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Comparing Stress and Arousal Systems in Response to Different Social Contexts in Children with ASD

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Abstract

Response to psychological stress can vary based on the extent to which the context is perceived as stressful, especially under different social conditions. The purpose of this preliminary study was to compare physiological stress (cortisol) and regulation (respiratory sinus arrhythmia, RSA) of 10–12 year old children with autism spectrum disorder (ASD, n=31) or typical development (TD, n=25) when exposed to two social stress protocols. The extent to which perceived emotion (affect recognition) and anxiety (state and trait) mediate the stress response was also explored. Results revealed different patterns of stress responses dependent on the type of stressor. During a friendly social interaction, both groups generally showed an adaptive, synergistic response between cortisol and RSA. In response to social evaluation, however, the ASD group did not show correlating responses between physiological systems, which was likely due to a blunted stress response to the social evaluative stressor. The ability to recognize neutral faces mediated the relationship between diagnostic group and physiological response to social evaluation, indicating that perception of threat is essential to triggering a stress response. The current study emphasizes the need to consider the important role of social context, social perception, and perceived anxiety when examining social interaction and stress.

Keywords

autism spectrum disorder; cortisol; HPA; RSA; stress; facial affect

Introduction

Children with autism spectrum disorder (ASD) exhibit core impairment in social communication and a repertoire of repetitive, restricted interests and behaviors (APA, 2013). A recent report by the Center for Disease Control estimates that 1 in 59 children are diagnosed with ASD in the United States (Baio, 2018), making it a significant health, fiscal,

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and societal concern impacting thousands of children and their families. Humans are fundamentally social and face a multitude of dynamic encounters every day, and the extent to which individuals respond is highly dependent on how one perceives, interprets and responds to the context. As a result of core deficits in social competence, children with ASD may experience significant stress and anxiety in various social situations.

One of the primary stress systems, the Hypothalamic Pituitary Adrenal (HPA) axis, regulates several vital biological processes and interactions to include physiological response to stress (Herman & Cullinan, 1997). Stress can be defined as an actual or anticipated disruption of homeostasis or an anticipated threat to well-being (Ulrich-Lai & Herman, 2009).

The HPA axis can be activated by *systemic* (i.e., threats to survival) and *processive* (i.e., perceived threat) (Herman & Cullinan, 1997) stressors. The primary glucocorticoid in humans, cortisol, is released from the adrenal cortices following activation of the HPA axis in response to extreme physiological or psychological stress (Herman & Cullinan, 1997). Key characteristics of processive stressors are situations perceived as novel, unpredictable, and uncontrollable or are a threat to the self, such as during social evaluation (Dickerson & Kemeny, 2004; Mason, 1968). The limbic system, which includes the amygdala, is involved in the acute processing of threatening information and plays an excitatory, modulatory role on the HPA axis (Hand et al., 2002; Herman, Ostrander, Mueller, & Figueiredo, 2005; Klimes-Dougan et al., 2014; Ulrich-Lai & Herman, 2009; Van de Kar & Blair, 1999).

Examination of the relationship between perceived and physiological stress is an emerging area of significant interest, complexity, and divergent findings. Response to psychosocial stress can vary based on environmental (e.g., social perception), idiosyncratic (e.g., genetics) and developmental (e.g., puberty) factors (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Rosmalen et al., 2005; Rotenberg, McGrath, Roy-Gagnon, & Tu, 2012). Likewise, the context in which a stressor occurs is of high importance, especially with regards to social evaluation, which most perceive to be stressful. A well-established paradigm, the Trier Social Stress Test (TSST) (Buske-Kirschbaum et al., 2003; Kirschbaum, Pirke, & Hellhammer, 1993), capitalizes on this common stressor by exposing people to a public speaking task in front of unresponsive raters who exhibit neutral facial expressions. Most people find the lack of responsivity to be unsupportive and threatening, resulting in activation of the HPA axis with strong convergence between HPA axis response and psychological factors during public speaking (Gaab, Rohleder, Nater, & Ehlert, 2005). For example, determinants of physiological stress (e.g., cortisol, respiratory sinus arrhythmia) and perceived stress were compared in children (N=363) and adolescents (N=344), and it was *perceived* stress that predicted cortisol responsivity in adolescents (Evans et al., 2013). In other words, in order for a situation to provoke a stress response it must be perceived as threatening to the individual.

A growing body of research has emerged over the last few decades examining the activation of the HPA axis in children and adolescents with ASD (Muscatello & Corbett, 2018; Taylor & Corbett, 2014). Although the majority of the studies have been conducted on the reactivity of the HPA axis in children (Corbett, Schupp, & Lanni, 2012; Lanni, Schupp, Simon, & Corbett, 2012; Nir et al., 1995; Schupp, Simon, & Corbett, 2013; Tani et al., 2005; Tordjman

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et al., 2009) studies with adolescents are emerging (Edmiston, Blain, & Corbett, 2017). Higher cortisol levels have been found in children with ASD in response to non-social stimuli (e.g., (Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006; Corbett, Mendoza, Wegelin, Carmean, & Levine, 2008; Spratt et al., 2012)). Because ASD is marked by impairment in social abilities, it is not surprising that social scenarios often result in activation of the HPA axis during school integration (Richdale & Prior, 1992), social interaction with peers in a playground (Corbett et al., 2012; Corbett, Schupp, Simon, Ryan, & Mendoza, 2010), and engagement with unfamiliar children (Lopata, Volker, Putnam, Thomeer, & Nida, 2008).

Importantly, not all social contexts are salient for children and youth with ASD. For example, the TSST– Child version (Buske-Kirschbaum et al., 2003), has failed to provoke a stress response in many participants with ASD, whereas TD peers generally show increased physiological response (Corbett et al., 2012; Jansen et al., 2000; Lanni et al., 2012; Levine et al., 2012). While the findings suggest that individuals with ASD do not interpret this social evaluation as threatening, it underscores the importance of simultaneously measuring perceived stress alongside physiological stress (e.g., cortisol) and regulation (e.g., Respiratory sinus arrhythmia, RSA).

The autonomic nervous system (ANS) has been hypothesized to be a primary biobehavioral regulator (Porges, 2001). The parasympathetic (PNS) component of the ANS is involved with states of rest, recovery, and restoration, and its activation results in decreased heart rate in addition to pupillary restriction and increased digestive processes. Much like the HPA axis, response of the ANS may be influenced by perception of the environment. For example, during non-threatening situations, the PNS may be upregulated to promote social approach and engagement (Porges, 2003, 2007). However, during stress, parasympathetic regulation will withdrawal, allowing for increased cardiac output to respond to the stressor (Porges, 1995). PNS regulatory effects on heart rate variability (HRV) can be measured via respiratory sinus arrhythmia (RSA), a measure of HRV associated with spontaneous respiration (Bernston et al., 1994). High baseline RSA has been associated with adaptive emotion regulation (Beauchaine, Gatzke-Kopp, & Mead, 2007; Calkins, 1997), social competence (Doussard-Roosevelt, Porges, Scanlon, Alemi, & Scanlon, 1997) and social interactions (Hastings, Kahle, & Nuselovici, 2014) in both typically developing children (Patriquin, Lorenzi, Scarpa, & Bell, 2013) as well as those with communicative disorders, such as ASD (Patriquin, Lorenzi, & Scarpa, 2013; Patriquin, Scarpa, Friedman, & Porges, 2013) and stuttering (Jones et al., 2014). Changes in RSA from baseline are interpreted to reflect the degree of physiological mobilization in support of active engagement with environmental stimuli and have been closely linked to the level of social disengagement (Shahrestani, Stewart, Quintana, Hickie, & Guastella, 2014).

Recent evidence supports ANS dysfunction in ASD (for review see (Benevides & Lane, 2013)), including possible differences in baseline PNS regulation relative to TD peers (Bal et al., 2010; Ming, Julu, Brimacombe, Connor, & Daniels, 2005; Vaughan Van Hecke et al., 2009) and altered RSA response to stressors (Althaus, Mulder, Mulder, Aarnoudse, & Minderaa, 1999; Daluwatte et al., 2012; Toichi & Kamio, 2003; Vaughan Van Hecke et al., 2009). In studies requiring social engagement, children with ASD tend to show reduced

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parasympathetic response (e.g. (Neuhaus, Bernier, & Beauchaine, 2016; Vaughan Van Hecke et al., 2009)). For example, Vaughan Van Hecke and colleagues found that children with ASD, relative to TD children, showed overall lower RSA to unfamiliar, as well as familiar, persons while increased PNS regulation was associated with greater social skills and fewer problem behaviors (Vaughan Van Hecke et al., 2009). Similarly, children with ASD have shown lower RSA overall relative to those without autism when interacting with a novel partner (Neuhaus et al., 2016). One of the few studies to assess RSA response to social play in children with ASD found higher baseline RSA was associated with more gestures and sharing behavior during play with an adult actor (Patriquin, Scarpa, et al., 2013). During social evaluative threat, when a more typical stress response would be expected with a decrease in RSA, individuals with autism demonstrate blunted RSA change in response to the TSST. This blunted response may be associated with comorbid symptoms such as social problems (Edmiston, Jones, & Corbett, 2016) or anxiety (Hollocks et al., 2014; Mikita et al., 2015). Despite the evidence for altered PNS response in ASD, research thus far has revealed conflicting results, emphasizing the need to further understand the impact of perceived stress on physiological response, as well as to identify other factors that may influence these stress response pathways.

Children with ASD often have difficulty perceiving facial expressions (e.g., (Adolphs, Sears, & Piven, 2001; Ashwin, Chapman, Colle, & Baron-Cohen, 2006; Berggren, Engstrom, & Bolte, 2016; Kuusikko et al., 2009). Functional MRI studies show atypical activation of the amygdala during emotion processing including diminished (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Bookheimer, Wang, Scott, Sigman, & Dapretto, 2008; Corbett et al., 2009; Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007) as well as elevated (Dalton, Kalin, Grist, & Davidson, 2005; Monk et al., 2010; Weng et al., 2011) amygdala activation. Some investigations have noted specific difficulty with ambiguous emotions, such as neutral faces, as well as with happy faces (Berggren et al., 2016; Dawson, Webb, & McPartland, 2005; Humphrey, 2007; Kuusikko et al., 2009). A recent fMRI study showed that amygdala activation was greatest for children with ASD during forced viewing of neutral faces, which were generally confused for negatively valenced emotions (Tottenham et al., 2014). Since facial affect recognition is the ability to infer emotional states from other people's faces, impairment may affect the extent to which a child with ASD perceives and responds to the social situation.

It is plausible that the ability to perceive the emotional states of others may be a mediating factor in determining a stress response. Indeed, a recent study explored the association between emotion recognition and stress response to the TSST and showed that participants who were better able to perceive emotions exhibited a higher and more prolonged cortisol response to social evaluation (Bechtoldt & Schneider, 2016). Conversely, it is plausible that an *inability* to detect emotions such as the neutral facial expressions of raters during the TSST, could result in diminished stress response. In this way, the extent to which children with ASD are able to detect neutral emotions may in turn predict physiological response to threatening social situations.

To more thoroughly examine social stress response, it has been recommended that researchers should examine change in response to naturalistic stressors (Adam, 2006). For

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example, using the ecologically valid Peer Interaction Playground (PIP) paradigm (Corbett et al., 2010), previous research has reported that many children with ASD evidence a significant increase in cortisol in response to benign social interactions with novel peers (Corbett et al., 2012). Moreover, a direct comparison of children with TD and ASD exposed to both the TSST and PIP (Corbett et al., 2012; Corbett et al., 2010) resulted in a double dissociation; TD children evidenced a significant rise in cortisol to the TSST whereas children with ASD showed heightened cortisol to play with peers and a blunted cortisol response to the TSST. Importantly, the PIP exposes the participant to other children during play using research confederates, thereby recreating an everyday social context. Since non-threatening social interaction with novel peers has been shown to be stressful for children with ASD (Corbett et al., 2010; Corbett et al., 2013), the inclusion of a "friendly" TSST (TSST-F; (Wiemers, Schoofs, & Wolf, 2013)) will allow direct comparison between two social contexts. Specifically, we will compare social evaluative threat (TSST) and social interaction (TSST-F) to determine if the context is an important variable in physiological response. As in our previous research, the TSST-F may result in increased cortisol reactivity (Corbett et al., 2012), as well as decrease parasympathetic regulation, during social engagement with peers.

The current study was aimed at better understanding the role of perceived stress and arousal across two contexts and two physiological systems. In other words, we compared the baseline and responsivity of children with ASD to both social evaluative threat and social interaction and the extent to which the HPA and PNS respond to these different contexts. The primary between-group and within-group hypotheses included the following: 1) Based on previous research, it was hypothesized that at baseline, children with and without ASD would show similar cortisol values (Corbett et al., 2012; Corbett et al., 2010). RSA profiles were hypothesized to be similar between groups based upon mixed findings in the literature, which do not clearly support differences in resting parasympathetic regulation (e.g. (Condy, Scarpa, & Friedman, 2017; Kushki, Brian, Dupuis, & Anagnostou, 2014; Levine et al., 2012; Watson, Roberts, Baranek, Mandulak, & Dalton, 2012). 2) Similar to previous findings for cortisol (e.g., (Corbett et al., 2012; Lanni et al., 2012)) and RSA (Edmiston et al., 2016; Neuhaus et al., 2016; Vaughan Van Hecke et al., 2009), it was predicted that children with ASD would show enhanced cortisol response and lower RSA to the TSST-F and a blunted cortisol and RSA response to the TSST. Additionally, we examined the relationship between perceived affect and physiological stress during the TSST by determining if the perception of neutral faces mediated the stress response (cortisol and RSA). 3) We hypothesized that perception of neutral faces would mediate the physiological response for the TSST. 4) Finally, we explored the relationship between self-reported trait and state anxiety and the physiological measures across the two social contexts; no specific hypotheses were made a priori.

Materials and Methods

Participants

Participants included 56 children between 10–12 years of age, 31 with ASD (mean age = 11.17) and 25 children with typical development (TD; mean age = 11.09). In the ASD

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group, there were 20 males and 11 females, and in the TD group, there were 18 males and 7 females. Families were recruited from the community through research registries, other autism-related studies, ASD diagnostic clinics, and local autism/disability organizations. Participants were required to have an intelligence quotient (IQ) score ≥ 70. Demographic information for each age group is presented in Table 1.

Diagnostic Criteria

The diagnosis of ASD was based on the Diagnostic and Statistical Manual-5 (APA, 2013) and established by: (1) a previous diagnosis by a psychologist, psychiatrist, or behavioral pediatrician with autism expertise; (2) current clinical judgment, and (3) corroborated by the Autism Diagnostic Observation Schedule (ADOS-2; (Lord et al., 2012)), administered by research-reliable personnel.

The research was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Vanderbilt Institutional Review Board approved the study. In compliance with the Vanderbilt Institutional Review Board determinations, informed written consent/assent was obtained from all study participants and care providers prior to inclusion in the study. Participation required two research visits to the University. The diagnostic and cognitive measures were administered during visit 1. The participants and family members were also trained on the salivary collection methods (see below). On visit 2, participants were exposed to the two social paradigms, with the same study research escort implementing the physiological procedures for both the TSST and the TSST-F.

Diagnostic Procedures

Autism Diagnostic Observation Schedule-Second Edition—(ADOS-2; (Lord et al., 2012)) is a semi-structured, play and interview-based instrument used to support the diagnosis of autism spectrum disorder. The ADOS was administered by research-reliable clinicians. A score of 7 or above on Module 3 (fluent speech) was required for inclusion in the study.

Wechsler Abbreviated Scale of Intelligence, Second Edition—(WASI-II, (Wechsler, 2011)) is a measure of cognitive ability that was used to obtain a quick, reasonable estimate of the child's intellectual functioning (IQ ≥ 70 required).

Social Stress Paradigms

During the second visit, participants completed the social interaction and social evaluation paradigms (described below). Due to cortisol diurnal rhythm, stress paradigms were conducted in the afternoon. Following arrival, participants first completed the TSST-F, followed by the TSST. The order of the paradigms was chosen to prevent possible changes in social behavior during the more friendly social interaction (TSST-F) due to violation of social norms and expectations in the TSST (LePoire & Yoshimura, 1999). All participants completed both social paradigms in one visit to the lab.

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Trier Social Stress Test (TSST)-Child Version

(Buske-Kirschbaum et al., 2003; Kirschbaum et al., 1993) is a well-validated, experimentally induced psychosocial stressor known to reliably activate the HPA axis in typically developing populations (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004). The TSST combines several elements shown to activate the HPA axis including social evaluative threat, unpredictability, and uncontrollability to produce moderate stress in a majority of children, adolescents and adults (Dickerson & Kemeny, 2004; Kirschbaum et al., 1993). The TSST is a 20-min task divided into four subcomponents including: 1) Intro/Preparation, 2) Present Speech, 3) Serial Subtraction, and 4) Debriefing. The protocol involves a scenario in which the participant must deliver the ending to a short story in front of a panel of judges (unresponsive judges showing neutral lacking supportive affect) who will, purportedly, be judging the child's performance against that of other children. The 5-minute speech task is followed by a serial subtraction task. The TSST results in a profound increase of salivary cortisol in 70–80% of participants (Kirschbaum et al., 1993; Kudielka et al., 2004).

TSST- Friendly (TSST-F)

(Wiemers et al., 2013) consists of a more "friendly" protocol in which the participant describes him or herself and/or a favorite book or movie in front of a novel peer of the same sex that shows encouragement (smiles, nods shows interest, follow-up questions). This "friendly" modification of the TSST does not lead to an increase in cortisol in TD individuals (Wiemers et al., 2013) and parallels our peer interaction paradigm (Corbett et al., 2010; Corbett et al., 2013). Participants had 5 minutes to prepare what they wanted to say to the peer and subsequently engaged in a 10-minute conversation, followed by a 5 minute debriefing period. The 20-minute protocol requires reciprocal social interaction with a novel peer, which may be a more potent stressor for children with ASD.

Importantly each paradigm was conducted in a different room with novel raters (TSST) and novel peers (TSST-F) for each condition. Raters are thoroughly trained and monitored to maintain consistent implementation of the protocols. Each administration of the TSST and TSST-F are recorded and routinely checked to ensure raters maintain neutral affect and social interest, respectively. If deviations in the protocol are noted, booster training sessions are provided to the rater. The same research lab member escorted the participant and collected the physiological data for both paradigms.

Similar to previous findings (e.g., (Corbett et al., 2012; Lanni et al., 2012)), it was predicted that children with ASD would show enhanced cortisol response and lower RSA to the TSST-F and a blunted cortisol and RSA response to the TSST.

Dependent Measures

Salivary cortisol.

Salivary cortisol can be measured reliably and non-invasively utilizing small amounts of saliva, making it an ideal measure in studies of children and youth (Kirschbaum & Hellhammer, 2000). Basal salivary cortisol was collected 4 times per day (Edwards, Evans,

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Hucklebridge, & Clow, 2001; Kudielka & Kirschbaum, 2003; Wilhelm, Born, Kudielka, Schlotz, & Wust, 2007), from the home over 3 consecutive week days using established procedures (Corbett et al., 2006; Corbett et al., 2008); however, these data are not part of the current study. Participants were provided with direct instruction, a mini-manual and a DVD of step-by-step passive drool procedures. They were instructed to avoid food and drink consumption prior to sample collection. Cortisol has a 20-min lag of detection in saliva; thus, samples were collected in at least 20-min intervals to assess baseline (2 samples) and exposure to social stress (4 samples, which also includes two 10 min samples immediately following the TSST-F and TSST – see Figure 1).

Cortisol assay.

Prior to assay, samples were stored at −20°C. Salivary cortisol assay was performed using a Coat-A-Count® radioimmunoassay (RIA) kit (Siemens Medical Solutions Diagnostics, Los Angeles, CA) modified to accommodate lower levels of cortisol in human saliva relative to plasma. Saliva samples were thawed and centrifuged at 3460 rpm for 15 min to separate the aqueous component from mucins and other suspended particles. All samples were duplicated. The coated tube from the kit was substituted with a glass tube into which 100ml of saliva, 100ml of cortisol antibody (courtesy of Wendell Nicholson, Vanderbilt University, Nashville, TN), and 100ml of ^{125}I-cortisol were mixed. After incubation at 4ºC for 24h, 100ml of normal rat serum in 0.1% PO4/ EDTA buffer (1:50) and precipitating reagent (PR81) were added. The mixture was centrifuged at 3460 rpm for 30 min, decanted, and counted. Serial dilution of samples indicated a linearity of 0.99. Interassay coefficient of variation was 1.97%.

Respiratory sinus arrhythmia (RSA).

Participants wore MindWare Mobile Impedance Cardiograph units during the social stress paradigms for collection of synchronized electrocardiography (ECG) and respiration data. Seven sensors were placed on the child’s torso after arrival and initial collection of salivary cortisol. Five minutes of baseline signal were acquired prior to each of the social stress paradigms. Participants wore the mobile unit for the remainder of the protocol.

RSA was derived in accordance with the guidelines by the Society for Psychophysiological Research committee on heart rate variability (Berntson et al., 1997) and calculated on a minute-by-minute basis. ECG signal was sampled at 500 Hz and analyzed using the Heart Rate Variability Software Suite provided by MindWare Technologies (MindWare Technologies LTD, Gahanna, OH). The suite automatically identifies R peaks, which were visually inspected to confirm the presence of R peaks. Time-domain series were submitted to a Fast Fourier Transform (FFT) to derive the spectral distribution (MindWare HRV Module, Gahanna, OH). RSA was quantified as the integral power within the respiratory frequency band (0.12 to 0.40 Hz), and respiration was monitored by impedance cardiography (Ernst, Litvack, Lozano, Cacioppo, & Berntson, 1999). The respiration signal was processed similarly by FFT and displayed to ensure that the values were within the designated respiratory frequency band. Respiratory frequency was confirmed to lie within the high frequency/RSA band (0.12–0.40 Hz) for all participants. Additionally, there was no statistically significant difference in respiratory frequency between the ASD and TD groups

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($p > 0.05$). Two participants in the ASD group did not have complete autonomic data due to an inability to tolerate the electrodes. Data were lost for an additional participant in the ASD group during the TSST due to equipment malfunction. Of the total collected data, 1.1% were excluded due to excessive motion artifact or cardiac arrhythmias. RSA was measured in ln (ms^2). In all analyses for the TSST, RSA Stressor was measured as the average RSA during the 5-minute speech portion of the task.

Perceived affect recognition.

Emotion recognition or the ability to identify the expressed facial expressions of others, has been linked to activation of the HPA axis and higher levels of cortisol reactivity to social evaluative stressors (Bechtoldt & Schneider, 2016). The following measure was used to assess the participant's ability to recognize facial affect, especially neutral expressions.

NEPSY *Affect Recognition* (Korkman, Kirk, & Kemp, 2007) is a neuropsychological measure of facial affect recognition that requires the child to identify, match and remember faces showing happy, sad, neutral, angry, fearful, and disgust expressions. In addition to a total score, individual raw error scores are generated for each emotion. For the current study, the measure was administered to assess the child's ability to perceive neutral affect since the TSST requires raters to convey neutral facial expressions to the participant during the performance of the protocol. For completeness, we also compared the between group differences for the other emotions. The raw error scores were used in the analyses.

Perceived anxiety.

An individual's evaluation of a processive stressor is paramount for the activation of the HPA axis (Evans et al., 2013). The following measure was used to capture state and trait anxiety immediately following each stressor.

State-Trait Anxiety Inventory for Children—(STAIC) (Spielberger, 1973) is a self-report measure of anxiety, completed by participants, in which an individual describes how he/she is currently feeling (state) and how he/she usually feels (trait). The psychometric properties of this commonly used instrument have been well established in a number of studies. The STAIC has been used in studies of children and adolescents with TD and ASD to identify and differentiate state versus trait anxiety (Lanni et al., 2012). Previous research has shown that high-functioning children with ASD are able to self-report Trait anxiety especially during occasions of physiological arousal (Simon & Corbett, 2013) and the index is sensitive to treatment response in ASD (Corbett, Blain, Ioannou, & Balser, 2016). Internal consistency for the STAIC was good ($\alpha = 0.90$ for STAIC-State; $\alpha = 0.91$ for STAIC-Trait).

Statistical Analyses

First, independent sample t-tests were conducted to test for differences between the groups in demographic and diagnostic variables. If the assumption of normality was violated, the equivalent nonparametric test was used. The assumption of homogeneity of variance was tested with Levene's test of homogeneity, and the Welch degree of freedom approximation was used when the assumption was violated. Due to cortisol samples being positively skewed, all cortisol values were log transformed prior to analysis. After log transformation,

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one outlier remained in the ASD group; however, it was not >3 SD and removal of the participant did not alter the findings; therefore, the data were retained. The remaining dependent variables, including RSA and NEPSY findings, were free of extreme outliers. Cortisol and RSA values for both groups are provided in Table 2.

General linear model (GLM) analyses were performed to compare cortisol and RSA initial Baseline (S14) values between the groups. Following Baseline comparison, GLM was used to compare Interaction (TSST-F) and Stress (TSST) with Diagnosis as the between-subject factor and Baseline as the covariate. Subsequently, we examined within-group cortisol and RSA levels across the two social contexts using Paired-Samples t-tests for Baseline, Stress, and Recovery.

To examine associations between physiological stress (Cortisol) and regulation (RSA) levels during stress induction, Pearson Product correlations were conducted at Baseline, Preparation, and Stress for the TSST-F and TSST protocols. Pearson correlation coefficient r values of 0.10, 0.30, and 0.50 were considered small, medium, and large effects, respectively (Cohen, 1988). No a priori hypotheses were made.

To test the hypothesis that perception of neutral faces mediates the relationship between the diagnostic groups and stress response to social evaluative threat, a mediation analysis (Preacher & Hayes, 2004) was conducted using the PROCESS macro for SPSS (Hayes, 2013). Bias-corrected 95% confidence intervals were calculated with 5000 bootstrapped samples. In cases of non-normally distributed data or count data, the PROCESS macro is able to handle count mediators to estimate model coefficients (Hayes, 2013), and bootstrapping does not assume normally distributed data. To determine the type of errors made when presented with Neutral faces, the incorrect emotion label was recorded and cross tab ratios were calculated. Finally, independent samples t-tests and Pearson correlations were used to examine between-group differences in state and trait anxiety, and the extent to which these indices were correlated with cortisol and RSA, respectively.

Results

There were no significant differences between the groups based on age or pubertal development (see Table 1). While there was a significant difference based on IQ, it was not correlated with any of the dependent measures and therefore was not controlled for in the analyses (all $p>0.05$).

Baseline Differences

It was hypothesized that children with and without ASD would show similar cortisol and RSA values at baseline. In regards to cortisol, there were no significant differences at baseline $F(1,53) = 0.80$, $p = 0.37$. Similarly, there were no significant differences at baseline for RSA, $F(1,52) = 0.20$, $p = 0.65$, confirming the hypothesis.

Physiological Response Differences

It was predicted that children with ASD would show enhanced cortisol response and lower RSA to the TSST-F and a blunted cortisol and RSA response to the TSST.

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TSST-F Cortisol: Using GLM, there were no between-group differences for Interaction $F(1,52) = 0.05$, $p = 0.83$. For the ASD group, paired sample t-tests showed no significant differences from Baseline to Preparation or Interaction; however, there was a significant difference at Recovery $t(30) = 2.94$, $p = 0.01$. Similarly, for the TD group, there were no differences from Baseline to Preparation or Interaction; however, there was also a significant difference to Recovery $t(24) = 3.11$, $p = 0.01$. These results did not confirm the hypothesis. The cortisol profiles are presented in Figure 2.

TSST Cortisol: Using GLM, there were no between-group differences for Stress $F(1,53) = 0.08$, $p = 0.78$. For the ASD group, there were no significant differences from Baseline to the Preparation, Stress or Recovery (all $p>0.05$), confirming the hypothesis for the TSST. For the TD group, there was a significant difference from Baseline to Stress $t(24) = -2.58$, $p = 0.02$, but no difference for Preparation or Recovery for the TSST (see Figure 3).

TSST-F RSA: For the TD group, there were significant differences from Baseline for Interaction $t(24) = -4.12$, $p<0.001$ and a trend for Recovery $t(24) = -2.03$, $p = 0.05$. For the ASD group, there were significant differences from Baseline to Interaction $t(28) = -2.89$, $p = 0.01$, which confirms the hypothesis. There were no differences for Preparation or Recovery ($p>0.05$).

TSST RSA: For the TD group, there were significant differences from Baseline to Preparation $t(24) = -3.74$, $p =0.001$, to Interaction $t(24) = -4.12$, $p = 0.002$, and Recovery $t(24) = -5.01$, $p<0.001$. For the ASD group, there were significant differences for the Preparation $t(27) = -4.65$, $p = 0.001$ and Recovery $t(27) = -4.74$, $p = 0.001$, but no difference for Stress ($p>0.05$). Thus, results partially confirmed the hypothesis such that the TD group showed significant differences in physiological response whereas the ASD group did not.

Associations between cortisol and RSA

TSST-F: Pearson Product correlations between stress (cortisol) and regulation (RSA) were conducted for the TSST-F time points; namely, Baseline, Preparation, Interaction, and Recovery. The Total sample showed a moderate negative correlation with Baseline ($r = -.381$, $p = 0.01$), indicating that both groups exhibit a moderate association between the HPA and ANS indices prior to the social interaction. Additionally, for the Total sample there were moderate correlations for Preparation ($r = -.329$, $p =0.02$)). There were no significant associations for Interaction ($r = -.235$, $p = 0.09$) or Recovery ($r = -.186$, $p = 0.18$).

To look at the associations separately across the sample, within-group analyses showed strong correlations for the ASD group at Baseline ($r = -.499$, $p = 0.01$) and Preparation ($r = -.466$, $p =0.01$), moderate correlations at Interaction ($r = -.396$, $p = 0.03$; see Figure 5), but no significant correlation at Recovery ($p>0.05$). For the TD all $p>0.05$.

TSST: Pearson Product correlations were conducted across the TSST time points (Baseline, Preparation, Stress, and Recovery) for the Total sample. There were significant correlations during Stress ($r = -.299$, $p = 0.03$) but no significant associations at Baseline, Preparation or Recovery ($p>0.05$). Within group analyses revealed no association between cortisol and

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RSA across time points for the ASD group (p >0.05). However, for the TD children there was a significant negative correlation for Stress (r = −.484, p = 0.01) (see Figure 6) indicating strong associations between HPA stress response and PNS regulation during social evaluative threat. There were no associations for Preparation or Recovery (p>0.05).

Social Perception

To examine the impact of social perception on TSST and TSST-F, affect recognition analyses were conducted. Normality testing revealed the NEPSY scores were not normally distributed. Mann Whitney tests demonstrated significant between-group differences on NEPSY Affect Recognition for Neutral Errors between ASD (Mdn = 1.00) and TD (Mdn = 1.50), U = 501.00, z = 2.21, p = 0.03 (see Table 3). In addition, differences were observed on the Happy and Sad errors. As predicted, Neutral Faces negatively correlated with ASD Stress (cortisol) response to TSST (r_s = −.27, p = 0.04, see Figure 7), but not for the TSST-F, and there was no correlation for the TD group (all p>0.05).

Perceived affect and physiological response

Mediation analysis was conducted to examine the extent to which facial affect recognition of Neutral Faces mediates physiological response to the TSST (RSA and cortisol). A significant total association between Dx and RSA including Neutral Faces was observed F(2,49) = 4.27, p = 0.01, R^2= 0.15. Mediation analyses further demonstrated the association was partially accounted for by Neutral face errors at the bootstrapped 95% confidence interval (CI) [0.031, 0.502]. The direct association between Dx and RSA was not significant t(52) = −1.42, p = 0.16, bootstrapped 95% CI [−0.8308, 0.1374]. Thus, results showed that the perception of neutral faces mediated the relationship between diagnostic group membership and RSA response. For cortisol, the total association including Neutral Faces was at trend F(2,52) = 2.79, p = 0.07, R^2 = 0.10; however, the bootstrapped 95% CI [−0.209, −0.015] for the indirect effect did not include zero while the direct association between Dx and cortisol was not significant t(55) = 0.21, p = 0.84, bootstrapped 95% CI [−0.1911, 0.2513].

To determine the type of errors made when presented with Neutral faces, cross tab ratios were calculated. For Neutral errors, the ASD group misidentified (perceived) the neutral faces as being sad 76.6% of the time; whereas the TD group misidentified neutral faces as being sad 84% of the time. Thus, both groups revealed a negative bias, and predominantly misidentified neutral as sad roughly 80% of the time.

Associations between anxiety and physiological response

There were significant differences between the groups for trait anxiety following the TSST with children with ASD endorsing more trait anxiety, but not for state anxiety (see Table 1). For the TSST-F, there were significant differences for both trait and state anxiety showing children with ASD reporting higher levels of anxiety after the social interaction. Pearson correlations were conducted to examine associations between cortisol and RSA with self-reported state and trait anxiety. There were no significant correlations between anxiety and cortisol or RSA for TSST-F or the TSST-S (p>0.05).

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Discussion

The purpose of this preliminary study was to compare the stress response (cortisol) and physiological regulation (RSA) of children with and without ASD exposed to two social stress protocols. Additionally, the role of perceived emotion (affect recognition) and anxiety (state and trait) were explored. For the initial hypothesis, it was predicted there would be no baseline differences for children with and without ASD such that they would show similar HPA and RSA profiles, and this hypothesis was confirmed. However, as illustrated in Figure 4, children with ASD evidenced a moderate negative correlation at baseline across these physiological systems; but the TD group did not show a similar profile. In other words, while cortisol was low, RSA was high demonstrating a state of rest and relaxation for children with ASD. Thus, there does not appear to be a fundamental impairment in baseline regulation of either the HPA or ANS under conditions of rest. While the TD group did not show a similar significant association, it may be due to the relatively limited variability, especially for RSA, within the TD group. Previous studies with larger samples of similarly aged children have found negative correlations between baseline cortisol and RSA (El-Sheikh, Arsiwalla, Hinnant, & Erath, 2011), suggesting that current findings may be affected by the relatively small sample.

Under conditions of social stress, it was hypothesized that children with ASD would show a differential stress response to the TSST-F and the TSST for cortisol and RSA. For the TSST-F, which consists of a social *interaction* with a same-age peer, the ASD group showed a negative correlation between cortisol and RSA, such that when cortisol levels are low, RSA regulation is higher suggesting synergistic response and regulation for HPA and PNS, respectively. In the TD group, there was a lack of significant association between the physiological responses, likely due to a lack of variability and minimal stress response in the group overall. However, during the TSST, which consists of social *evaluation*, only the TD group showed a strong association between cortisol and RSA. Conversely, children with ASD did not show a correlation across physiological systems. It appears this lack of relationship was driven by a diminished stress response to the stressor in the ASD group. During direct comparison, there were no between group differences for the TSST-F or the TSST. However, based on within-group analyses, distinct profiles emerged. Similar to previous findings using pairwise comparisons, children with ASD exhibited a blunted cortisol and RSA response, a finding consistently observed in other studies of children and adolescents with ASD (e.g.,(Edmiston et al., 2017; Lanni et al., 2012; Levine et al., 2012)). In contrast, the TD children showed an adaptive stress response and enhanced regulation when socially evaluated by others.

While it is clear that many youth with ASD do not perceive the TSST to be stressful, the factors that contribute to the lack of enhanced arousal in response to social evaluative threat are unclear. One plausible explanation for diminished response is that they do not perceive the evaluation by the raters to be threatening, ostensibly due to social cognitive deficits in reading the emotional states of others. Previous studies have reported that children with ASD have difficulty identifying facial affect, especially neutral and happy faces (Berggren et al., 2016; Jarvinen et al., 2015; Tottenham et al., 2014). Jarvinen and colleagues compared children with ASD, Williams syndrome, and TD, and examined autonomic activity and

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emotion identification showing that the ASD group showed higher arousal relative to the TD group specifically in response to happy and neutral faces.

Subsequently, we examined the relationship between affect perception (neutral faces) and physiological response (cortisol and RSA) during the two stressors. The TSST is designed to provoke a stress response by having raters exhibit neutral expressions during a speech, which is considered by most to be unsupportive and threatening. People who are high on emotional intelligence (EI) exhibit enhanced ability to recognize facial affect (Davies, Stankov, & Roberts, 1998; Joseph & Newman, 2010), and EI has been associated with higher cortisol reactivity in social contexts like the TSST (Bechtoldt & Schneider, 2016). Therefore, if children with ASD do not accurately perceive neutral faces they may not experience the same arousal as TD individuals.

In the current sample, children with ASD indeed showed a reduced ability to identify neutral faces compared to the TD group, resulting in more errors. Moreover, a negative correlation between the ability to detect neutral faces and higher cortisol response to the TSST was only observed in the ASD group indicating that children with ASD who show better ability to perceive neutral facial expressions exhibit higher cortisol response to social evaluation. Conversely, children with ASD who demonstrate difficulty identifying neutral affect showed reduced stress and arousal to the social evaluation paradigm.

Subsequently, we examined the extent to which neutral faces mediates physiological response during the TSST. Results showed that diagnosis alone does not predict RSA or cortisol levels, but ASD diagnosis can explain the inability to identify neutral faces, which in turn mediates RSA (and cortisol levels at trend) in response to the TSST. For children who do not accurately identify neutral affect, the TSST is unlikely to be interpreted as threatening and therefore does not trigger activation of the PNS or HPA.

Tottenham and colleagues showed that youth with ASD were less accurate at identifying neutral faces; however, when forced to look in the eye region they showed enhanced amygdala response compared to TD participants (Tottenham et al., 2014). As the amygdala has been shown to activate the HPA axis stress response during psychological stress (Hand et al., 2002; Herman et al., 2005), this inability to recognize and focus on the eye region for neutral faces may conceivably contribute to the differential responses seen in the current study.

Avoiding eye contact explicitly to neutral faces has been reported in ASD (Kliemann, Dziobek, Hatri, Baudewig, & Heekeren, 2012). Additionally, when children with ASD do observe neutral faces, they often show a negative bias (Herrington et al., 2017; Tottenham et al., 2014). Examination of the type of errors made revealed that the ASD group misidentified neutral faces as being sad 76.6% of the time. Similarly, the TD group also misidentified neutral faces as being sad 84% of the time (although they made significantly fewer errors). Both groups revealed a negative bias predominantly misidentifying neutral as a sad facial expression nearly 80% of the time. Therefore, it makes sense that if the participants perceive the raters during the TSST as being sad, it would not provoke a stress response. Importantly,

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since so many participants with ASD mislabeled neutral faces, it is questionable as to whether they should be utilized in experiments as control stimuli (Tottenham et al., 2014).

In regards to the self-reported perception of anxiety across the two social contexts, there were significant between-group differences for trait anxiety for both paradigms. Children with ASD endorsed more persistent anxiety and it was indistinguishable for social evaluation or social interaction. However, the endorsement of state anxiety was differentiated across the groups and across context; children with ASD reported more state anxiety when socially interacting with peers yet did not report higher levels of anxiety during social evaluation, which is largely consistent with other findings (Lanni et al., 2012). There were no correlations between anxiety and physiological measures for TSST-F or the TSST for either group. Thus, even though physiological arousal was present under certain circumstances and anxiety was endorsed for the ASD group, the lack of associations between physiological systems and self-reported symptoms of arousal suggest distinct systems.

Even so, there were significant differences between the groups, which is a frequent finding in the literature. The presence of anxiety in ASD is widely reported with estimates ranging from 20% – 80% (Simonoff et al., 2008; van Steensel, Bogels, & Perrin, 2011; White, Oswald, Ollendick, & Scahill, 2009). One of the reasons for the broad range of reports is that anxiety in ASD may be typical or atypical based on diagnostic criteria (Kerns et al., 2014). For example, it has been reported that some children with ASD show increased social anxiety without fear of negative evaluation (Kerns et al., 2014). This unique observation may be in line with current findings showing endorsement of persistent anxiety even though the children with ASD do not report enhanced state anxiety during social evaluative threat.

Taken together, children with ASD do not show enhanced physiological arousal to being socially evaluated as previously reported (Corbett et al., 2012; Jansen et al., 2000; Lanni et al., 2012; Levine et al., 2012). The current study advanced these reports by showing that the perception of neutral faces mediated the HPA stress response and the upregulation of the PNS. Since many of the children with ASD misperceived neutral faces (primarily as sad), it apparently did not trigger a stress response or endorsement of anxiety on the TSST.

The extent to which these physiological findings may be translated into meaningful and relevant clinical information is important to consider. The current study replicates reports that children with ASD fail to show an adaptive increase in stress and arousal in response to social evaluation (Corbett et al., 2012; Edmiston et al., 2017; Lanni, 2012 #2157;Levine, 2012 #2058}. It is important to highlight that an absence of stress within the context of social judgement is concerning and renders the child with ASD vulnerable to misperceiving potentially threatening social situations (e.g., being poorly evaluated by others). Secondly, the stress response was mediated by the ability to perceive facial affect; namely, neutral faces. These results underscore the importance of teaching the interpretation of key social cues, such as facial affect, especially in a dynamic, interactive manner embedded within social situations. It would be interesting to see if interventions aimed at modifying the ability to perceive affect would also result in changes in physiological response.

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An encouraging finding is that children with ASD did not show stress or poor regulation during social interaction with novel peers as has been found in some social situations (e.g. (Corbett et al., 2010); (Lopata et al., 2008)). Children with ASD in the current study demonstrated a similar physiological profile as TD children suggesting they were comfortable engaging with the novel peer. Finally, it is important to acknowledge the notable heterogeneity in ASD, the variability in stress responsivity, as well as the complexity of social contexts. Therefore, the aforementioned clinical implications may not apply to a given child or situation.

Despite the compelling findings, there are important limitations to acknowledge. Notably, the study may be viewed as preliminary as it included a relatively small sample size. There was also no eye tracking used to determine if participants were actually looking in the eyes of the raters during the TSST. It is part of next steps to implement behavioral coding of videotaped sessions to determine the extent to which participants are viewing or avoiding the raters, including their facial affect. Additionally, the inclusion of more natural, dynamic stimuli for comparison may have been even more valuable than the use of standardized pictures of affect recognition. Previous research has shown that during natural viewing of the eyes, children with ASD do not look in the eye region; however, when forced to look at faces, eye contact is found to be negatively associated with amygdala activation and an increase in threat ratings (Tottenham et al., 2014). The study would have benefitted from direct observation of social behavior during the TSST-F. Similar to the point above, next steps include implementation of behavioral coding to assess relationships between stress response and observable behavior. Finally, future studies would benefit from more comprehensive assessment of anxiety symptoms, including parent- and clinician-report, and a much larger sample to extend these preliminary findings.

Social context determines the extent to which children with ASD experience psychological and physiological stress, as differential patterns of stress response are evident during social interaction versus social evaluation. Moreover, the atypical response to social evaluative threat in children with ASD is influenced by misperception of neutral faces, which are often perceived as sad and therefore do not promote a stress response or increased anxiety. In summary, the current study emphasizes the need to consider the important role of social context, social perception, and perceived anxiety when examining social interaction and stress, especially in children with ASD.

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Highlights

- Children with ASD show atypical response to different social situations.
- Social context determines the extent to which children with ASD experience stress.
- Important to consider social perception when studying social interaction and stress.
- Misperception of neutral faces mediates the stress response during social evaluation.
- Children with ASD misperceive neutral faces questioning their use in paradigms.

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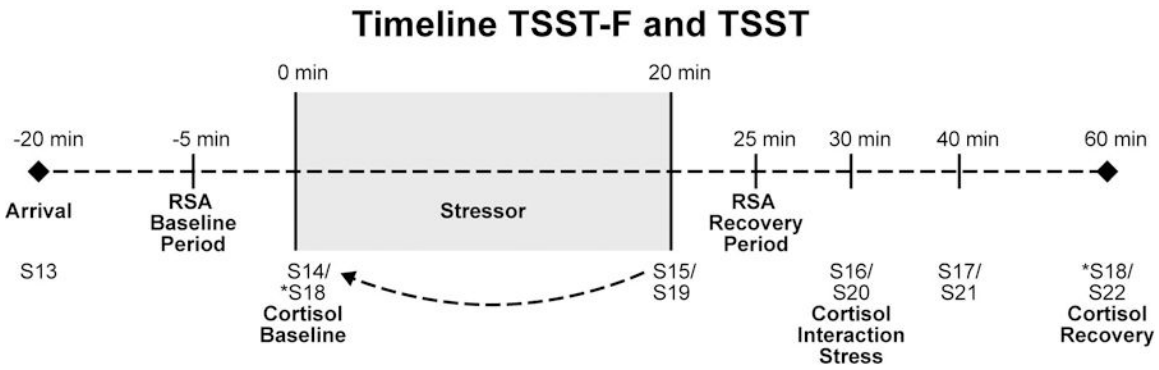

Figure 1.

Timeline Schematic for TSST and TSST-F for Cortisol and RSA Collection. S14 is the TSST Baseline.

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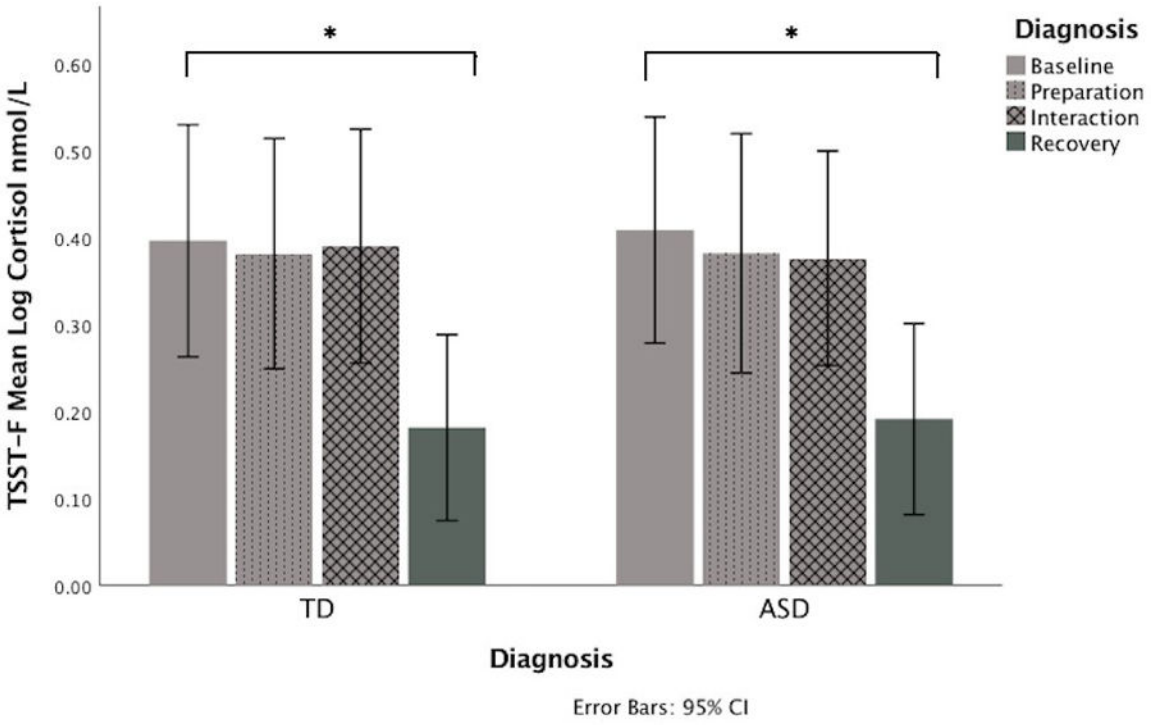

Figure 2.

Mean Log Cortisol Levels on the TSST-F for Children with TD and ASD. The figure shows a similar pattern across the groups with a significant difference between Baseline levels and Recovery indicating a reduction in cortisol after the social interaction protocol.

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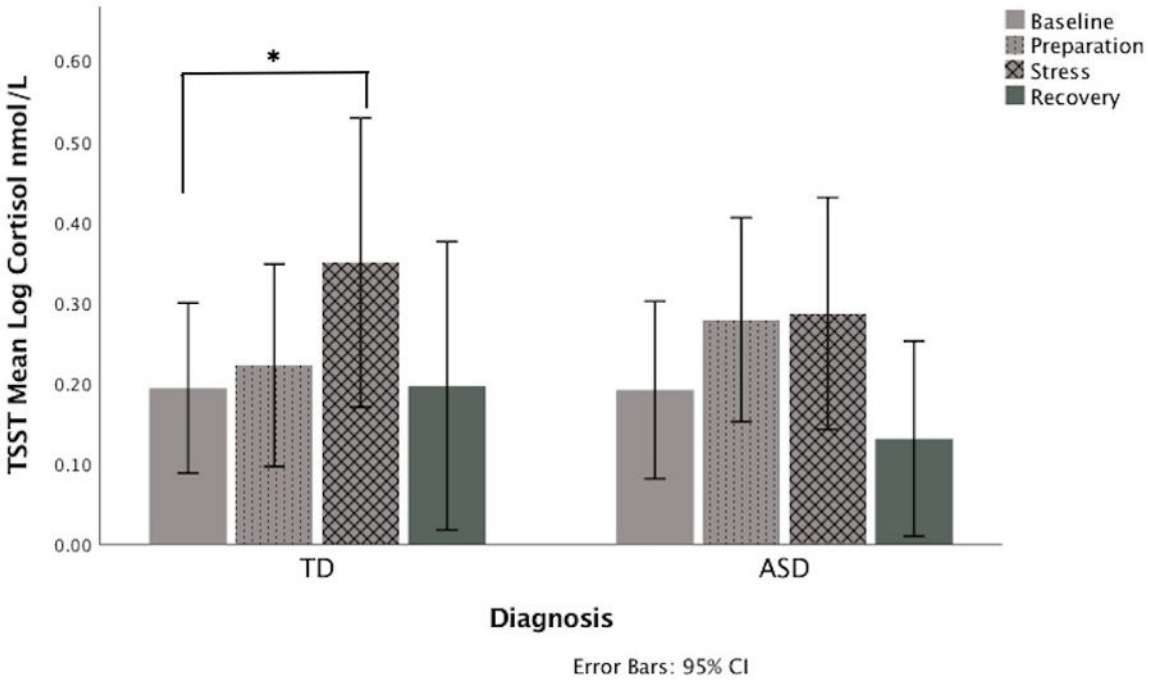

Figure 3.

Mean Log Cortisol Levels on the TSST for Children with TD and ASD. The figure shows a similar Baseline. However, the TD group shows a significant cortisol response to the TSST followed by a sharp return to Baseline levels, a predictable adaptive response to the stressor. In contrast, the ASD group shows a non-significant rise in cortisol during Preparation that plateaus and drops below Baseline levels during Recovery.

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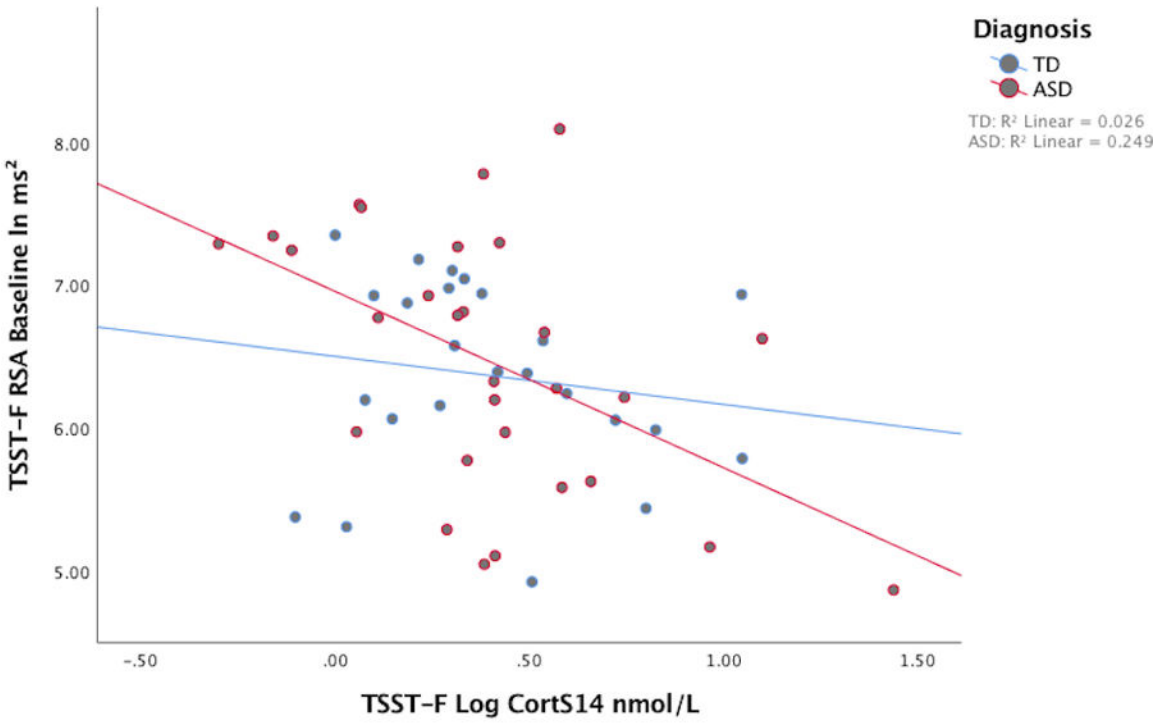

Figure 4.

Association between Baseline RSA and Cortisol. Baseline cortisol and RSA show strong negative correlations for children with ASD (r = −.499), but TD did not reach significance.

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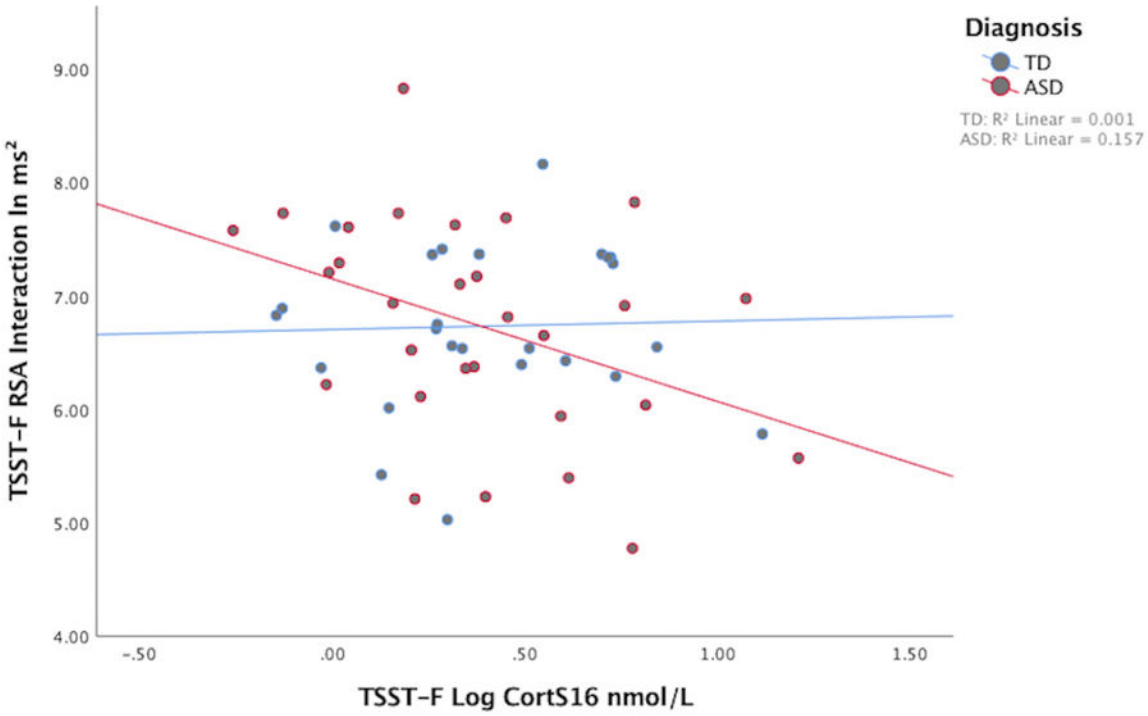

Figure 5.

Correlations between RSA and Cortisol During TSST-F for ASD and TD. The results show moderate correlations between cortisol and RSA during the TSST-F for children with ASD ($r = -.396$).

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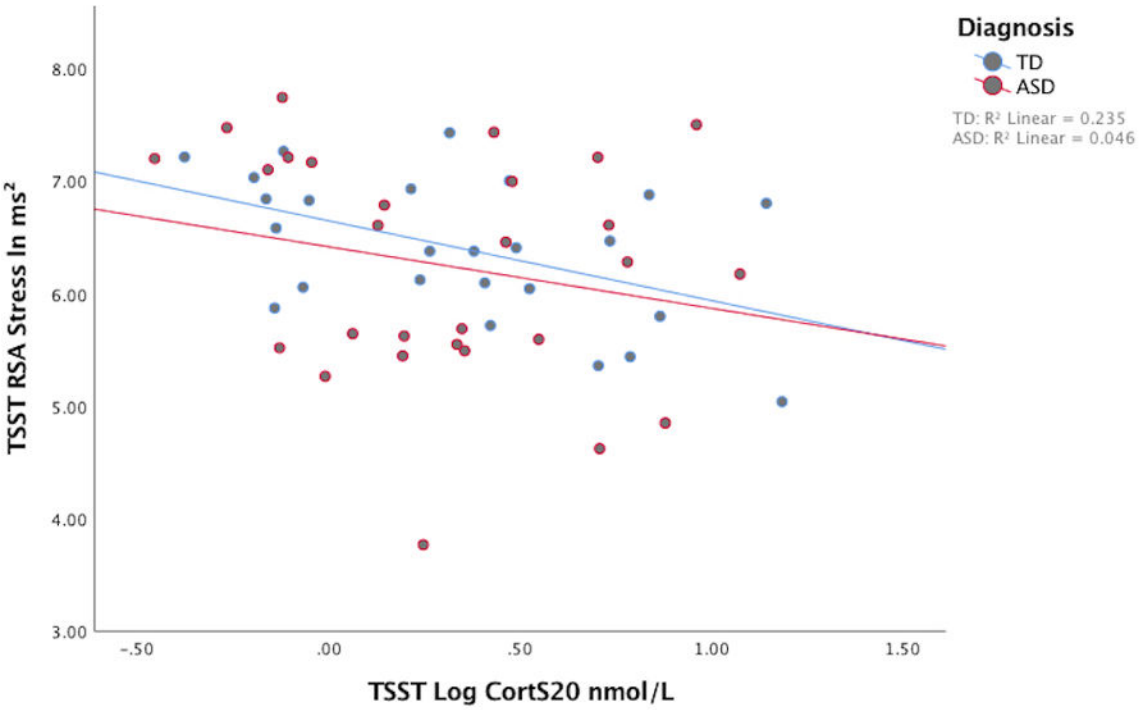

Figure 6.

Lack of correlations between RSA and Cortisol During TSST for ASD Group. The results show a lack of an association between cortisol and RSA for the TSST in children with ASD. However, there was a strong negative correlation between RSA and cortisol in TD (r = −. 484).

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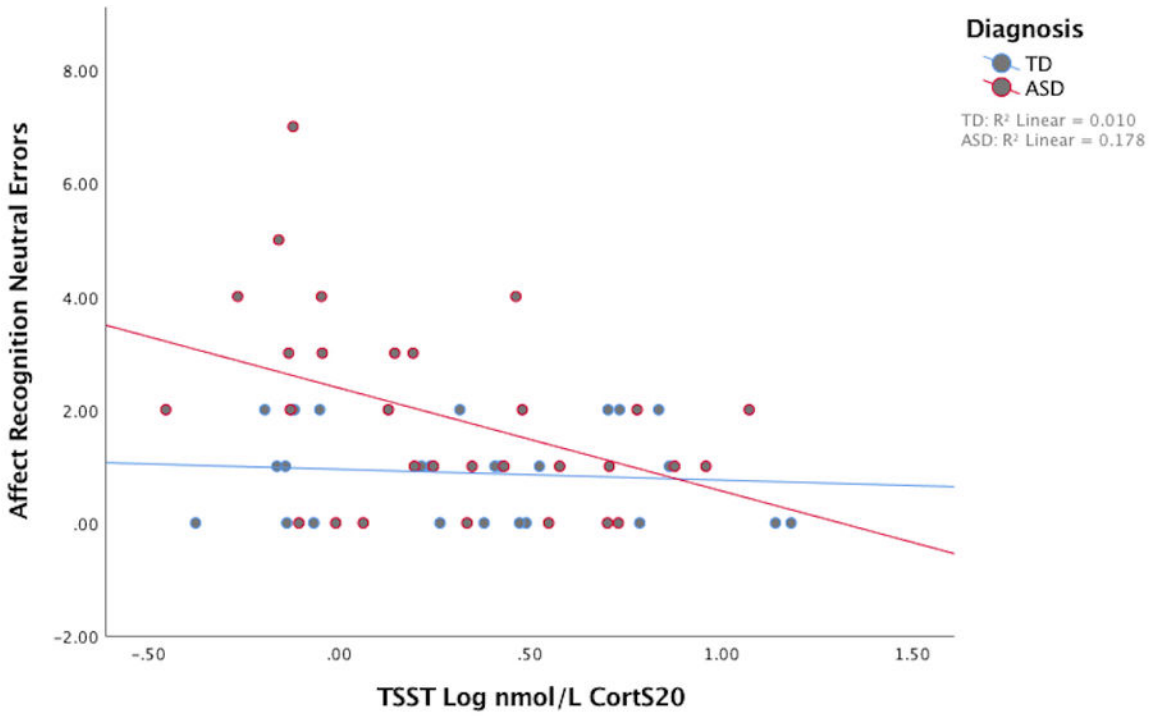

Figure 7.

Negative correlation between Neutral Face Perception Errors and Cortisol during the TSST in Children with ASD. There was a negative correlation between the ability to detect neutral faces and higher cortisol response to the TSST only in the ASD group. Thus, children with ASD who show better ability to perceive neutral facial expressions (demonstrated by fewer errors) exhibit higher cortisol response to social evaluation.

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Table 1.

Demographic Data

Variable	TD		ASD		t	p
	M	SD	M	SD		
Age	11.09	0.91	11.17	1.08	−0.29	0.78
IQ	113.76	16.57	98.29	20.27	3.07	0.01
ADOS			11.21	4.35		
PDS Average	1.68	0.55	1.87	0.65	−1.14	0.26
STAIC-State: TSST	32.00	7.41	29.90	5.59	1.21	0.23
STAIC-Trait: TSST*	27.42	4.75	33.32	8.18	−3.55	0.002
STAIC-State: TSST-F*	27.20	3.73	30.16	5.90	−2.18	0.03
STAIC-Trait: TSST-F*	28.72	4.55	34.52	7.82	−3.46	0.001
					-	

Note: TD = typical development, ASD = autism spectrum disorder, M = mean; SD = standard deviation, ADOS = autism diagnostic observation schedule, IQ = intelligence quotient, PDS = Pubertal Development Scale, STAIC= State-Trait Anxiety Inventory for Children, TSST = Trier Social Stress Test, TSST-F = Trier Social Stress Test – Friendly.

* $p<0.05$

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Table 2.

Means and Standard Deviations for Cortisol and RSA for ASD and TD Groups

Variable	ASD (N = 31)		TD (N = 25)	
	M	***SD***	**M**	***SD***
Cortisol: Arrival				
S13	0.466	0.354	0.385	0.310
Cortisol: TSST-F				
S14	0.409	0.355	0.397	0.316
S15	0.382	0.375	0.393	0.312
S16	0.376	0.337	0.404	0.319
S17	0.282	0.313	0.318	0.300
***S18**	0.192	0.300	0.194	0.255
Cortisol: TSST				
***S18**	0.192	0.300	0.194	0.255
S19	0.279	0.344	0.222	0.304
S20	0.287	0.392	0.349	0.434
S21	0.247	0.369	0.305	0.444
S22	0.131	0.330	0.197	0.433
Respiratory Sinus Arrhythmia: TSST-F				
Baseline	6.46	0.90	6.36	0.65
Preparation	6.37	0.94	6.20	0.75
Interaction	6.74	0.95	6.73	0.72
Recovery	6.52	0.89	6.58	0.68
Respiratory Sinus Arrhythmia: TSST				
Baseline	6.05	0.89	5.58	0.73
Preparation	6.86	1.05	6.51	0.81
Stress Speech	6.25	1.01	6.40	0.64
Math	6.01	0.92	6.20	0.66
Recovery	6.65	1.08	6.44	0.71

Note: TD = typical development, ASD = autism spectrum disorder, M = mean; SD = standard deviation; TSST-F = Trier Social Stress Test-Friendly; TSST = Trier Social Stress Test

*S18: Sample 18 represents recovery sample for TSST-F as well as initial sample for TSST. See Figure 1 for timing of cortisol sampling. All cortisol values are log (base 10) transformed. RSA measured in ln (ms^2).

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Table 3.

Between-Group Values for NEPSY Affect Recognition Raw Error Scores

NEPSY Errors	TD	ASD	z	p
	M SD	M SD		
Neutral *	0.88 (0.83)	1.87 (1.72)	2.21	0.03
Fear	0.76 (0.97)	0.97 (1.60)	0.50	0.62
Happy *	0.40 (0.20)	0.47 (0.78)	2.71	0.01
Sad *	1.84 (1.03)	2.90 (1.45)	2.81	0.01
Anger	1.88 (1.39)	2.23 (1.59)	0.87	0.38
Disgust	1.68 (1.11)	2.20 (1.19)	0.10	0.10

Note: TD = typical development, ASD = autism spectrum disorder, M = mean; SD = standard deviation.

* $p<0.05$