2017-07-01

The Relationship Between Auditory Habituation and Anxiety in Autism Spectrum Disorder

David Nicholas Top
Brigham Young University

The Relationship Between Auditory Habituation and Anxiety in Autism Spectrum Disorder

David Nicholas Top Jr.

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

Master of Science

Mikle South, Chair
Steven Luke
Rebecca Lundwall

Department of Psychology

Brigham Young University

ABSTRACT

The Relationship Between Auditory Habituation and Anxiety
in Autism Spectrum Disorder

David Nicholas Top Jr.
Department of Psychology, BYU
Master of Science

Many individuals with autism spectrum disorder (ASD) have atypical sensory processing and behaviors including sensory sensitivity and low registration of sensory stimuli as well as sensory seeking and avoiding behaviors. Additionally, many individuals with ASD have clinically distressing levels of anxiety. Previous research suggests that there is a link between abnormal sensory processing, anxiety, and ASD. The purpose of this study was to experimentally observe auditory sensory processing using pupillometry methods, between ASD, control, and high-anxious control groups. While a difference in tonic pupil size was observed, there were no reactivity or habituation differences between the groups. There were no significant correlations between the pupillometry measures and behavioral measures of emotional distress and anxiety. These results do not indicate a relationship between anxiety and unimodal auditory response in ASD. Implications and directions for future research are discussed.

Keywords: autism spectrum disorder, anxiety, pupillometry, habituation

TABLE OF CONTENTS

Abstract ii

List of Tables v

List of Figures vi

Manuscript: The Relationship Between Auditory Habituation and Anxiety in Autism Spectrum Disorder 1

Methods 7

Participants 7

Behavioral measures 7

Autism Spectrum Quotient. 7

Intolerance of Uncertainty Scale-12. 7

Penn State Worry Questionnaire. 8

Adolescent/Adult Sensory Profile 8

Eye-Tracking Apparatus and Measurement 8

Auditory Habituation Protocol 9

Data cleaning and preparation 10

Results 10

Tonic Pupil Size 10

Initial Response to the Sound Stimuli 11

Auditory Habituation to the Sound Stimuli 11

Between Group Differences of Behavioral Measures 12

Behavioral Correlates..... 13

Discussion..... 13

References..... 18

LIST OF TABLES

Table 1 *Difference Between Groups On Behavioral Measures* 33

Table 2 *Unconditional Growth Model Fit Indices For Sound1* 34

Table 3 *Unconditional Growth Model Fit Indices For Sound2* 35

Table 4 *HLM Results Sound1 With Natural Log Transformation Of Time* 36

Table 5 *HLM Results Sound2 With Natural Log Transformation Of Time* 37

Table 6 *Spearman's Rho Correlation Coefficients* 38

LIST OF FIGURES

Figure 1. Tonic pupil size across all 10 trials of the Silence condition. 39

Figure 2. Pupil responses to Sound1 across all 10 Sound1 trials. 40

Figure 3. Pupil responses to Sound2 across all 10 Sound2 trials.. 41

The Relationship Between Auditory Habituation and Anxiety in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social reciprocity, social communication, and repetitive/restricted behaviors or interests, affecting approximately one of every 68 Americans (American Psychiatric Association, 2013; Christensen et al., 2016). The most recent editions of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) classify atypical sensory processing as a restricted/repetitive behavior (American Psychiatric Association, 2013). Atypical sensory processing is relatively common in individuals with ASD, affecting 45–95% of the ASD population (Baker, Lane, Angley, & Young, 2007; Baranek et al., 2007; D. Green, Chandler, Charman, Simonoff, & Baird, 2016; Leekam, Nieto, Libby, Wing, & Gould, 2006; Tomchek & Dunn, 2007; Tomchek, Huebner, & Dunn, 2014). Sensory processing in ASD is heterogeneous and complex, with both increased sensitivity and reduced responsiveness often observed within the same individual (Baranek et al., 2007; Crane, Goddard, & Pring, 2009; Hirstein, Iversen, & Ramachandran, 2001). For example, individuals with ASD show significantly high levels of distress to low-threshold sensory stimuli (Tomchek & Dunn, 2007; Tomchek et al., 2014). They can also exhibit a reduced responsiveness or registration of sensory stimuli and engage in sensory seeking behaviors (Kern et al., 2007).

Although not a core feature of ASD, many individuals with ASD meet criteria for a comorbid anxiety disorder (Buck et al., 2014; van Steensel, Bögels, & de Bruin, 2013; van Steensel, Bögels, & Perrin, 2011; White, Oswald, Ollendick, & Scahill, 2009). These anxiety symptoms can cause additional impairment for these individuals, including exacerbated levels of problematic behaviors (Gotham et al., 2013; Rodgers, Glod, Connolly, & McConachie, 2012),

impaired decision making skills (Luke, Clare, Ring, Redley, & Watson, 2012), and considerable stress on family systems (Conner, Maddox, & White, 2013). While some anxious individuals with ASD manifest anxiety in ways that suggest the presence of comorbid anxiety disorders, more research is needed to understand the unique presentation of anxiety found in ASD samples (Kerns et al., 2014). A recent study by Kerns and collagues (2014) suggests that youth with ASD express anxiety in ways both similar and dissimilar to current definitions of anxiety disorder. Basic etiological research exploring the potential underlying mechanisms that link anxiety with the core symptoms of ASD, like atypical sensory processing, is an important step towards developing targeted anxiety interventions for individuals with ASD (Rodgers et al., 2012; White et al., 2014).

Researchers examining the relationship between sensory processing and anxiety suggest that sensory processing sensitivity is an important factor contributing to the 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). Additionally, a number of studies have shown evidence of an association between atypical sensory features, anxiety symptoms, and ASD symptoms (Ben-Sasson et al., 2008; Green & Ben-Sasson, 2010; Lidstone et al., 2014; Liss, Mailloux, & Erchull, 2008; Neil, Olsson, & Pellicano, 2016; Pfeiffer, Kinnealey, Reed, & Herzberg, 2005; Uljarević, Carrington, & Leekam, 2016). For example, Liss and collegues (2008), using a large non-ASD sample, found that multiple sensory processes (e.g., ease of excitation, low sensory threshold, and aesthetic sensitivity) were related to self-reported levels of autism symptoms and anxiety. Other studies utilizing self-report measures with ASD and typical developing young adult samples

found significant relationships between sensory sensitivity and anxiety levels (Milosavljevic et al., 2016; Uljarević, Carrington, & Leekam, 2016).

Studies utilizing parent report measures in children and adolescent samples have found similar results. Lidstone and colleagues (2014) found that sensory avoidance and sensory sensitivity are related to anxiety and ASD symptoms. Other studies reported significant relationships between sensory under-responsiveness and sensory sensitivity, levels of anxiety, and ASD symptoms (Neil et al., 2016; Wigham & McConachie, 2014). Green et al. (2012), in one of the landmark studies on this topic, reported that sensory over-responsivity emerges earlier than anxiety in ASD and was found to predict anxiety symptoms. Although very informative, the previously mentioned studies rely on self/parent report measures, and do not utilize any psychophysiological methods (e.g., skin conductance, cardiac impedance, or pupillometry) or use experimental sensory paradigms to examine the relationship between anxiety and atypical sensory processing in individuals with ASD. Psychophysiological measures of basic sensory processes allow researchers to observe participants' physiological reaction to sensory stimuli and thus provide more objective measurement than self/parent report measures. The purpose of the present study was to experimentally observe a sensory processing phenomenon, namely auditory habituation, using a psychophysiological measure among typically developing individuals (CON), typical developing individuals with elevated levels of anxiety (ANX), and individuals with ASD.

For the purposes of this study, habituation is defined as the exponential decrement of a response to the same and initially novel stimulus presented repeatedly over time (Madsen, Bilenberg, Cantio, & Oranje, 2014; Sinclair, Oranje, Razak, Siegel, & Schmid, 2016). Research examining the habituation to sensory stimuli in ASD has yielded mixed results. For instance,

habituation studies in children and adolescents with ASD have suggested that individuals with ASD show reduced/atypical habituation (or increased sensitization, which is the opposite of habituation) to auditory (Green et al., 2013a; Järvinen et al., 2015; Madsen et al., 2014; Ornitz, Lane, Sugiyama, & de Traversay, 1993), tactile (Puts, Wodka, Tommerdahl, Mostofsky, & Edden, 2014), and visual stimuli (Green et al., 2013). A study examining auditory habituation in infants with a high risk of ASD showed reduced habituation compared to typically developing infants (Guiraud et al., 2011). A recent study by Green and collegues (Green et al., 2015) found atypical habituation to multiple sensory stimuli (e.g., tactile and auditory stimulation at the same time) in the ASD group. This finding became more prominent when the ASD group was split into sensory overresponsive and sensory non-overresponsive groups, with the overresponsive sensory group showing reduced neural habituation to multiple stimuli. However, this study is limited by the small sample size in each group (splitting a small *n* of 19 into two smaller groups) and may not have sufficent power to be generalizable. By contrast, other reseachers have not found differences in habituation when comparing ASD and typically developing youth samples. For example, Takahashi et al. (2015) did not find differences in habituation using a acoustic startle response paradigm, but did find that the ASD group had a larger response to the mild stimuli and a longer peak-startle latency. Additionally, Ornitz and collegues (1993) did not find differences in short-term habitution to startle amplitude or long-term habituation to auditory stimuli. According to our knowledge, only one study examined sensory habituation in adults with ASD (Musurlian, 1995). This study reported evidence for reduced auditory habituation in adults with ASD. Due to the lack of data in the adult ASD population, a recent literature review by Sinclair et al. (2016) argues that habituation protocols deserve further investigation in adults with ASD.

Previous habituation studies in ASD used a variety of psychophysiological arousal measures including galvanic skin response, electromyography (eye-blink startle response), or functional magnetic resonance imaging. Pupillometry is another psychophysiological measure linked to autonomic nervous system arousal and is considered a valid measure of auditory stimulation and habituation (Shiga & Ohkubo, 1980; Sirois & Brisson, 2014; Steiner & Barry, 2011). A recent study by Wiemer, Mühlberger, and Pauli (2014) found that pupil dilation increased as sounds became more aversive, indicating that pupillometry is an accurate measure of auditory processing. Additionally, changes in pupil dilation have been shown to accurately reflect emotional arousal (Blackburn & Schirillo, 2012; Bradley, Miccoli, Escrig, & Lang, 2008; Kuchinke, Schneider, Kotz, & Jacobs, 2011; Partala, Jokiniemi, & Surakka, 2000) and autonomic arousal elicited by other sensory stimuli (Aguillon-Hernandez et al., 2015). Recent studies have found an assosication between pupillometry and activation of the locus coeruleus (Alnæs et al., 2014; Murphy, O'Connell, O'Sullivan, Robertson, & Balsters, 2014), a region of the brain that has a major role in arousal and stress responses (Benarroch, 2009; Laeng, Sirois, & Gredebäck, 2012; Samuels & Szabadi, 2008). Because of the strong link between pupillometry and autonomic arousal that is directly associated with a brain structure, pupillometry is considered an objective index of autonomic nervous system arousal that is especailly useful in clinical populations and interventions (Anderson & Colombo, 2009; Laeng et al., 2012; Lahiri, Bekele, Dohrmann, Warren, & Sarkar, 2015).

Previous studies using pupillometry in ASD have yielded mixed results. For example, some studies have found that individuals with ASD have a larger tonic pupil size than typical developing controls (Anderson & Colombo, 2009; Anderson, Colombo, & Unruh, 2013), while others have found the opposite trend (Martineau et al., 2011) or no differences (Nuske, Vivanti,

& Dissanayake, 2015). Additionally, pupillometry has been used in ASD to measure basic physiological reactions to light (Daluwatte et al., 2013; Daluwatte, Miles, Sun, & Yao, 2015), faces (Anderson, Colombo, & Shaddy, 2006; Falck-Ytter, 2008; Nuske, Vivanti, & Dissanayake, 2014; Sepeta et al., 2012), cognitive load (Martineau et al., 2011), and emotional stimuli (Nuske, Vivanti, & Dissanayake, 2013; Nuske et al., 2015; Nuske, Vivanti, Hudry, & Dissanayake, 2014). To date, no study has used pupillometry to experimentally examine the relationship between sensory processing, anxiety, and ASD symptoms.

As mentioned earlier, the purpose of this study was to experimentally observe auditory habituation (a sensory process) among typically developing adults (CON), typically developing adults with elevated levels of anxiety (ANX), and adults with ASD, using pupillometry as the index of autonomic arousal. We tested three specific hypotheses in this study. **Hypothesis 1**: Given the current state of the research, our working theory of anxiety in ASD assumes that sensory sensitivities in ASD significantly contribute to the anxiety experienced in this population. If this is the case, then these sensitivities should be manifest in the pupillary response. Thus, we hypothesized a larger pupil response to the initial auditory stimuli in the ASD groups compared to the ANX and CON groups. **Hypothesis 2:** Existing literature has suggested that the anxiety in ASD is due to atypical habituation of sensory stimuli, leading us to hypothesize that the ASD group would show reduced habituation to the auditory stimulus compared to the CON and ANX groups. **Hypothesis 3:** We hypothesized that we should replicate and expand upon previous research by finding significant correlations between anxiety, ASD symptoms, and atypical sensory processing as measured by the pupillometry and behavioral measures.

Methods

Participants

A total of 94 volunteers participated in our study: 35 typically developing controls (CON), 31 individuals with autism (ASD), and 28 typically developing individuals with elevated levels of (ANX). Members in the ASD group had a confirmed diagnosis of autism spectrum disorder as validated by the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2000). The ADOS-2 was administered by clinician who is research reliable. Ages ranged from 18 to 37 years (see Table 1). Proportion by sex for each group were as follows: CON group was 63% male, ASD group was 76% male, and ANX was 40% Male. The ASD group (M = 24.47) was significantly older then the ANX (M = 21.90) and CON (M = 20.94) groups ($F(2,92) = 6.62$, $p = .002$). There were no significant differences in intellectual functioning as measured by the Wechsler Abbreviated Scale of Intelligence – II ($F(2,92) = 2.32$, $p = .010$). All participants who agreed to participate in this study were able to complete the auditory habituation protocol.

Behavioral Measures

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 ASD phenotype. The ASQ has been used as a dimensional measure of ASD-symptoms in clinical populations and in the general public, and has been demonstrated to be sensitive to subclinical ASD symptoms (Bishop et al., 2004).

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 was used in the current study. The IUS-12 has been successfully used to show an association between IU and anxiety in children and adolescents diagnosed with ASD (Boulter, Freeston, South, & Rodgers, 2014; Chamberlain et al., 2013).

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 (e.g., the Beck Depression Inventory) and general anxiety (e.g., State Trait Anxiety Inventory); and to be sensitive to cognitive orientated treatment (Dear et al., 2011; Meyer et al., 1990).

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 a previous study examining the relationship between atypical sensory processing, anxiety, and ASD symptoms (Milosavljevic et al., 2016).

Eye-Tracking Apparatus and Measurement

Pupils were recorded via an SR Research Eyelink 1000 Plus tower mount eye tracker (spatial resolution of 0.01°) sampling at 1000 Hz. Subjects were seated 60 cm away from a 24" LCD screen. Head movements were minimized with a chin and headrest. 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 SR Research Experiment Builder software.

Auditory Habituation Protocol

After the eye-tracking equipment was calibrated to the participant, participant was shown the instructions for the task. The instructions were presented on the computer screen while the experimenter read the instructions out loud to the participants. The instructions were as follows, "During this experiment, you will be staring at the fixation cross in the center of the screen. While staring at the cross you will be hearing noises in the headphones. Please keep your eyes focused on the cross throughout the experiment. Failure to look at the fixation cross will pause the experiment. Do you have any questions?" After answering any questions the participant had, the experimenter would start the auditory habituation protocol.

The auditory habituation protocol consisted of three blocks with 10 trials per block for a total of 30 trials. For each trial, after a 500ms delay, the corresponding sound (Silence, Sound1, or Sound2) was presented for approximately two seconds (the sound duration was jittered, ranging from 1.8–2.2 seconds). This was followed by a 20-second jittered inter-trial-interval ranging from 18–22 seconds. Each block of trials corresponded with the tones presented to the participants. In the first block of trials, participants were exposed to ten trials of "silence," an audio file with no sound presented on the identical schedule as in the following blocks. The second block of trials utilized a 60db, 2000Hz sinewave tone (Sound1). An 80db 2000Hz sawtooth tone (Sound2) was presented during the third block. Each participant received each block in order (Silence, Sound1, then Sound2). During the experiment, the fixation-cross remained on screen continuously, and there were no visual changes to the screen to indicate that

one trial had ended and another had begun. Additionally, the eye-tracker was programmed so that if the eyes left a pre-defined invisible area around the fixation cross, the experiment would pause until the eyes returned to the fixation cross.

Data Cleaning and Preparation

As mentioned previously, pupillometry data was collected at a 1000hz rate throughout the experiment. Because the data were originally in arbitrary area units, we converted the data to mm diameter by running the experiment with a 10mm artificial pupil and using the resulting data to compute pupil diameter of the actual participants. Data were then cleaned, by removing samples that occurred during blinks and saccades, and then smoothed using a loess filter with a span of 0.25. Pupil size at time 0 (the moment before the sound onset) was used as a baseline, and pupil size change was computed by subtracting this baseline value from each sample. Finally, before analysis, outlier samples greater than or less than 2.5 standard deviations from the participant's mean were removed (less than 4% of the total data were removed), and the pupil data were grouped into 250ms bins via averaging (Sirois & Brisson, 2014).

Results

Tonic Pupil Size

All analyses were performed using STATA 14. To investigate the average tonic pupil size for each group, we first calculated the average pupil size across all 10 trials of the Silence condition. Normality testing showed that the distribution of average tonic pupil sizes was non-normal. We attempted to perform data transformations with no success. Visual inspection of the data showed that for all three groups the data were positively skewed and similarly shaped. We proceeded with a Kruskal-Wallis equality of populations rank test to compare the tonic pupil size between groups. The Kruskal-Wallis test is a non-parametric alternative to the one-way ANOVA

test that uses the ranking of scores to determine if there are differences between the groups (Ruxton & Beauchamp, 2008). Analysis revealed there were significant differences between the groups ($\chi 2$ (2) = 6.26, p = .0001; see Table 1). We performed post-hoc analysis by performing Dunn's test of multiple comparisons of rank sums using the "dunntest" package of STATA 14. Post-hoc analysis showed that there were no significant differences between the CON and ANX groups. However, the ASD group had a significantly greater tonic pupil size than the CON group and the ANX group (see Figure 1). Results were not different when an ANOVA was performed.

Initial Response to the Sound Stimuli

We used the first six seconds of each trial during the Sound1 and Sound2 blocks to extract the peak pupil response to the stimulus. To examine the initial pupil response to the sounds, we used the peak pupil change for the first trial of each block (Sound1 and Sound2). Normality analysis showed that Sound1 responses were non-normal and no data transformation would successfully normalize the data. Because of this, we performed the Kruskal-Wallis test to examine potential differences between groups. This analysis yielded no difference between the three groups ($\chi 2$ (2) = 1.75, p = .42). We used a one-way ANOVA to examine initial response of Sound2 because it was normally distributed. The analysis revealed no differences between the groups for Sound2 (F (2,92) = 2.29, p = .11). Overall, there were no differences in the initial response to the tones between the ASD, ANX, and CON groups.

Auditory Habituation to the Sound Stimuli

Because the data set included multiple trials per participant, we used Hierarchal Linear Modeling (HLM) analyses to control for random inter-individual variability that was common to all trials performed by the same participant. Visual inspection of the data and testing unconditional growth models indicated that a natural log transformation of trial ["ln(trial)"]

variable was a better fit of the data than the linear model for both Sounds (see Figures 2 & 3 and Tables 2 & 3). Natural log functions are frequently used in psychotherapy outcome research in which the effect of time on the dependent variable is steep at first, then gradually levels out (Warren, Brown, Layne, & Nelson, 2011; Warren & Salazar, 2014). For the purpose of interpretation, we coded the groups as follows, CON = 0, ANX = -1, and ASD = 1. This coding method allowed us to use CON as the normative group, and thus observed how the ASD and ANX groups differed from the CON group. The final model for the peak change in pupil size across Sound1 included fixed effects of group and trial, as well as the group-by-trial interaction and the random effects of trial. Results showed a significant effect for trial, but non-significant effects for the group or group-by-trial interaction, suggesting that all three groups successfully habituated to Sound1 at similar rates. The final model for the peak change in pupil size across Sound2 was the same as Sound1. Similarly, we saw a strong habituation response in all three groups, but non-significant group main effects or group-by-trial interaction effects (see Tables 4 & 5).

Between Group Differences of Behavioral Measures

We examined the differences between the groups on the behavioral measures. Normality test showed that the following variables were normally distributed: Penn State Worry Questionnaire, and the *low registration, sensory seeking*, and *sensory avoiding* subscales of the Adult/Adolescent Sensory Profile. For these scales, we used one-way ANOVAs followed by Tukey's honest significant difference post-hoc analyses. The Autism Quotient, Intolerance of Uncertainty total score, and the *sensory sensitivity* subscale of the Adult/Adolescent Sensory Profile had non-normal distributions. We used the Kruskal-Wallis test and Dunn's post-hoc test for these scales. The results of these analyses are presented in Table 1. The CON group has

significantly lower levels of intolerance of uncertainty ($F(2,85)$ = 19.91, p = .0001), autism symptoms ($\chi 2(2)$ = 34.73, p = .0001), and sensory sensitivity ($\chi 2(2)$ = 24.24, p = .0001), than both the ASD and ANX groups who did not differ from each other. The CON group (M = 52.69) showed higher levels of sensory seeking behaviors (F (2, 77) = 24.40, p = .0001) than both the ANX and ASD groups, with the ANX group (M = 44.95) having higher levels than the ASD group (M = 38.67). The ASD group showed significantly higher levels of low registration ($F(2, 77)$ = 11.82, p = .0001) and sensory avoidant behaviors (F (2,77) = 14.22, p = .0001) than the CON and ANX groups. The ANX group had the highest levels of anxiety (F (2, 86) = 14.62, p = .0001) compared to the ASD and CON groups, who did not differ from each other.

Behavioral Correlates

Because the pupillometry measurements and some of the behavioral measurements were non-normal, we performed Spearman's *rho* correlations using a Sidak correction for multiple comparisons to examine the relationships between the initial pupil responses to the tones and other behavioral data. The results are presented in Table 6. Correlation analyses reveal that there were no significant correlations between any of the pupillometry measurements and the other behavioral measures. We found significant positive correlations between the autism symptoms and the low registration (ρ = .45), sensory sensitivity (ρ = .49), and sensory avoidance (ρ = .59) domains of the Sensory Profile. The AQ was also negatively associated with sensory seeking behaviors (ρ = -.64). The IUS showed the same pattern of associations as the AQ. Participants' anxiety as measured by the PSQ was positively correlated with the sensory sensitivity (ρ = .42), autism symptoms (ρ = .44), and intolerance of uncertainty (ρ = .57).

Discussion

The goal of this study was to determine if the anxiety commonly reported in ASD is related to atypical sensory processes in ASD, specifically auditory processing and habituation. We did this through experimental observation of auditory habituation, among typically developing individuals (CON), typically developing individuals with elevated levels of anxiety (ANX), and individuals with ASD using pupillometry techniques as our measure of sensory sensitivity and autonomic arousal. We hypothesized that the ASD group would show a heightened physiological response due to their sensory sensitivities, as manifest by larger pupil responses, to the initial presentation auditory stimuli compared to the ANX and CON groups. The results of this study do not support this hypothesis, as there were no differences between the three groups, indicating that the ASD group's responses to auditory stimuli are physiologically similar to the responses of typically developing adults. This may suggest that the anxiety observed in ASD may not be due to the to the single stimulus itself, but the high-level processing (e.g., learning or memory) of said stimulus or atypical integration of multiple stimuli.

We also theorized that the anxiety found in ASD was due to the atypical habituation of sensory stimuli. Thus, we also hypothesized that the ASD group would show reduced habituation to the auditory stimuli compared to the CON and ANX groups. Since the groups did not habituate to the sounds at different rate from one another, similar to previous studies (Ornitz et al., 1993; Takahashi et al., 2015), this hypothesis was also not supported. This suggests that anxiety experienced by those in the ASD group is unlikely to be due to deficits in auditory habituation.

We also sought to replicate and expand upon previous research by finding significant correlations between anxiety, ASD symptoms, and atypical sensory processing as measured by the pupillometry and behavioral measures. The results from the behavioral measures indicate that

anxiety is significantly associated with ASD symptoms and sensory sensitivity, replicating the results of previous research (Lidstone et al., 2014; Liss et al., 2008; Milosavljevic et al., 2016; Neil et al., 2016; Uljarević et al., 2016; Wigham & McConachie, 2014). However, unlike previous literature (Lidstone et al., 2014; Neil et al., 2016; Wigham et al., 2015), sensory avoidance, sensation seeking, and low registration were not associated with anxiety scores. Furthermore, anxiety was not related to any of the psychophysiological measures including tonic pupil size, pupil response to the initial sounds, or habituation rates, making it unlikely that this hypothesis was accurate. The only significant psychophysiological finding that replicates the effect of previous studies is that the ASD group have larger tonic pupil sizes than the ANX and CON groups (Anderson & Colombo, 2009; Anderson et al., 2013). However, it is unclear whether the larger tonic pupil size in the ASD group indicates 1) heightened physiological arsoual in ASD or 2) that people with ASD just have naturally larger pupils.

Although the results of this study suggest that anxiety experienced by those with ASD may not be directly influenced to atypical processing of and habituation to auditory stimuli, there are a number of limitations that need to be considered. Firstly, the compositions of our groups were different on multiple levels. For instance, the ASD group was significantly older than the ANX and CON groups. However, this age difference is not likely to be clinically significant for 2 reasons. First, all members in the group are within the same developmental range and it was two members of the ASD group that drove the age difference. Second, age was not a significant predictor of pupil responses as part of our HLM model. There were also more females in the ANX group than in the ASD or CON groups. This may have been a problem since females have been found to have larger pupil responses than males to neutral stimuli (Partala & Surakka, 2003). However, our results yielded no differences between the three groups despite having more

females in the ANX group. Another possible reason that we did not find significant correlations between anxiety, autism symptoms, and other sensory abnormalities is because the measures we used only captured one aspect of the construct that constrains the effect. Furthermore, the anxiety measure used in this study (as well as nearly all other anxiety measures for adults that were available at the time of the project) has yet to be validated in an adult ASD population. However, this limitation is inherent in most, if not all, published studies examining the relationships between autism and anxiety symptoms. Thus, future research investigating the issue of sensory sensitivity and habituation in autism should attempt to better match control groups and find a validated measure of anxiety or use several measures to improve construct validity.

This study also has some strengths. We recruited a sizable anxious control group to examine differences in the psychological response between the three groups, which is important for research investigating how anxiety experienced by individuals with ASD is different from the anxiety experienced by individuals with anxiety disorders. Additionally, the adoption of pupillometry, a simple and non-invasive physiological measure, meant that we did not have any participant attrition, with all of our participants finishing the auditory habituation task. Additionally, the auditory habituation task was the simplest possible protocol to test our hypotheses, examining very basic sensory processes without requiring the use of higher-level cognitive processes to complete.

This study is one of the first to examine the role of auditory sensitivity and habituation in ASD and its relations to anxiety. The rejection of our hypotheses and the overall pattern of null findings suggest that it is unlikely that atypical auditory sensitivity or habituation is directly influenced the anxiety experienced by those with ASD. However, this does not rule out the possibility that habituation to other sensory modalities (i.e., visual, tactile, or olfactory) or multi-

sensory modalities may contribute to the heightened anxiety in ASD. Future studies should examine this possibility by replicating this design using other sensory modalities and utilizing other behavioral measures and psychophysiological methods (i.e., skin conductance) to further investigate these relationships.

If sensory sensitivity/habituation is not the cause of anxiety in Autism, then what might be? One possible explanation is that atypical learning processes associated with sensory input, and not the initial response to that sensory input, are to blame. In other words, the meanings and associations made between the sensory stimuli and other objects, meanings, and events might be what leads to heightened anxiety in ASD. Indeed, past studies investigating fear conditioning in ASD suggest that individuals with ASD show atypical fear conditioning compared to typical developing controls (Gaigg & Bowler, 2007; South, Larson, White, Dana, & Crowley, 2011; South, Newton, & Chamberlain, 2012; Top et al., 2016). Although this seems to be a reliable finding, it is unclear if fear conditioning abnormalities in ASD are due to learning deficits (i.e., they are unable to or take longer to learn to the differences between safe and threatening stimuli) or a failure to extinguish. Additionally, these previous studies only used partial reinforcement schedules, making it plausible that their results were due to the uncertainty component of the fear conditioning paradigm rather than a failure to learn the association all together. In a recent commentary, Marin & Milad (2016) argue that fear conditioning studies may be particularly helpful to study fear learning and emotional regulation abilities in ASD and other related disorders. This is another direction for future research that may help demystify the mechanisms of the unique anxiety in experienced by individuals with ASD.

References

Aguillon-Hernandez, N., Naudin, M., Roché, L., Bonnet-Brilhault, F., Belzung, C., Martineau, J., & Atanasova, B. (2015). An odor identification approach based on event-related pupil dilation and gaze focus. *International Journal of Psychophysiology*, *96*(3), 201–209. https://doi.org/10.1016/j.ijpsycho.2015.03.009

Ahadi, B., & Basharpoor, S. (2010). Relationship between sensory processing sensitivity, personality dimensions and mental health. *Journal of Applied Sciences*, *10*(7), 570–574. https://doi.org/10.3923/jas.2010.570.574

Alnæs, D., Sneve, M. H., Espeseth, T., Endestad, T., van de Pavert, S. H. P., & Laeng, B. (2014). Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. *Journal of Vision*, *14*(4), 1–20.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-V*. Washington, D.C.: American Psychiatric Association Publishing.

Anderson, C. J., & Colombo, J. (2009). Larger tonic pupil size in young children with autism spectrum disorder. *Developmental Psychobiology*, *51*(2), 207–211. https://doi.org/10.1002/dev.20352

Anderson, C. J., Colombo, J., & Shaddy, D. J. (2006). Visual scanning and pupillary responses in young children with autism spectrum disorder. *Journal of Clinical and Experimental Neuropsychology*, *28*(7), 1238–1256. https://doi.org/10.1080/13803390500376790

Anderson, C. J., Colombo, J., & Unruh, K. E. (2013). Pupil and salivary indicators of autonomic dysfunction in autism spectrum disorder. *Developmental Psychobiology*, *55*(5), 465–482. https://doi.org/10.1002/dev.21051

Aron, E. N., & Aron, A. (1997). Sensory-processing sensitivity and its relation to introversion and emotionality. *Journal of Personality and Social Psychology*, *73*(2), 345–368.

Baker, A. E. Z., Lane, A., Angley, M. T., & Young, R. L. (2007). The relationship between sensory processing patterns and behavioural responsiveness in autistic disorder: A pilot study. *Journal of Autism and Developmental Disorders*, *38*(5), 867–875. https://doi.org/10.1007/s10803-007-0459-0

Baranek, G. T., Boyd, B. A., Poe, M. D., David, F. J., Watson, L. R., & MacLean Jr., W. E. (2007). Hyperresponsive sensory patterns in young children with autism, developmental delay, and typical development. *American Journal on Mental Retardation*, *112*(4), 233–245.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal Of Autism And Developmental Disorders*, *31*(1), 5–17.

Benarroch, E. E. (2009). The locus ceruleus norepinephrine system: Functional organization and potential clinical significance. *Neurology*, *73*(20), 1699–1704. https://doi.org/10.1212/WNL.0b013e3181c2937c

Benham, G. (2006). The highly sensitive person: Stress and physical symptom reports. *Personality and Individual Differences*, *40*(7), 1433–1440.

Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S. A., Engel-Yeger, B., & Gal, E. (2008). A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(1), 1–11. https://doi.org/10.1007/s10803-008-0593-3

Bishop, D. V. M., Maybery, M., Maley, A., Wong, D., Hill, W., & Hallmayer, J. (2004). Using self-report to identify the broad phenotype in parents of children with autistic spectrum disorders: A study using the Autism-Spectrum Quotient. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *45*(8), 1431–1436. https://doi.org/10.1111/j.1469-7610.2004.00849.x

Blackburn, K., & Schirillo, J. (2012). Emotive hemispheric differences measured in real-life portraits using pupil diameter and subjective aesthetic preferences. *Experimental Brain Research*, *219*(4), 447–455. https://doi.org/10.1007/s00221-012-3091-y

Boulter, C., Freeston, M., South, M., & Rodgers, J. (2014). Intolerance of uncertainty as a framework for understanding anxiety in children and adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *44*(6), 1391–1402. https://doi.org/10.1007/s10803-013-2001-x

Bradley, M. M., Miccoli, L., Escrig, M. A., & Lang, P. J. (2008). The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology*, *45*(4), 602–607. https://doi.org/10.1111/j.1469-8986.2008.00654.x

Brown, C., Tollefson, N., Dunn, W., Cromwell, R., & Filion, D. (2001). The Adult Sensory Profile: Measuring patterns of sensory processing. *American Journal of Occupational Therapy*, *55*(1), 75–82. https://doi.org/10.5014/ajot.55.1.75

Buck, T. R., Viskochil, J., Farley, M., Coon, H., McMahon, W. M., Morgan, J., & Bilder, D. A. (2014). Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *44*(12), 3063–3071. https://doi.org/10.1007/s10803-014-2170-2

Carleton, R. N., Norton, M. A. P. J., & Asmundson, G. J. G. (2007). Fearing the unknown: A short version of the Intolerance of Uncertainty Scale. *Journal of Anxiety Disorders*, *21*(1), 105–117. https://doi.org/10.1016/j.janxdis.2006.03.014

Chamberlain, P. D., Rodgers, J., Crowley, M. J., White, S. E., Freeston, M. H., & South, M. (2013). A potentiated startle study of uncertainty and contextual anxiety in adolescents diagnosed with autism spectrum disorder. *Molecular Autism*, *4*(1), 31. https://doi.org/10.1186/2040-2392-4-31

Christensen, D. L., Baio, J., Braun, K. V. N., Bilder, D., Charles, J., Constantino, J. N., … Yeargin-Allsopp, M. (2016). Prevalence and characteristics of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR. Surveillance Summaries*, *65*(3), 1–23. https://doi.org/10.15585/mmwr.ss6503a1

Conner, C. M., Maddox, B. B., & White, S. W. (2013). Parents' state and trait anxiety: Relationships with anxiety severity and treatment response in adolescents with autism spectrum disorders. *Journal Of Autism And Developmental Disorders*, *43*(8), 1811–1818. https://doi.org/10.1007/s10803-012-1728-0

Crane, L., Goddard, L., & Pring, L. (2009). Sensory processing in adults with autism spectrum disorders. *Autism*, *13*(3), 215–228. https://doi.org/10.1177/1362361309103794

Daluwatte, C., Miles, J. H., Christ, S. E., Beversdorf, D. Q., Takahashi, T. N., & Yao, G. (2013). Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *43*(8), 1910–1925. https://doi.org/10.1007/s10803-012-1741-3

Daluwatte, C., Miles, J. H., Sun, J., & Yao, G. (2015). Association between pupillary light reflex and sensory behaviors in children with autism spectrum disorders. *Research in Developmental Disabilities*, *37*, 209–215. https://doi.org/10.1016/j.ridd.2014.11.019

Dear, B. F., Titov, N., Sunderland, M., McMillan, D., Anderson, T., Lorian, C., & Robinson, E. (2011). Psychometric comparison of the Generalized Anxiety Disorder Scale-7 and the Penn State Worry Questionnaire for measuring response during treatment of generalised anxiety disorder. *Cognitive Behaviour Therapy*, *40*(3), 216–227. https://doi.org/10.1080/16506073.2011.582138

Desmond, J. E., & Glover, G. H. (2002). Estimating sample size in functional MRI (fMRI) neuroimaging studies: Statistical power analyses. *Journal of Neuroscience Methods*, *118*(2), 115–128.

Dunn, W. (1997). The impact of sensory processing abilities on the daily lives of young children and their families: A conceptual model. *Infants and Young Children*, *9*(4), 23–35.

Falck-Ytter, T. (2008). Face inversion effects in autism: A combined looking time and pupillometric study. *Autism Research*, *1*(5), 297–306. https://doi.org/10.1002/aur.45

Gaigg, S. B., & Bowler, D. M. (2007). Differential fear conditioning in Asperger's syndrome: Implications for an amygdala theory of autism. *Neuropsychologia*, *45*(9), 2125–2134.

Goldsmith, H. H., Van Hulle, C. A., Arneson, C. L., Schreiber, J. E., & Gernsbacher, M. A. (2006). A population-based twin study of parentally reported tactile and auditory

defensiveness in young children. *Journal of Abnormal Child Psychology*, *34*(3), 393–407. https://doi.org/10.1007/s10802-006-9024-0

Gotham, K., Bishop, S. L., Hus, V., Huerta, M., Lund, S., Buja, A., … Lord, C. (2013). Exploring the relationship between anxiety and insistence on sameness in autism spectrum disorders. *Autism Research: Official Journal Of The International Society For Autism Research*, *6*(1), 33–41. https://doi.org/10.1002/aur.1263

Green, D., Chandler, S., Charman, T., Simonoff, E., & Baird, G. (2016). Brief Report: DSM-5 sensory behaviours in children with and without an autism spectrum disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-016-2881-7

Green, S. A., & Ben-Sasson, A. (2010). Anxiety disorders and sensory over-responsivity in children with autism spectrum disorders: Is there a causal relationship? *Journal of Autism and Developmental Disorders*, *40*(12), 1495–1504. https://doi.org/10.1007/s10803-010-1007-x

Green, S. A., Ben-Sasson, A., Soto, T. W., & Carter, A. S. (2012). Anxiety and sensory over-responsivity in toddlers with autism spectrum disorders: Bidirectional effects across time. *Journal of Autism and Developmental Disorders*, *42*(6), 1112–1119. https://doi.org/10.1007/s10803-011-1361-3

Green, S. A., Hernandez, L., Tottenham, N., Krasileva, K., Bookheimer, S. Y., & Dapretto, M. (2015). Neurobiology of sensory overresponsivity in youth with autism spectrum disorders. *JAMA Psychiatry*, *72*(8), 778–786. https://doi.org/10.1001/jamapsychiatry.2015.0737

Green, S. A., Rudie, J. D., Colich, N. L., Wood, J. J., Shirinyan, D., Hernandez, L., … Bookheimer, S. Y. (2013). Overreactive brain responses to sensory stimuli in youth with

autism spectrum disorders. *Journal Of The American Academy Of Child And Adolescent Psychiatry*, *52*(11), 1158–1172. https://doi.org/10.1016/j.jaac.2013.08.004

Guiraud, J. A., Kushnerenko, E., Tomalski, P., Davies, K., Ribeiro, H., & Johnson, M. H. (2011). Differential habituation to repeated sounds in infants at high risk for autism. *NeuroReport: For Rapid Communication of Neuroscience Research*, *22*(16), 845–849.

Hirstein, W., Iversen, P., & Ramachandran, V. S. (2001). Autonomic responses of autistic children to people and objects. *Proceedings of the Royal Society of London B: Biological Sciences*, *268*(1479), 1883–1888. https://doi.org/10.1098/rspb.2001.1724

Järvinen, A., Ng, R., Crivelli, D., Neumann, D., Arnold, A. J., Woo-VonHoogenstyn, N., … Bellugi, U. (2015). Social functioning and autonomic nervous system sensitivity across vocal and musical emotion in Williams syndrome and autism spectrum disorder. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21335

Kern, J. K., Garver, C. R., Carmody, T., Andrews, A. A., Trivedi, M. H., & Mehta, J. A. (2007). Examining sensory quadrants in autism. *Research in Autism Spectrum Disorders*, *1*(2), 185–193. https://doi.org/10.1016/j.rasd.2006.09.002

Kerns, C. M., Kendall, P. C., Berry, L., Souders, M. C., Franklin, M. E., Schultz, R. T., … Herrington, J. (2014). Traditional and atypical presentations of anxiety in youth with autism spectrum disorder. *Journal Of Autism And Developmental Disorders*, *44*(11), 2851–2861. https://doi.org/10.1007/s10803-014-2141-7

Kuchinke, L., Schneider, D., Kotz, S. A., & Jacobs, A. M. (2011). Spontaneous but not explicit processing of positive sentences impaired in Asperger's syndrome: Pupillometric evidence. *Neuropsychologia*, *49*(3), 331–338. https://doi.org/10.1016/j.neuropsychologia.2010.12.026

Laeng, B., Sirois, S., & Gredebäck, G. (2012). Pupillometry: A window to the preconscious? *Perspectives on Psychological Science*, *7*(1), 18–27. https://doi.org/10.1177/1745691611427305

Lahiri, U., Bekele, E., Dohrmann, E., Warren, Z., & Sarkar, N. (2015). A physiologically informed virtual reality based social communication system for individuals with autism. *Journal of Autism and Developmental Disorders*, *45*(4), 919–931. https://doi.org/10.1007/s10803-014-2240-5

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2006). Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders*, *37*(5), 894–910. https://doi.org/10.1007/s10803-006-0218-7

Lidstone, J., Uljarević, M., Sullivan, J., Rodgers, J., McConachie, H., Freeston, M., … Leekam, S. (2014). Relations among restricted and repetitive behaviors, anxiety and sensory features in children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, *8*(2), 82–92. https://doi.org/10.1016/j.rasd.2013.10.001

Liss, M., Mailloux, J., & Erchull, M. J. (2008). The relationships between sensory processing sensitivity, alexithymia, autism, depression, and anxiety. *Personality and Individual Differences*, *45*(3), 255–259. https://doi.org/10.1016/j.paid.2008.04.009

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., … Rutter, M. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, *30*(3), 205–223.

Luke, L., Clare, I. C. H., Ring, H., Redley, M., & Watson, P. (2012). Decision-making difficulties experienced by adults with autism spectrum conditions. *Autism: The*

International Journal Of Research And Practice, *16*(6), 612–621. https://doi.org/10.1177/1362361311415876

Madsen, G. F., Bilenberg, N., Cantio, C., & Oranje, B. (2014). Increased prepulse inhibition and sensitization of the startle reflex in autistic children. *Autism Research*, *7*(1), 94–103. https://doi.org/10.1002/aur.1337

Marin, M.-F., & Milad, M. R. (2016). Extending the examination of the fear extinction network beyond anxiety and fear-based disorders: Insight into autism spectrum disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *1*(4), 302–304. https://doi.org/10.1016/j.bpsc.2016.05.002

Martineau, J., Hernandez, N., Hiebel, L., Roché, L., Metzger, A., & Bonnet-Brilhault, F. (2011). Can pupil size and pupil responses during visual scanning contribute to the diagnosis of autism spectrum disorder in children? *Journal of Psychiatric Research*, *45*(8), 1077–1082. https://doi.org/10.1016/j.jpsychires.2011.01.008

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, *28*(6), 487–495.

Milosavljevic, B., Carter Leno, V., Simonoff, E., Baird, G., Pickles, A., Jones, C. R. G., … Happé, F. (2016). Alexithymia in adolescents with autism spectrum disorder: Its relationship to internalizing difficulties, sensory modulation and social cognition. *Journal of Autism and Developmental Disorders*, *46*(4), 1354–1367. https://doi.org/10.1007/s10803-015-2670-8

Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Human Brain Mapping*, *35*(8), 4140–4154. https://doi.org/10.1002/hbm.22466

Musurlian, H. S. (1995, May). *Autonomic nervous system responses of electrodermal activity and heart rate response to an auditory stimulus: A comparison of individuals with autism and normal controls* (Doctoral dissertation). Retrieved from ProQuest Information & Learning, US.

Neal, J. A., Edelmann, R. J., & Glachan, M. (2002). Behavioural inhibition and symptoms of anxiety and depression: Is there a specific relationship with social phobia? *British Journal of Clinical Psychology*, *41*(4), 361–374. https://doi.org/10.1348/014466502760387489

Neil, L., Olsson, N. C., & Pellicano, E. (2016). The relationship between intolerance of uncertainty, sensory sensitivities, and anxiety in autistic and typically developing children. *Journal of Autism and Developmental Disorders*, *46*(6), 1962–1973. https://doi.org/10.1007/s10803-016-2721-9

Nuske, H. J., Vivanti, G., & Dissanayake, C. (2013). Are emotion impairments unique to, universal, or specific in autism spectrum disorder? A comprehensive review. *Cognition & Emotion*, *27*(6), 1042–1061. https://doi.org/10.1080/02699931.2012.762900

Nuske, H. J., Vivanti, G., & Dissanayake, C. (2014). Reactivity to fearful expressions of familiar and unfamiliar people in children with autism: An eye-tracking pupillometry study. *Journal of Neurodevelopmental Disorders*, *6*. https://doi.org/10.1186/1866-1955-6-14

Nuske, H. J., Vivanti, G., & Dissanayake, C. (2015). No evidence of emotional dysregulation or aversion to mutual gaze in preschoolers with autism spectrum disorder: An eye-tracking

pupillometry study. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-015-2479-5

Nuske, H. J., Vivanti, G., Hudry, K., & Dissanayake, C. (2014). Pupillometry reveals reduced unconscious emotional reactivity in autism. *Biological Psychology*, *101*, 24–35. https://doi.org/10.1016/j.biopsycho.2014.07.003

Ornitz, E. M., Lane, S. J., Sugiyama, T., & de Traversay, J. (1993). Startle modulation studies in autism. *Journal of Autism and Developmental Disorders*, *23*(4), 619–637. https://doi.org/10.1007/BF01046105

Partala, T., Jokiniemi, M., & Surakka, V. (2000). Pupillary responses to emotionally provocative stimuli. In *Proceedings of the 2000 Symposium on Eye Tracking Research & Applications* (pp. 123–129). New York, NY, USA: ACM. https://doi.org/10.1145/355017.355042

Partala, T., & Surakka, V. (2003). Pupil size variation as an indication of affective processing. *International Journal of Human-Computer Studies*, *59*(1-2), 185–198. https://doi.org/10.1016/S1071-5819(03)00017-X

Pfeiffer, B., Kinnealey, M., Reed, C., & Herzberg, G. (2005). Sensory modulation and affective disorders in children and adolescents with Asperger's disorder. *American Journal of Occupational Therapy*, *59*(3), 335–345. https://doi.org/10.5014/ajot.59.3.335

Puts, N. A. J., Wodka, E. L., Tommerdahl, M., Mostofsky, S. H., & Edden, R. A. E. (2014). Impaired tactile processing in children with autism spectrum disorder. *Journal of Neurophysiology*, *111*(9), 1803–1811. https://doi.org/10.1152/jn.00890.2013

Rodgers, J., Glod, M., Connolly, B., & McConachie, H. (2012). The relationship between anxiety and repetitive behaviours in autism spectrum disorder. *Journal Of Autism And*

Developmental Disorders, *42*(11), 2404–2409. https://doi.org/10.1007/s10803-012-1531-y

Ruxton, G. D., & Beauchamp, G. (2008). Some suggestions about appropriate use of the Kruskal–Wallis test. *Animal Behaviour*, *76*(3), 1083–1087. https://doi.org/10.1016/j.anbehav.2008.04.011

Samuels, E. R., & Szabadi, E. (2008). Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the regulation of arousal and autonomic function part I: Principles of functional organisation. *Current Neuropharmacology*, *6*(3), 235–253. https://doi.org/10.2174/157015908785777229

Sepeta, L., Tsuchiya, N., Davies, M. S., Sigman, M., Bookheimer, S. Y., & Dapretto, M. (2012). Abnormal social reward processing in autism as indexed by pupillary responses to happy faces. *Journal of Neurodevelopmental Disorders*, *4*(1), 1–9. https://doi.org/10.1186/1866-1955-4-17

Shiga, N., & Ohkubo, Y. (1980). Pupillary reflex dilation to the auditory stimuli: The effects of parasympathetic activity on the pattern of the pupillary reflex dilatation. *Tohoku Psychologica Folia*, *39*(1-4), 31–39.

Sinclair, D., Oranje, B., Razak, K. A., Siegel, S. J., & Schmid, S. (2016). Sensory processing in autism spectrum disorders and Fragile X syndrome-From the clinic to animal models. *Neuroscience and Biobehavioral Reviews,* 76(Pt B), 235-253. https://doi.org/10.1016/j.neubiorev.2016.05.029

Sirois, S., & Brisson, J. (2014). Pupillometry. *Wiley Interdisciplinary Reviews: Cognitive Science*, *5*(6), 679–692. https://doi.org/10.1002/wcs.1323

South, M., Larson, M. J., White, S. E., Dana, J., & Crowley, M. J. (2011). Better fear conditioning is associated with reduced symptom severity in autism spectrum disorders. *Autism Research*, *4*(6), 412–421. https://doi.org/10.1002/aur.221

South, M., Newton, T., & Chamberlain, P. D. (2012). Delayed reversal learning and association with repetitive behavior in autism spectrum disorders. *Autism Research: Official Journal Of The International Society For Autism Research*, *5*(6), 398–406. https://doi.org/10.1002/aur.1255

Steiner, G. Z., & Barry, R. J. (2011). Pupillary responses and event-related potentials as indices of the orienting reflex. *Psychophysiology*, *48*(12), 1648–1655. https://doi.org/10.1111/j.1469-8986.2011.01271.x

Takahashi, H., Komatsu, S., Nakahachi, T., Ogino, K., & Kamio, Y. (2015). Relationship of the acoustic startle response and its modulation to emotional and behavioral problems in typical development children and those with autism spectrum disorders. *Journal of Autism and Developmental Disorders,* 46(2):534-543). https://doi.org/10.1007/s10803-015-2593-4

Tomchek, S. D., & Dunn, W. (2007). Sensory processing in children with and without autism: A comparative study using the short sensory profile. *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association*, *61*(2), 190–200.

Tomchek, S. D., Huebner, R. A., & Dunn, W. (2014). Patterns of sensory processing in children with an autism spectrum disorder. *Research in Autism Spectrum Disorders*, *8*(9), 1214–1224. https://doi.org/10.1016/j.rasd.2014.06.006

Top Jr, D. N., Stephenson, K. G., Doxey, C. R., Crowley, M. J., Kirwan, C. B., & South, M. (2016). Atypical amygdala response to fear conditioning in autism spectrum disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *1*(4), 308–315. https://doi.org/10.1016/j.bpsc.2016.01.008

Uljarević, M., Carrington, S., & Leekam, S. (2016). Brief Report: Effects of sensory sensitivity and intolerance of uncertainty on anxiety in mothers of children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *46*(1), 315–319. https://doi.org/10.1007/s10803-015-2557-8

van Steensel, F. J. A., Bögels, S. M., & de Bruin, E. I. (2013). Psychiatric comorbidity in children with autism spectrum disorders: A comparison with children with ADHD. *Journal of Child and Family Studies*, *22*(3), 368–376. https://doi.org/10.1007/s10826-012-9587-z

van Steensel, F. J. A., Bögels, S. M., & Perrin, S. (2011). Anxiety disorders in children and adolescents with autistic spectrum disorders: A meta-analysis. *Clinical Child and Family Psychology Review*, *14*(3), 302–317. https://doi.org/10.1007/s10567-011-0097-0

Warren, J. S., Brown, C. R., Layne, C. M., & Nelson, P. L. (2011). Parenting self-efficacy as a predictor of child psychotherapy outcomes in usual care: A multi-dimensional approach. *Psychotherapy Research*, *21*(1), 112–123. https://doi.org/10.1080/10503307.2010.531405

Warren, J. S., & Salazar, B. C. (2014). Youth self-efficacy domains as predictors of change in routine community mental health services. *Psychotherapy Research: Journal of the Society for Psychotherapy Research*, 1–12. https://doi.org/10.1080/10503307.2014.932464

White, S. W., Mazefsky, C. A., Dichter, G. S., Chiu, P. H., Richey, J. A., & Ollendick, T. H. (2014). Social-cognitive, physiological, and neural mechanisms underlying emotion regulation impairments: Understanding anxiety in autism spectrum disorder. *International Journal of Developmental Neuroscience*, *39*, 22–36. https://doi.org/10.1016/j.ijdevneu.2014.05.012

White, S. W., Oswald, D., Ollendick, T., & Scahill, L. (2009). Anxiety in children and adolescents with autism spectrum disorders. *Clinical Psychology Review*, *29*(3), 216–229. https://doi.org/10.1016/j.cpr.2009.01.003

Wiemer, J., Mühlberger, A., & Pauli, P. (2014). Illusory correlations between neutral and aversive stimuli can be induced by outcome aversiveness. *Cognition and Emotion*, *28*(2), 193–207. https://doi.org/10.1080/02699931.2013.809699

Wigham, S., & McConachie, H. (2014). Systematic review of the properties of tools used to measure outcomes in anxiety intervention studies for children with autism spectrum disorders. *PloS One*, *9*(1), e85268. https://doi.org/10.1371/journal.pone.0085268

Wigham, S., Rodgers, J., South, M., McConachie, H., & Freeston, M. (2015). The interplay between sensory processing abnormalities, intolerance of uncertainty, anxiety and restricted and repetitive behaviours in autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *45*(4), 943–952. https://doi.org/10.1007/s10803-014-2248-x

Table 1
Difference Between Groups On Behavioral Measures

Variable	Mean values (SD)			*F*-value or χ2-value*	*p*-value	df	Direction of Significance
Group	CON	ANX	ASD				
Age	20.94 (1.72)	21.90 (2.80)	24.47 (6.14)	6.62	.0021	(2,92)	CON<ASD ANX<ASD
Full-Scale IQ (WASI-II)	112.38 (5.83)	108.36 (5.12)	105.67 (8.34)	2.32	.0982	(2,92)	
Tonic Pupil Size*	3.63 (.42)	3.59 (.28)	3.92 (.54)	6.26*	.0364	2	CON<ASD ANX<ASD
Initial Change in pupil size Sound1*	.298 (.34)	.272 (.32)	.311 (.33)	1.75*	.4153	2	
Initial Change in pupil size Sound2	.905 (.57)	.667 (.37)	.715 (.45)	2.29	.1075	(2,92)	
Intolerance of Uncertainty	28.00 (7.13)	40.89 (9.56)	38.96 (10.08)	19.91	.0001	(2,85)	CON<ANX CON<ASD
Low Registration	31.91 (5.85)	32.20 (7.14)	39.83 (7.14)	11.82	.0001	(2,77)	CON<ASD ANX<ASD
Sensory Seeking	52.69 (6.54)	44.95 (8.80)	38.67 (8.36)	24.40	.0001	(2,77)	CON>ANX CON>ASD ANX>ASD
Sensory avoidant	37.19 (5.56)	39.85 (9.49)	48.75 (9.46)	14.22	.0001	(2,77)	CON<ASD ANX<ASD
Sensory Sensitivity*	33.22 (6.75)	39.25 (9.90)	44.91 (10.11)	24.24*	.0001	2	CON<ANX CON<ASD
Penn State Worry Questionnaire	46.69 (11.98)	63.11 (8.75)	50.92 (15.01)	14.62	.0001	(2,86)	CON<ANX ANX>ASD
STAI – Trait	n/a	52.67 (8.96)	42.38 (12.46)	9.88	.0031	(1,41)	ANX>ASD
Autism Quotient*	15.61 (5.42)	23.33 (7.18)	27.77 (8.96)	34.73*	.0001	2	CON<ANX CON<ASD

Note: * indicates Kruskal-Wallis test used instead of ANOVA

Table 2
Unconditional Growth Model Fit Indices For Sound1

Variable	AIC	BIC
Trial	118.71	157.54
ln(Trial)	99.93	138.76

Table 3
Unconditional Growth Model Fit Indices For Sound2

Variable	AIC	BIC
Trial	565.68	604.47
ln(Trial)	505.14	544.93

Table 4
HLM Results Sound1 With Natural Log Transformation Of Time

Variable	Coefficient	Std. Error	z-value	*p*-value	95% Confidence Interval
Group	.025	.0313	.83	.407	-.0354 – .0874
ln(Trial)	-.084	.013	-6.26	.000	-.1106 – -.578
Group* ln(Trial)	.004	.0171	-.26	.794	-.0379 – .0290
Intercept	.421	.0246	17.07	.000	.3730 – .4697

Table 5
HLM Results Sound2 With Natural Log Transformation Of Time

Variable	Coefficient	Std. Error	z-value	*p*-value	95% Confidence Interval
Group	.023	.0426	0.52	.606	-.0665 – .1141
ln(Trial)	-.142	.0182	-7.79	.000	-.1778 – - .1063
Group* ln(Trial)	-.003	.0231	-0.15	.880	-.0488 – .0418
Intercept	.644	.0363	17.75	.000	.5735 – .7159

Table 6
Spearman's Rho Correlation Coefficients

Variables	PSQ	AQ	IUS	Low Registration	Sensation Seeking	Sensory Sensitivity	Sensory Avoidance	Initial Reaction Sound1	Initial Reaction Sound2	Tonic Pupil Size	Habituation Sound1	Habituation Sound2
PSQ	1.00											
AQ	.44*	1.00										
IUS	.57*	.66*	1.00									
Low Registration	.23	.45*	.33	1.00								
Sensation Seeking	-.12	-.64*	-.48*	-.21	1.00							
Sensory Sensitivity	.42*	.49*	.57*	.45*	-.51*	1.00						
Sensory Avoidance	.27	.59*	.58*	.45*	-.52*	.75*	1.00					
Initial Reaction Sound1	-.10	-.22	-.10	-.08	.15	-.09	-.10	1.00				
Initial Reaction Sound2	-.09	-.09	-.07	-.06	-.05	.01	.01	.19	1.00			
Tonic Pupil size	-.11	-.26	-.12	-.30	.23	-.11	-.04	-.11	-.21	1.00		
Habituation Sound1	-.02	-.07	-.14	.10	.07	-.10	-.23	.07	-.07	-.14	1.00	
Habituation Sound2	-.01	-.04	-.07	-.05	.16	-.13	-.14	-.15	-.83*	.26	.06	1.00

Note: * Indicates statistical significance at $p<.05$ after Sidak correction for multiple comparisons

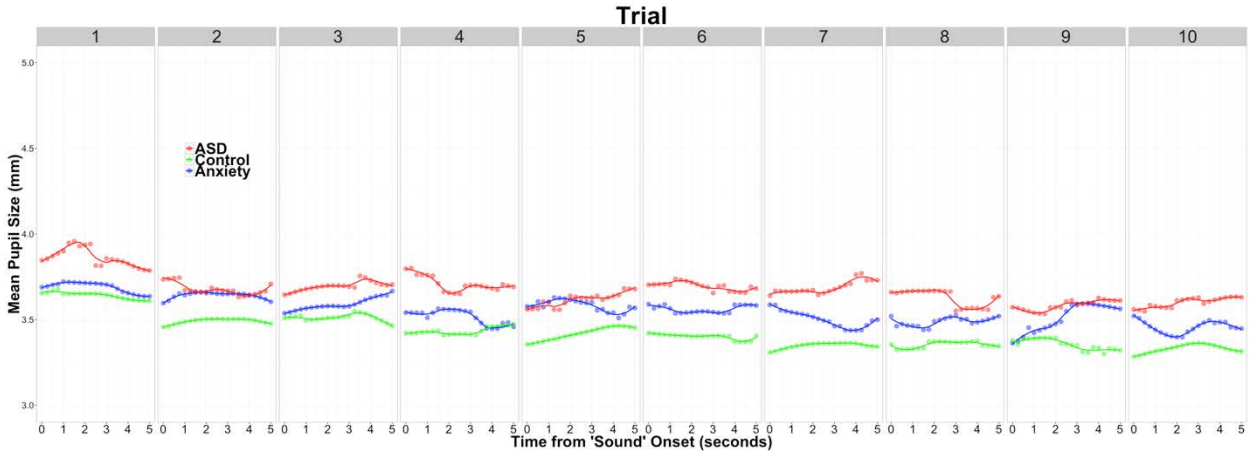

Figure 1. Tonic pupil size across all 10 trials of the Silence condition.

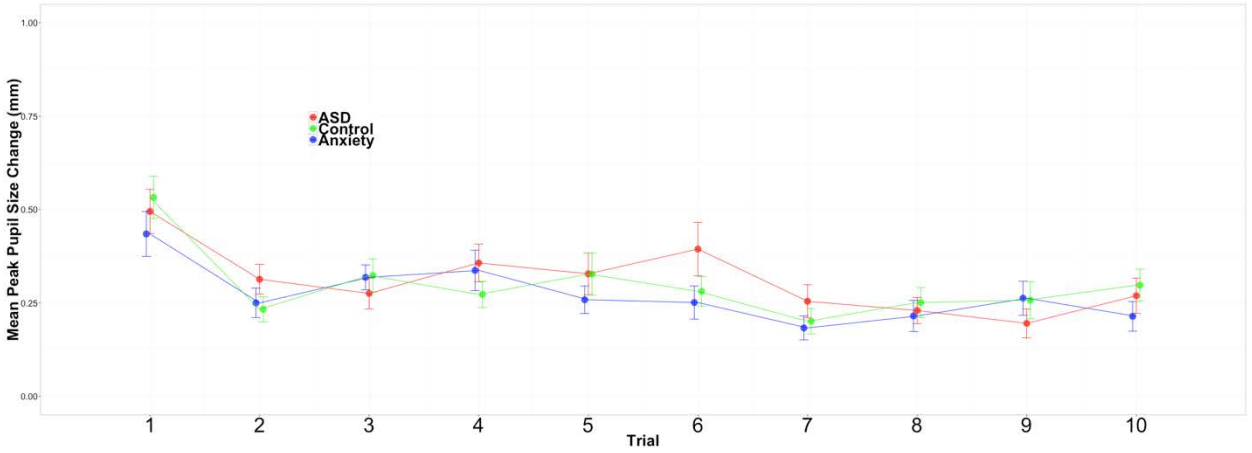

Figure 2. Pupil responses to Sound1 across all 10 Sound1 trials.

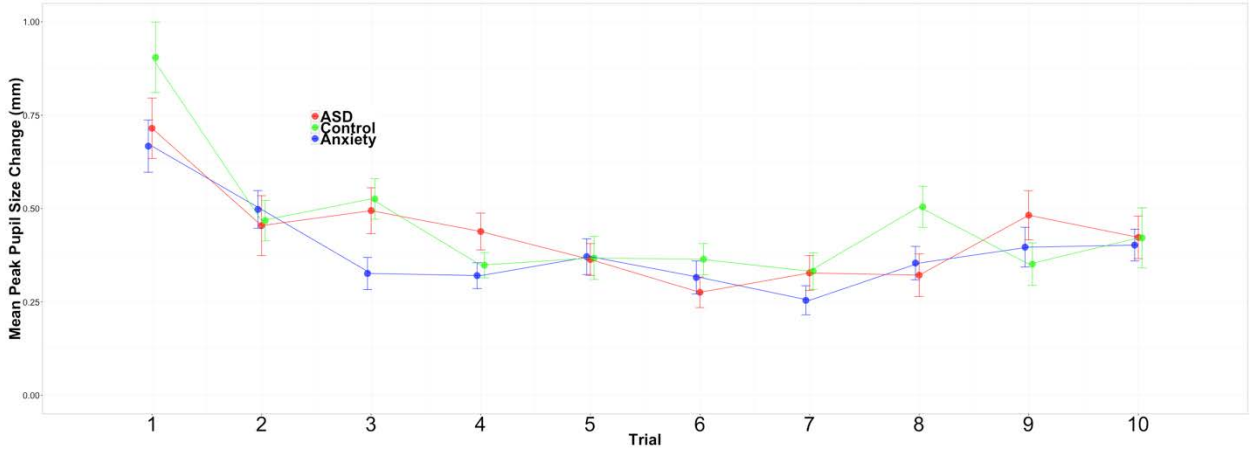

Figure 3. Pupil responses to Sound2 across all 10 Sound2 trials.