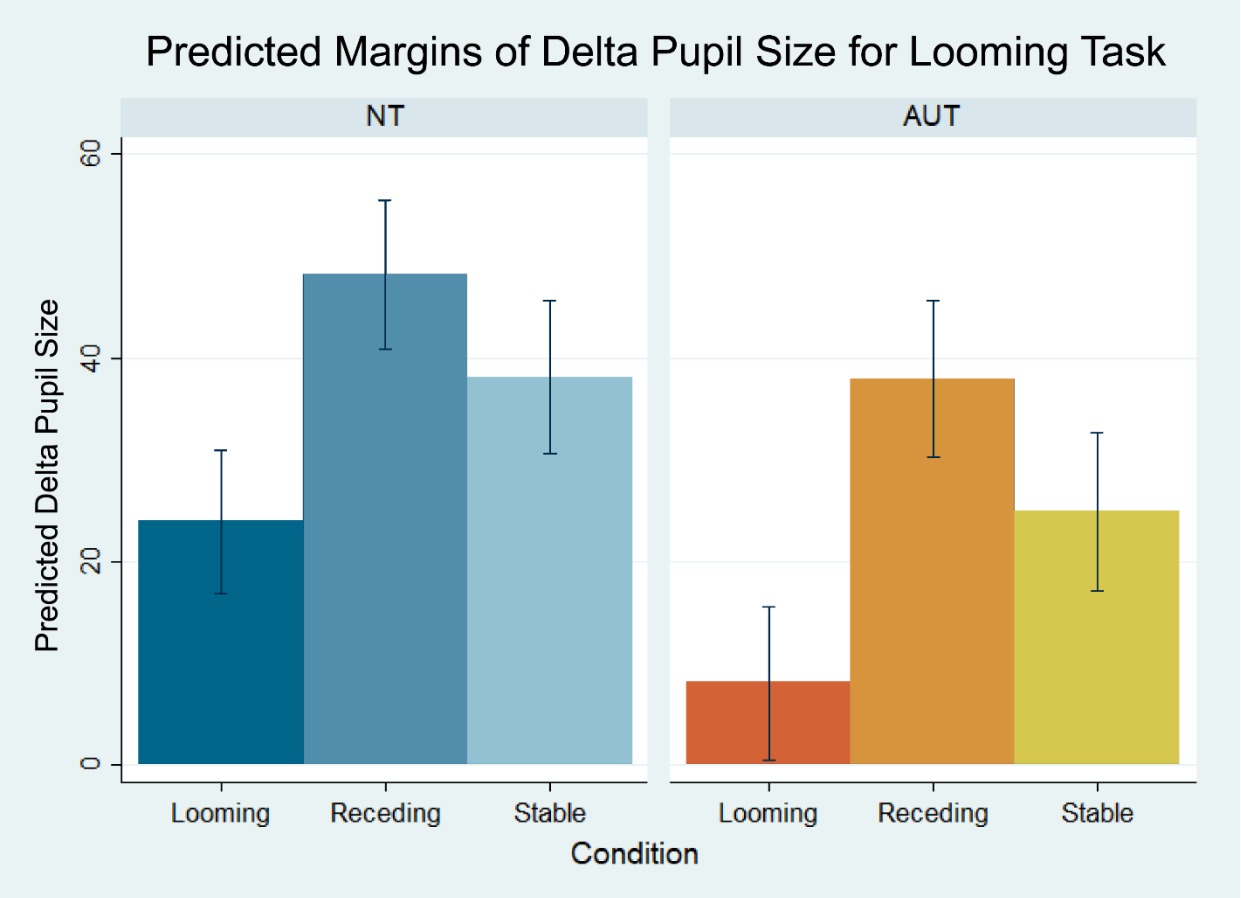


*Figure 13.* AUT vs NT: HLM of delta pupil size for auditory looming task. NT = neurotypical group. AUT= autism group.

Table 41
*Low IU vs High IU: HLM Analysis of Pupil Data for the Contrast of Looming and Receding Stimuli for Auditory Looming Task . High IU n = 21 (AUT n = 13) Low IU n = 23 (AUT n = 6)*

| Predictors | Coefficient | Standard Error | z | *p*-value | Confidence Intervals | Effect |
|---|---|---|---|---|---|---|
| Condition: | | | | | | |
| Vs. Recede | 22.55 | 9.23 | 2.44 | .015 | [4.46, 40.66] | Recede > Loom |
| Vs. Stable | 12.21 | 9.30 | 1.31 | .189 | [-6.03, .30.46] | |
| Group | -6.21 | 10.69 | -0.58 | .561 | [-27.16, 14.73] | |
| Condition x Group: | | | | | | |
| Vs. AUT & Recede | 9.73 | 13.83 | 0.70 | .482 | [-17.38, 36.85] | |
| Vs. AUT & Stable | 6.96 | 13.94 | 0.50 | .617 | [-20.36, 34.28] | |
| Constant | 19.25 | 7.15 | 2.69 | .007 | [5.23, 33.26] | |

ROI analysis of the looming showed a main effect for condition with the looming stimuli having greater activation than the receding stimuli in the right and left superior temporal gyrus (see Table 42). Analyses also revealed a significant main effect for group with the AUT group having greater activation than the NT group in the following brain structures: right insula (see Figure 14), right and left superior temporal gyrus, and right temporal plane. No significant interaction effect was found. Analysis using the High IUS and Low IUS group had main effect for groups (looming > receding) in the following areas: left and right Brodmann area 41, left and right superior temporal gyrus, and left Brodmann Area 22 (see Table 43). Unlike the AUT vs NT comparison, there were no significant difference between the High IUS and Low IUS groups. There were no interaction effects for the IUS grouping analysis.

Table 42
*AUT vs NT: Contrast of Looming and Receding Stimuli in a priori ROIs for Auditory Looming Task. AUT n = 26; NT n = 33*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Superior Temporal Gyrus | R | 44, -24, 8 | 97.47 | <.001 | Threat > Safe |
| | | 50, -32, 12 | 84.48 | <.001 | Threat > Safe |
| | | 54, -10, 0 | 79.69 | <.001 | Threat > Safe |
| Superior Temporal gyrus | L | -40, -32, 10 | 91.95 | <.001 | Threat > Safe |
| | | -50, -28, -4 | 76.18 | <.001 | Threat > Safe |
| | | -48, -16, 2 | 75.38 | <.001 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Superior Temporal Gyrus | L | -62, -8, 0 | 22.71 | .009 | AUT > NT |
| Superior Temporal Gyrus | R | 60, 0, 4 | 42.11 | <.001 | AUT > NT |
| Insula | R | 42, -16, 4 | 37.13 | <.001 | AUT > NT |
| | | 50, -28, 14 | 21.59 | .014 | AUT > NT |
| Temporal Plane | R | 40, -28, 12 | 27.31 | .001 | AUT > NT |
| **Interaction Effect: Group*Condition** | | | | | |
| Null | | | | | |

Table 43

*Low IU vs High IU: Contrast of Looming and Receding Stimuli in a priori ROIs for Auditory Looming Task Using High IU and Low IU. High IU n = 25 (AUT n = 15) Low IU n = 34 (AUT n = 11).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Brodmann Area 41 | L | -40, -32, 10 | 111.58 | <.001 | Threat > Safe |
| Brodmann Area 22 | L | -48, -16, 2 | 99.70 | <.001 | Threat > Safe |
| Superior Temporal Gyrus | L | -56, -28, 8 | 89.52 | <.001 | Threat > Safe |
| Superior Temporal Gyrus | R | 46, -24, 8 | 111.14 | <.001 | Threat > Safe |
| | | 52, -10, 0 | 105.58 | <.001 | Threat > Safe |
| Brodmann Area 41 | R | -50, -32, 12 | 107.76 | <.001 | Threat > Safe |
| | | -48, -16, 2 | 75.38 | <.001 | Threat > Safe |
| **Main Effect: Group** | | | | | |
| Null | | | | | |
| **Interaction Effect: Group*Condition** | | | | | |
| Null | | | | | |

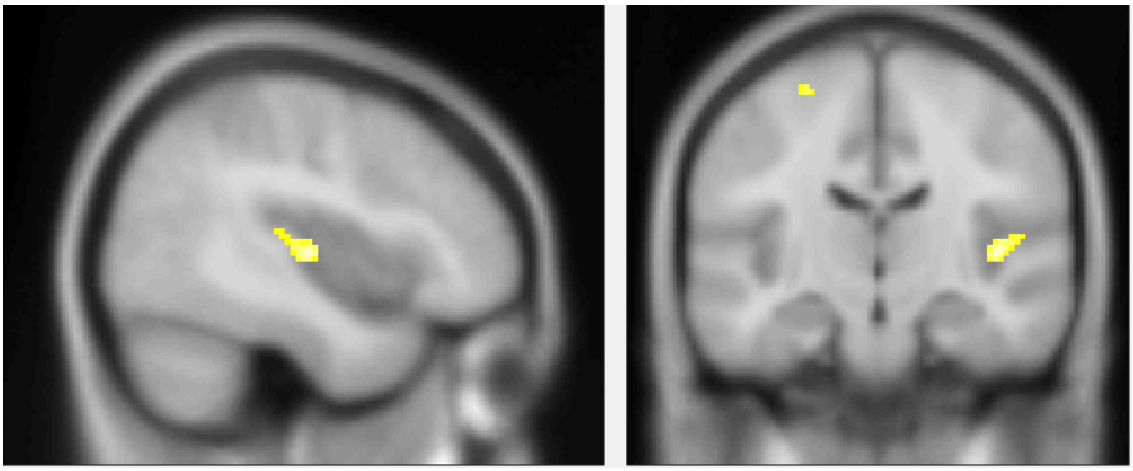

*Figure 14.* AUT vs NT: Greater right insula activation in autism group compared to neurotypical group during auditory looming task.

The exploratory whole brain analysis showed a significant main effect for condition in the following areas (see Table 44 & Figure 1): right superior temporal gyrus, left superior temporal gyrus, right and left Brodmann area 41, left Brodmann area 22, and right Brodmann area 6. The exploratory analysis also showed a significant main effect for group with the AUT group having greater activation than the NT group in the following areas: right Brodmann area 22, right transverse temporal gyrus, left culmen, and right and left postcentral gyrus. The interaction effect was not significant. The main effect for condition was similar splitting the groups by High IUS and Low IUS with the addition of the inferior frontal gyrus activation (see Table 45). There were multiple clusters of activation, with High IUS having greater activation than the Low IUS group in the following areas: left and right extra-nuclear, left corpus collosum, left Brodmann area 21, and right parahippocampal gyrus. There were no significant interactions effects.

Table 44
*AUT vs NT: Exploratory Whole Brain Analysis of the Contrast of Looming and Receding Stimuli for the Auditory Looming Task. AUT n = 26 NT n = 33*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Superior Temporal Gyrus | R | 44, -24, 8 | 97.47 | <.001 | Loom > Recede |
| | | 54, -10, 0 | 79.69 | <.001 | Loom > Recede |
| Superior Temporal Gyrus | L | -50, -28, 4 | 76.18 | <.001 | Loom > Recede |
| Brodmann Area 41 | R | 50, -32, 12 | 84.48 | <.001 | Loom > Recede |
| Brodmann Area 41 | L | -40, -32, 10 | 91.95 | <.001 | Loom > Recede |
| Brodmann Area 22 | L | -48, -16, 2 | 75.38 | <.001 | Loom > Recede |
| Brodmann Area 6 | R | 52, 0, 48 | 30.96 | .003 | Loom > Recede |
| **Main Effect: Group** | | | | | |
| Brodmann Area 22 | R | 60, 0, 4 | 42.11 | <.001 | AUT > NT |
| Transverse Temporal Gyrus | R | 40, -28, 12 | 27.31 | .014 | AUT > NT |

| | | | | | |
|---|---|---|---|---|---|
| Culmen | L | -38, -46, -26 | 31.68 | .002 | AUT > NT |
| Postcentral Gyrus | R | 18, -34, 74 | 31.23 | .003 | AUT > NT |
| Postcentral Gyrus | L | -60, -12, 16 | 31.11 | .003 | AUT > NT |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

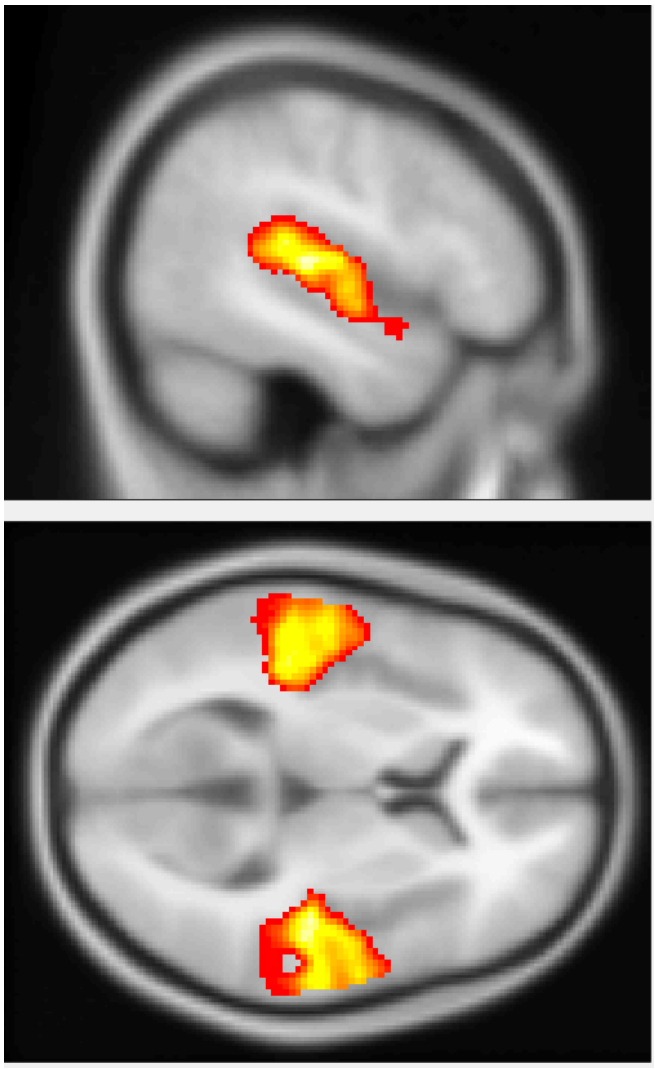

*Figure 15.* AUT vs NT: Significant clusters of activation during auditory looming task during exploratory whole-brain analysis.

Table 45
*Low IU vs High IU: Exploratory Whole Brain Analysis of the Contrast of Looming and Receding Stimuli for the Auditory Looming Task. High IU n = 25 (AUT n = 15) Low IU n = 34 (AUT n = 11).*

| Structure | Hemisphere | Peak Coordinates | *F* | Corrected *p* | Effect |
|---|---|---|---|---|---|
| **Main Effect: Condition** | | | | | |
| Superior Temporal Gyrus | R | 46, -24, 8 | 111.14 | <.001 | Loom > Recede |
| | | 52, -10, 0 | 105.58 | <.001 | Loom > Recede |
| Superior Temporal Gyrus | L | -56, -28, 8 | 89.52 | <.001 | Loom > Recede |
| Brodmann Area 41 | R | 50, -32, 12 | 84.48 | <.001 | Loom > Recede |
| Brodmann Area 41 | L | -40, -32, 10 | 111.58 | <.001 | Loom > Recede |
| Brodmann Area 22 | L | -48, -16, 2 | 99.70 | <.001 | Loom > Recede |
| Brodmann Area 6 | R | 52, 0, 48 | 36.76 | <.001 | Loom > Recede |
| Inferior Frontal Gyrus | R | 48, 30, 0 | 27.02 | .016 | Loom > Recede |
| **Main Effect: Group** | | | | | |
| Extra-Nuclear | R | 20, 28, 6 | 54.05 | <.001 | High IUS > Low IUS |
| Parahippocampal Gyrus | R | 33, -42, -5 | 24.24 | .013 | High IUS > Low IUS |
| Brodmann Area 21 | L | -38, 10, -36 | 38.83 | <.001 | High IUS > Low IUS |
| Corpus Callosum | L | -16, -44, 6 | 31.80 | .002 | High IUS > Low IUS |
| Extra-Nuclear | L | -22, 2, 28 | 29.96 | .004 | High IUS > Low IUS |
| **Interaction: Condition x Group** | | | | | |
| Null | | NS | NS | NS | |

### *Predicting Anxiety*

Results of the Spearman's correlation examine the relationship between the brain/psychophysiological measures and the anxiety/intolerance of uncertainty measures are presented in Table 46. No significant correlations were identified in the analysis at the corrected

or uncorrected level. Logistic regression were not performed because of the lack of significant correlations in the Spearman correlation.

Table 46
*Spearman Correlation Analysis for Auditory Looming Task with Sidak's Correction.*

| Physiological Measure | DASS | PSWQ | IUS |
|---|---|---|---|
| Amygdala Activation Receding Cues | .06 | -.06 | -.02 |
| Amygdala Activation Looming Cues | -.01 | -.06 | -.07 |
| Insula Activation Receding Cues | .14 | -.04 | .05 |
| Insula Activation Looming Cues | -.03 | -.07 | -.09 |
| SCR Activation Receding | .04 | .13 | .22 |
| SCR Activation Looming | .17 | .07 | .07 |
| Pupil Activation Receding | -.22 | -.04 | -.19 |
| Pupil Activation Looming | .10 | .05 | .13 |

Note: * indicates p-value <.05 after Sidak's correction for multiple comparisons. ** indicates uncorrected p-value of <.05.

**Auditory Looming Conclusions**

The purpose of the second study was to identify the brain and physiological response differences between autistic and neurotypical adults to an auditory looming task according to the predictions established by the emotional regulation model of anxiety in autism (White et al., 2014). We first hypothesized that there would be a significant group-by-condition interaction effect wherewith the AUT group would show greater amygdala and insula activation to both looming and receding stimuli, while the NT group would show greater amygdala and insula activation to the looming stimuli only. Our findings do not support this hypothesis, as there were no significant interaction effects for any of our ROIs. However, we did find significant group effects with the AUT having greater activation than the NT group in the insula, temporal gyrus, the temporal plane, transverse temporal gyrus, post-central gyrus, culmen, and Brodmann area 22

The greater insula, temporal gyrus, and temporal plane activation in the AUT group suggest interesting insights into the relationship between sensory processing and anxiety in autism. Berntson et al. (2011) proposes that the insula plays a broader role in the integration of

affective and cognitive processing of stimuli. Additionally, Bach et al. (2008) reported that the superior temporal gyrus and temporal plane are brain areas used to differentiate looming from receding sounds. The increased activation of mentioned brain areas in the AUT group during the auditory looming task suggest greater cognitive effort and use of neural resources in the AUT group to process the auditory stimuli. The more effortful processing of auditory stimuli may distract from other sources of social and emotional information provided by their environment, reducing the amount of contextual information autistic person has to make sense of their world, which in turn increases the amount of uncertainty and amount of anxiety autistic persons experience. This finding and interpretation is congruent with South and Rodgers (2017) model of anxiety in autism.

Similar to the hypothesis for the fMRI data, we also hypothesized that there would be a group-by-condition interaction effect for the pupillometry and SCR measurements. The data did not support this hypothesis. Interestingly, there was a significant group effect with the AUT having a greater SCR response to the stimuli compared to the NT group, but no differences in the pupil data. This difference between the SCR and pupil measures highlights the potential errors that may arise when researchers assume different psychophysiological will yield the same results. There was a significant main effect for condition with the Receding stimuli having a greater SCR and pupil responses than the Looming sounds. These results run contrary to previous auditory looming studies using pupillometry (Fletcher et al., 2015) and SCR measures (Bach et al., 2008). This may be due to the difference in auditory stimuli used (we used auditory stimuli from Neuhoff (2016)) and the adapted protocol design from the Bach et al. (2008) that found amygdala and intraparietal sulcus activation to the looming stimuli. Another possible reason for these discrepancies is the loud MRI environment. Previous studies utilizing SCR or

pupillometry did not collect their data in an MRI environment, a very loud testing environment, which could have affected the psychophysiological response of the participants. Although we attempted to control for this using active noise cancelling head phones, it is possible that the lower volume at the beginning of a looming trial was drowned out by scanner noise. Thus, A participant may not have been able to recognize the Looming trial until the stimulus was halfway over, attenuating the SCR or pupil response. Furthermore, the Receding sounds started louder than the Looming sounds, likely resulting in a higher SCR or pupil response near the beginning of the trial that was maintained during the course of the trial. Future studies are needed to determine how task protocol (e.g., inclusion of other sounds to reduce habituation, number of trials, etc.), stimuli differences (e.g., types of looming stimuli, 2 second looming sound vs 4 second looming sound, etc.), and testing environment (e.g., MRI environments vs quiet laboratory environments) may lead to differential SCR or pupillometry responses.

When testing the South and Rodgers (2017) model of anxiety in autism, we hypothesized that there would be a group-by-condition interaction effect with the High IUS group responding to both greater amygdala and insula activation to both looming and receding stimuli, while the Low group would show greater amygdala and insula activation to the looming stimuli only. This hypothesis was rejected. Unlike the AUT vs NT group split, there were no group differences in the ROIs between the High IUS and Low IUS groups. Thus, it seems that there is something beside the intolerance of uncertainty that is driving the difference in brain activation in the autism group, such as atypical sensory processing or alexithymia (South & Rodgers, 2017). Other potential mechanisms explaining the brain activation differences to auditory looming between autistic individuals and neurotypical individuals need be further explored in future studies.

Lastly, we hypothesized that the amygdala and insula activation to the Receding and Looming and the psychophysiological measures would significant correlated with the anxiety and intolerance of uncertainty levels, as suggested about the White et al (2014) and South & Rodgers (2017) models. This hypothesis was rejected. This lack of association between the brain activation/psychophysiological measures and the behavioral measures will be discussed further in the general discussion section.

## General Discussion

These two studies aimed to evaluate several possible contributors to anxiety in autism, including both cognitive and physiological models. We used tasks that involved learning and no-learning conditions and we modified the reinforcement contingencies from our earlier foray into fear conditioning. We analyzed support for the possibility of 1) atypical, hyperactive amygdala activation in autism (e.g., White et al. 2014); 2) and 2) a distracting role for uncertainty, possibly related to atypical sensory processing (e.g., South & Rogers, 2017).

One of the most interesting findings of these studies was that fear conditioning and extinction seem to be intact in autism in this study, where the reinforcement of the threat stimulus was 100%. This finding suggests that the atypical amygdala activation found in Top Jr et al. (2016) is possibly due to anxious distraction caused by the partial reinforcement (uncertainty) of the threat stimulus. Additionally, in this study we found that although the AUT group was able to differentiate between the Receding and Looming stimuli to the same degree as the NT group, the AUT group showed atypical insula response regardless of the auditory stimulus condition. This may fit with the uncertainty hypothesis, as the participants did not have any information of when and what type of stimuli would be presented during the task. Future

auditory looming studies in autism may benefit from providing visual or other clues to inform the client what stimulus they will be presented and see if this finding can be replicated.

We make these conclusions tentatively, as this is the first fMRI fear conditioning study in autism to use a 100% reinforcement schedule, as well as the first auditory looming study in autism that also collected psychophysiological data simultaneously. Thus, future research should attempt to replicate and refine these findings.

While using brain responses to the tasks to predict behavioral anxiety was one of the purposes of the study, LeDoux and Pine (2016) suggest that expecting neuro-/psycho-physiological measures to predict self-report measures is an unrealistic assumption to place on ours or similar data. They suggest that the "fear network" activated during experimental tasks is separate from the "anxiety network" that is activated in an individual's everyday experience, and that research participants filling our behavioral measures of anxiety are reflecting on their everyday experience of anxiety. Thus, they argue that there is an ontological gap between a participant's neuro-/psycho-physiology measured in the lab and their behavioral measures, making it unlikely researchers will be able to find meaningful correlations between these types of data. The disconnect between lab response and behavioral responses in autism research has led to a call for experimental designs with more ecological validity and the creation of behavioral measures reflect what is being measures in the laboratory setting (Geurts, Corbett, & Solomon, 2009; South & Rodgers, 2017). Furthermore, there is a measurement issue in autism research where many of the anxiety measures typically used in autism research do not have measurement invariance between neurotypical and autistic youth (Glod et al., 2017; Schiltz et al., 2019; White et al., 2015). To date, no anxiety measures have been tested for measurement invariable in an autistic adult sample. Future research would benefit from assessing the measurement invariance

of anxiety measures in autistic samples or the creation of an autism specific anxiety measure in an adult population.

An important element to consider is the different temporal properties of our dependent measures sometime leading to differential results. SCR and fMRI have relatively low temporal resolution compared to the high temporal resolution of pupillometry. It may be the case that there are no differences between autism and neurotypical controls when using the measures with slower temporal resolution because those with autism reactions are able to catch up to the responses of the neurotypical population by the end of the trial. On the other hand, measures with high temporal resolution (e.g., pupillometry or electroencephalogram) may be able to detect during the early moments of stimulus onset that may be washed out by the end of the trial. Indeed, other work we are doing with pupillometry suggests that there are group differences in signal very early (first 1000ms) in the AUT group that resolve by the middle part of the trial (Bennion et al., 2019). It may be profitable for future studies of anxiety in autism to examine psychophysiological differences across the time course of a condition/trial, as opposed to using the total change or mean response across the condition or trial.

**Clinical Implications**

This set of studies lead to some clinical insights for those working with anxiety in autism. As mentioned earlier, the results from the fear conditioning study provides promising evidence for the utilization of exposure therapies for the treatment of phobias. Specifically, this study showed that the autistic and neurotypical person have relatively similar brain and physiological responses to fear conditioning and fear extinction when the reinforcement of the feared stimulus is absolutely certain. Given the results of this study, autistic individuals seeking treatment for

phobias that were developed and maintained via conditioning are likely to benefit from behavioral therapies.

However, anxiety in autism often takes a more generalized form that is often unrelated to classical fear conditioning and has more to do with uncertainty about their environment (Kerns et al., 2014). Given this more generalized form of anxiety due to the uncertainty about the environment, these results as well as the Top Jr et al. (2016) results suggests behavioral therapies may be less effective for this generalized presentation of anxiety. This implication is further supported by Morriss et al. (2018) who reported that increased intolerance of uncertainty reduced the effectiveness of fear extinction protocols for adults with generalized anxiety disorder. Additionally, Keefer et al. (2016) found that intolerance of uncertainty moderated the outcomes of cognitive behavioral therapy for anxiety with an adolescent autistic youth sample, in that children with higher baseline levels of intolerance of uncertainty did not benefit from the anxiety treatment to the same degree. Furthermore, the structural equation modeling of anxiety in autism from Maisel et al. (2016) reported that alexithymia and experiential avoidance mediated the relationship between autism symptoms and anxiety, suggesting that mindfulness- and acceptance-based interventions may be promising for treating anxiety in autism.

Another clinical implication from these studies highlights the importance for clinicians to pay attention to the role of sensory sensitivities and other atypical sensory processing factors that may uniquely contribute to the anxiety in autism. Many of the mainstream treatments for anxiety do not include modules for helping clients address their sensory concerns (South & Rodgers, 2017). Treatment models that help address these sensory difficulties including promotion interoceptive awareness (Garfinkel et al., 2016) and mindfulness (Maisel, Stephenson, Cox, &

South, 2019; Spek, van Ham, & Nyklíček, 2013) will likely be beneficial for clients with autism seeking treatment for anxiety.

**Limitations**

Although these studies shed light on the anxiety in autism, there are a number of limitations that should be addressed in future studies. First, while this study had a reasonable sample size, a larger sample size is needed to investigate the intricacies of anxiety presentation in autistic persons. For example, Herrington et al. (2016) found that atypical amygdala response in autism was a function of anxiety rather than a true difference between their autism group (n = 81) and neurotypical group (n = 67). Unlike our study, Herrington had a large enough sample to split their autism group into high anxiety and low anxiety groups and retain enough statistical power to find differences. Additionally, Gotham et al. (2018) found that when comparing autism adults with/without depression to neurotypical adults with/without depression, the level of depressive symptoms was a stronger predictor of the psychophysiological response to a task than the autism vs neurotypical group distinction. Our study would have benefited from having a larger AUT and NT groups that we could split into high anxiety and low anxiety groups to examine for differential brain or psychophysiological responses as a function of anxiety level. Additionally, a larger sample size would have allowed us to run additional and more complex anxiety models without sacrificing statistical power.

Second, many studies of fear conditioning in humans use more aversive unconditioned stimuli including mild shock. While there are significant ethical concerns about using aversive methods in vulnerable samples, there may be a disconnect between the intensity of our air burst stimulus and the intensity of threatening stimuli in an individual's everyday experience (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013). Alternative UCS presentations, such as a cold

pressor, that appear to be tolerable even for pediatric samples may provide a good middle ground for future studies (Birnie, Noel, Chambers, von Baeyer, & Fernandez, 2011).

A third limitation of these studies stems from Boubela et al. (2015) findings that typical echo-planar imaging (EPI) may not be sensitive enough to find reliable amygdala activation. Specifically, they reported that traditional EPI sequences, like the one used in this study, are likely to suffer from signal dropout and "activation contamination" from the blood flow in the basal vein of Rosenthal when there is a visual component to the task (Boubela et al., 2015). As our fear conditioning paradigm used visual cues as the threat and safe stimuli, it is possible that our lack of main effects or interaction effects in the amygdala may be due to this phenomenon. As recommended by Boubela et al. (2015), future fear conditioning studies should use non-visual stimuli when using typical EPI sequences, or utilize low-TR multiband EPI sequences to increase measurement sensitivity of the amygdala when visual cues are part of the task protocol.

An important limitation of this study is the lack of amygdala activation in both paradigms that were specifically chosen because they were likely to activate the amygdala. As mentioned earlier in this paper, the Fullana et al. (2016) meta-analysis of fear conditioning in neurotypical adults found that amygdala activation is less robust and less reliable in human samples, compared to the robust and reliable activation of the insula. In regard to the looming protocol, and to the best of our knowledge, there has only been one fMRI looming study in humans and the original looming study had a relatively small sample size compared to our sample. While we may have tested the insula activation predictions of White et al. (2014) model, the protocol used in this study does not seem sufficient to test the amygdala activation predictions of the White et al. (2014) model.

**Future Directions**

Future research can expand upon this study in a number of ways. First, it will be important to replicate these results using similar designs and stimuli. Second, An interesting direction for future research is to see if fear conditioning/extinction with 100% reinforcement starts to break down as the task becomes more complex. An example of this would be using multimodal conditioning protocols or conditioning protocols with variable reinforcement rates, as an individual's learned fear response to different stimuli in the "real world" is rarely created and maintained with such simplicity as this fear conditioning task. Reversal fear learning protocols, in which the threatening and the safe conditioned stimuli is switched half through the task, requiring the participants to learn a new association while extinguishing the previous association simultaneously may further our understanding of anxiety in autism (Schiller et al., 2008; South et al., 2012). According to our knowledge, the has not been a reversal learning paradigm in an adult autistic population or while using fMRI.

Additional sensory processing tasks, including multimodal sensory tasks, will help researchers to delineate the relationship between atypical sensory processing and anxiety in autisms. Helpful tasks may include visual looming or combined auditory and visual looming tasks. Multi-modal habituation tasks may also yield interesting findings.

As mentioned in the limitations section, the many of anxiety measures typically used in autism research have not shown measurement invariance between neurotypical and autistic populations (Glod et al., 2017; Schiltz et al., 2019; White et al., 2015). Future research would benefit from assessing the measurement invariance of anxiety measures in autistic samples or the creation of an autism specific anxiety measure in an adult population. Once these measures have

been created and validated, can be used in a SEM model to directly compare the White et al. (2014) and South & Rodgers (2017) models for model fit.

In the clinical domain, studies performing randomized controlled trials of anxiety treatments in autistic populations can provide direct information that can help clinicians attempting to help their clients. A recent study by Wood et al. (2019) compared treatment-as-usual, Cognitive Behavioral Therapy, and modified Cognitive Behavioral Therapy for autistic youth found and found that the modified Cognitive Behavioral Therapy lead to improved outcomes compared to the other two conditions. Future randomized control trials should assess if clinicians utilizing interventions to address intolerance of uncertainty and sensory processing difficult lead to improved treatment outcomes.

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