

VERBAL ABILITY AND SOCIAL STRESS IN CHILDREN WITH  
AUTISM AND TYPICAL DEVELOPMENT

By

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Abstract

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Autism is characterized by severe and persistent impairment in social interaction, communication, and restricted repetitive and stereotyped patterns of behavior. In addition, children with autism demonstrate a significantly higher prevalence of anxiety, particularly social anxiety, than children with other developmental disabilities or chronic health conditions. Physiological indices of stress portray irregularities in the diurnal rhythm of the neuroendocrine system and variability in the LHPA axis response to acute stress in children with autism. The Trier Social Stress Test–Child version (TSST-C) is a standardized, social-evaluative stress protocol designed to evoke a significant physiological stress response in healthy participants and is a widely used technique for evaluating the LHPA axis in clinical populations. The purpose of the current study was to investigate the neuroendocrine (cortisol) and psychological (anxiety) response to performance of the TSST-C in children with autism, relative to typical development, and to determine the association between physiological stress and anxiety. Because the TSST-C involves the completion of tasks that employ verbal communication and executive functioning skills, two abilities that are often implicated in autism, the Delis Kaplan Executive Function System (DKEFFS) Verbal Fluency Test and NEPSY Narrative Memory test were considered as predictor variables. Two groups, each comprised of fifteen children between the ages of 8 and

12, underwent neuropsychological testing, extended home cortisol sampling, and completed the TSST-C experiment. Results indicated that verbal ability did not predict the stress or anxiety (STAIC: State Form) responses for either diagnostic group. Children with autism and typical development demonstrated similar baseline levels of cortisol, but varied in their responses to the stressor; Typically developing children demonstrated a significantly increased level of cortisol following the task, however, this was not observed in children with autism. Self-reported levels of acute anxiety did not correlate with the physiological stress response exhibited by either group. The overall findings are interpreted within the context of the larger literature on social and cognitive functioning in autism with a particular emphasis on impaired social cognition. Clinical implications pertaining to the relationship between stress and anxiety as well as the importance of structured treatment to optimize performance are discussed.

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## CHAPTER ONE

### INTRODUCTION

Autistic Disorder (commonly referred to as autism) is a Pervasive Developmental Disorder characterized by severe and persistent impairment in social interaction (delays or abnormal functioning), communication (receptive and expressive social communication), and restricted repetitive and stereotyped patterns of behavior. This triad of core symptoms must begin prior to the age of three (APA, 2000). Autism spectrum disorder (ASD) is a term often used in scientific literature to describe the group of individuals who meet criteria for one of the following diagnoses: Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS). These three neurodevelopmental disorders each fall within the category of Pervasive Developmental Disorders (PDD) according to the *Diagnostic and Statistical Manual, Fourth Edition, Text Revision* (DSM-IV-TR) (APA, 2000) and share overlapping symptoms, but maintain distinct criteria (e.g., presence/absence of language delay, number of symptoms required for diagnosis, age of symptom onset). In this manuscript, the term autism is reserved to refer exclusively to individuals diagnosed with Autistic Disorder while autism spectrum disorder (or ASD) is used to describe research on the combined diagnostic group (PDD). Within this introduction, the literature pertaining to physiological stress, social anxiety, and executive functioning in children with autism spectrum disorders is reviewed as the background for a study designed to explore how these variables may be related in both children with autism and typically developing children.

#### *Autism Spectrum Disorders and Behavioral Stress*

In addition to the triad of core symptoms, individuals with ASDs tend to respond to stress with variable levels of intensity (APA, 2000; Muris, Steerneman, Merckelbach, Holdrinet, &

Meesters, 1998). For example, social situations that may be perceived as stressful to typically developing children may seemingly be underresponded to (e.g. lack of empathy in response to a sibling's death) or overresponded to (e.g. repeated tantrums in response to changing classrooms midyear) by a child with autism. Stress is also associated with an increase in symptoms in children with autism (Kanner, 1943; Thomas, et al., 1998). Core symptoms of autism such as stereotyped, repetitive behavior or insistence on sameness may become heightened in the face of uncertain circumstances in the environment. Presently, some researchers postulate that these behaviors may serve as a mechanism by which children with autism sooth themselves in challenging situations (Howlin, 1997, 1998; Thomas, et al., 1998). For example, children with autism may resort to increased motor stereotypies (e.g., hand flapping, twirling, rocking) or become insistent on routines or obsessively preoccupied with a circumscribed interest as a means of coping with unpredictable circumstances and find the interruption of these behaviors intensely distressing. Although not part of the diagnostic criteria, these behavioral observations have led researchers to further analyze stress and anxiety in children with ASDs (e.g. Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006; Corbett, Mendoza, Wegelin, Carmean, & Levine 2008b; Corbett, Schupp, Levine, & Mendoza, 2009c; Jansen, et al., 2000; Jansen, Gispens-de Wied, van der Gaag, & van Engelen, 2003; Lopata, Volker, Putnam, Thomeer, & Nida, 2008; White, Oswald, Ollendick, & Scahill, 2009b).

### *Stress versus Anxiety – Defined*

Stress and anxiety, while often used interchangeably in laymen's terms, remain two distinct constructs in scientific literature and must be considered separately when evaluating individuals with ASDs. In his book, *The Wisdom of the Body*, physiologist and stress research pioneer, Walter Cannon (1932) initially demonstrated the sympathetic nervous system's role in

responding to environmental threats and popularized the term homeostasis, describing "...the existence of agencies which are ready to operate correctively when the normal state of the organism is upset" (pg. 20-21). Seyle (1956) also highlighted the physiological nature of stress in his definition of the "general adaptation syndrome," described as a "nonspecific response of the body to any demands" (pg. 472). Seyle introduced the idea that stress may be considered any deviation from homeostasis and is credited with proposing a role for the adrenal glands in the stress response. The importance of both the adrenal and sympathetic nervous system in regulating the physiological stress response continue to be widely accepted (McEwen, 2000).

The physiological components of the stress response are just one aspect of stress research. The role of psychological factors in the activation of the stress response has also been investigated. The importance of considering the influence of psychological factors on stress has long been acknowledged (Seyle, 1956), and researchers over the years have demonstrated numerous psychological variables associated with stress (Corbett, et al., 2008b; Hennessey & Levine, 1979; McEwen, 2000; Weiss, 1970). For example, Weiss (1970, 1972) provided evidence that stress is associated with the occurrence of events that are unpredictable. Levine and colleagues (Hennessey & Levine, 1979; Levine, 2000) determined that stress results from a state of uncertainty, when an individual's cognitive appraisal of an event is inconsistent with his/her expectation of the event (or mental representation). Corbett and colleagues (2008b) specified the importance of cognitive appraisal and ascribed emotional meaning in the individual's comparison of the current situation to past experience. In consideration of the multifaceted nature of stress, McEwen (2000) incorporated the importance of both physiological and psychological factors into the following definition: "a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioral responses.

In biomedicine, stress often refers to situations in which adrenal glucocorticoids (GCs) and catecholamines are elevated because of an experience” (pg. 508).

In contrast to the physiological nature of stress, anxiety is classified as an emotion or individual-difference trait. As an emotion, anxiety can be induced by stress, although stress does not always precede anxiety. Spielberger (1972, 1973) distinguished between two types of anxiety, termed state anxiety and trait anxiety. He defined state anxiety as emotional arousal in the face of threatening environmental stimuli while trait anxiety is a stable, individual difference in the tendency towards responding to environmental stimuli with state anxiety. It is important to note that while anxiety may often be a normal emotional response, it is also the defining feature of a class of psychiatric disorders when it results in clinically significant distress and disability (APA, 2000).

Although there is a distinction between stress and anxiety, these terms are linked as anxiety is a potential consequence of stress (Endler, 1997). Stress, particularly when it is severe or prolonged, is a predisposing factor towards psychiatric illness, including anxiety disorders (McEwen, 2003; Sachar, Hellman, Fukushima, & Gallagher, 1970). This review intends to clarify how both stress and anxiety pertain to children with ASDs and will discuss each construct separately.

#### *Anxiety in ASD*

Children with autism experience a higher incidence of anxiety disorders than typically developing children (Achenbach, 1985; Gillott, Furniss, & Walter, 2001; Sutton, et al., 2005), children from other developmentally disabled groups (e.g., Specific Language Impairment: Gillott, et al., 2001), and children with chronic medical conditions (e.g., Asthma: Vila, Nollet-Clemencon, de Blic, Mouren-Simeoni, & Scheinmann, 2000). A recent review of the literature,

revealed an 11-84% prevalence rate for anxiety in children and adolescents with autism spectrum disorders, concluding that the expression of anxiety in this population is dependent on multiple factors including age and cognitive ability (White, et al., 2009b). Sutton and colleagues (2005) found that children with high functioning autism demonstrate increased social anxiety, social stress, and awareness of interpersonal difficulties on self-report measures, compared to typically developing children. Similarly, Gillott and colleagues (2001) determined that children with autism report significantly higher levels of anxiety, particularly social anxiety, separation anxiety and obsessive compulsive disorder, than children with Specific Language Impairment. These reviews indicate that social anxiety is a common form of anxiety experienced by children with ASDs.

*Social Anxiety Disorder.* Social anxiety disorder is defined by the DSM-IV-TR as a marked, persistent fear of at least one social performance situation that exposes the individual to either unfamiliar people or possible evaluation (APA, 2000). The individual with social anxiety disorder primarily fears that his/her behavior will lead to embarrassment and humiliation which leads him/her to avoid social interaction or endure it with dread. The DSM-IV-TR distinguishes between avoidance of social interaction in individuals with pervasive developmental disorders versus social anxiety disorder based on the underlying motivation factor (i.e. avoidance due to lack of interest versus avoidance due to anxiety, respectively) (pg. 455). Furthermore, for a child to be diagnosed with social anxiety disorder, he/she must have at least one age-appropriate friend, and symptoms of social anxiety or avoidance must not be better accounted for by another disorder (e.g., Major Depressive Disorder). The implication of this is that it is difficult to diagnose comorbid social anxiety disorder in individuals with PDD according to the current classification system.

Nonetheless, social anxiety is a prevalent concern as researchers have attempted to characterize anxiety in children with autism spectrum disorders (Gillott, et al., 2001; Kuusikko, et al., 2008; Lopata, et al., 2008; Simonoff, et al., 2008; Sutton, et al., 2005). For example, Sukhodolsky and colleagues (2008) used a parent-report measure to determine that 43% of children in their sample met criteria for an anxiety disorder. Similarly, Simonoff and colleagues (2008) used a parent-interview measure to evaluate the prevalence of psychiatric disorders in 112 children (10-14 years old) with autism spectrum disorders, finding that 41.9% of their sample met criteria for at least one anxiety disorder. The most prevalent anxiety disorder found in this study was social anxiety disorder (29.2%). By comparison, the lifetime prevalence of Social Anxiety Disorder in the general population is estimated to range from 3-13 % (APA, 2000). The higher prevalence of social anxiety disorder in children with autism spectrum disorders may be related to the core symptoms of the disorder, particularly social impairment (e.g., Kuusikko, et al., 2008; Lopata, et al., 2008; Sutton, et al., 2005).

*Social Impairment and Anxiety.* Social impairment is one of the core features of autism and is described as an inability to utilize nonverbal behavior to appropriately regulate social interactions, lack of social and emotional reciprocity, and failure to develop age-appropriate peer relationships. Symptoms of social impairment may change over the course of development, spanning from resistance to cuddling during infancy to lack of spontaneous shared enjoyment with others during adolescence into adulthood (APA, 2000). Although symptoms of social impairment may appear to improve as a result of natural development and/or behavioral treatment, these characteristic symptoms never remit. For example, a school-aged child may improve from complete social withdrawal and avoidance towards the acceptance of social play initiated by a peer (while remaining unable to initiate this cooperative social interaction).

Natural development and increased experience with social interaction may lead a child with autism towards increased insight into his own and other's emotional experiences as well as result in increased anxiety surrounding his own social deficits (Lopata, et al., 2008). This developmental progression has been hypothesized to contribute to increased social and evaluative anxiety as a child with autism enters adolescence (Kuusikko, et al., 2008). Kuusikko and colleagues documented this pattern in a sample of children and adolescents with high functioning autism, Asperger's disorder, and typical development. They demonstrated that social and evaluative anxiety increased with age in the participants with autism spectrum disorders (while symptoms of social anxiety decreased with age for the typically developing children). It was hypothesized that the initial delay of social development in children with HFA and Asperger's disorder may have contributed to this pattern (i.e. as the quality of social interaction increased, social anxiety increased). In addition, the authors noted a discrepancy in symptom-reporting between child/parent dyads for those with autism spectrum disorders, particularly prior to the age of twelve. They identified that children with autism spectrum disorders tend to under-report symptoms of anxiety, relative to parent-report. Gillott and colleagues (2001) observed this same distinction between child- and parent-reports. Both groups of researchers concluded that this artifact may be due to the child's limited insight into his/her level of social impairment and anxiety, particularly early in the course of development, determining that progressing social and emotional development may narrow this gap between the child- and parent-reports and align observed anxiety with the child's recognition of this emotional experience (Gillott, et al., 2001; Kuusikko, et al., 2008).

Sutton and colleagues (2005) also provided evidence of the influence of development and social skills on social anxiety. They demonstrated that children with autism whose parents

reported a low level of social impairment tend to self-report increased awareness of social difficulties and greater social anxiety than children with autism whose parents report a high level of social impairment (i.e. increased ability to interact socially was associated with increased awareness of social difficulties and greater social anxiety). A recent review by White and colleagues (2009b) determined that factors related to anxiety in children with autism spectrum disorders include diagnosis (pervasive developmental disorder > high functioning autism > autism), cognitive ability (high>low), and degree of social impairment. In contrast, Sukhodolsky and colleagues (2008) did not find differences in anxiety level based on diagnosis. However, their data did demonstrate a relationship between increased anxiety and higher level of intelligence, greater social impairment, and increased use of functional language according to the Autism Diagnostic Interview – Revised (ADI-R: Lord, Rutter, & Couteur, 1994).

*Limitations of Previous Research.* Previous research has provided abundant evidence that children with autism experience comorbid symptoms of anxiety, particularly social anxiety. Several limitations evident in this work include the use of cross-sectional research designs, heterogeneous diagnostic groups, and reliance on self-report and parent-report measures. The use of self-report measures may presently be the most difficult limitation to remedy as core features of the disorder likely interfere with an individual with autism’s ability to understand the question being asked (e.g. impaired verbal comprehension) or refrain from perseverative responding. In addition, difficulty with personal introspection may influence a child with autism’s ability to self-report internal emotional states (Baron-Cohen, Leslie, & Frith, 1985; Capps, Yirmiya, & Sigman, 1992). The validity of parent-report measures may also be threatened due to the internal nature of anxiety and reliance on the parent’s observation of behaviors that are interpreted by the parent to be anxiety-related. In consideration of the observed discrepancies between child- and



parent-reports of anxiety (Gillott, et al., 2001; Kuusikko, et al., 2008), the possibility that parent-reports of anxiety are documenting anxiety that does not truly exist within the child cannot be ruled out. Nevertheless, it is common practice to measure anxiety with self- and parent- reports, and it is not recommended that their use be abandoned. A high prevalence of children with comorbid anxiety disorders have been identified, and preliminary evidence for the efficacy of psychological treatment for anxiety in this population has also been provided through the use of these instruments (Chalfant, Rapee, & Carroll, 2007; Ooi, et al., 2008).

One way to broaden our understanding of anxiety in autism without exclusive reliance on self-report and parent-report measures is to examine one precipitant of anxiety, the stress response (Endler, 1997). Neuroendocrine markers of stress reactivity provide an objective criterion that can be compared and contrasted with concurrently reported anxiety and observations of behavior to more precisely determine triggers of anxiety as well as the biological underpinnings that may sustain anxiety in children with autism spectrum disorders. Evans, Canavera, Kleinpeter, Maccubbin, and Taga (2005) recently recommended the use of physiological measures of anxiety to avoid threats to validity associated with self- and parent-report measures in this population. Previous researchers have utilized this method to evaluate the Limbic-Hypothalamic-Pituitary-Adrenal (LHPA) axis in children with autism (Corbett, et al., 2006, 2008b, 2009c; Jansen, et al., 2000, 2003; Lopata, et al., 2008; Richdale & Prior, 1992), and there is some evidence that physiological indices of stress are positively correlated with parent-reports of daily stress (Corbett, et al., 2009c).

#### *Stress and the LHPA Axis – General Description.*

The LHPA axis is a complex neural system that is activated and inhibited via specific neurochemicals and involves numerous anatomical structures. While this system has traditionally

been known as the HPA axis, the prominent role of the limbic system in perceiving threatening environmental events that stimulate activation of this system has led to its being increasingly referred to as the LHPA axis (Levine, 2005). To briefly summarize its activity, when an individual encounters an environmental event (physical or psychological) that is perceived as novel or unfamiliar, the hypothalamus releases two neurochemicals, corticotrophin releasing factor (CRF) and arginine vasopressin (AVP). CRF and AVP then activate corticotrophs located in the pituitary to stimulate the release of adrenocorticotrophic hormone (ACTH). ACTH stimulates the release of glucocorticoids (cortisol in humans) from the adrenal which are then discharged into general circulation. When the LHPA axis is functioning properly, the increased level of glucocorticoids in the bloodstream alerts the brain and pituitary to cease production of CRF and ACTH, allowing the organism's glucocorticoids to return to a normal basal level via negative feedback, terminating the acute stress response (Levine, 2005).

Outside of the acute stress response, basal levels of cortisol vary according to a circadian rhythm which is well-structured within the first few months of life (Price, Close, & Fielding, 1983; Vermes, et al., 1980). Basal cortisol levels are naturally highest in the morning, peak 30 minutes after awakening, and then decline throughout the later morning (rapid decline) and afternoon hours (slow decline) towards the body's lowest level of cortisol in the evening and night.

Cortisol, released from the adrenal following LHPA activation, is a widely used biomarker of the endocrine stress response, as it is consistently found to be elevated when an individual encounters what is perceived to be a novel or unfamiliar situation (Gunnar & Donzella, 2002; Hennessy & Levine, 1979). The integrity of the LHPA system is vital to the health of the organism, and individuals vary significantly in terms of LHPA functioning

(McEwen, 1998). These individual differences are expressed through increased vulnerability or resistance towards exhibiting the stress response when faced with an unfamiliar circumstance. Factors known to contribute to individual variability include early developmental experiences (Levine, 1957; Meaney, Aitken, Viau, Sharma, & Sarrieau, 1993) and exposure to chronic stress (McEwen, 2004). When a disruption occurs within any of these three regulatory processes (circadian rhythm, activation in response to acute stress, return to baseline via negative feedback) it compromises the overall health of the organism (McEwen, 1998; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996).

#### *Stress and the LHPA Axis in ASDs*

Kanner's (1943) initial clinical description of autism documented a notable increase in symptoms in response to stress and marked difficulty in responding to novel situations. Consistent with this long-standing observation as well as our present understanding of psychological factors that trigger the LHPA stress response (i.e. novelty, unfamiliarity, uncertainty), irregularities in the neuroendocrine system and LHPA axis have been demonstrated in autism (Corbett, et al., 2006, 2008b, 2009c; Lopata, et al., 2008; Naber, et al., 2007; Richdale & Prior, 1992; Tordjman, et al., 1997; Yamazaki, Saito, Okada, Fujieda, & Yamashita, 1975). Dysregulation of the LHPA axis in children with ASDs is evident in both regulation of the circadian rhythm (e.g., Corbett, et al., 2006, 2008b, 2009c; Yamazaki, et al., 1975) and response to acute stress (e.g., Hoshino, et al., 1987; Tordjman, et al., 1997).

*Circadian Rhythm.* In 1975, Yamazaki and colleagues demonstrated deviations from the normal circadian rhythm of cortisol in their evaluation of seven children with autism. Further evidence that children with autism exhibit variability in circadian rhythm has been documented by Corbett and colleagues (2006) who evaluated salivary cortisol levels at three points

throughout the day (upon awakening, afternoon, evening) for two consecutive days. They demonstrated higher within-group variability in daily cortisol levels in children with autism than in typically developing children, as well as significant differences in circadian rhythm between the two groups. The authors hypothesized that higher variability amongst the children with autism may be due to increased sensitivity to daily changes and unpredictable environmental events, symptoms that are characteristic of autism. Further evaluation of circadian rhythmicity in children with autism using a more rigorous protocol over a six day period with a much larger sample (Corbett, et al., 2008b) replicated the results of their previous study (2006) and revealed that morning values of cortisol declined steadily over time while the evening values remained consistently elevated in the children with autism, relative to children with typical development. In addition to between-group and within-group variability, a high level of within-subject variability was found in this investigation. The authors proposed that consistency in diurnal rhythm might also be an important variable to consider when evaluating the LHPA axis in children with autism (Corbett, et al., 2008b). Further analyses of this sample (Corbett, et al., 2009c) revealed a positive relationship between parent-reported daily stress on the Stress Survey Schedule (SSS; Groden, et al., 2001), particularly on the Changes subscale, and elevated evening cortisol (an indication of “cumulative arousal” in response to unexpected events or changes in expected routine). They also determined that increased daily stress on this measure was associated with lowered morning cortisol (an indication of chronic stress or insecure social relationships). In addition, multiple relationships were determined between parent-reported sensory sensitivity on the Short Sensory Profile (SSP; Dunn, 1999) and morning cortisol (i.e., auditory filtering and movement sensitivity were related to lower morning cortisol; energy and visual-spatial sensitivity were related to higher morning cortisol). Together, these findings

accentuate the importance of extended home sampling to establish a baseline for the comparison of a cortisol response during an experimental task as well as the value of designing studies to investigate factors that contribute to the activation and exacerbation of the stress response in children with autism.

*Acute Stress Response – Social.* Richdale and Prior (1992) evaluated cortisol in 18 children with autism and 19 typically developing children over the course of two days. While they did not find significant differences between the groups in their circadian rhythm of cortisol, they did observe an increased level of daytime cortisol in the children with autism who had been integrated into regular classrooms. The authors hypothesized that this subgroup may be hyperresponsive to environmental stress (i.e. classroom integration). In a laboratory setting, Jansen and colleagues (2000, 2003) performed a series of experiments utilizing a modified version of a standardized, social-evaluative stressor (Trier Social Stress Test – Child Version; Buske-Kirschbaum, et al., 1997) known for its ability to reliably activate the LHPA axis (Kirschbaum, Pirke, & Hellhammer, 1993). The authors observed that children with an “autistic-like” disorder (Multiple Complex Developmental Disorder, MCDD; Cohen, Paul, & Volkmar, 1986) demonstrated an attenuated stress response, relative to typically developing children (2000), and that children with autism did not demonstrate a significantly different stress response than typically developing children (2003). In addition, the authors reported that children with autism demonstrated a significant elevation in cortisol in response to a “control condition” that was described as identical to the experiment session with the exception of the stress task. The control condition entailed staying “as relaxed as possible, for instance by talking, drawing, or playing a game” (pg. 585). Neither the group with MCDD or typical development demonstrated a stress response during this condition. These two studies (Jansen, et al., 2000, 2003) provide

some insight into the functioning of the LHPA axis in children with ASDs, however, future replication and extension of these findings might allow researchers to disentangle what factors may have contributed to the finding that children with autism demonstrated stress in response to the control condition as well as the finding that children with autism, despite being more socially impaired than children with MCDD, demonstrated a more similar acute stress response to the typically developing group than the children with MCDD.

In a more natural setting, Lopata and colleagues (2008) designed an experiment to evaluate the cortisol response following social interaction with a familiar or unfamiliar peer. Thirty-three children with high functioning ASDs were recruited from a six-week day camp. During week five of the camp, participating children engaged in two separate twenty-minute game sessions, one to interact with a familiar peer and one to interact with an unfamiliar peer. Results indicated a significant order-effect, such that children who interacted with the familiar peer prior to the unfamiliar peer demonstrated increased cortisol following interaction with the unfamiliar peer relative to the familiar peer (while the participants who interacted with the unfamiliar peer first did not demonstrate a change in cortisol from one day to the next). One explanation for these findings could be that children who interacted with the familiar peer first did not anticipate the second day's social interaction with an unfamiliar peer. In addition, Lopata and colleagues documented a mild-to-moderate correlation between cortisol level and subjective self-reported stress on a researcher-developed scale.

*Acute Stress Response – Non-Social.* While the previous studies (Richdale & Prior, 1992; Jansen, et al., 2000, 2003; Lopata, et al., 2008) examined the acute stress response to various social stressors, Corbett and colleagues (2006, 2008b, 2009c) utilized a novel, non-social stressor (i.e. twenty minute exposure to a mock-MRI) to evaluate the LHPA axis in children with autism

and typical development, minimizing the likelihood that social impairment might influence the stress response. Results indicated a significant elevation in cortisol for children with autism, while typically developing children demonstrated a decrease in cortisol, following exposure. Interestingly, this increase in cortisol occurred in the absence of observable behavioral agitation, highlighting the importance of evaluating neuroendocrine response to stress in children with autism (rather than depending solely on observed behavior or parent- or self-reported symptoms of stress and anxiety). To evaluate the stress response to the mock MRI further, Corbett and colleagues (2008b) performed a second study with a larger group of children and the addition of a repeat exposure to the mock MRI in order to determine if a habituation or sensitization effect might occur. In contrast to their initial findings (2006), no significant differences between groups were observed upon initial exposure to the mock MRI (although cortisol levels in the group of children with autism were relatively higher than those in the comparison group). They did find, however, that children in both groups demonstrated a significant elevation in cortisol upon arrival to the second mock MRI scan as compared to their previous cortisol level (collected upon arrival at the initial mock MRI scan). This anticipatory stress response did not occur in response to the stressor itself, but resulted from the child's cognitive appraisal of a situation that he had previously associated with an emotional response. The authors recommended that future research efforts be directed towards replicating these findings with repeated exposure to additional stress paradigms and to determining factors that mediate responsiveness of the LHPA axis. Following this recommendation, Corbett and colleagues (2009c) analyzed the contribution of sensory sensitivity and psychological stress in the previous sample (2008b). The psychological variables (parent-reported stress and sensory sensitivity) were not significantly related to responder status (based on demonstrated increase in cortisol twenty minutes following exposure to the stressor)

within or between the diagnostic groups. However, the psychological variables were significantly related to differences in the diurnal rhythm between diagnostic groups as previously discussed.

*Acute Stress Response – Physical.* In addition to research evaluating the acute stress response following social and non-social stressors, acute stress following physical exercise has also been evaluated in children with ASDs (Jansen, et al., 2003). Jansen and colleagues (2003) compared the cortisol levels of 10 children with autism, 11 children with MCDD, and 15 healthy controls following ten minutes of exercise on a stationary bicycle. Children with autism did not differ from the remaining two groups in their cortisol response to this task.

*Acute Stress Response – Physiological.* Several researchers have evaluated the LHPA axis by triggering an acute stress response, physiologically (Hoshino, et al., 1987; Yamazaki, et al., 1975). For example, Yamazaki and colleagues (1975) evaluated the cortisol stress response following pyrogen injection in a sample of seven children with autism and determined that it was not abnormal. In contrast to the previous finding, Hoshino and colleagues (1987) evaluated fifteen children with autism (10 high functioning and 5 low functioning, based on IQ) and demonstrated that children with autism (particularly those who were lower functioning) showed an abnormal response to the dexamethasone suppression test (DST). The DST involves measuring cortisol following the ingestion of ACTH and is useful for examining whether the negative feedback system of the LHPA axis is functioning properly, with normal functioning entailing suppression of cortisol production following ACTH ingestion. Ten of the fifteen participants with autism were characterized as “nonsuppressors” (defined by continued production of cortisol), indicating that the negative feedback system was not functioning properly. This finding of a dysfunctional negative feedback system may be consistent with



Corbett and colleague's (2009c) discussion of elevated evening cortisol as an indication of "cumulative arousal" following multiple incidences of acute stress throughout the day as continued production of cortisol in the absence of the initial stressor could contribute to an elevated evening level.

*Acute Stress – Hyperresponsivity versus Chronic Hyperarousal.* The previous research documents abnormalities in the circadian rhythm (Corbett, et al., 2006, 2008b, 2009c), acute stress response (Corbett, et al., 2006; Jansen, et al., 2000), and negative feedback system (Hoshino, et al., 1987) of the LHPA axis for children with ASDs; However, it is also important to identify whether evidence suggests a pattern of hyperresponsivity to acute stress or chronic hyperarousal. Tordjman and colleagues (1997) addressed this question by measuring multiple physiological indicators of stress. They measured morning cortisol, ACTH, and  $\beta$ -endorphin (BE) via venipuncture in ninety children and adolescents (48 with autism, 16 with mental retardation or cognitive impairment, and 26 with typical development). While the children with autism demonstrated elevated ACTH and BE relative to the remaining two groups, their basal cortisol level did not differ significantly. Since cortisol, a slower acting stress hormone than ACTH and BE, was not elevated, the authors concluded that the autism group demonstrated a pattern of heightened response to acute stress rather than chronic hyperarousal.

#### *Stress and Anxiety – Summary*

Research to date documents that children with autism demonstrate significant variability in the diurnal rhythm of cortisol (Corbett, et al., 2006, 2008b, 2009c), a pattern of hyperresponsivity to acute stress rather than chronic hyperarousal (Tordjman, et al., 1997), and abnormalities in the negative feedback system following activation of the LHPA axis (Hoshino, et al., 1987). In addition, children with ASDs vary substantially in their responses but do not

differ as a whole from typically developing children in their response to acute nonsocial stress (mock-MRI; Corbett, et al., 2008b; but see Corbett, et al., 2006 for evidence of variability), anticipation of repeated exposure to nonsocial stress (mock-MRI; Corbett, et al., 2008b), or physical stress (exercise; Jansen, et al., 2003).

A complex picture emerges when children with autism are exposed to social stress. In two studies limited by the exclusion of typically developing comparison groups, children with autism appeared to demonstrate a heightened stress response under conditions in which they were required to interact socially (Lopata, et al., 2008; Richdale & Prior, 1992). Following performance of a standardized laboratory-based social stressor (TSST-C; Jansen, et al., 2003), children with autism showed a similar elevation in cortisol to typically developing children while children with an autism-like disorder (MCDD) demonstrated a blunted cortisol response (Jansen, et al., 2000).

The findings described by Jansen and colleagues (2000, 2003) contribute to our understanding of the functioning of the LHPA axis in children with ASDs, while simultaneously posing questions for further inquiry. For example, the finding that children with autism, a more socially impaired group than children with MCDD, demonstrated an acute stress response that did not differ from the typically developing comparison group contradicted the authors' initial hypothesis that children with autism would demonstrate an even further attenuated stress response than children with MCDD. The authors had initially reasoned that social impairment would preclude the children with autism from recognizing the socially stressful nature of this task. One possible explanation for this unanticipated result is that a factor (or factors) other than social impairment might have influenced the children with autism's stress response as well as the children with MCDD's attenuated response. This may be particularly likely in lieu of the finding

that children with autism also demonstrated stress in response to the control condition. Another possibility is that the methodology employed in these studies resulted in findings that are not replicable using the standardized TSST-C protocol. A careful evaluation of the TSST-C and methods employed by Jansen and colleagues (2000, 2003) must occur in order to fully understand the utility and task-demands of this stress protocol as well as limitations encountered in this previous work. Future replication and extension of the work presented by Jansen and colleagues (2000, 2003) may allow further interpretation of these findings in the context of our present understanding of acute stress in autism.

#### *Trier Social Stress Test – Child Version (TSST-C)*

The Trier Social Stress Test (TSST; Kirschbaum, et al., 1993) is a standardized psychosocial stress protocol that is known for its ability to reliably activate the LHPA axis, inducing a 2-4 fold increase in salivary cortisol level and concentration relative to baseline, in a laboratory setting. The TSST is a well-validated protocol that has been utilized to distinguish differences in the stress responses of healthy individuals compared to those with conditions such as schizophrenia (Brenner, et al., 2009), depression (Chopra, et al., 2009), and social anxiety disorder (Roelofs, et al., 2009). In addition to distinguishing between diagnostic groups, this highly sensitive protocol has been used to identify factors that contribute to differences in the stress response of healthy individuals, including age and gender (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004), social support and oxytocin (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), and personality (O’Leary, Loney, & Eckel, 2007; Tyrka, et al., 2007). Buske-Kirschbaum and colleagues (1997) adapted the TSST for use with children and have subsequently utilized this tool to examine the function of the LHPA axis amongst children with medical conditions in which symptoms can be exacerbated by stress (Atopic Dermatitis;

Buske-Kirschbaum, et al., 1997; Asthma; Buske-Kirschbaum, et al., 2003) as well as those having experienced stressful early-life events known to influence the development of the LHPA axis (Former Preterm Infants; Buske-Kirschbaum, et al., 2007). To summarize, the TSST-C is a twenty-minute task requiring the participant to stand at a microphone in front of two evaluators while creating the ending to a standardized short-story and completing a mental-arithmetic task. When the participant's performance is not acceptable (e.g. finishing the short story too early or stating an incorrect number), the evaluators prompt the participant to complete the task as requested.

*TSST/TSST-C and Autism Spectrum Disorders.* The first experiment by Jansen and colleagues (2000) examined the stress response in children with MCDD and typical development following a modified version of the TSST-C. The typically developing children showed a significant increase in cortisol following performance of the stressor while the children with MCDD failed to demonstrate an acute stress response. The second experiment by Jansen and colleagues (2003) used the same modified version of the TSST-C to evaluate the stress response in a group of children with autism, who demonstrated a stress response that did not differ significantly from the typically developing children, although their peak cortisol value was lower relative to the comparison group. The protocol in each study required the participant to prepare and deliver a speech on a topic of his/her choosing in front of “a ‘jury’ of at least three ‘teachers’” (Jansen, et al., 2003, pg. 584) who were purportedly sitting behind a one way mirror, outside of view, to judge the participant's performance. Notably, the authors observed a significant positive correlation between communication impairment based on the Autism Diagnostic Interview (ADI; Le Couteur, et al., 1989) and peak cortisol value (40 minutes after beginning the speech task) for the children with autism.

To expand their previous findings with children, Jansen and colleagues (2006) performed a similar study utilizing a modified version of the TSST to examine the autonomic and endocrine stress response in adults with autism and typical development. Both groups demonstrated an increased cortisol level following task performance, and the two groups did not differ significantly from each other, although the adults with autism demonstrated a more modest increase in cortisol than the typically developing adults.

*Limitations of Previous Studies Evaluating Children with ASDs.* Multiple methodological limitations make the previous studies evaluating the stress response of children with ASDs following performance of the TSST-C difficult to interpret. Specifically, the protocol used in each study significantly deviated from the well-documented, highly reliable and validated, TSST-C. It is unknown how the modifications in the previous studies may have influenced the validity of the TSST-C; However, it is likely that the stressfulness of this standardized test was altered as participants were given the opportunity to speak on a topic of their choosing rather than an assigned topic, the serial subtraction portion of the task was omitted, and the members of the evaluating committee were not sitting in the same room as the participant. While this doesn't mean that the protocol used by Jansen and colleagues (2000, 2003) was not stressful, it does limit the ability to compare their findings to other studies that have used the TSST-C to evaluate the LHPA axis. In addition to modifying the protocol, the authors used the cortisol response to measure stress while failing to exclude participants who presently used antipsychotic medication, which is known to influence basal cortisol levels in children by flattening the morning-to-evening slope (Hibel, Granger, Cicchetti, & Rogosch, 2007). Six of the ten children in the MCDD group were taking this type of medication (Jansen, et al., 2000). It was not stated whether the children with autism were taking any medication (Jansen, et al., 2003). Furthermore, neither

study measured basal cortisol levels prior to the experiment session to determine if the baseline cortisol level used upon arrival to the experiment was a valid baseline relative to each participant's regular afternoon cortisol level. Instead, the authors employed a control condition that arguably placed similar demands on the participants, requiring them to be removed from their regular routine and interact socially with an experimenter, playing games or talking. In addition, the typically developing comparison group consisted of six boys and six girls, while the MCDD group was comprised of ten boys and the children with autism included eight boys and two girls. Cortisol is a hormone with demonstrated differences in activity between the sexes (Kudielka, Hellhammer, & Wust, 2009), therefore, comparison groups comprised of both male and female participants likely introduced unnecessary variability. In terms of the diagnostic groups, MCDD is a research category described by Cohen and colleagues (1986) that includes features of ASDs, but it is not a clinical disorder included in the DSM-IV-TR. Therefore, it is difficult to generalize findings pertaining to this group, although, the authors did acknowledge that each member of the MCDD group also met clinical criteria for PDD-NOS. For the study evaluating the stress response in children with autism (Jansen, et al., 2003), the data used for the typically developing comparison group was the same data collected in conjunction with the MCDD group (Jansen, et al., 2000). The absence of simultaneous data collection for the children with autism and typically developing children comparison groups increases the likelihood that extraneous variables influenced the results of the study (e.g., different research assistants administering the protocol, data collected during different seasons of the year).

Despite these imperfections, the work by Jansen and colleagues does provide preliminary groundwork and direction for future researchers to investigate factors that contribute to acute stress in children with ASDs. Of particular relevance to the present discussion is the finding that

communication impairment was associated with peak cortisol in children with autism. This finding lends credence to the argument that, although the TSST-C is primarily considered a social stress task because it requires the performance of a speech in front of an evaluative committee, additional factors may contribute to the stress response following this task. In other words, a combination of both cognitive and social demands may contribute to the stressful nature of this task, particularly for children with autism.

*TSST/TSST-C and Cognition.* Though performance of the TSST is cognitively demanding, the present authors know of only one study to date that directly examined the contribution of cognition on the stress response following completion of this task (Fiocco, Jooper, & Lupien, 2007). In this empirical study, Fiocco and colleagues examined the relationship between performance on several tests of executive functioning (i.e. verbal fluency and digit span) and education level and cortisol reactivity following performance of the TSST in typically developing, middle-aged adults. As expected, adults with higher levels of education (i.e. postsecondary education above junior college) performed better on tests of verbal fluency than adults with lower levels of education. In contrast, the two groups performed similarly on a test of verbal working memory (digit span). Following performance of the TSST, adults who had completed lower levels of education displayed higher increases in cortisol, relative to baseline, compared to their more highly educated peers. In contrast to the significant difference between groups in their cortisol response to the task, no group differences on subjective ratings of stress were found. The authors concluded that, because the TSST is an oral task, lower verbal fluency and a lower level of education may heighten the stressful nature of this task.

It is presently unknown if lower verbal ability heightens the stress response to this task similarly in children, as this has never been tested. If this were the case, it might be expected that

children with autism would find this task particularly stressful given that they often demonstrate impaired verbal ability relative to typically developing children on tests of verbal fluency (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004; Spek, Schatorje, Scholte, & van Berckelaer-Onnes, 2009; Turner, 1999; Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2005), although there is also evidence that verbal fluency is not universally impaired (Corbett, et al., 2009b; Manjiviona & Prior, 1999). While the hypothesis that impaired verbal ability may heighten the stress response for children with autism is consistent with the previous finding of an exaggerated stress response for this group relative to children with MCDD (a higher functioning group), this line of reasoning does not readily explain the lower stress response of children with autism relative to typically developing children (Jansen, et al., 2000, 2003). Still, it is possible that the children with autism demonstrated a similar stress response to children with typical development, albeit for different reasons. It could be argued that a complex interplay of features related to the disorder (communication, social, and repetitive patterns of behavior) likely influenced the differences in the stress response of each group. For example, perhaps the two diagnostic groups enrolled in the work by Jansen and colleagues (2000, 2003) were both sufficiently impaired, socially, to prevent social stress in response to the TSST-C, but only the children with autism were sufficiently impaired, verbally, to exhibit a stress response following this task. It remains just as plausible that, rather than impaired verbal ability, children with autism were more sensitive than children with MCDD to the changes in routine required to attend and participate in the experiment rather than their regular afternoon activities. These possibilities highlight the importance of evaluating multiple factors in addition to social impairment that may contribute to the stress response in children with autism and typical development following performance of the TSST-C. One natural place to begin would be to



extend previous work implicating the role of cognition in the stress response following this task (Fiocco, et al., 2007; Jansen, et al., 2003) by evaluating executive functioning abilities thought to be related to both communication ability and completion of the TSST-C.

### *Executive Functioning and Autism*

In addition to the core symptoms of autism, impaired executive functioning has been theorized to be a central feature of autism spectrum disorders (Ozonoff, Pennington, & Rogers, 1991; Pennington & Ozonoff, 1996). Executive functioning includes a range of cognitive skills (e.g., working memory, planning, set shifting, initiation, cognitive flexibility, inhibition, fluency) that are critical for problem-solving and maintenance of goal-directed behavior when an individual is faced with a novel situation (Ozonoff & Strayer, 1997; Pennington & Ozonoff, 1996; Welsh & Pennington, 1988). Deficits in executive functioning have been frequently observed across multiple domains including set shifting and planning (Ozonoff & Jensen, 1999), switching and initiation (Kleinmans, Akshoomoff, & Delis, 2005), working memory (Barnard, Muldoon, Hasan, O'Brien, & Stewart, 2008), and fluency (Geurts, et al., 2004; Spek, et al., 2009; Turner, 1999; Verte, et al., 2005), although there is presently a lack of consensus regarding the pattern of executive dysfunction in autism (Hill & Frith, 2003).

Inasmuch as the nature of executive functioning is to guide purposeful behavior in novel situations, there is fundamental reason to evaluate the association between executive skills and social impairment, stress, and anxiety in children with autism as they are required to function in a social world that is in constant fluctuation. Difficulty with executive functioning (i.e. tendency to perseverate, inability to generate novel responses, lack of behavioral inhibition) has been proposed as one mechanism resulting in the restricted, repetitive behavior that is characteristic of autism (Turner, 1997), and evidence associating deficient executive functioning (e.g. cognitive

flexibility) with this symptom domain has been documented (Lopez, Lincoln, Ozonoff, & Lai, 2005; South, Ozonoff, & McMahon, 2007), though not consistently (see Geurts, Corbett, & Solomon, 2009 for review). It has also been hypothesized by several researchers that symptoms of behavioral rigidity, repetition, and “insistence on sameness” may predispose children with autism to anxiety as they are required to interact with people who are unfamiliar or navigate an environment that is unpredictable (Church, Alisanski, & Amanullah, 2000; Gillott, et al., 2001; Lopata, et al., 2008). Evidence provided by Corbett and colleagues (2009c) of a relationship between changes in daily routine and elevated evening cortisol (an indication of accumulated stress) in children with autism lends support to this hypothesis.

Executive functioning is a heterogeneous construct representing numerous cognitive abilities, and a detailed account of how each of these abilities may be impacted in autism is beyond the scope of this paper. Therefore, two abilities that are relevant to communication ability and performance of the TSST-C, verbal fluency and verbal working memory, will be discussed as these skills could potentially contribute to stress and perceived anxiety.

#### *Verbal Fluency – General*

Verbal fluency tasks are considered one of the most sensitive assessments of frontal lobe integrity and executive functioning (Benton, 1968; Parker & Crawford, 1992). Performance relies on executive processes such as organization of word-retrieval, self-monitoring of previous responses, inhibition of responses that do not fit the stated criteria, initiation of novel search strategies, switching, mental flexibility, attentional control, conflict monitoring, and working memory (Crawford & Henry, 2005; Rosser & Hodges, 1994). In addition to the executive system, both speed of information processing and the integrity of semantic memory can impact

performance, as the task must be completed within a given time constraint and the participant must have access to specific words, respectively.

Verbal fluency tasks can assess both phonemic and semantic fluency. To complete these tasks, the examinee is instructed to generate as many words as possible in a specified category within one minute (e.g. generating words that begin with the letter, F; generating words that are animals). Tests of phonemic fluency require utilization of search strategies based on lexical representation while semantic fluency tests require the search of categorical associations within the lexicon (Delis, Kaplan, & Kramer, 2001). Additional cognitive abilities also play a role in performance and can be evaluated utilizing fluency tasks. For example, similarly deficient performance on both tasks of phonemic and semantic fluency indicate problems with the executive system or processing speed, while deficient performance on phonemic fluency or semantic fluency tasks indicate deficient access or integrity of phonetic memory or semantic memory, respectively (Henry & Crawford, 2004; Rosser & Hodges, 1994). Other factors that have documented effects on performance include working memory capacity (Daneman, 1991), depression (Fossati, Guillaume le, Ergis, & Allilaire, 2003), and anxiety (Delis, et al., 2001).

*Verbal Fluency – Autism.* Tests of verbal fluency have often been employed to assess executive functioning ability in children with autism (Boucher, 1988; Geurts, et al., 2004; Turner, 1999; Williams, Moss, Bradshaw, & Rinehart, 2002). A review of current literature on verbal fluency ability amongst individuals with autism revealed mixed findings. Generally, phonemic fluency ability is found to be impaired (Corbett, et al., 2009b; Geurts, et al., 2004; Kleinhans, et al., 2005; Kleinhans, Muller, Cohen, & Courchesne, 2008; Rumsey & Hamburger, 1988, 1990; Spek, et al., 2009; Turner, 1999; Verte, et al., 2005; but see Barnard, et al., 2008; Manjiviona & Prior, 1999; Minshew, Goldstein, & Siegel, 1997; Scott & Baron-Cohen, 1996)

while semantic fluency remains intact (Boucher, 1988; Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009b; Dunn, Gomes, & Sebastian, 1996; Manjiviona & Prior, 1999; Kleinhans, et al., 2005; Kleinhans, et al., 2008; but see Geurts, et al., 2004; Spek, et al., 2009; Turner, 1999; Verte, et al., 2005). Variables thought to lead to discrepant findings between published studies include heterogeneity of the experimental group (e.g. inclusion of PDD-NOS, Asperger's Disorder), participant age, comparison group (e.g. neurotypical control versus developmental disorder), and overall level of functioning (Corbett, et al., 2009b; Geurts, et al., 2009). In addition, Lopez and colleagues (2005) made the important point that researchers must not neglect effect size, urging that studies be designed with sufficient power to detect an effect size greater than 0.50 which may help to resolve inconsistent findings in the fluency literature. Regardless of the discrepancies, a general pattern emerges where children with autism spectrum disorders display greater difficulty retrieving information organized phonetically than semantically (Kleinhans, et al., 2008), providing evidence that abnormalities in phonemic memory stores likely contribute significantly to their impaired performance on verbal fluency tasks.

#### *Verbal Working Memory – General*

Working memory is defined as a limited-capacity system that is used for storing and manipulating information, guiding cognitive processing (Baddeley & Hitch, 1974; Baddeley, 1986, 2000, 2003), and selecting appropriate responses in novel situations (Pennington, 1994). Baddeley and Hitch proposed a widely-used model of working memory that consists of three components: the central executive, the articulatory/phonological loop, and the visuospatial sketchpad. Following this proposal, Baddeley added a fourth component, the episodic buffer (Baddeley, 2000). The central executive component directs attention and manipulates information, coordinating the two slave systems (articulatory/phonological loop and visuospatial

sketchpad) as needed, depending on the form of information (auditory/verbal versus visuospatial information). The episodic buffer is important for complex processing and temporary storage when multiple modes of information (e.g. visual and auditory) must be processed in concert or linked with information stored in long-term memory (e.g., phonemic memory, semantic memory, episodic memory).

Neuropsychological tests of verbal working memory (requiring proper functioning of the phonological loop, episodic buffer, and central executive components) include nonword repetition (e.g. Nonword Repetition Test; Dollaghan & Campbell, 1998), digit span (e.g. Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), Digit Span; Wechsler, 2003), word recall (e.g. California Verbal Learning Test, Immediate Recall; Delis, Kramer, Kaplan, & Ober, 1987), sentence span (e.g. Stanford Binet Intelligence Scales, Fifth Edition, Memory for Sentences; Roid, 2003), and immediate recall of a short story (e.g., NEPSY, Narrative Memory; Korkman, Kirk, & Kemp, 1998) (Baddeley, 2003). Beyond clinical testing and language, proper functioning of the phonological loop is also likely to influence behavioral control (e.g. subvocalization while learning social dance or driving an unfamiliar route) (Baddeley, 2003). Extraneous factors that may influence performance of verbal working memory tasks (e.g. digit span) include anxiety, attention, and semantic memory (Baddeley, 2003; Nakahachi, et al., 2006).

*Verbal Working Memory in Autism.* Baddeley and Hitch's (Baddeley & Hitch, 1974; Baddeley, 1986, 2000, 2003) model of working memory has been utilized by researchers examining verbal and visual-spatial working memory in autism (e.g. Williams, Happé, & Jarrold, 2008). Pennington and colleagues (1997) argued that working memory is a core deficit in autism spectrum disorders; However, other researchers have documented evidence that working

memory is not sufficiently impaired to be considered a core deficit (Ozonoff & Strayer, 2001; Russell, Jarrod, & Henry, 1996; Williams, Goldstein, Carpenter, & Minshew, 2005; Williams, Goldstein, & Minshew, 2006a; Williams, et al., 2008).

Verbal working memory and spatial working memory must be distinguished when interpreting impairment in working memory. For example, a review by Pennington and Ozonoff (1996) determined that verbal working memory is impaired in children with autism relative to typically developing children as well as those with other developmental disorders. Conversely, researchers evaluating working memory using spatial working memory tasks have found no differences in working memory for children with autism relative to children with typical development (Edgin & Pennington, 2005; Joseph, Steele, Meyer, & Tager-Flusberg, 2005b; Ozonoff & Strayer, 2001), ADHD (Geurts, et al., 2004; Goldberg, et al., 2005; Happé, Booth, Charlton, & Hughes, 2006, but see Corbett, et al., 2009b) or Tourette Syndrome (Verte, et al., 2005; Verte, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006).

Research studies evaluating working memory utilizing verbal tasks have reported both deficient (Bennetto, Pennington, & Rogers, 1996; Joseph, McGrath, & Tager-Flusberg, 2005a; Joseph, et al., 2005b; Lopez, et al., 2005; Pennington & Ozonoff, 1996) as well as intact (Koshino, et al, 2005, 2008; Nakahachi, et al., 2006; Williams, et al., 2005, 2006a, 2008) working memory in children with autism, relative to typically developing children. Similar variables that account for the discrepancies in studies evaluating verbal fluency performance also contribute to discrepant findings related to verbal working memory in children with autism (e.g., diagnosis, overall level of functioning). Further complicating matters, verbal working memory can be measured by a variety of tasks that vary in extraneous task-demands (e.g., digit span versus letter-number sequencing) and complexity (word-recall versus sentence recall).

Of particular interest to the TSST-C is passage-recall, or ability to store relevant details of a short-story in working memory for the purpose of retelling it. The few studies evaluating verbal working memory using measures of story-recall have found it deficient in individuals with autism spectrum disorders (Fein, et al., 1996; Gabig, 2008; Rumsey & Hamburger, 1990; Williams, et al., 2006b). For example, Rumsey and Hamburger (1990) compared adults with autism, dyslexia, and typical development and determined that adults with autism were significantly impaired on immediate recall of a short story (Wechsler Memory Scale-Revised, Logical Memory; Wechsler, 1987) relative to a healthy control group, though they performed similarly to the group with dyslexia. No differences between these groups were found on additional measures of verbal working memory (digit span and word fluency tasks).

Research examining similar (though less complex) tasks such as word-recall and sentence-recall has extended our understanding of this specific verbal working memory deficit (i.e. passage-recall) in autism spectrum disorders. Though children with autism remain able to perform word-list learning tasks similarly to typically developing peers, they demonstrate impairment as material increases in complexity (e.g. repetition of digits versus repetition of a sentence versus repetition of a short story). This effect has been shown in preschoolers (Fein, et al., 1996), school-aged children (Williams, et al., 2006b), and adults (Rumsey & Hamburger, 1990) with autism spectrum disorders. Furthermore, a recent study by Gabig (2008) evaluated language ability and verbal working memory in children with autism, determining that the task demands of simple verbal working memory tasks (e.g. sentence repetition) also contribute to impairment on more complex tasks (e.g. story retelling).

One factor underlying deficient performance on verbal working memory tasks may be inability to initiate an organizational strategy to manipulate semantic information for memory

storage (e.g. grouping items together according to categories, such as vegetables or articles of clothing). Several researchers have documented evidence that children with autism perform similarly to typically developing children on tasks of word list-learning, however, they do not engage in spontaneous use of semantic organizational strategies to aid memory recall (Frith, 1970a, 1970b; Fyffe & Prior, 1978; Hermelin & O'Connor, 1970). Further investigation has determined that while children with autism do not utilize these strategies spontaneously, they do benefit when organizational strategies are presented externally (Tager-Flusberg, 1991). The previous findings suggest that as the working memory demands increase, requiring the use of organizational strategies, children with autism fail to perform at the level of their typically developing peers.

Beyond clinical testing, Bennetto and colleagues (1996) provided evidence of a preliminary link between verbal working memory and the symptoms of autism. They compared children and adolescents with autism to those with a non-autistic learning disorder and determined that children with autism performed more poorly on a task of verbal working memory (e.g., Sentence Span; Siegel & Ryan, 1989), relative to the comparison group. In addition, they found a correlation between the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1986) and the Sentence Span task. Bennetto and colleagues (1996) commented that “A general deficit in [working memory] would make later understanding of the social world difficult, since social interaction is transient, context-specific, and requires the integration of information from diverse sources” (p. 1831). As suggested by the previous authors, the working memory demands associated with deciphering appropriate responses in the social world greatly exceed the demands posed by performance of the described clinical tasks and likely contribute to symptoms of social impairment.



*Executive Functioning and Autism – Inconsistencies in the Literature.* As evidenced by this brief review, a complicated picture emerges when evaluating executive functioning in children with autism spectrum disorders. Inconsistencies in the literature have been addressed by several authors (e.g., Geurts, et al., 2009; Kenworthy, et al., 2008; Lopez, et al., 2005; Minshew, et al., 1997). For example, Geurts and colleagues (2009) highlighted the influence of measurement techniques (e.g. employing tasks that require use of multiple abilities simultaneously, precluding researchers from distinguishing what factor underlies deficient performance) as well as the heterogeneity in symptoms in individuals diagnosed with autism. Lopez and colleagues (2005) discussed a model of relative strengths (working memory, response inhibition) and weaknesses (cognitive flexibility, planning) in autism. Alternatively, Kenworthy and colleagues (2008) concluded that children with autism may demonstrate impairment when task-completion requires coordination of multiple executive skills simultaneously (e.g., Tower Test requires multiple skills, including cognitive flexibility and planning). They also noted that the modality of executive function tasks (e.g. verbal versus visuospatial) must be considered, particularly when evaluating executive functioning in a population with impaired language ability. For example, an experiment by Joseph and colleagues (2005b) found spatial working memory to be spared while verbal working memory was impaired. White, Burgess, and Hill (2009a) documented evidence that executive tasks that are more “open-ended” in nature may be particularly difficult for children with autism who may be less able to generate spontaneous responses or decipher implicit socio-communicative demands made by an experimenter. Another explanation for inconsistent findings has been offered by Minshew and colleagues, who characterize autism, and its associated neuropsychological profile, as a disorder of complex information processing (Minshew, et al., 1997; Minshew & Goldstein, 2001; Williams, et al.,

2006b). This model of the disorder accounts for evidence that simple working memory tasks appear to be spared (e.g. digit span) while more complex tasks (e.g. passage-recall) are impaired in autism (Fein, et al., 1996; Gabig, 2008; Williams, et al., 2006b). Despite the previous reviews, the field presently lacks a single, cohesive theoretical model to accommodate the existing evidence. As such, there is room for future investigators who adhere to the recommendations provided by previous researchers (e.g., Geurts, et al., 2009) to advance our understanding of executive functioning in children with autism spectrum disorders.

### *Summary*

Children with autism, due to the nature of this condition, experience symptoms of social and communication impairment. In addition to these characteristic symptoms, the disorder is associated with variability in the regulation of the LHPA axis as well as symptoms of behavioral stress and social anxiety. Factors that may perpetuate dysregulation of the LHPA axis in children with autism remain incompletely understood as well as unknown. Previous research examining the response of the LHPA axis to stress in children with autism has often utilized physiological and nonsocial stressors, and, while these studies contribute to our knowledge of the physiological processes implicated in this disorder, they do not increase our understanding of the stress response following interactions that require communication and social skills. In particular, there is a paucity of research to date evaluating the influence of important factors related to the disorder (e.g., executive functioning) and stress and anxiety following social interaction. The handful of studies that have evaluated the physiological stress response following social stressors have significant methodological limitations, therefore, replication is needed prior to drawing firm interpretations.

The TSST-C offers a standardized method of evaluating social stress while requiring the completion of tasks that employ executive functioning skills. The purpose of the current investigation is to examine the stress response of children with autism following the completion of this protocol, while also evaluating the contribution of two executive functioning abilities that are relevant to communication and performance of the TSST-C, verbal fluency and verbal working memory. The intent of the present study is to replicate and extend the previous findings reported by Jansen and colleagues (2000, 2003) utilizing more stringent diagnostic categorization and exclusionary criteria as well as adhering more closely to the original stress protocol designed by Buske-Kirschbaum and colleagues (1997).

#### *Current Study*

The current study is designed to investigate communication and social functioning in children with autism by evaluating neuroendocrine (cortisol) and psychological (anxiety) responses following completion of a verbal, social-evaluative stress test (TSST-C). Communication skills required for performance of this task, verbal fluency (Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency Test; Delis, et al., 2001) and verbal short term memory (NEPSY Narrative Memory) will be considered as predictor variables, as they may influence stress and anxiety in response to the stressor. Finally, the association between acute physiological stress and acute psychological anxiety (State-Trait Anxiety Inventory for Children (STAIC); Spielberger, 1973) will be determined. The resulting findings will contribute to the existing literatures pertaining to the physiological, psychological, and cognitive functioning in children with autism spectrum disorders as well typical development.

*Aims and hypotheses.* The first aim (Aim 1A) is to evaluate the *physiological stress response* (cortisol response) following the TSST-C and (Aim 1B) to determine its relation to

verbal fluency and verbal short-term memory abilities (DKEFS Verbal Fluency Task; NEPSY Narrative Memory) in children with autism and typically developing children. The second aim (Aim 2A) is to examine the cognitively perceived, *self-reported anxiety response* (STAIC: State anxiety) following the TSST-C and (Aim 2B) to determine its relation to verbal fluency and verbal short term memory abilities (DKEFS Verbal Fluency Task; NEPSY Narrative Memory) in children with autism and typically developing children. The third aim (Aim 3) is to determine the *correlation* between the *physiological stress response* (cortisol response) and the *self-reported anxiety response* (STAIC: State anxiety) in children with autism and typically developing children.

*Hypotheses for Aim 1A.* The purpose of this aim is to evaluate the change in cortisol following the TSST-C relative to baseline cortisol between the two groups (i.e. the cortisol response). It is hypothesized that both groups will demonstrate significantly elevated cortisol following the TSST-C relative to baseline. Based on previous research, it is expected that children with autism will demonstrate a more moderate increase in cortisol following the TSST-C than typically developing children, who will demonstrate a more dramatic increase, but the two groups will not differ (Jansen, et al., 2000, 2003).

*Hypotheses for Aim 1B.* The purpose of this aim is to determine whether performance on the verbal ability measures predicts the cortisol response following the TSST-C for each group. It is hypothesized that children with autism will demonstrate significantly lower verbal ability (Narrative Memory SS, Phonemic Fluency SS, Category Fluency SS, Category Switching Fluency SS, and Category Switching Total Switching Accuracy SS) relative to typically developing children. Furthermore, verbal ability is hypothesized to predict the cortisol response for both children with autism and typically developing children.

*Hypotheses for Aim 2A.* The purpose of this aim is to evaluate self-reported state anxiety following the TSST-C between the two groups and to compare state anxiety to trait anxiety within each group. It is hypothesized that both groups of children will demonstrate comparable levels of acute anxiety following the TSST-C (STAIC: State form). Despite reporting a similar level of acute anxiety (STAIC: State form), it is expected that children with autism will demonstrate significantly higher self-reported anxiety on a measure of general, persistent anxiety (STAIC: Trait form) than typically developing children. In other words, it is hypothesized that while typically developing children will report significantly increased state anxiety relative to trait anxiety, children with autism will demonstrate a more moderate increase in state anxiety that is statistically comparable to their usual, trait level of anxiety.

*Hypotheses for Aim 2B.* The purpose of this aim (Aim 2B) is to determine whether performance on the verbal ability measures predict state anxiety following the TSST-C. It is hypothesized that children with autism will demonstrate a significantly lower level of verbal ability relative to typically developing children (as stated in Aim 1B). Furthermore, verbal ability is expected to predict self-reported state anxiety in both children with autism and typically developing children.

*Hypotheses for Aim 3.* As stated, it is hypothesized that both children with autism and neurotypical children will demonstrate a significant physiological response to stress (increased cortisol relative to baseline) and comparable levels of state anxiety following the TSST-C. Within-group analyses for anxiety are expected to reveal a significant increase in state anxiety (relative to trait anxiety) for typically developing children while children with autism will report statistically similar levels of state and trait anxiety. It is further hypothesized that there will be a significant, positive correlation between cortisol response and state anxiety in typically

developing children. In contrast, it is hypothesized that the correlation between the cortisol response and state anxiety will be positive, but not significant, in children with autism. It is acknowledged that a weak correlation for this group could simply reflect significant variability in the magnitude of responses (both physiological stress and self-reported anxiety) for the children with autism due to the known heterogeneity of deficits characterizing this disorder.

## CHAPTER TWO

### METHODS

#### *Participants*

Two groups, each comprised of fifteen male participants, completed the study protocol. For participants in the group with autism, diagnosis was determined by interview with the parent, classification score of autism on the ADOS, and meeting the diagnostic criteria for Autistic Disorder according to the DSM-IV-TR (APA, 2000). Exclusionary criteria for this group included a full scale intelligence score (FSIQ) lower than 70 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) or a more comprehensive measure of intelligence if recently completed (N=3) (Roid, 2003; Wechsler, 2003), presence of comorbid neurological (e.g., seizures) or genetic disorder (e.g., Fragile X Syndrome), pubertal development as determined by a score of 6 or higher (midpubertal level) on the Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988), and the use of medication known to influence the secretion of cortisol (e.g. antipsychotic medication). In addition to the aforementioned criteria, exclusionary criteria for participants in the typical development group included diagnosis of a learning disability, neurodevelopmental disorder (e.g., Autism, ADHD), or psychiatric disorder (previous or current).

Group differences for age, intelligence, and pubertal development were assessed using independent two sample t-tests (see Table 1). The groups were similar with regard to age [ $t(28) = -0.396$ ,  $p > 0.05$ ] and onset of puberty [ $t(26) = -0.697$ ,  $p > 0.05$ ]. Group differences were found for intelligence: FSIQ [ $t(28) = 8.63$ ,  $p < 0.001$ ]. Therefore, the present study used FSIQ as a covariate in statistical analyses.

#### *Measures*

*Autism Diagnostic Observation Schedule* (ADOS; Lord, Rutter, DiLavore, & Risi, 1999).

The ADOS is a diagnostic classification tool that is designed to solicit communication and social interaction through a flexible, interactive, semi-structured interview. It is intended to provide the clinician with multiple opportunities for direct observation of behavior that may suggest the diagnosis of an autism spectrum disorder. The ADOS consists of four modules, one of which is pre-selected by the examiner based on the examinee's age and language ability. Module 3 was selected for use with the present sample, as it is appropriate for children and adolescents (preschool to age 16) who are verbally fluent (estimated expressive language of a typical 4 year old). Module 3 consists of 14 activities (e.g., Description of a Picture, Conversation and Reporting, Emotions) that yield a total of 28 ratings, 11 of which are used to calculate the algorithm for diagnostic classification. The overall goal in observation for this module is to catalogue the examinee's ability to engage in spontaneous, social-communicative behavior (e.g., reciprocal conversation, appropriate use of facial expressions to communicate affect, insight into the nature of social relationships) while documenting a sample of language (e.g., delayed echolalia, highly repetitive utterances) and taking note of stereotypical/repetitive behaviors (e.g. unusual sensory interests, compulsions/rituals). Immediately following administration, behaviors are coded to calculate the algorithm for diagnostic classification as autism, autism spectrum disorder, or nonspectrum. The resulting ADOS classification can be used in conjunction with additional measures and clinical judgment to determine an examinee's overall diagnosis (e.g., Autism, Asperger's Disorder, PDD-NOS). The current study utilized the participant's composite score on the Communication-Social Interaction Total and classification of autism as one criterion to determine inclusion in the study. Internal consistency for the Communication-Social



Interaction Total is very high (Cronbach's alpha=.91-.94) for all four modules. Interrater agreement for ADOS classification is 81% (Lord, et al., 1999).

*Pubertal Development Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988).* The PDS is a six-item self-report measure of pubertal development; However, for the present study, the PDS was completed via parent-report. Stage of pubertal development is classified, for boys, according to the following three items: deepening of voice, growth of pubic hair, and growth of facial hair. Each item is ranked on a four point scale denoting level of developmental change (i.e., 1=no change; 2=barely started to change; 3=change is definitely underway; 4=change is complete). The combined score for the three items is calculated to determine the individual's placement in one of five pubertal stages: prepubertal (score=3), beginning pubertal (score=4-5), midpubertal (score=6-8), advanced pubertal (score=9-11), postpubertal (score=12). Internal consistency for the PDS is adequate (Alpha coefficients range from .68-.78 for boys).

*State-Trait Anxiety Inventory for Children (STAIC; Spielberger, 1973).* The STAIC is a self-report questionnaire designed to measure anxiety in children, ages 9-12. Following publication of the administration manual (Spielberger, 1973), research evaluating the psychometric properties of the STAIC has extended the age range for individual administration to kindergarten through sixth grade children (Papay & Spielberger, 1986). It has two forms, one to provide a measure of anxiety as a transient, acute state (State form) and one to measure anxiety as a stable, individual difference trait in tendency to respond to situations with acute anxiety (Trait form). The State form contains twenty "I feel..." questions that must be answered on a three-point, Likert-type scale based on intensity (e.g., very relaxed, relaxed, not relaxed). The Trait form contains twenty statements (e.g., "I worry too much") that must be answered on a three-point, Likert-type scale based on frequency (i.e., hardly ever; sometimes; often). Internal

consistency is satisfactory for both State ( $r=.74-.76$ ) and Trait ( $r=.82-.84$ ) forms (Papay & Spielberger, 1986).

*Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999). The WASI is a short and reliable instrument that can be used to obtain an estimate of general intellectual ability for individuals ages 6-89 in situations where a more comprehensive assessment would be excessive or impractical (e.g., matching groups based on cognitive ability in a research study, retesting individuals who are referred for psychiatric evaluation following a previous assessment). The WASI consists of four subtests (Vocabulary, Block Design, Similarities, Matrix Reasoning), and norms are provided that determine an estimate of Full Scale IQ based on the four subtests as well as based on completion of two subtests (Vocabulary and Matrix Reasoning). The two subtest version of the WASI was used in the current study. The Vocabulary subtest measures an individual's expressive vocabulary and verbal knowledge, requiring the examinee to verbally identify pictures and describe the meaning of words (42 items possible). The Matrix Reasoning subtest is an assessment of nonverbal reasoning consisting of incomplete patterns that the examinee must complete by selecting one of five pieces presented simultaneously within each item (35 items possible). Reliability coefficients for the two-subtest version of the WASI are high (Full Scale IQ:  $r=.92-.95$ ; Vocabulary:  $r=.86-.93$ ; Matrix Reasoning:  $r=.89-.94$ ), signifying a low degree of measurement error (actual score versus true score) for typically developing children, ages 8-12. Test-retest reliability is adequate for typically developing children, ages 6-16 ( $r=.83-.87$ ). A sample of 176 children and adolescents (age:  $M=11.45$ ,  $SD=3.04$ ) demonstrated that the Full Scale IQ obtained from the two-subtest version of the WASI is moderately correlated ( $r=.81$ ) with the Full Scale IQ obtained from the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991).

*NEPSY: Narrative Memory (NEPSY; Korkman, Kirk, & Kemp, 1998)*. The NEPSY is a battery of tests designed to examine neuropsychological development in children, ages 3-12, across five functional domains (Attention/Executive Functions, Language, Sensorimotor, Visuospatial Processing, Memory and Learning). The subtests included in each domain are designed to assess a range of functional ability from simple to more complex processing. The Narrative Memory subtest is a complex processing task included within the Memory and Learning domain. It is a short story recall task that can be used to assess auditory short term memory. Following the presentation of a short story, the examinee is required to recite the story, receiving full credit for free recall and partial credit for cued recall of the story's components. Total score is derived from the combination of the free and cued recall conditions. Performance on this task requires attention, organizing and sequencing, semantic and syntactic language skills, comprehension of underlying themes in addition to specific details, and short term memory (encoding, storage, and retrieval). Information provided during free recall reflects intact encoding, storage and retrieval processes while information recalled during the cued condition reflects intact encoding and storage but difficulty with retrieval of semantic information. Factors leading to poor performance under both free and cued recall conditions include difficulty with auditory processing, impaired short term memory (encoding, storage, and retrieval), inattention, anxiety, or lack of motivation. Internal consistency for the Narrative Memory subtest is adequate for children ages 8-12 ( $r=.68-.86$ ), and test-retest reliability is also adequate for children ages 5-12 ( $r=.60$ ).

*Delis-Kaplan Executive Function System: Verbal Fluency Test (Delis, Kaplan, & Kramer, 2001)*. The Delis-Kaplan Executive Function System (D-KEFS) is a battery of nine tests, each derived from existing measures, that is designed to assess various components of

executive functioning. The Verbal Fluency Test is a measure of word-productivity (Strauss, Sherman, & Spreen, 2006), containing three conditions (i.e. letter fluency, category fluency, and category switching) during which the individual is required to name as many words as possible in sixty seconds. Letter fluency is the first condition, during which the participant is asked to name as many words as possible in 60-seconds that begin with a specific letter. There are three trials in this condition: F, A, and S. Category fluency is the second condition, which requires the participant to name as many objects as possible in a specific category. There are two trials in this condition: animals and boys' names. Category switching is the third condition and requires the participant to switch between two categories: fruit and furniture. For example, the participant first says a type of fruit, then a piece of furniture, then a type of fruit, and so on. Dependent variables include total correct letter fluency, total correct category fluency, total correct category switching, and total switching accuracy. Internal consistency is high for letter fluency ( $r=.80-.89$ ) and marginal for category and category switching fluency ( $r=.60-.69$ ). Test-retest coefficients are high for letter fluency ( $r=.80-.89$ ), adequate for category fluency ( $r=.70-.79$ ), and low for category switching ( $r=<.59$ ).

*TSST-C (Buske-Kirschbaum, et al., 1997)*. The TSST-C is a version of the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) that has been modified for use with children. This psychosocial stress protocol is known for reliably activating the LHPA axis (2-4 fold increase in salivary cortisol level and concentration) in a controlled, laboratory setting. The twenty-minute task is subdivided into four components (introduction and speech preparation, speech delivery, serial subtraction, debriefing). Participants undergoing the procedure are escorted to a sterile, examination room with two committee members sitting behind a large table, wearing white lab coats, and holding clipboards. The two committee

members remain affectively neutral throughout the procedure, regardless of the participant's performance. Next to the committee members is a videocamera (two were used in the present study for behavioral and facial coding), and there is a standing microphone in the center of the room that the participant is instructed to stand behind. As the participant stands behind the microphone in front of the committee members, one of the committee members provides the participant with instructions for his task. The committee member tells the participant that the introduction to a short story will be read, and five minutes time will be allotted for him to exit the room and prepare the ending for the short story. Upon his return, he is instructed to stand behind the microphone and deliver the ending to the story as a speech in front of the committee who will, purportedly, be judging his performance relative to the performance of other children. If the participant finishes his story before the end of five minutes, he is instructed to continue speaking as he still has time remaining. Following the speech delivery period, one committee member provides the participant with instructions for the next task: serial subtraction (i.e. subtracting 7's from 758). Should the participant make an error in calculation during this five minute period, he is instructed to start again with the initial number. When the serial subtraction period has ended, the two committee members warmly congratulate the participant for his performance and provide debriefing from the task (including acknowledgment that they were not truly judging his performance in comparison with other children).

### *Procedure*

Participants were recruited through the University of California, Davis, Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute Subject Tracking System database, IRB approved flyers distributed locally, and community outreach events (i.e. advertisement booths at two local conferences on autism as well as a local recreation center) in

the Sacramento region. Participation entailed three major components: neuropsychological testing, home sampling, and completion of the experiment. Approval for the current study was obtained from the Institutional Review Board at the University of California, Davis. Informed written consent was obtained from parents in addition to verbal assent from children (and written assent from children who were 12 years old) for each participant prior to enrollment.

*Neuropsychological Testing.* All testing occurred at the UC Davis M.I.N.D. Institute and the UC Davis Center for Mind and Brain, depending on which location was most convenient for the participant. Neuropsychological testing was completed by trained graduate students (primarily KL) and a postdoctoral research assistant under the supervision of a licensed clinical psychologist (BAC). Testing occurred in one session, and participants were allowed to take breaks as needed. Research reports describing how each participant performed on the standardized measures were provided to each child's parent/legal guardian.

*Home Sampling.* Each participant collected (1.00 ml) saliva samples at home which determined his natural rhythm of cortisol and provided a baseline from which to compare salivary cortisol on the afternoon of the experiment. Participants were instructed to collect saliva four times per day (i.e., immediately upon awakening, thirty minutes after awakening, in the afternoon between 1PM and 4PM, and in the evening within thirty minutes of going to bed) for three consecutive days (i.e., Monday, Tuesday, Wednesday) over two consecutive weeks. This sampling schedule provided a total of twenty-four samples over six days.

Participants and parental guardians received training on the saliva sampling procedure and were given a collection kit (which included an instructional DVD, twenty-four pre-printed labels, a permanent marker, twenty-four collection tubes, twenty-four straws, twenty-four pieces of Trident Original sugarless gum, a small ziplock bag to store saliva samples in the refrigerator,

and two diaries to document sleep and overall health on each collection day) at their first visit for neuropsychological testing. This procedure entailed chewing the Trident gum (the components of which have been previously assayed to determine it does not contain cortisol (Corbett, et al., 2006)) for approximately thirty seconds to stimulate saliva, placing the straw into the collection tube, emitting saliva into the tube through the straw, writing the time and date on a pre-printed label (printed with the participant's identification number and sample number), placing the label onto the collection tube, and storing the sampling tube in the refrigerator until submitting it to the researcher on the day of the experiment. Participants were instructed not to eat, drink, or brush their teeth for one hour prior to each sampling, as these activities could unduly influence the level of salivary cortisol.

An alternate method of saliva collection was utilized in the case where a participant was unable to emit saliva through a straw (N=3). For this procedure, grape-flavored KoolAid (previously assayed to determine it does not contain cortisol) was provided in lieu of Trident gum along with twenty-four cotton rolls and twenty-four plastic syringes. Following the placement of KoolAid on the participant's tongue, the participant savored a cotton roll inside his mouth. The saturated cotton roll was then inserted into the syringe which was used to extract the saliva directly into the collection tube. Labeling and storage for this saliva collection method followed the identical procedure of the method previously described.

*Experiment (TSST-C).* Upon arriving at the M.I.N.D. Institute, the participant and his parental guardian were escorted by the researcher to a quiet testing room in the research clinic, similar to the room in which the participant underwent initial neuropsychological testing. Immediately upon arrival, a saliva sample was collected from the participant. After a twenty-minute resting period, a second saliva sample was collected, and a separate research assistant

arrived to escort the participant to the examination room next door where he was given instructions for the experimental task (TSST-C). Following completion of this twenty-minute task, the participant was reunited with his parental guardian and the research assistant he was greeted by in the initial testing room for a one-hour resting period. During this hour, the participant completed several self-report questionnaires (including the STAIC) and provided additional saliva samples. In total, six salivary cortisol samples were taken during the experiment at twenty minutes intervals, beginning upon arrival. Following completion of the experiment session, participants were thanked and paid modestly for their time.

*Cortisol Storage and Assays.* As described in previous research (Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006; Corbett, Mendoza, Wegelin, Carmean, & Levine, 2008; Corbett, Mendoza, Baym, Bunge, & Levine, 2008; Corbett, Schupp, Levine, & Mendoza, 2009c), refrigerated saliva samples were transported from the M.I.N.D. Institute to the Endocrine Laboratory at the University of California, Davis, California National Primate Research Center. Samples were stored in a freezer (-20 degrees Celsius), then thawed, and centrifuged (3000 rpm for twenty minutes) to separate aqueous components from mucins and other suspended particles before being assayed. Salivary concentrations of cortisol were estimated in duplicate using commercial radioimmunoassay kits (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Assay procedures were modified to accommodate overall lower levels of cortisol found in human saliva relative to plasma. Specifically, standards were diluted to concentrations ranging from 2.76 to 345 nmol/L, sample volume was increased to 200  $\mu$ l, and incubation times were extended to 3 hours. Serial dilution of samples indicated that the modified assay displayed a linearity of 0.98 and a least detectable dose of 1.3854 nmol/L. Intra- and inter-assay coefficients of variation were 3.91 and 5.26, respectively.



### *Data Analyses*

Based on previous research (Jansen, et al., 2000), a power analysis was performed indicating that 15 participants in each of the two groups yielded 80% power to detect an effect size of 0.85.

*Demographics & Neuropsychological Measures.* Group (children with autism, typically developing controls) differences on age, level of pubertal development, and intelligence were calculated using independent two sample t-tests (see Table 1). Because intelligence (FSIQ) was found to differ significantly between the groups, this variable was covaried when determining group differences on the neuropsychological measures (Verbal Fluency: Phonemic Total, Category Total, Category Switching Total, Total Switching Accuracy; Narrative Memory: Total score) using univariate analyses of covariance (ANCOVAs). Scaled scores on the neuropsychological variables were used for these analyses.

*Aim 1A.* Since cortisol is known to be highly right skewed (Corbett, et al., 2006; Richdale & Prior, 1992; Tordjman, et al., 1997), thus violating assumptions of normality, each cortisol variable was transformed by computing a log transformation (base e) in SPSS prior to undergoing statistical analyses in order to attain approximate normality. ANCOVA was performed to determine if the baseline cortisol values (mean afternoon, experiment arrival, and 20 minutes post-arrival) were comparable at each measurement between the two diagnostic groups. Then, to determine physiological response (change in cortisol) following performance of the TSST-C, a maximum-minus-minimum change score was computed as the difference between each participant's maximum cortisol level (0 minutes post-TSST-C or 20 minutes post-TSST-C) and minimum cortisol level (experiment arrival or 20 minutes post-arrival). The maximum-

minus-minimum was used to determine each participant's cortisol response following performance of the TSST-C.

In order to evaluate the validity of the minimum cortisol value (or experimental baseline) used in the maximum-minus-minimum change score, mean afternoon cortisol (across the six home sampling days) was compared to both cortisol upon arrival and cortisol 20 minutes following arrival on the afternoon of the experiment using paired sample t-tests for the whole sample. Difference variables were computed (mean afternoon cortisol-minus-arrival cortisol; mean afternoon cortisol-minus-cortisol 20 minutes after arrival; arrival cortisol-minus-cortisol 20 minutes after arrival) to determine if the average difference was significantly different from zero for each participant. Since this involved multiple comparisons of related cortisol variables, a Bonferroni correction was applied to determine the significance ( $p=0.05/3$ ) of each paired sample t-test. The paired sample t-tests revealed that the three measurement times did not differ significantly.

Once the change score to identify cortisol response was computed, ANCOVA was performed with FSIQ as a covariate to determine if there was a difference between the two groups in their physiological response to the stressor. One-sample t-tests were used to determine if the cortisol response was significantly different from zero (i.e., no change) for each of the diagnostic groups.

*Aim 1B.* A step-wise regression model was used to determine if verbal ability (Narrative Memory SS, Phonemic Fluency SS, Category Fluency SS, Category Switching Fluency SS, Category Switching Total Switching Accuracy SS) predicted cortisol response. Prior to interpreting this model, the verbal ability variables were checked for multicollinearity. The verbal ability variables were highly correlated, so a cumulative verbal ability score was

computed and used as the independent variable. The cumulative verbal ability score was the mean scaled score based on each of the verbal tasks (Narrative Memory SS, Phonemic Fluency SS, Category Fluency SS, Category Switching Fluency SS, Category Switching Total Switching Accuracy SS).

*Aim 2A.* ANCOVA, with intelligence as the covariate, was used to evaluate differences between diagnostic groups on acute anxiety response following the TSST-C (STAIC: State form) as well as group differences for general anxiety level (STAIC: Trait form). In addition, within-group differences were evaluated for acute anxiety (STAIC: State form) and general anxiety (STAIC: Trait form) using paired sample t-tests.

*Aim 2B.* To determine if verbal ability (Narrative Memory SS, Phonemic Fluency SS, Category Fluency SS, Category Switching Fluency SS, Category Switching Total Switching Accuracy SS) predicted acute anxiety (STAIC: State form) following the TSST-C, a step-wise regression model was conducted. Prior to interpreting this model, the verbal ability variables were checked for multicollinearity (as performed in Aim 1B). Since the verbal ability variables were highly correlated, a cumulative verbal ability score was computed (calculating the average SS across the five variables) and used as the independent variable.

*Aim 3.* To determine the association between physiological stress and self-reported anxiety, Pearson correlation coefficients were calculated both for the overall sample and for each group separately. Correlations were performed using the following variables: cortisol response, STAIC: State Form, and STAIC: Trait Form. Partial correlations (controlling for FSIQ) were also performed using these same variables.

## CHAPTER THREE

### RESULTS

Appropriate tests of normality (e.g., Shapiro-Wilk's) were used to assess each of the dependent variables used in the parametric tests (e.g., t-tests). For the independent two sample t-tests, the assumption of equal variances was tested using Levene's test.

#### *Neuropsychological Measures*

Group differences on the neuropsychological measures (Verbal Fluency: Phonemic Total, Category Total, Category Switching Total, Total Switching Accuracy; Narrative Memory: Total score) were evaluated using ANCOVAs, with intelligence (FSIQ) as the covariate (see Table 2). The children with autism and typically developing children did not differ significantly from each other on Phonemic Total [ $F(1,26)=0.174, p>0.05$ ], Category Total [ $F(1,26)=3.774, p>0.05$ ], or Category Switching Total [ $F(1,26)=2.600, p>0.05$ ]. Performance did differ significantly between the groups on Total Switching Accuracy [ $F(1,26)=10.249, p<0.01$ ] and Narrative Memory [ $F(1,26)=5.416, p<0.05$ ].

#### *Aims*

*Aim 1 A.* The normality assumption was confirmed for each of the dependent variables (STAIC: State Form; STAIC: Trait Form; Mean Afternoon Cortisol; Arrival Cortisol; 20 Minutes After Arrival Cortisol; mean afternoon cortisol-minus-arrival cortisol; mean afternoon cortisol-minus-cortisol 20 minutes after arrival; arrival cortisol-minus-cortisol 20 minutes after arrival) using the appropriate tests of normality.

The following cortisol measurements were compared between the two diagnostic groups using ANCOVA, with intelligence as the covariate: Mean Afternoon Cortisol, Arrival Cortisol, 20 Minutes After Arrival Cortisol. There were no significant differences found between the

groups for mean afternoon cortisol [ $F(1,27)=0.002$ ,  $p>0.05$ ], cortisol upon arrival [ $F(1,27)=0.505$ ,  $p>0.05$ ], or cortisol twenty minutes after arrival [ $F(1,27)=0.495$ ,  $p>0.05$ ].

Difference variables (mean afternoon cortisol-minus-arrival cortisol; mean afternoon cortisol-minus-cortisol 20 minutes after arrival; arrival cortisol-minus-cortisol 20 minutes after arrival) were computed, and paired sample t-tests revealed that the differences did not deviate significantly from zero for each participant when analyzed at both the sample and group levels. The difference between mean afternoon cortisol and cortisol upon arrival did not differ significantly for the sample as a whole [ $t(29)=-1.977$ ,  $p>0.05$ ], the group with autism [ $t(14)=-2.102$ ,  $p>0.05$ ], or the typically developing group [ $t(14)=-0.729$ ,  $p>0.05$ ]. The difference between mean afternoon cortisol and cortisol twenty minutes after arrival did not differ significantly for the sample as a whole [ $t(29)=-2.393$ ,  $p>0.05$ ], the group with autism [ $t(14)=-1.834$ ,  $p>0.05$ ], or the typically developing group [ $t(14)=-1.557$ ,  $p>0.05$ ]. The difference between cortisol upon arrival and cortisol twenty minutes after arrival did not differ significantly for the sample as a whole [ $t(29)=-0.633$ ,  $p>0.05$ ], the group with autism [ $t(14)=-0.229$ ,  $p>0.05$ ], or the typically developing group [ $t(14)=-0.618$ ,  $p>0.05$ ].

Based on the previous analyses for Aim 1A, a minimum value for the maximum-minus-minimum change score was selected to be the lowest cortisol value for each participant taken from the beginning or end the initial twenty minute rest period (i.e., upon arrival or twenty minutes after arrival) on the day of the experiment. The minimum cortisol value was subtracted from the maximum cortisol value (taken from zero minutes post-experiment or twenty minutes post-experiment) to determine cortisol response to TSST-C for each participant.

Using ANCOVA (with FSIQ as the covariate), it was determined that cortisol response to the TSST did not differ significantly between the diagnostic groups [ $F(1,27)=0.140$ ,  $p>0.05$ ]. It

is noteworthy that similar results were found using ANOVA [ $F(1,28)=1.991, p>0.05$ ], indicating that controlling for group differences in intelligence did not alter the outcome. One-sample t-tests revealed that the cortisol response for the typically developing children differed significantly from zero [ $t(14)=2.703, p<0.05$ ] while the cortisol response for the children with autism did not differ significantly from zero [ $t(14)=1.443, p>0.05$ ] (See Figure 1).

*Aim 1B.* The verbal ability measures were checked for multicollinearity and found to be highly correlated for the overall sample (all variables correlated at  $p<0.05$ ), therefore, a composite verbal ability score was computed for use in the step-wise regression model. ANCOVA determined that the verbal ability composite score differed significantly between the two groups [ $F(1,27)=6.732, p<0.05$ ], and a general linear model was used to test for an interaction between diagnosis and the verbal ability composite score with cortisol response as the dependent variable. Since the interaction term was not significant [ $F(1,5)=2.194, p>0.05$ ], it was removed from the model. The resulting main effects model, which included diagnosis and the verbal ability composite score as predictor variables, was not found to be significant [ $F(2,27)=0.978, p>0.05$ ]. The least significant variable, the verbal ability composite [ $t(27)=-0.185, p>0.05$ ], was removed, and the model was retested. The final main effects model, which included diagnosis as the predictor variable, was not found to be significant [ $F(1,28)=1.991, p>0.05$ ], as would be expected based on the results from Aim 1A.

*Aim 2A.* Group differences on trait and state anxiety were evaluated using ANOVA as well as ANCOVA, with intelligence as the covariate (see Table 3). Using ANOVA, significant group differences were found for trait anxiety [ $F(1,26)=10.658, p<0.01$ ] in which children with autism reported significantly greater trait anxiety than typically developing children. No significant differences were found between groups for state anxiety following performance of the

TSST [ $F(1,26)=0.547, p>0.05$ ]. Because FSIQ differed significantly between the two groups, ANCOVA was performed to determine group differences on trait and state anxiety with FSIQ as the covariate. Results indicated no differences between groups for trait anxiety [ $F(1,25)=1.342, p>0.05$ ] or state anxiety [ $F(1,25)=0.002, p>0.05$ ], once intelligence was controlled.

Paired sample t-tests were used to determine differences within each group on state versus trait anxiety on the STAIC. The children with autism reported significantly lower state anxiety than trait anxiety [ $t(12)=-4.467, p<0.01$ ] while the typically developing children reported similar levels of state and trait anxiety [ $t(14)=-0.872, p>0.05$ ].

*Aim 2B.* As stated under Aim 1B, the verbal ability measures were found to be highly correlated (all variables correlated at  $p<0.05$ ), therefore, a composite verbal ability score was used in the step-wise regression model. A general linear model was used to test for an interaction between diagnosis and the verbal ability composite score with state anxiety as the dependent variable. Since the interaction term was not significant [ $F(1,5)=0.175, p>0.05$ ], it was removed from the model. The resulting main effects model, which included diagnosis and the verbal ability composite score as predictor variables, was not found to be significant [ $F(2,25)=0.638, p>0.05$ ]. The least significant variable, the verbal ability composite [ $t(25)=0.857, p>0.05$ ], was removed, and the model was retested. The final main effects model, which included diagnosis as the predictor variable, was not found to be significant [ $F(1,26)=0.547, p>0.05$ ], as would be expected based on the results from Aim 2A.

*Aim 3.* Pearson correlation coefficients were calculated to determine the association between physiological stress and self-reported anxiety. For the sample as a whole, cortisol response was not correlated with state anxiety ( $r=-0.153, p>0.05$ ) or trait anxiety ( $r=-0.119, p>0.05$ ). For the group with autism, cortisol response was not correlated with state anxiety

( $r=0.246$ ,  $p>0.05$ ) or trait anxiety ( $r=-0.126$ ,  $p>0.05$ ). And for the typically developing group, cortisol response was not correlated with state anxiety ( $r=-0.292$ ,  $p>0.05$ ) or trait anxiety ( $r=0.061$ ,  $p>0.05$ ). For the sample as a whole, there was a significant association between state anxiety and trait anxiety ( $r=0.380$ ,  $p<0.05$ ), indicating a positive relationship between state and trait anxiety (i.e. high levels of trait anxiety correlated with high levels of acute anxiety following performance of the TSST-C). However, this association was not significant when a partial correlation was conducted, controlling for FSIQ ( $r=0.350$ ,  $p>0.05$ ). At the group level, the association between state and trait anxiety was not significant for children with autism ( $r=0.197$ ,  $p>0.05$ ) or typically developing children ( $r=0.453$ ,  $p>0.05$ ).

#### *A Priori Hypotheses*

*Aim 1A.* It was hypothesized that both children with autism and typically developing children would demonstrate significantly elevated cortisol following the TSST-C (0- or 20-minutes post-experiment) relative to baseline (0- or 20-minutes post-arrival). In addition, it was hypothesized that children with autism and typically developing children would not differ significantly in cortisol response following the TSST-C, though it was expected that children with autism would demonstrate less of an increase in cortisol following the TSST-C than typically developing children. As expected, an ANCOVA revealed that children with autism and typically developing children did not differ significantly in their cortisol response to the stressor [ $F(1,27)=0.140$ ,  $p>0.05$ ]. However, the hypothesis that both children with autism and typically developing children would demonstrate significantly elevated cortisol following the TSST-C relative to baseline was not confirmed for the children with autism. One-sample t-tests revealed that while the cortisol response for typically developing children was significantly different from zero [ $t(14)=2.703$ ,  $p<0.05$ ], the cortisol response for children with autism was not significantly



different from zero [ $t(14)=1.443$ ,  $p>0.05$ ]. These one-sample t-tests confirm the hypothesis that the magnitude of increase in cortisol for children with autism would be lower than the increase for typically developing children.

*Aim 1B.* It was hypothesized that children with autism would demonstrate significantly lower verbal ability than typically developing children. ANCOVA, with intelligence as the covariate, confirmed that the two groups differed significantly on the verbal ability composite score [ $F(1,27)=6.732$ ,  $p<0.05$ ], with children with autism performing more poorly than typically developing children. It was also hypothesized that performance on the verbal ability measures would predict cortisol response following performance of the TSST-C for each group. A step-wise regression model, which included diagnosis and the verbal ability composite score as predictor variables, did not confirm this hypothesis [ $F(2,27)=0.978$ ,  $p>0.05$ ].

*Aim 2A.* It was hypothesized that children with autism and typically developing children would demonstrate comparable levels of acute anxiety (STAIC: State form) following the TSST-C. The results of ANCOVA were not significant [ $F(1,25)=0.002$ ,  $p>0.05$ ], therefore, confirming this hypothesis. It was also hypothesized that children with autism would report a significantly higher level of general, persistent anxiety (STAIC: Trait form) than typically developing children. Though the results of an ANOVA indicated that children with autism reported significantly greater trait anxiety than typically developing children [ $F(1,26)=10.658$ ,  $p<0.01$ ], an ANCOVA determined there was no difference between groups on trait anxiety when controlling for intelligence [ $F(1,25)=1.342$ ,  $p>0.05$ ]. Therefore, the hypothesis that children with autism would report significantly greater trait anxiety than typically developing children was not supported. Lastly, it was hypothesized that typically developing children would demonstrate a significant increase in state anxiety, relative to trait anxiety, following the TSST-C while

children with autism would report similar levels of state and trait anxiety. The conducted paired sample t-tests did not support this hypothesis, revealing that children with autism reported significantly lower state anxiety than trait anxiety [ $t(12)=-4.467, p<0.01$ ] and typically developing children reported similar levels of trait and state anxiety [ $t(14)=-0.872, p>0.05$ ].

*Aim 2B.* As stated under Aim 1B, it was hypothesized that children with autism would demonstrate significantly lower verbal ability than typically developing children, and ANCOVA confirmed this hypothesis. It was also hypothesized that verbal ability would predict self-reported state anxiety, following performance of the TSST-C, in both children with autism and typically developing children. A step-wise regression model, which included diagnosis and the verbal ability composite score as predictor variables, did not confirm this hypothesis [ $F(2,25)=0.638, p>0.05$ ].

*Aim 3.* A significant, positive correlation between cortisol response and state anxiety (STAIC: State form) following performance of the TSST-C was expected for typically developing children. Pearson correlation coefficients were performed and did not support this hypothesis ( $r=-0.292, p>0.05$ ), yielding a negative correlation that was not significant. In contrast, it was hypothesized that there would not be a significant correlation between cortisol response and state anxiety for children with autism. This hypothesis was supported ( $r=-0.246, p>0.05$ ).

## CHAPTER FOUR

### DISCUSSION

#### *Neuropsychological Functioning*

The present study compared children with autism to typically developing children on several executive functioning tasks. Despite having a significantly lower FSIQ than typically developing children, the children with autism performed similarly to the typically developing children on both phonemic and semantic verbal fluency tasks demonstrating comparable verbal fluency skills. On a task requiring the participants to produce words while switching between two semantic categories, the children with autism were able to produce a similar number of words as typically developing children, however, they were less able to accurately switch between categories on this task. This pattern of performance indicates that children with autism had significant difficulty with one component of executive functioning, switching, rather than language fluency. A similar pattern of performance by adults and adolescents diagnosed with either high functioning autism or Asperger's disorder was documented by Kleinmans, Akshoomoff, and Delis (2005).

Performance on a test assessing auditory short-term memory for semantic components of a short-story also differed significantly between the two groups, with children with autism demonstrating marked difficulty relative to typically developing children. This finding is consistent with previous research portraying impaired auditory short-term memory (story recall) in children with autism (Fein, et al., 1996; Gabig, 2008; Rumsey & Hamburger, 1990; Williams, et al., 2006b).

The purpose of assessing these neuropsychological abilities in the present study was to determine if these specific cognitive skills (verbal fluency, switching, and story recall) would

predict physiological stress or perceived anxiety following performance of the TSST-C. Results of regression analyses determined that there was no significant relationship between stress or anxiety and these cognitive abilities. Based on these findings, difficulty remembering the short story presented during the experimental task and decreased ability to flexibly switch between concepts during the speech portion of the task failed to contribute significantly to the observed stress and anxiety responses.

One caveat worth mentioning is that the TSST-C protocol included the provision of a written copy of the short story for use during the five-minute preparation period of the task, while the neuropsychological test used to assess narrative memory was exclusively auditory. We cannot rule out the possibility that the written copy of the short story provided during the experiment allowed for further encoding of the semantic components of the story to memory than what was observed during neuropsychological testing. However, behavioral observations during the experiment (e.g. many participants did not attend to the provided copy of the story) make it unlikely that the children with autism's retention significantly improved as a result of this additional exposure.

### *Physiological Stress Response*

Although results from the neuropsychological testing suggest that the TSST-C posed significant cognitive demands for the children with autism, relative to typically developing children, this cannot be equated with the conclusion that the children with autism found the TSST-C to be more stressful. In fact, the data indicated that the children with autism did not demonstrate significantly increased stress following performance of this task. While the typically developing children demonstrated a significant increase in cortisol, relative to baseline, the children with autism maintained a relatively stable level of cortisol throughout the experiment

and subsequent rest period. Furthermore, despite lowered performance on the narrative memory and verbal switching tasks, regression analyses indicated that cumulative performance on the verbal ability measures did not predict the stress response to the TSST-C in children with autism. In other words, difficulty remembering the story or switching between tasks did not trigger increased cortisol for children with autism. It could be argued that the children with autism did not find the task stressful because their lower cognitive ability prohibited them from understanding the task requirements. However, this possibility is unlikely due to the fact that these were children with high functioning autism whose verbal comprehension was sufficient to complete the initial neuropsychological testing.

Several additional interpretations may also explain the blunted cortisol response observed in children with autism, including social impairment, abnormal social cognition, dysfunction of the LHPA axis, habituation, and level of induced structure. In regards to social impairment, the anxiety literature portrays a trend for children with autism to report higher levels of anxiety as they become increasingly higher functioning and less socially impaired (White, Oswald, Ollendick, & Scahill, 2009b). Although the present sample of children with autism was selected because they were “high functioning,” and their mean FSIQ was in the average range, statistical analyses determined their FSIQ to be significantly lower than that of children in the typically developing group. Furthermore, the age range of the children enrolled in this study is somewhat younger than the age at which many prior studies find a significant increase in anxiety in individuals with autism, which is typically during adolescence (Kuusikko, et al., 2008; White, Oswald, Ollendick, & Scahill, 2009b). Thus, it is conceivable that despite being “high functioning,” the children with autism enrolled in the present study had not yet reached a level of development and social ability that would allow them to recognize the socially stressful

components of this task. Therefore, they may not have experienced significant acute anxiety or stress. In further support of the hypothesis that social impairment might have precluded a classic physiological stress response to the TSST-C, Naber and colleagues (2007) also observed a lowered cortisol response in toddlers with autism who had higher symptom severity utilizing the Strange Situation Procedure, a standardized protocol requiring interaction with an unfamiliar adult. Although the authors did not specifically state that social impairment contributed to the blunted cortisol response, they did hypothesize that inability to recognize the stressful nature of the situation may have limited the toddler's stress response.

In addition to the previous work outlining the relationship between social impairment and anxiety, the literature on social cognition in autism also contributes to our understanding of the data from the present study. As previously discussed, the key element of the TSST-C that induces a cortisol response in typically developing individuals is social-evaluative threat. Research on social cognition in autism has documented abnormalities in social perception (Corbett, et al., 2009a; Schultz, 2005) and decreased accuracy in detecting social threat (Krysko & Rutherford, 2009), relative to typically developing children. Given that the evaluators in the TSST-C remain affectively neutral throughout the task, it may have been particularly difficult for children with autism to detect the component of social-evaluative threat in this experimental protocol. Therefore, the lack of increased cortisol in the children with autism following the TSST-C could be explained by an inability to perceive the critical stress-provoking component of this task. If this were the case, the TSST-C may not be as relevant a way to induce social stress in children with autism as it is for children with typical development or children with medical conditions in which social perception is not implicated (e.g., asthma). Perhaps a more

ecologically valid experimental protocol is necessary to explore how children with autism are responding physiologically to social interactions experienced in their everyday life.

In addition to social impairment and social cognition, a third explanation for the present findings is the possibility that underlying LHPA dysfunction contributed to the blunted cortisol response in children with autism. A high level of variability in the rhythm (Corbett, et al., 2006, 2008b, 2009c) and response (Corbett, et al, 2006, 2008b) of the LHPA axis has been previously documented in children with autism, and perhaps variability in the present sample (see Figure 2) contributed to a mean cortisol response that was not statistically significant. This interpretation would allow for the possibility that the nature of the task was indeed stressful for some children with autism, despite a lack of significance for the group as a whole. Unfortunately, our limited sample size prohibits us from further differentiating the children in the group with autism into children who may have exhibited a stress response to this task (“responders”) and those who did not (“non-responders”) to fully evaluate this potential argument.

Furthermore, while it is reasonable to recognize that a subgroup of children with autism in our sample may have demonstrated a significant stress response to the TSST-C, this consideration must be tempered with the fact that, as a group, children with autism are capable of demonstrating a marked acute physiological stress response in the face of non-social stress (Corbett, et al, 2006, 2008b; Yamazaki, et al., 1975). The robust cortisol response demonstrated by children with autism to nonsocial stress lends additional credibility to the hypotheses that social impairment or abnormal social cognition accounted for the overall lack of stress response to this social-evaluative task.

Another explanation worth considering is that the absence of a physiological stress response demonstrated by children with autism symbolized a habituated stress response. By

definition, a habituated stress response occurs when the stress response of an organism declines following repeated exposure to specific stressful stimuli (Harris, 1943). As a result of habituation, the organism exhibits an attenuated response upon exposure to the stimuli, no longer appearing to be stressed. Prior research documenting the propensity for children with autism to demonstrate an anticipatory stress response (Corbett, et al., 2006, 2008b), provides evidence that their neuroendocrine system is sufficiently adaptive to prior emotional experiences to also be capable of exhibiting a habituated stress response.

One critical limitation of the interpretation that the data from the present study represents a habituated stress response is that the children with autism in our sample had previously never completed the TSST-C. However, previous researchers utilizing the TSST to evaluate the stress response of individuals with anxiety-based psychiatric disorders have also proposed that the attenuated stress response observed in their samples might be characteristic of a habituated response to social stress, even upon initial exposure (Panic Disorder: Petrowski, et al., 2010; Social Anxiety Disorder: Shirotaki, et al., 2009). For example, Shirotaki and colleagues (2009) administered the TSST to college students with high social anxiety and observed an attenuated cortisol response, relative to students with low social anxiety. They hypothesized that the physiological response in socially anxious individuals may have lessened as a result of repeated, daily exposure to circumstances that an individual with social anxiety would deem socially stressful. Similarly, adults with Panic Disorder demonstrated a normal cortisol awakening response but attenuated acute stress response to the TSST (Petrowski, et al., 2010). Petrowski and colleagues argued that these results were characteristic of a habituated response to acute stress, hypothesizing that the threatening elements of the TSST may not be perceived as novel to an individual with a history of repeated, acute panic attacks in situations that are perceived to be



uncontrollable. The authors also discussed unpublished data from their lab indicating that this finding does not appear to differ depending on the course of the disorder, with newly diagnosed participants with Panic Disorder responding similarly to participants who had previously undergone successful treatment. While the authors argued that underlying hyporesponsivity of the LHPA axis to stress might predispose individuals to Panic Disorder, this finding also lends itself towards the argument that despite the individual's learned ability to overcome subjective distress, the underlying hyporesponsivity of the LHPA axis associated with Panic Disorder persisted.

In a similar fashion, it could be argued that the children with autism in the current study have also experienced sufficient daily anxiety in the context of the social environment to have dampened their physiological response to an uncontrollable and stress-provoking psychosocial stressor. However, previous literature on the physiological responses exhibited by children with autism when they are required to interact socially does not provide supporting evidence for this argument. Specifically, one could argue that if children with autism were truly habituated to social-evaluative stress to an extent that could generalize to the TSST-C experiment, we would not expect to observe the documented evidence of increased cortisol in children with high functioning autism who are integrated into traditional classrooms (Richdale & Prior, 1992), interacting with an unfamiliar peer unexpectedly (Lopata, et al., 2008), or completing a modified version of the TSST-C (Jansen, et al., 2003). The significant physiological stress responses demonstrated in these additional social scenarios highlight the importance of further considering what aspect of the TSST-C might have uniquely led to the blunted cortisol response observed in children with autism.

In an attempt to further disentangle what aspect of the current social stress protocol might have led to the blunted cortisol response in children with autism relative to other social stress protocols, it is worth revisiting the findings described by Jansen and colleagues (2000, 2003). One component of our experimental protocol that differs from the one used in their previous work is that our protocol employed a greater degree of structure. Specifically, children completing our experiment were provided with the topic on which they were to speak (i.e. short story) while the children completing the experiment in the study by Jansen and colleagues (2003) were encouraged to speak on a topic of their choosing. Previous research on executive functioning has demonstrated that children with autism have more difficulty on “open-ended” tasks, performing optimally on tasks that provide clearly defined structure with less reliance on the need to decipher implicit socio-communicative demands from an experimenter (White, Burgess, & Hill, 2009a). While the task of creating the ending to a short story is open-ended in nature, it is more restricted in scope than a free speech task. In addition to the specifications of the speaking task, the children in our study received structured, consistent social feedback from face-to-face evaluators. In contrast, the children enrolled in the study by Jansen and colleagues (2003) were asked to perform the speech task in a room in which the evaluators were physically absent, supposedly seated in another room behind a one-way mirror. This modification introduced a component of novelty, performance for an evaluator located outside of view, that is not included in the standardized version of the TSST-C. Therefore, it is possible that the difference between the findings of the current study and the work by Jansen reflects the differing level of structure employed in each protocol. For example, the standard TSST-C protocol utilized in the current study provides the participant with concrete social roles, a defined task, and consistent social feedback whereas the protocol implemented in the previous work requires the

participant to interact in a highly unusual, abstract social scenario in which his performance is being evaluated by an unobserved rater. Future research protocols with varying levels of structured social interactions, differing both in the structure of social roles (teacher-student versus peer-peer) and in the structure of the performed activity (e.g. free play versus a card game with clearly outlined rules) could address the credibility of this hypothesis.

### *Trait Anxiety*

In contrast to previous literature, the children with autism in the current study reported a baseline, trait anxiety level that was comparable to children with typical development, rather than a higher level of trait anxiety. An important caveat to this finding is that the trait anxiety data was analyzed while controlling for group differences in FSIQ. When group differences in intelligence were not considered, the children with autism appeared to report significantly higher trait anxiety than typically developing children, as would be expected based on prior research. Nonetheless, this study is not the first to report similar levels of anxiety in children with ASDs and typical development (e.g., Williamson, Craig, & Slinger, 2008).

### *Acute Anxiety in Response to the TSST-C*

In concordance with the children with autisms' lack of cortisol response following performance of the TSST-C, they also did not report a significantly elevated level of state anxiety, relative to their reported level of trait anxiety. An important caveat to this finding is that their reported level of acute anxiety following performance of the TSST-C was significantly *lower* than their level of trait anxiety, despite a relatively stable level of cortisol. In comparison, the children with typical development reported no difference in state anxiety relative to trait anxiety, despite a significant increase in cortisol. Data analyses suggested that neither group reported a subjective level of anxiety that correlated with their physiological response to the task.

It is interesting that there was a discrepancy between the physiological stress response and psychologically perceived and reported anxiety, particularly for the typically developing children. This finding suggests that the internal, physiological stress response did not translate to perceived anxiety for typically developing children and calls into question the validity of the self-report measure as an indicator of acute stress for both groups. Furthermore, although multiple self-report measures of anxiety, including the STAIC, have been psychometrically validated for administration to typically developing children, many authors remain skeptical of the utility of self-report measures in children with autism (e.g., Baron-Cohen, Leslie, & Frith, 1985; Capps, Yirmiya, & Sigman, 1992; White, et al., 2009b). For example, a recent review by White and colleagues (2009b) examining anxiety in ASDs recommended “healthy skepticism” (p. 226) when considering results from the current instruments that are available for measuring anxiety in children with ASDs. Within the context of the present study, the results from the STAIC highlight the importance of discriminating between stress and anxiety as separate constructs, rather than referring to stress and anxiety as synonymous.

Although the STAIC did not appear to be an indicator of anxiety in relation to physiological stress in this study, it is noteworthy that the children with autism utilized this instrument to report two significantly different states of emotion. One emotion was their high, trait level of anxiety, and the other was a lower, acute level of anxiety following performance of the TSST-C. In the absence of a significant physiological stress response following the TSST-C, it could be argued that the children with autism demonstrated emotional insight when completing this self-report measure. Although this reasoning is compelling, the statistical analyses utilized in the current study do not support a relationship between self-reported anxiety and physiological stress. Nonetheless, the children with autism demonstrated an ability to subjectively differentiate

between two different levels of the same emotion. This finding is clinically relevant, providing evidence that children with autism have the underlying skills to be taught how to distinguish between two intensities of a single emotion. Furthermore, they may have sufficient emotional insight to engage in psychotherapy for anxiety (e.g., Cognitive Behavioral Therapy).

#### *Relationship between Stress and Anxiety*

Stress and anxiety are two constructs that share considerable theoretical overlap in scientific literature and are commonly considered equivalent by the layperson. However, the data from the present study indicated that there was no correlation between physiological stress and subjective anxiety in either group of children. In a similar study with adults, Fiocco and colleagues (2007) also failed to find a correlation between physiological stress and subjective anxiety. Jansen and colleagues (2000) also did not find a relationship between indices of physiological stress and self-reported anxiety in children with MCDD. Romanczyk and Gillis (2006) discussed the possibility that the complexity of physiological stress and the limitations of self-reported anxiety measures complicate the ability to document an association between these two processes (Romanczyk & Gillis, 2006), and perhaps the data from the present study along with the previously cited research reflect that stress and anxiety are two distinct, though sometimes overlapping, constructs.

#### *Overall Interpretation – Impaired Social Cognition and Optimal Structure*

Within the context of the overall literature on stress in autism, two of the previously discussed arguments appear particularly compelling: impaired social cognition and the absence of stress under conditions of optimal structure. In a disorder characterized by social impairment and documented abnormalities in social cognition, the argument that the children with autism did not perceive the TSST-C to represent a condition of social-evaluative threat has considerable

merit. Given the difficulty children with autism have in perceiving social threat, the TSST-C may not be a pertinent way to evaluate social stress in this clinical group.

At the same time, it cannot be ignored that a previous study utilizing a modified version of the TSST-C did find that children with autism demonstrated a significant physiological response (Jansen, et al., 2003), leading to the interpretation that a critical component may have differed between the methodology of the two studies. As discussed above, this component may have been the difference in the level of imposed structure in the variations of the TSST-C employed. Jansen and colleagues (2003) argued that the children with autism in their study did not appear to fully comprehend the social-evaluative nature of the task based on the fact that this group of children exhibited a lowered heart rate during the speech preparation period (as opposed to the increased heart rate observed in typically developing children). In lieu of their decreased heart rate, the authors concluded that the increased level of cortisol following performance of the TSST-C was not evidence of a normal stress response to the task but instead characteristic of the hyperresponsivity of the LHPA axis observed in this clinical group (Tordjman, et al., 1997). In light of the findings from the current study, it may instead be the case that while they were unable to fully recognize the component of social-evaluative threat embedded in the task as Jansen and colleagues discussed (2003), the children with autism in their study exhibited a stress response based on the more abstract and open-ended nature of the required task. It is also noteworthy that the same study by Jansen and colleagues (2003) reported that children with autism had an increased cortisol response during the control condition of their experiment. This condition entailed sitting with a research assistant and talking or playing a game, providing further evidence of the tendency for children with autism to exhibit a physiological stress response when engaging in social interactions comprised of less structured activities and social

feedback than the standardized TSST-C. To summarize, the standardized TSST-C protocol utilized in the present study may represent a benign social scenario for children with autism because they are unable to perceive social-evaluative threat, particularly in a context of highly structured social roles, clearly outlined tasks, and consistent social feedback.

### *Limitations*

The present study utilized a standardized protocol in which social-evaluation occurred based on cognitive performance. Although several aspects of neuropsychological functioning were assessed in the initial session, this study did not include a verbal comprehension task. Therefore, it is not possible to determine whether level of understanding of the short story presented during the stress protocol could have been related to the children with autism's physiological response. In addition, the TSST-C includes a serial subtraction task, and the study did not include a measure to assess computational ability. Based on previous research, it is assumed that computational ability in children with autism would be highly correlated with IQ (Mayes & Calhoun, 2003) and would not differ significantly from the ability of typically developing peers (Minshew, Goldstein, Taylor, & Siegel, 1994). Furthermore, one previous study (Fiocco, et al., 2007) included a numerical working memory task (i.e. Digit Span) in their evaluation of healthy adults and found it to be nonsignificant, identifying only the verbal fluency task to be related to physiological stress. Still, we recognize the value of including a computational ability measure as a covariate in future studies evaluating stress following performance of the TSST-C in children with autism.

In regards to anxiety, the instrument utilized to measure trait and state anxiety in the present study is limited in scope as it is designed to be a general screening tool and does not differentiate between differing types of anxiety (e.g. social anxiety, performance anxiety, phobia,

panic disorder). Furthermore, it would have been valuable to know whether the children in our sample met criteria for Social Anxiety Disorder or another comorbid anxiety disorder (e.g. Panic Disorder). In addition, the present study did not include multiple measurements of state anxiety, for example, a baseline measurement of state anxiety taken upon arrival to the experiment to compare with the measurement of state anxiety immediately following TSST-C performance.

Lastly, the lack of a clinical comparison group also limits the interpretations that can be drawn from the resulting data. For example, the inclusion of a group of typically developing children with social anxiety disorder would contribute to our understanding of how social anxiety influences the physiological response to the TSST-C in children who do not have autism.

### *Clinical Implications*

Research evaluating the LHPA axis in children with autism has provided clinicians with a glimpse into the complicated mental and emotional state of these individuals in a variety of stress-provoking situations. The fact that completion of an evaluated, cognitively-challenging task did not evoke a marked physiological stress response in children with autism provides evidence that the daily, one-on-one, behavioral treatment sessions that are considered the “gold standard” in early-intervention treatment (Dawson, et al., 2010; Lovaas, 1987) are not likely to be perceived as stressful for a child with autism. The results from the current study further emphasize the importance of the highly structured methods of treatment employed by these programs. Nevertheless, while these treatment programs are inarguably efficacious in reinforcing social interaction and cognitive skills in children with autism, it could also be the case that early, repetitive exposure to an environment designed to teach the child to both acclimate and interact in situations that are novel, cognitively challenging, unpredictable, and behaviorally-based has also effectively trained the neuroendocrine system to initiate a habituated stress response in



similarly structured social interactions. It is currently unknown whether very young children with autism demonstrate a physiological stress response upon initiation of behavioral treatment that later resolves. However, this could be determined by way of a longitudinal study beginning in early childhood with the purpose to evaluate cortisol pre-intervention and at several points post-initiation of a behavioral treatment program. Lastly, the present study provides further evidence that the self-report of anxiety in both children with autism and typical development should be interpreted cautiously as the validity of these measures for use evaluating stress is questionable.

#### *Directions for Future Research*

Several important implications for future research arise from the current study. First, there is a need to disentangle the relationship between physiological stress and self-reported anxiety in children. While the current results indicate a dissociation between stress and anxiety in a social-evaluative context, perhaps situations can be identified in which stress and anxiety are more aligned.

In terms of research methodology, the present study suggests that it may be worthwhile for future researchers to consider the role of intelligence in self-reported emotional states. In the literature on executive functioning, it is common practice to control for intelligence when comparing children with autism and typical development (e.g., Corbett, et al., 2009b; Liss, et al., 2001; Ozonoff, Pennington, & Rogers, 1991). In fact, Liss and colleagues (2001) have argued that intelligence should be covaried even when there is not a significant difference, statistically, between these two groups to avoid inflating group differences. While researchers evaluating anxiety in ASD have evaluated within-group differences in level of cognitive functioning (e.g., Sukhodolsky, et al., 2008), it may be worthwhile for future researchers to use intelligence as a

covariate variable when evaluating group differences in anxiety, even when the difference in intelligence between groups is not statistically significant.

Lastly, there is a need for future research to continue evaluating the functioning of the LHPA axis in children with autism and observing their stress responses in a variety of social, nonsocial, experimental, and real-world contexts. It is of particular importance for this work to reveal whether a marginal physiological response to stress in a given context might be characteristic of habituation or physiological desensitization and exhaustion (Cyr & Romero, 2009). The resulting findings would equip clinicians with invaluable information for providing optimal behavioral, psychological, and pharmaceutical treatment of autism.

In addition to evaluating the cortisol response to stress, there is a need for future studies to identify the etiology of the observed physiological responses to stress, both across disorders and within healthy populations. Clearly, multiple underlying causes could lead to the attenuated cortisol response observed in children with autism following performance of the TSST-C. Although children with autoimmune disorders (e.g. Atopic Dermatitis, Allergic Asthma) and adults with Panic Disorder and social anxiety exhibit a similar attenuated cortisol response to this task as children with autism, it is likely that these clinical conditions could be differentiated according to the underlying cause that results in the observed cortisol response. A recent review by Foley and Kirschbaum (in press) outlined a variety of factors associated with attenuated cortisol in response to the TSST, including biomedical factors (e.g., chronic inflammation; autoimmune dysfunction; hypoglycemia), genetic factors (e.g., glucocorticoid receptor gene polymorphism BclI GG, in men only; dopamine D4 receptor gene allele DRD4 7R), and psychological factors (e.g., sexual abuse; behavioral stress management training). Future research to dissociate the interplay of each of these domains in the described populations,

including autism, would provide the groundwork for establishing efficacious treatment aimed at restoring proper functioning of the LHPA axis.

### *Summary and Conclusion*

The current study evaluated the physiological stress response in children with high functioning autism and typical development following completion of a well-validated, reliable social stress protocol. It was determined that executive functioning, specifically verbal fluency and verbal short-term memory, was not predictive of the physiological stress response or acute anxiety in children with autism or typical development. Children with autism did not exhibit a stress response to the TSST-C while typically developing children demonstrated a significant physiological stress response, relative to baseline. The absence of a physiological stress response in children with autism was attributed to impaired social cognition, limiting their ability to perceive the element of social-evaluative threat. It was also argued that the TSST-C is distinct from other social stress protocols in its high level of structure, both in terms of the activities engaged in by the participant and the consistency of social feedback. Children with autism reported similar levels of trait anxiety to typically developing children, and reported significantly lower acute anxiety relative to their trait anxiety level. Furthermore, the physiological stress response was not associated with a subjective self-report measure of acute anxiety for either group.

Overall, the present study provides insight into one aspect of emotional and physiological functioning in children with autism: the response to acute psychosocial stress. The task for future research is to further reveal the pathophysiology of autism and its variable manifestations in individuals with different subtypes of the disorder (Sutton, et al., 2005; Bonde, 2000; Volkmar et al., 1989; Wing & Gould, 1979) as well as varying situations within a single individual (Corbett,

under review; Lopata, et al., 2008). This work contributes to a collection of literature on the neuroendocrinology of autism spectrum disorders which can ultimately be used to provide tangible recommendations for individuals with autism, their families, and the clinicians who devote professional service towards breaking through the enigma of autism spectrum disorders.

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Table 1  
*Demographics*

	High Functioning Autism	Typical Development
Information	M(SD)	M(SD)
WASI**	92.77(12.29)	124.87(9.17)
ADOS (Communication + SI)	14.07(3.99)	N/A
Age	9.77(1.26)	9.55(1.65)
Pubertal Development Scale	3.46(0.88)	3.27(0.59)

\*p<0.05

\*\*p<0.01

Table 2  
*Neuropsychological Test Performance*

	High Functioning Autism	Typical Development
Information	M(SD)	M(SD)
DKEFS Verbal Fluency		
Letter Fluency	7.31(3.15)	10.73(3.08)
Category Fluency	6.92(4.05)	11.47(2.88)
Category Switching (Total Correct)	6.23(4.76)	11.33(2.82)
Category Switching** (Total Switching Accuracy)	4.38(2.76)	11.47(2.23)
NEPSY Narrative Memory*	3.69(3.90)	11.93(2.60)

\*p<0.05

\*\*p<0.01

Table 3  
*Self-Reported Anxiety*

	High Functioning Autism	Typical Development
Information	M(SD)	M(SD)
STAIC		
Trait Anxiety***	38.77(4.94)	32.07(5.80)
State Anxiety	32.00(3.51)	30.80(4.84)

\*p<0.05

\*\*p<0.01

\*\*\*p<0.01, w/o controlling for FSIQ (p=n.s, when group difference in FSIQ controlled)

Figure 1  
*Cortisol Response*

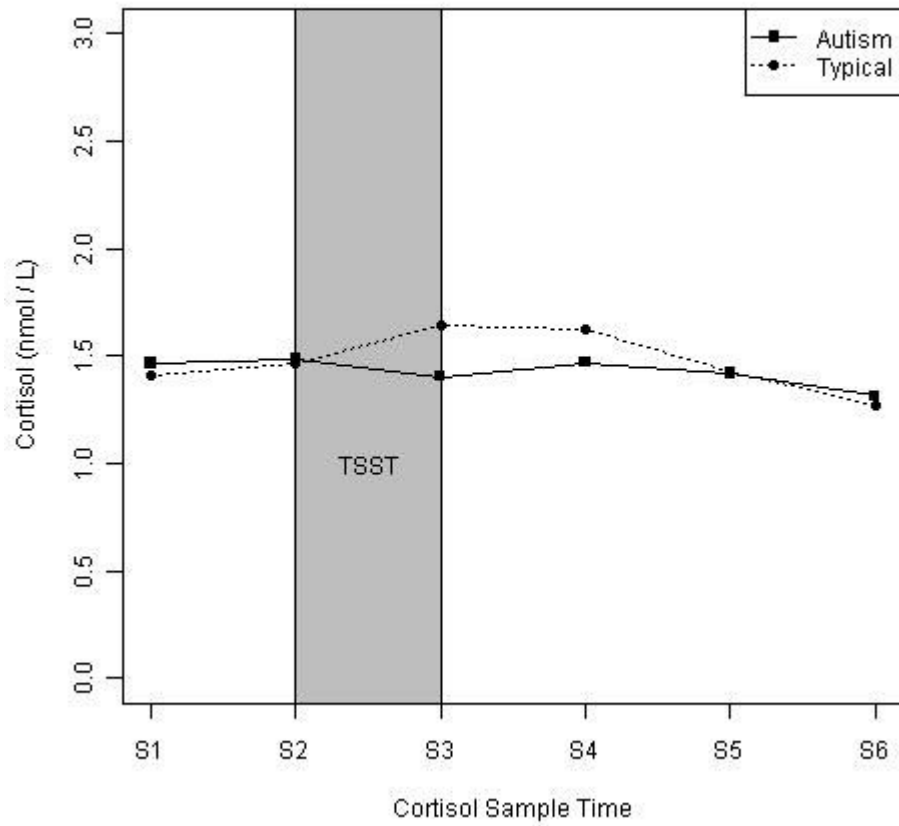


Figure 2  
*Cortisol Variability*

