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## Understanding Stress Reactivity in Schizophrenia

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UNDERSTANDING STRESS REACTIVITY IN SCHIZOPHRENIA

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## ABSTRACT

The role of stress has long been recognized in schizophrenia; several theories have identified the role of stress as an important factor in the etiology of schizophrenia. A handful of studies have used laboratory psychosocial stressors to examine cortisol stress response in schizophrenia; the results obtained have consistently suggested that the stress response is attenuated in people with schizophrenia. Present study set out to examine stress responsivity in schizophrenia relative to healthy controls. A laboratory stress test was used to investigate cortisol response, heart rate and task appraisal in a sample of 17 healthy controls and 16 men diagnosed with schizophrenia who were clinically stable at the time of testing.

No group differences were found in task appraisal of the TSST or heart rate. Nevertheless, similar to previous research, an attenuated cortisol response was observed in the schizophrenia group, implicating potential disruption of the HPA axis in schizophrenia.

Associations between cortisol response and performance on measures of social cognition and everyday functioning skills were also examined. Lastly, the relationship between childhood trauma and cortisol stress response was examined.

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## CHAPTER 1

### INTRODUCTION

Schizophrenia is a neurodevelopmental disorder characterized by psychosis, negative symptoms, and impairments in cognitive functioning and social cognition. Psychotic disorders are arguably the most devastating of the psychiatric illnesses, resulting in long-term disability, and high costs incurred both by the individual and society (Foster & Goa, 1999). The impact of stress on individuals with schizophrenia is monumental. The diastasis-stress model proposes that schizophrenia emerges in the context of a biological predisposition to develop the disorder and environmental stress. The hypothalamic-pituitary-adrenal (HPA) axis has been identified as an endocrine structure that triggers physiological responses to a subjective experience and is commonly investigated via cortisol secretion (e.g., Walker & Diforio, 1997; Nuechterlein & Dawson, 1982).

Stress has been implicated as both a contributing factor in the onset of psychosis and as a factor in the exacerbation of its course. A meta-analysis of 41 studies which included 79,000 individuals concluded that people with childhood trauma were nearly three times (odds ratio = 2.75-2.99) more likely to exhibit psychotic symptoms than those who did not experience childhood trauma (Varese et al., 2012). Additionally, stress has been implicated in exacerbating the course of psychotic illness. Social stressors exacerbate psychotic symptoms and are associated with higher relapse rates and more hospitalizations (Remington et al., 2013; Doering et al., 1998) and symptomatic relapse is associated with worse psychosocial functioning (Stefanopoulou et al., 2011).

While the body of literature examining HPA axis response to laboratory-based psychosocial stressors in schizophrenia is fairly small, the findings have been largely consistent.

Patients with chronic schizophrenia generally match or exceed healthy controls on measures of autonomic arousal (e.g., heart rate, blood pressure) and subjective self-report of stress during the laboratory psychosocial stressors; however, patients had attenuated cortisol levels in response to laboratory induced psychosocial stress (Brenner et al., 2009; Jansen et al., 2000; Jansen et al., 1998). Similar findings have been reported in first episode patients (van Venrooij et al., 2012) and those at ultra-high risk (UHR) for developing schizophrenia (Pruessner et al., 2013), suggesting that attenuated cortisol response is not the direct result of exposure to psychotropic medications, disease chronicity or other associated factors, such as institutionalization, decrease opportunity for appropriate social interactions, among others. Interestingly, cortisol responses to physiological stressors such physical exercise (Jansen et al., 2000) and metabolic stressors have been similar in patients and healthy controls, suggesting a potentially unique HPA axis response to social stressors in schizophrenia (Jansen et al., 2000; Jansen et al., 1998).

Despite the consistency of these findings, their interpretation remains unclear. In order to clarify and extend prior findings, the present study's goals were to further examine the aforementioned attenuation in cortisol response in relationship to 1) objective measures of social functioning, 2) history of childhood adversity, and 3) subjective experience of stress. The study will also address potential methodological confounds that may have caused inconsistencies in the results of prior studies. Each of these goals are explained below.

The first aim, or to examine the relationship between cortisol response and measures of social functioning, is intended to provide additional information for how judgment and subjective experience impact hormonal responding in schizophrenia. Some aspects of psychosocial functioning have been examined among people with schizophrenia who have undergone laboratory psychosocial stressors. For example, people with schizophrenia report

greater use of passive or avoidant coping strategies in general (Jansen et al., 2000; Jansen et al., 1998) and when asked to evaluate hypothetical social scenarios (Jansen et al., 1998). Patients reported greater use of confrontive and avoidant coping strategies during the psychosocial laboratory stressor (Jansen et al., 2000).

The present study intends to extend this goal by examining the relationship between social cognition, task appraisal, and physiological stress response. Impairment in social cognitive functioning is well established in schizophrenia (e.g., Pinkham et al., 2014). Additionally, there is strong evidence for defeatist performance beliefs and poor self-efficacy in schizophrenia. Because task appraisal has direct effects on the stress response, the current study will examine how objective measures of social cognition and defeatist performance beliefs can be used to understand the cortisol stress response in schizophrenia.

The second aim, to examine the relationship between childhood adversity and cortisol response to laboratory stressors, has not been directly investigated in the existing literature and may assist with differentiating whether abnormal cortisol response could be better understood as the result of early environmental stressors or as a direct expression of schizophrenia pathology. Exposure to early adversity has deleterious effects on the neurobiological mechanisms that underlie HPA axis mediated stress responsivity. Blunted cortisol response has been documented among healthy controls with a history of child abuse free of clinical diagnoses (e.g., Carpenter et al., 2007). This finding was interpreted as the result of desensitization of the HPA axis following long-term activation due to chronic stress. Given the high prevalence of childhood adversity in schizophrenia it is not clear whether the observed attenuation is due to schizophrenia specific pathology, a result of childhood trauma, or an interaction of the two.

Lastly, the present study aims to replicate past research using a *live* evaluative panel instead of an imagined one. The studies conducted with schizophrenia did not use live confederates in the room, but have obtained the observed results by either leading the participants to believe that they are being currently observed and evaluated during a performance task. While an imagined panel has been demonstrated to increase autonomic response to some degree, at least one study has demonstrated that the cortisol responses obtained in healthy controls with imagined judges were significantly lower than those obtained from subjects who were asked to speak in front of a live audience (Kelly et al., 2007).

The present study will focus on the stress response of men only to preserve the heterogeneity of the study sample, as research has indicated that males and females have characteristically dissimilar responses (Kudielka, B.M., Hellhammer, D.H., & Wüst, S, 2009) and have shown differential associations with variables of interest (e.g., Smeets et al., 2009).

A potential limitation with the present body of research is the use of overly generalized scales to examine distress. Difference between challenge and threat depends on whether an individual appraises personal resources as adequate or not to meet a specific challenge (Blascovich & Tomaka, 1996). Dickerson and Kemeny (2004) did not find a relationship between subjective self-report of distress and cortisol response in response to laboratory stressors. Similarly, two other meta-analyses did not find a relationship between subjective self-report and immune system outcomes in everyday settings (Seegerstrom & Miller, 2004; Herbert & Cohen, 1993). Denson and colleagues (2009) have suggested that these findings were not significant due to the use of overly generalized scales, or that classifying emotions into broad dimensions (e.g., positive and negative) may obscure relationships between specific emotions and the stress response. This meta-analysis replicated the lack of relationship between global

mood states and cortisol responses, and used statistical models to demonstrate that types of cognitive appraisals are significantly associated with cortisol responses.

Studies have indicated that subjective interpretation of day-to-day experience may differ for people with schizophrenia: individuals diagnosed with schizophrenia are more likely to perceive both positive and negative events as more stressful, less controllable, and handled less skillfully than healthy controls (Horan et al., 2005). This is particularly relevant considering the fact that studies in healthy controls have reported an association between anxiety and magnitude of cortisol stress response using a more nuanced measure of threat and challenge (Gaab, Rohleder, Nater, & Ehlert, et al., 2005). In summary, these studies suggest that understanding stress responsivity in schizophrenia may have broad implications for symptom management.

Based on these considerations, the current study proposes to examine changes in cortisol levels in schizophrenia in response to laboratory based stress, and associations with social cognitive abilities and the presence of childhood trauma. In this context, social cognitive abilities, and particularly social cognition, are thought to mediate stress response and cortisol level fluctuations in schizophrenia such that those individuals with deficient social perception will experience greater stress and larger fluctuations in cortisol levels. The presence or absence of childhood trauma is expected to influence baselines levels of cortisol and be associated with blunted response to laboratory stressors.

In the following sections, relevant literature regarding HPA axis, childhood trauma, schizophrenia, social cognition, and findings from laboratory based stress procedures are discussed to provide a basis for the study hypotheses.

## CHAPTER 2

### REVIEW OF RELATED LITERATURE

#### **Conceptualizing Stress**

Early models conceptualized stress as an all-or-nothing mechanism: Selye (1973) stated, “stress producing factors ... are different, and yet they all produced essentially the same biologic stress response” (p. 692). According to Weiner (1992), Selye was biased by the unavoidable or overpowering stimuli used in his research, which override the nuanced differences in behavior or physiological responses; additionally Selye overestimated the role of stress in causing the non-specific (e.g., lethargy, loss of appetite) symptoms of illness in humans. Conceptualizations of stress shifted in later years as scientists realized that organisms must have more finely tuned response systems to survive, and that stressors, such as hunger, thirst, or social threat must elicit different responses for an animal to be effective. Following WWII researchers started examining stress from a psychosocial perspective. This perspective was warranted as one-third of the American soldiers returning from the war did not sustain any physical injury, but suffered from exposure to loud noise, extreme fear, exertion, or grief following deaths of colleagues (Weiner, 1992).

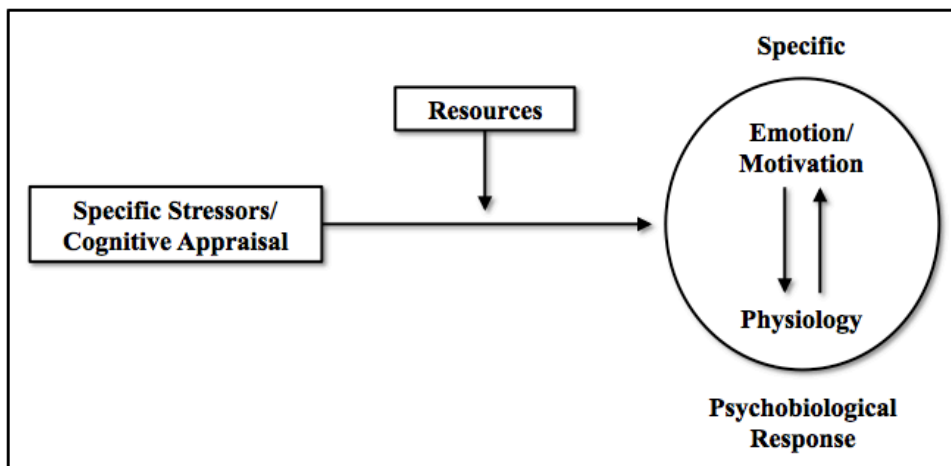
Based on their work with animals, Sawchenko, Li, & Ericsson (2000) argue for the existence of a dichotomous responding system to *interoceptive*, responsive to internal environments, and *exteroceptive*, responsive to external environments, stressors. The interoceptive system, which is mediated by subcortical regions and is largely reflexive, does not require conscious perception of the stressor in order for it to impact the HPA axis. This would include such stressors as temperature, physical activity, or metabolic stressors. The exteroceptive

system is activated by stressors that must be perceived and elicit cognitive or emotional processing, as demonstrated by animal studies using restraint. In humans the exteroceptive system is responsive to psychological and psychosocial stressors and can be examined via laboratory psychosocial stressors where perceived control and social evaluation are associated with the magnitude of the cortisol response (e.g., Schlotz, Hammerfald, Ehlert, & Gaab, 2011). Even for stress responses that are mediated by the exteroceptive system, animal models indicate distinct behavioral responses for different classes of stress responses such as fighting, fleeing, or submitting (Weiner, 1992). These considerations call for a more nuanced approach to the study of the HPA axis and stress responses in humans.

The integrated specificity model posits that distinct emotions are associated with unique physiological responses (Dickerson, Gruenewald, & Kemeny 2004; Kemeny 2003; Weiner, 1992). Figure 1 illustrates how appraisal can impact emotional and physiological functioning (Diagram adapted from Kemeny, 2003).

Figure 1

*Relationship between Cognitive Appraisal and Physiological Response*





Psychological stressors can be characterized as threats or challenges. If the demands of the stressor are assessed to exceed the resources of the organism the stressor can be considered a “threat;” however, if the organism appraises its resources as adequate the stressor can be classified as a “challenge” (Blascovich & Tomaka, 1996). This requires the simultaneous assessment of task demands (primary assessment) and one’s capabilities (secondary assessment). Threat and challenge create distinct physiological responses in the individual perceiving the situation: while both states are associated with autonomic activation, challenge is associated with increased peripheral resistance, resulting in increased blood pressure (Kemny, 2003). Thus, these findings further demonstrate that cognitive appraisal can have direct effects on physiological responses. Weiner (1992) listed several determinants of the stress response: situational novelty and unpredictability, previous experience, role of the participant, appraisal of performance, and individual coping mechanisms.

### **HPA Axis Function**

The human body works to preserve homeostasis in response to threats to well-being, or stressors. Stressors can be chronic or short-term, and can include both psychological and physical elements, such as perceived threat to the physical self or one’s social standing, infection, starvation, and fatigue, to name a few. Several physiological mechanisms work together to in response to stress.

The hypothalamic-pituitary-adrenal (HPA) axis initiates physiological responses to stress by orchestrating a hormonal cascade that starts within minutes or hours after encountering a stressor (Walker, Mittal, & Tessner, 2008; Sawchenko et al., 2000). Once a stressor is recognized, the periventricular nucleus (PVN) of the hypothalamus releases corticotrophin-releasing hormone (CRH), which triggers the release of the adrenocorticotrophic hormone

(ACTH) from the pituitary gland, which in turn triggers release of glucocorticoids (GC), including cortisol, from the adrenals.

Under normal conditions cortisol plays a major role in homeostasis; under stressful conditions cortisol production increases and facilitates an adaptive physiological response. Cortisol production is regulated by circadian rhythms: there is a sharp elevation in production upon awakening, and steady decline throughout the day (Weitzman et al., 1971). Most human cells have mineralocorticoid (MR) cortisol receptors, thereby allowing the hormone to regulate a variety of bodily systems including metabolic, immune, and cardiovascular functioning (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009). Under normal conditions, cortisol is secreted at a rate of 10 milligrams per day; in response to a stressor cortisol levels can increase 10-fold (Schimmer & Parker, 1996). Unless there are elevations in production, cortisol is mainly involved in homeostatic functioning due to the high affinity of MR receptors. Increased concentrations of cortisol allow for it to bind to lower affinity GC receptors and activate mechanisms that promote short-term survival of the organism in response to stress by: 1) increasing the supply of oxygen and glucose to the skeletal muscles, heart and brain to bolster physiological functioning; 2) conserving energy by shutting down the reproductive, immune, and digestive systems; 3) promoting analgesia; and 4) activating the peripheral autonomic nervous system (Sapolsky 2000).

Prolonged cortisol elevation is believed to have detrimental effects on neurophysiology, particularly the hippocampal functioning (King & Hegadoren, 2002) and is associated with lower levels of brain derived neurotropic factor (BDNF; Hansen et al., 2006). The hippocampus is particularly sensitive to GC-mediated neurotoxicity because it has the highest GC receptor density of any brain region. Hippocampal damage in turn may exacerbate cortisol dysregulation

because it provides negative feedback for corticosteroid production (Jankord & Herman, 2008). While the exact nature of the resulting dysfunction is unclear, several mechanisms have been proposed. McEwen (1998) proposed a glucocorticoid-cascade hypothesis suggesting that chronic stress leads to hippocampal “wear and tear,” resulting in HPA axis dysregulation and cognitive impairment. Repeated or chronic stress may lead to increased negative feedback through sensitization to GC activity and result in up-regulation in the number of GC receptors thereby increasing negative feedback and resulting in hypo-cortisolism (King & Hegadoren, 2002). Others have suggested that chronic stress leads to hyper-cortisolism by increasing the central tone of the HPA axis, down regulation to GC receptors in key feedback regions, and facilitation of corticosteroid responses to stressors (Jankord & Herman, 2008).

The effects of psychosocial stressors are modulated by limbic circuits, which involve the amygdala, hippocampus, and orbital/medial prefrontal cortex. The stressor is appraised by the prefrontal cortex and anterior cingulate. Subcortical structures, including the hippocampus and amygdala, also participate in stressor appraisal. Signal integration has been observed to occur at the hypothalamic and brain stem structures.

Interpretation of findings is further complicated by the fact that cortisol production is regulated through negative feedback at various levels of the HPA axis. Negative signaling occurs at the hypothalamus and pituitary gland when increased levels of free cortisol are detected and halts of the release of CRH and ACTH. The effects of these mechanisms are gradual: unbound levels of cortisol continue to increase for 15 to 20 minutes following a stressor’s cessation (Kirschbaum & Hellhammer, 2000).

*Methods for studying the HPA axis*

Cortisol is the most frequently sampled hormone and can indicate dysfunction at several levels of the HPA axis. Cortisol is often studied as a proxy measure of HPA axis functioning because it is the final product of the HPA axis in humans, it plays a critical role in maintaining homeostasis, and it is relatively easy to sample using minimally invasive procedures such as saliva and urine sampling, and blood draws. Salivary sampling is relatively common as it is a practical, reliable, non-stressful, and non-invasive approach. Additionally, because salivary cortisol is 100% unbound, it reflects the substrates available for interaction with receptors and is arguably the most relevant measure of bioactive cortisol (Hellhammer, Wüst, & Kudielka, 2009). In addition to these methods, cortisol levels can also be examined in the cerebrospinal fluid (CSF). Salivary, urinary, and plasma cortisol levels are highly correlated (Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999).

Several techniques have been used to investigate cortisol levels. Some methods are more passive where natural levels of cortisol are observed during resting condition, known as “basal levels,” such as when a person is just waking up, or during the afternoon. Another approach has been to examine response to stressors, or challenge studies, used to investigate HPA axis response capacity. Researchers have also used physiological challenge studies, or activation of the HPA axis under controlled conditions, such as pharmacological agents with known effects on the HPA axis, as stressors to examine HPA axis functioning.

The best known among the pharmacological challenge tests is the dexamethasone suppression test (DST). Some forms of HPA axis hyperactivity are thought to be due to reduced sensitivity to dexamethasone, a glucocorticoid that provides negative feedback on the production adrenocorticotrophic hormone and cortisol. By binding to receptors distributed throughout the HPA axis, glucocorticoids provide negative feedback, or suppression of synthesis and release of

CRH in the PVN (Owens & Nemeroff, 1993). DST examines the effects of negative-feedback of dexamethasone through anterior pituitary GR activation (Pariante & Miller, 2001). DST is ingested before which is taken right before bed. Cortisol is sampled the following morning and afternoon and compared to the samples obtained when no pharmaceutical agent was administered. Reduced levels of cortisol the morning after ingestion are interpreted as evidence of successful negative feedback of the HPA axis. Non-suppression following DST administration is more common among patients with Cushing's syndrome, and depression, to name a few (Walker et al., 2008). Other sets of patients have shown a response known as hyper-suppression, or depressed levels of cortisol following DST test. Hyper-suppression is more typically found among individuals who have sustained a trauma, such as veterans, natural disaster victims, and adults who have histories of sexual abuse (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Dickerson et al., 2004).

Other pharmacological challenges assess adrenal cortex functioning by administering synthetic ACTH. Smaller doses are used to assess receptor sensitivity, while larger doses can be used to examine maximum adrenal capacity. Physiological and environmental stressors can also be used to examine cortisol responding. Stressors such as physical exercise, keeping one's hand in cold water, or uncontrollable background noise (e.g., Albus, Ackenheil, Engel, & Müller, 1982) can be used to elicit a cortisol responses. Response to physiological stressors does not appear to be impacted by habituation as suggested by similar responses seen across multiple time points (O'Connor & Corrigan, 1987). Laboratory based procedures to induce psychological stress include mental calculation tasks and public speaking tasks. The most commonly used is the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993).

The TSST is an acute, naturalistic stress protocol used in laboratories to induce social stress. The task is unique because it does not rely on self-report, which is susceptible to reporting and cognitive biases. Generally, the task requires the participant to compose and deliver a speech in front of a panel. This allows sampling of several phases of the stress response including baseline measures of stress hormones following a period of habituation, anticipation anxiety, peak stress response, and resolution.

Converging lines of evidence indicate that the TSST is effective at eliciting a stress response. TSST is subjectively stressful as indicated by participant self-report and physiological indicators of stress including increased heart rate, increased stress hormones, and immune system functioning (Dickerson & Kemeny, 2004). The TSST and modified versions of the laboratory stressor, appear to have robust effects and have been used with several clinical and non-clinical populations including patients with mood disorders (Houtepen et al., 2013; Steen et al., 2011), post-traumatic stress disorder (Simeon, Knutelska, et al., 2007; Simeon, Yehuda, et al., 2007), healthy controls with a history of childhood trauma (Carpenter et al., 2007; Elzinga et al., 2007), schizophrenia (Jansen et al., 1998, 2000), anxiety disorders (Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010; van Veen et al., 2009), and first-degree relatives of people with mood disorders (Houtepen et al., 2013; Ellenbogen et al., 2006), to name a few.

A meta-analysis of 208 studies of healthy controls on acute psychological laboratory stress tasks analyzed these tasks to determine which components are more effective at eliciting a stress response (Dickerson & Kemeny, 2004). The tasks reviewed fit broadly into the following five categories: cognitive tasks; public speaking/verbal interaction; public speaking/cognitive tasks; emotion induction; and noise exposure. Findings suggest that only the first three categories were demonstrated to have significant impact on the stress response. Further analyses revealed

that uncontrollability and social evaluation were each significant predictors of cortisol production, presumably because these conditions create situations that threaten the participants' social standing.

Effective components of the TSST have also been examined through systematic modification of the task. Experimental variation of the TSST has suggested that the response elicited by the social stressor is incremental, and affected by the participant's subjective experience, individual factors, and nature of the stressor. Gruenewald and colleagues (2004) determined that social stress, and not the task of delivering a speech, is associated with the stress response. There were significant differences in subjective and physiological responses of healthy controls asked to deliver a speech in front of an audience compared to those of subjects asked to deliver the same speech alone. Interestingly, while both groups reported comparable increases of anxiety and performance esteem, the group exposed to an audience reported more shame and less social self-worth. The group exposed to an audience had significant increases of salivary cortisol following the task and within this group greater increases in shame and greater reductions of social self-worth were associated with greater rises in cortisol. This suggests that different emotions may cause increases in salivary cortisol.

Other researchers examined the effect of the physical presence of a judging panel, and the interaction between the presence & absence of a judging panel and gender. Kelly and colleagues (2007) found that exposure to a panel in the room, an imagined panel (behind a one way mirror), and a virtual reality panel all caused rises in cortisol level in a mixed gender sample of healthy controls. Although no differences in subjective appraisal of task difficulty were detected between the conditions, peak cortisol levels for participants in front of a live panel were significantly higher than the other conditions: the participants delivering the speech in front of a live panel

exhibited cortisol elevations that were on average 90% higher than baseline, while those delivering the speech to an imagined or virtual panel had increases of 30% and 20% from baseline, respectively. No gender differences were detected. In contrast, a study of healthy, young men did not find group differences in cortisol response between men assigned randomly to one of four conditions: two judges in the room ( $n=20$ ), two judges out of the room ( $n=20$ ), a judge in the room ( $n=10$ ), or a judge out of the room ( $n=10$ ) (Andrews et al., 2007). All of the subjects were told that their speech was being videotaped for future evaluation by an expert. The discrepancy in the findings may be due to the fact that Kelly et al. (2007) had a larger sample of participants (although the actual number of subjects per group was not reported, equal distribution among the conditions would indicate that this study had roughly 62 subjects per condition) or due to a greater number of panel members used (Kelly et al. (2007) had four). Interestingly, Andrews et al. (2007) findings were not replicated in a similar study of healthy, young women where subjects speaking in front of a live panel had a larger cortisol response than women delivering a speech to an imagined panel (Wadiwalla, et al., 2010). These findings may suggest that physical presence may differentially impact males and females. Notably, no differences were found when comparing subjects speaking about oneself (high ego involvement) vs. someone else (low ego involvement) (Wadiwalla, 2010).

While effective components of social stress tasks have been largely agreed upon, the emotional predictors of the stress response are not as understood. Denson, Spanovic, and Miller (2009) used high inference coding procedures in their meta-analytic review of laboratory stressors, and have found that exemplars of cognitive appraisals, basic emotions, rumination and worry, and social treat are significantly associated with physiological responses to laboratory stressors. These authors argue that negative affect is too broad a dimension to capture the



nuances of the physiological stress response, and attribute the field's lack of success in finding these predictors to use of broad global measures or behavioral categorizations (e.g., approach, avoidance). Authors recommended use of more measures that capture specific emotional states (e.g., anger, worry, relief).

Efforts have been made to understand the relationship between the stress response and performance. In healthy controls lower cortisol response when faced with a stressor has been associated with positive outcomes. Henry (1992) claimed that a lower adrenocortical response is associated with successful coping, and higher response tends to be an indicator of hopelessness or helplessness. Experimental evidence appears to support this finding as there was a significant negative association between self-esteem and cortisol response in subjects assigned to complete a difficult math test (Pruessner, Hellhammer, & Kirschbaum, 1999).

Gaab and colleagues (2005) found that anticipatory cognitive appraisal accounted for 35% of the variance in salivary cortisol response to a social stressor in a sample of male healthy controls. These authors also reported that the retrospective appraisal of TSST on visual analog scales was unassociated with the cortisol response, while general and specific personality scales were modestly related. Effects of stressor appraisal on cortisol response have also been examined. Similarly, Scholtz and colleagues (2011) found greater cortisol responding to a social stress test in healthy young men who found public speaking to be more threatening. Alexothymia was found to be associated with significantly elevated levels of cortisol at baseline but not during stress exposure in male college students (de Timary, Roy, Luminet, Fillée, & Mikolajczak, 2008).

To my best knowledge, only one study has examined the association between social cognition and salivary cortisol response. Smeets and colleagues (2009) reported better

performance on a complex social appraisal task among male college students with a higher cortisol response to the TSST compared to those with a lower response, and men who were not exposed to the TSST. Similarly, males with higher emotional intelligence (measured responses to a questionnaire asking about one's perception of his emotional intelligence) exhibited a lower cortisol response to the TSST compared to males with lower emotional intelligence scores (Mikolajczak, Roy, Luminet, Fillée, & de Timary, 2007). A different pattern was found among women for whom better performance was associated with a lower cortisol response (Smeets et al., 2009).

#### *Cognitive effects of psycho-social stressors*

Stress hormones easily permeate the blood-brain barrier and are therefore able to directly impact cognitive processes. Stress has been found to moderate complex cognition such as dual task performance, task switching, cognitive flexibility, creativity, estimation, and risk-related decision-making (Allen et al., 2014). Experimentally induced stress has been demonstrated to increase rate of false positives among semantically related distracter words on a recall task (Payne, Nadel, Allen, Thomas, & Jacobs, 2002). Additionally, impulsivity, as measured by performance on go-no-go paradigms, appears to increase following TSST (Scholz et al., 2009).

Performance on measures of emotional cognition has also been examined. High cortisol responders to the TSST showed worse delayed recall for emotional and neural pictures, while individuals without cortisol elevations in response to the TSST had improved memory for emotionally negative pictures (Buchanan & Tranel, 2008). Similarly, TSST stress resulted in reduced memory for emotionally neutral words, and unimpaired or enhanced recall of emotional words and events (Jelici, Geraerts, Merckelbach, & Guerrieri, 2004; Payne et al., 2006; Smeets, Jelicic, & Merckelbach, 2006). Others have also reported enhanced recall for material of similar

emotional valance: studies have found reduced recall of positively charged words (Domes et al., 2004) and enhanced memory for stressor-relevant material (Smeets et al., 2009). Overall, these studies suggest that the effects of TSST on cognition may be moderated by emotional valance.

#### *Social stress tests in psychological disorders*

HPA axis dysregulation has been found in schizophrenia, mood disorders, post-traumatic stress disorder, and other psychiatric conditions and has been suggested to function as a non-specific moderating system on symptom expression. Stress responsivity has been examined in both clinical and non-clinical populations. While the majority of the research has been conducted in depression, some studies have also been done with patients with bipolar disorder, healthy adults with a history of trauma, and panic disorder. Collectively, these findings suggest that abnormalities in endocrine response are not unique to schizophrenia, vary in their presentation, and may be present in individuals without any diagnosable psychopathology. Alternatively, some individuals with diagnosable psychopathology have a normalized stress response. This section briefly reviews this spectrum of pathology with the intention of understanding the hypo-responsivity in schizophrenia on a broader scale.

Mixed findings have been reported in panic disorder ranging from non- to hypo-responsivity to the TSST. Despite exhibiting similar increases in heart rate to healthy controls in response to the TSST, cortisol values obtained during the TSST did not differ from baseline values for all but three of the people diagnosed with panic disorder during the first TSST administration and all but one of the patients during the second administration (Petrowski et al., 2010). These findings were not replicated in a younger sample of individuals with panic disorder who had an attenuated cortisol response to the TSST (Petrowski, K., Wintermann, G. B., Schaarschmidt, M., Bornstein, S. R., & Kirschbaum, 2013). Findings were consistent in salivary and plasma cortisol.

Authors hypothesized that differences between studies may be due to more down regulation of the HPA axis overtime in older patients who have had panic disorder for a longer period of time. Cortisol responses greater exceeding baseline response were observed in adults with social phobia in after the TSST (van Veen et al., 2009) suggesting that non-responsiveness may be not be universal to all anxiety disorders. Due to lack of a control group, it is not clear whether these changes were normative. Despite endorsing greater subjective distress during the TSST, individuals with PTSD had normal cortisol responsiveness (Simeon, Knutelska, et al., 2007; Simeon, Yehuda, et al., 2007).

Adults with a history of childhood adversity exhibit a pattern of under responsiveness to psychosocial laboratory stressors quite similar to the one observed in schizophrenia. Elzinga and colleagues (2007) investigated the cortisol response to the TSST in healthy undergraduate students with a history of adverse events prior to the age of 18. Despite having elevations in heart rate, blood pressure, and subjective stress comparable to those of healthy controls, levels of salivary cortisol were significantly lower in people with a history of two or more traumatic events. These findings remained significant for the overall sample and male subjects, but not for females. Similarly, lower cortisol levels in response to laboratory psychosocial (Carpenter, Shattuck, Tyrka, Geraciotti, & Price, 2011; Kraft & Luecken, 2009; Pierrehumbert et al., 2009; Carpenter et al., 2007) and pharmacological (Carpenter et al., 2009) challenges have been reported in healthy adults with a history of childhood adversity including moderate to severe childhood abuse, sexual and physical abuse, and parental divorce. Damped responsivity to laboratory psychosocial stress tests at age 16 was associated with adversity sustained between the ages of 12-13 and 14-15 (Bosche et al., 2012).

Converging evidence indicates hippocampal pathology. As discussed in the previous section, childhood adversity has been associated with disruptions in hippocampal functioning. Additionally, similar patterns of responsivity were reported in a population of individuals with hippocampal damage. Preliminary evidence suggests that individuals with bilateral hippocampal lesion exhibit an attenuated cortisol response to a TSST in the context of otherwise normal physiological responding (e.g., elevated heart rate) and levels of subjective stress (Buchanan, Tranel, & Kirschbaum, 2009). Individual with lesions to parts of the brain other than the hippocampus showed similar responding to healthy controls.

Investigation of cortisol response to psychosocial stressors in bipolar disorder has yielded mixed results. Steen et al. (2011) reported attenuated cortisol response in patients with schizophrenia and bipolar disorder in response to a mental challenge task. No differences between the clinical populations were detected. Contrarily, Houtepen et al. (2013) found that differences in cortisol response between healthy controls and individuals with bipolar disorder became non-significant after including antipsychotic use a covariate in the analysis. Thus far, studies of first degree relatives of patients with bipolar disorder have indicated normal cortisol stress response in adult siblings (Houtepen et al., 2013) and adolescent children (Ellenbogen et al., 2006) of individuals with bipolar disorder.

Studies of depression converge on a largely normal cortisol response to psychosocial stress tests. Meta-analysis examining HPA axis reactivity to laboratory psychosocial challenges concluded that patients with non-psychotic depression cannot be distinguished from healthy controls on the basis of their stress response (Ciufolini et al., 2014). This is largely consistent with a previous meta-analysis of responses to stress tests in depression that reported elevations in cortisol levels during the recovery phase of the laboratory stress tasks only (Burke, Davis, Otte,

& Mohr, 2005). Normal stress responding has unsurprisingly also been reported in individuals who have been in remission from depression for at least six months (Lange et al., 2013).

#### *Impact of early adversity on HPA axis function*

There is a strong association between childhood trauma and psychosis. Meta-analysis of 41 studies indicated that individuals who had experienced adversity during childhood were almost three times more likely to exhibit psychotic symptoms than those who did not endorse childhood adversity (Varese et al., 2012). These associations remained significant after demographic, SES, family history of mental illness, and drug use were controlled for. Large-scale studies have concluded that the relationship is causal and dose dependent: more severe or frequent childhood abuse is associated with greater illness severity (Heins, et al., 2011; Lysaker, Beattie, Strasburger, Davis, 2005; Read, van Os, Morrison, Ross, 2005). Similarly, individuals with more impairing symptoms of psychosis are more likely to report more severe trauma in childhood (Saha et al., 2011; Janssen et al., 2004). Within schizophrenia childhood trauma also appears to interact with symptoms of schizophrenia: individuals with a history of childhood trauma had more hospitalizations, earlier onset of the disorder, and earlier first hospitalization (Alvarez, Oses, Foguet, Sola, Arrufat, 2011; Schenkel, Spaulding, DiLillo, Silverstein, 2005).

Psychological and biological approaches have been used to explain the link between psychosis and childhood trauma. Psychologically, researchers have suggested that early trauma impacts cognitive processes such as attributional biases, source-monitoring failures, dissociation, and disruption in attachment (Morrison, 2004; Morrison, Frame, & Larkin, 2003; Morrison, 2001). Traumatic experiences have been linked the presence of negative beliefs about the self, others, and the world.

Models of cognitive changes following stress exposure have been examined in animals. An animal is permanently changed by the experience of stress. As described by Weiner (1992) animals “may learn from the experience; they may habituate with its reception; or their reaction patterns may never again be the same.” (p. 159). Nonhuman primates with inconsistent parental contact early in life are more fearful and submissive, and are more likely to exhibit abnormalities in levels of key neurotransmitters such as serotonin, norepinephrine, and dopamine (Rosenblum & Andrews, 1994; Rosenblum et al., 1994).

The findings in human literature appear to converge with the animal research: childhood adversity has been associated with cognitive and behavioral disturbances. Studies of stress responsivity in children with a history of trauma also support disruption at the level of psychosocial threat appraisal and response regulation (Gunnar & Quevedo, 2007). An experience sampling study found that individuals with a history of childhood trauma report more negative affect and psychotic symptoms in response to everyday stressors than patients without childhood trauma (Lardinois, Lataster, Mengelers, Van Os, & Myin-Germeys, 2011). Furthermore, childhood trauma was found to be associated with recent adversity in a sample of psychotic individuals (Lataster, Myin-Germeys, Lieb, Wittchen, & Van Os, 2012).

Experience of trauma in childhood can be particularly impactful due to increased neuroplasticity. An interaction between sensitive developmental processes and extreme stress can have long-term effects. Grassi-Oliveira and colleagues (2008) explain that immature organisms try to adapt by making changes permanently, compared to mature organisms, which tend to make temporary compensational adjustments. Thus, traumatic early experiences may cause neurological “scars” which may underlie vulnerability to future psychopathology.

While the mechanisms underlying stress-sensitization are not well understood, several biological, neurobiological, and behavioral changes have been identified. Read and colleagues (2014) published a review of the literature examining biological mechanisms linking the experience of early adversity to psychosis that included 125 articles offering either direct confirmation or support of the link. The traumagenic neurodevelopmental model (Read, Perry, Moskowitz, & Connolly, 2001) posits that in some individuals early adversity leads to changes in neurobiological stress-responsivity, which underlie the biological vulnerability to develop symptoms of psychosis in adulthood. The 2014 review indicated that early adversity either leads to or is associated with heightened stress sensitivity, HPA axis dysfunction, abnormalities within the frontal lobes and hippocampus, lower levels of BDNF, increased sensitivity in mesocorticolimbic dopamine system, and cognitive dysfunction, particularly deficits in memory and executive functioning.

One of the mechanisms proposed to explain long-term HPA axis dysfunction is stress desensitization. Repeated stress may cause hypersecretion of cortisol following the childhood stressor(s), resulting in eventual desensitization of the HPA axis and leading to reduced responsivity in the long-term (Heim et al., 2000). Childhood abuse results in increased basal CRH levels, which lead to decreased pituitary sensitivity to CRH stimulation through down-regulation of CRH receptors (Grassi-Oliveira, Ashy, & Stein, 2008). Long-term CRH elevations lead to a relative adrenal insufficiency.

### **Schizophrenia**

As previously mentioned, the HPA axis has been investigated as the set of biological structures that mediate the relationship between stress and risk for developing mental illness. The HPA axis has also been proposed to trigger the series of biological events that contribute to the



emergence of psychotic symptoms, particularly positive symptoms (Walker, Mittal, & Tessner, 2008; Holtzman et al., 2013)). Gispén-Wied and colleagues (2000) note inconsistencies in the schizophrenia literature, as some studies report intact baseline cortisol levels, while others report evidence of hypercortisolemia in schizophrenia patients. Examination of cortisol in response to laboratory stressors has yielded more consistent findings.

#### *Baseline HPA axis function*

Given the fact that the HPA axis plays a major role in homeostasis, understanding diurnal rhythm has been of great interest. Baseline activity is a measure of HPA axis functioning outside of an immediate stressor. An organism's set points can change depending on its experience, therefore the term "baseline" must be considered in the context of one's history (Danese & McEwen 2012).

In an effort to understand the diurnal rhythm of cortisol secretion in schizophrenia, measures of cortisol have been taken at various time points during the day including morning, afternoon, and evening. Both blunted cortisol awakening response (CAR) and elevated levels of cortisol in schizophrenia have been reported in the morning (Girshkin, Matheson, Shepherd, & Green, 2014; Monteleone et al., 2014; Mondelli et al., 2010; Braehler et al., 2005). Elevations have also been reported in afternoon cortisol levels (Gallagher et al., 2007; Walsh et al., 2005; Ryan et al., 2004). Evidence suggests that hypercortisolemia predates onset of the disorder itself: Higher levels of cortisol have also been reported in a large sample of people who are at elevated risk of developing psychotic disorder (Walker et al., 2013) and in unaffected siblings of individuals with schizophrenia relative to healthy controls (Collip et al., 2011).

Meta-analysis of 64 studies of morning cortisol levels in schizophrenia and bipolar disorder concluded that there is moderate quality evidence of small to moderate elevations in

peripheral morning cortisol levels in both disorders relative to healthy controls, without significant differences between the two disorders (Girshkin, et al., 2014). In contrast to the CAR, which is a naturally occurring peak in cortisol occurring within the first 30-40 minutes after awakening, morning cortisol levels and has been argued to be a reaction to the mild stressor of waking up, which are sampled *immediately* after awakening reflect basal cortisol levels (Clow, Thorn, Evans, & Hucklebridge, 2004; Wust et al., 2000). Greater effect sizes in schizophrenia were reported for patients who are currently hospitalized, unmedicated, and those who have had more than one psychotic episode. While the majority of findings indicate similar levels of baseline cortisol between the genders (Girshkin et al., 2014; Mondelli et al., 2010), at least one study has found attenuations in men only (Pruessner et al., 2008).

Different correlations between diurnal cortisol levels were found in patients in healthy controls: in patients diurnal cortisol levels were negatively correlated with the number of recent stressors, while in healthy controls there was a positive association (Modelli et al., 2010). This study also found that awakening cortisol levels were blunted in the patients with first episode psychosis (FEP) irrespective of medication status relative to healthy controls. Awakening cortisol was positively correlated with history of childhood sexual abuse.

Acute use of anti-psychotics, particularly atypical ones, tends to decrease cortisol levels, an effect that appears to normalize with chronic use. Attenuated levels of plasma cortisol have been observed in healthy controls following administration of antipsychotic medications (Cohrs et al., 2006). Further evidence comes from comparing populations of schizophrenia patients: hypercortisolemia has been reported in unmedicated FEP patients (Ryan et al., 2004) and Modelli et al. (2010) reported that FEP patients with less than two weeks of treatment with atypical antipsychotics had higher diurnal levels of cortisol than FEP patients with two or more

weeks of treatment and healthy controls. No differences were reported between the latter groups, suggesting that two weeks of treatment may normalize morning hypercortisolemia. Chronic use of anti-psychotic medications cease to lower cortisol levels (Meador-Woodruff & Greden, 1998), as evidenced by studies of medicated and chronic schizophrenia patients have also reported elevations in baseline cortisol levels (Gallagher et al., 2007; Yilmaz et al., 2007). Others have reported normal cortisol levels in schizophrenia patients on and off medications (Rao et al., 1995), suggesting that differences may be due to disorder related heterogeneity.

Possible interpretations of HPA hyperactivity include results of chronic HPA axis dysregulation, compounding effects of illness, or fluctuations related to illness exacerbation. It has also been proposed that elevations in basal levels of cortisol are the result of an endophenotypic marker of illness (Cheng et al., 2010). Others have hypothesized elevations may be due to symptoms of depression or negative symptoms (Gispén-de Weid, 2000). Overall, findings regarding baseline levels of cortisol in schizophrenia remain mixed as several studies have reported cortisol values that are within normal limits (Jansen et al., 2000; Rae et al., 1995; Roy et al., 1986; Kemali et al., 1985), suggesting that further research is warranted.

### *Challenge Tests*

Unlike passive measures of baseline functioning, challenge tests investigate HPA axis functioning in response to a stressor. This type of testing has been argued to be more sensitive, representative of HPA axis functioning, and a better indicator of HPA axis dysfunction (Holsboer, 2001). As previously discussed, challenge tests may be in the form of pharmacological, physical, and psychosocial.

DST studies have been used to investigate HPA axis functioning in schizophrenia. Meta-analyses of 34 studies DST studies in schizophrenia reported that patients have significantly

higher rates (26.4%) of non-suppression (defined as responding above a cut-off value of 5 mcg/dL of cortisol the morning following administration) when administered 1-mg of dexamethasone compared to healthy controls (5.0%) and have greater variability of non-suppression values (Yeragani, 1990). This meta-analysis did not find relationships between non-suppression and symptoms of depression, severity of positive symptoms, or schizophrenia subtype. Tandon and colleagues (1991) reported that 39% of the 44 individuals who were admitted for inpatient treatment of schizophrenia were DST non-suppressors. These patients were off medications for a minimum of two weeks prior to study participation. Following four weeks of treatment using clinically determined doses of typical antipsychotic medications, 14% of the sample remained non-suppressors. Similarly, a study of FEP male patients found that acute treatment lowered the percentage of non-suppressors from 14% of the total sample to 5% (Ceskova, Kasparek, Zourkova, & Prikryl, 2006). These findings have not been replicated in chronic schizophrenia. Ismaili and colleagues (1998) did not find non-suppressors in a sample of medicated schizophrenia patients and similar levels of salivary cortisol were found following DST in healthy controls and schizophrenia patients (Jansen et al., 2000). Similarly, in a mixed sample of schizophrenia patients, 38% of the sample were non-responders, the majority of whom were unmediated (Lammers et al., 1995). Together these findings suggest that DST non-suppression may be responsive to pharmacological intervention, or is associated with acute distress in schizophrenia.

Other pharmacological challenge tests have indicated normal responsivity in schizophrenia. Jansen and colleagues (2000) did not find differences between people with schizophrenia and controls in cortisol levels following dexamethasone ingestion and hydrocortisone. Both tests were used because they reflect different aspects of HPA axis

functioning: dexamethasone is mainly active at the pituitary level while hydrocortisone has more affinity for supra-pituitary glucocorticoid receptors (De Kloet, 1991). Similarly, metabolic stress induced by 2-deoxy-D-glucose (2DG), a glucose analog that impairs glucose metabolism and causes a state similar to hypoglycemia, caused similar cortisol elevations in patients with schizophrenia and healthy controls (Ellman et al., 1998; Kathol et al., 1993; Breier & Buchanan, 1992). Additionally, *m*-chlorophenylpiperazine, a serotonin agonist that directly stimulates the HPA axis, induced a normal increase of pituitary-adrenal hormones (Kahn, Davidson, Siever, Sevy, & Davis, 1994).

One challenge in interpreting studies that utilize laboratory-based stressors to modify cortisol levels is that differential activation of the HPA axis occurs depending on unique characteristics of the stressor. For physical stressors, proxies of the exteroceptive stress system functioning, the most important factor is that stimuli intensity, while for psychological stressors, proxies of the interoceptive stress system, greater unpredictability, ego-involvement, novelty, and less controllability of the task will elicit a stronger HPA axis response (Gispens-de Wied, 2000). The following section will examine laboratory stressors by grouping them their respective dichotomy.

There have been few studies examining cortisol response to physical stressors in schizophrenia, and those that have been conducted have yielded mixed findings. Intact cortisol levels were observed following a physical exercise on a stationary bike (Jansen et al., 2000). Studies examining stress response due to medical procedures, however, have consistently found attenuation in response to surgical stress (Kudoh, Ishihara, & Matsuki, 1999; Kudoh, Kudo, & Ishihara, 1997), and lumbar puncture (Breier, Wolkowitz, Doran, Bellar, & Pickar, 1988). Thus, it may difficult to generalize, as it is not clear how anesthetics may interact with antipsychotic

medications. One study has reported greater cortisol stress responding in schizophrenia. Patients with primarily paranoid symptoms demonstrated an overall elevation in cortisol in response to a cold pressor test, active relaxation, noise test, and mental calculation relative to healthy controls (Albus, Ackenheil, Engel, & Müller, 1982). This study is somewhat difficult to interpret as authors have confounded the effects of physiologically and physically stressful events.

Given the mixed finding, results of studies of examining cortisol stress responding to mental and social stressors have yielded surprisingly consistent findings. Laboratory studies of HPA axis responsivity in schizophrenia found attenuated levels of cortisol in response to psychosocial stressors. To date three in-vivo studies examining social stress response have been conducted in schizophrenia (Brenner et al., 2009; Jansen, Gispen-de Wied, & Kahn, 2000; Jansen et al., 1998) and one examining cortisol response to a test of mental arithmetic (Steen et al., 2011), one study in first episode psychosis (van Venrooij et al., 2012), and one study in people at ultra high risk (UHR) for developing psychosis (Pruessner et al., 2013). Despite methodological differences, the findings are consistent: four studies found attenuated cortisol levels in response to the stressor in the clinical populations compared to healthy controls (Pruessner et al., 2013; Steen et al., 2011; van Venrooij et al., 2012; Jansen, Gispen-de Wied, & Kahn, 2000; Jansen et al., 1998). One study reported significantly lower cortisol values in schizophrenia for four of the time points examined (baseline, anticipatory, immediately after stressor and 15 minutes after the stressor) in male subjects only (Brenner et al., 2009). A meta-analysis of three studies of laboratory social stress tests (Van Venrooij et al., 2012; Brenner et al., 2011; Jansen et al., 2000) revealed that relative to healthy controls, schizophrenia subjects had lower levels of cortisol during the anticipatory phase and lower peak cortisol levels;

however, no significant differences in the recovery phase of the social stress test or in overall change in cortisol levels were found (Ciufolini, Dazzan, Kempton, Pariante, & Mondelli, 2014).

Holtzman and colleagues (2013) proposed three explanations to account for the dampened cortisol response when faced with social stressors: 1) ceiling effects on cortisol production; 2) experiencing external factors as less stressful after onset of psychosis; and 3) the psychosocial events that are threatening may become idiosyncratic. Each of the explanations are examined below.

It does not appear that there are ceiling effects in cortisol production in schizophrenia. The authors of meta-analytic study ruled out this possibility based on the fact that change in cortisol (difference between lowest values and peak values) and variability for all time points except the task recovery were equal for patients and controls (Ciufolini, et al., 2014). The meta-analysis did find a significant difference between healthy controls and schizophrenia patients in peak cortisol values during the laboratory social stressor was reported, which may be indicative of some differences of ceiling effects. van Venrooij et al. (2012) did not find differences in peak values between patients and controls. Unfortunately, analyses of differences in peak values were not reported in the other articles. Another potential confound is the fact that these studies were not conducted in front of a live panel, which, as previously mentioned, has been associated with significantly greater cortisol response compared to imagine panels (Kelly et al., 2007) and two of the studies recruited both males and females.

There is no empirical evidence to support the second claim, or that patients experience external events as less stressful. Patients' subjective ratings of anxiety and stress prior to and during the social stress tests are equal to or greater than those of healthy controls (van Venrooij et al., 2012; Jansen et al., 1998). Additionally, measures of autonomic activation were either

comparable or higher for patients than healthy controls, including increases in heart rate, and mean arterial pressure (van Venrooij et al., 2012; Brenner et al., 2009; Jansen et al., 1998). Patients reported experiencing significantly less control while speaking in public (van Venrooij et al., 2010), which is generally associated with increased anxiety, and endorsed the use of more confrontational and avoidant coping strategies during the psychosocial stressors than healthy controls (Jansen et al., 2000). These findings are consistent with other studies that found that individuals diagnosed with schizophrenia are more likely to perceive both positive and negative events as more stressful, less controllable, and are more likely to report that they handled the stressful situation poorly compared to healthy controls (Horan et al., 2005). Jointly these findings indicate that there may be differences in the subjective experience that may affect neurobiological regulation of the stress response; however, current evidence suggests that patients with schizophrenia experience *more* stress than healthy controls in the similar situations.

Finally, the third explanation, or that psychosocial events may become idiosyncratic for individuals with schizophrenia, has not been directly tested as it does not propose a hypothesis for how the idiosyncrasies are expected to impact HPA functioning.

One study that examined the relationship between current positive symptoms and cortisol response to a psychosocial stressor did not find a significant association (Jensen et al., 1998). Additionally, the fact that dampened responsivity was reported in first episode schizophrenia patients in a psychiatric hospital (van Venrooij et al., 2012), clinically stable chronic schizophrenia outpatients (Jansen et al., 1998, 2000), and UHR individuals who have never been psychotic (participants included on the basis of *attenuated* psychosis), would suggest that psychosis alone cannot account for this finding.



Furthermore, attenuated cortisol response to psychosocial stressors does not appear to be due to disease-chronicity or use of antipsychotic medications. As stated previously, attenuated cortisol levels were reported first episode patients and individuals who are UHR ( Pruessner et al., 2013; van Venrooij et al., 2012). Both groups are naïve to antipsychotic medication, suggesting that the differences in the cortisol response to psychosocial stress test predate medical usage.

This small body of literature is not without limitations. One confound in this research is smoking. Long-term nicotine dampens HPA axis responsivity (Kudilka, Hellhammer, & Wüst 2009), which is particularly concerning for this population given the high prevalence of smoking in schizophrenia. For example, one study found that 88% of individuals with schizophrenia smoke (Mitchell & Dahlgren, 1986), and rates of smoking in schizophrenia have been estimated to be 2-3 times higher than the general population (Kelly & McCreadie, 2000). van Venrooij and colleagues (2012) recruited nonsmoking controls, which increases the probability of finding a significant difference between the groups given that half of the schizophrenia sample smoked. This concern is somewhat mitigated by the fact that comparison of peak cortisol values of the smoking and non-smoking patients was non-significant. Pruessner et al.'s (2013) study of UHR subjects suggests that the attenuated responding is not due to smoking given that there were equally small numbers (3/21) of smokers in the UHR and healthy control samples, and that long-term smoking is less likely in this younger sample of subjects (mean age of subjects was about 20). Smoking status was not reported by the other studies (Jansen et al., 1998, 2000; Brenner et al., 2009).

Another complication is the use of mixed gender samples. Three of the studies (Pruessner et al., 2013; Brenner et al., 2008; Jansen, 2000;) used mixed gender samples and did

not correct for menstrual phase or report use of oral contraceptives. A large-scale review (Kanjantje & Philips, 2006) concluded that adult females generally show lower HPA axis responsiveness than men, greater responding during the luteal phase, and lower levels of salivary cortisol in women using oral birth control. Additionally, experimental manipulation of the stressful social situation has found differences in factors that impact responding in the genders (e.g., Smeets et al., 2009), suggesting that triggers may differ.

Therefore, it is possible that averaging across genders may obscure significant findings between groups and misrepresent the relationship between cortisol levels and other psychosocial variables of interest.

There is some evidence to support the hypothesis that predictors of cortisol response are different for people with schizophrenia and healthy controls. Coping style and stress reactivity explained an additional 20% of the variance in quality of life for schizophrenia but not healthy controls and that lower levels of cortisol in response to the TSST were associated with a higher self-reported quality of life in schizophrenia (Brenner et al., 2011). Pruessner and colleagues (2013) reported lower overall cortisol release during the TSST to be associated with higher self-reported stress over the past year in UHR participants but not healthy controls. Self-reported stress was measured by a single rating on a Likert scale from “not stressed” to “very stressed” in response to, “How stressed did you feel in the last year?” No associations were found between cortisol release, subjective stress during the task, or subjective stress during the last month. Additionally, those who rated the TSST to be more stressful tended to have lower self-esteem and reported use of fewer coping strategies.

Evidence suggests that there may be differences in subjective experience during the psychosocial stress test. Male first episode schizophrenia patients and controls were found to

have experienced similar levels of stress in the past month (van Venrooij et al., 2010). Patients reported higher levels of anxiety than controls during the task as measured by the Spielberger State Trait Anxiety Inventory. Ten-point visual analogue scales found no differences between patients and controls in terms of nervousness before or during the TSST, or the level of experienced control during the preparation phase. Patients were more nervous after the public speaking task and reported experiencing less control during the task than healthy controls. This finding was not always replicated despite the similarity in methodology. Similar ratings of anxiety were obtained in schizophrenia and healthy controls when asked to rate the stressfulness of the task (1= not stressed at all, 10=extremely stressed) (Brenner et al., 2009) and on the STAI (Jansen et al., 2000).

Only one schizophrenia study has examined the relationship between self-reported coping behaviors used during the TSST and the stress response. Trend level negative associations between self-reported use of escape/avoidance coping during the TSST and cortisol response was observed for the overall sample. Reported tendency to use passive coping strategies in day-to-day life was negatively correlated with cortisol and people with schizophrenia reported using more confrontive coping and escape/avoidance coping than healthy controls during the TSST. Previous study found that males with schizophrenia reported using more avoidant and passive coping strategies than healthy controls in a hypothetical social situation; however, no difference in coping strategy was found in problem solving a hypothetical non-social situation (Jansen et al., 1998). This suggests that people with schizophrenia may have both physiological and psychological difficulty coping with socially stressful situations.

*Social cognition in schizophrenia*

Social cognition is broadly defined as the mental operations that underlie social interactions. Attendees of a National Institute of Mental Health Workshop focused on social cognition in schizophrenia used the following definition of social cognition: “the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others” (Pinkham et al., 2013). A focus group of researchers examining social cognition in schizophrenia concluded that research can be divided into five partially-overlapping domains: theory of mind, social perception, social knowledge, attributional bias, and emotional processing (Green et al., 2008).

Impairments in social cognition are a defining feature of schizophrenia. Deficits in social cognition are often evident prior to illness onset and are more prevalent among non-affected first-degree relatives of people with schizophrenia compared to those without affected first degree relatives (Hans, Aurbach, Asarnow, Styr, & Marcus 2000; Dworkin, et al., 1993). Social cognition is conceptualized to be semi-independent of cognition, and its domains are differentially impacted (Silver, Bilker, Goodman, 2009; Mancuso, Horan, Kern, & Green, 2011). Impairments in social cognition have been linked to lower functional and occupational functioning and lower quality of life (Horan et al., 2011; Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011; Bell, Tsang, Grieg, & Bryson, 2009; Couture, Penn, & Roberts, 2006; Brune, 2005). It has also been observed that improvements in social cognition following specialized training are associated with improvements in day-to-day social functioning, social skills, relationships, and enhanced social adjustment (Eack, Greenwald, Hogarty, Keshavan, 2010; Combs, Adams, Penn, Roberts, Tiegreen, & Stem, 2007).

Studies of emotional processing found that people with schizophrenia experience higher levels of negative emotion than healthy controls and find social interactions to be less enjoyable.

Naturalistic studies of day-to-day experience such as random experience sampling have been used to examine self-reported emotions outside of the laboratory setting. People with schizophrenia were found to have more intense and variable negative emotions than healthy controls (Myin-Germeys, Delespaul, & deVries, 2000). Gard and Kring (2009) reported that while overall levels of emotion experienced are comparable, people with schizophrenia experience social interactions to be less pleasant and more activating compared to healthy controls. Similarly, patients reported more withdrawal and desire to be alone when around others compared to healthy controls (Oorschot, et al., 2011). A meta-analysis of naturalistic studies concluded that individuals with schizophrenia report more negative feelings following stressful situations compared to patients with depression, bipolar disorder, unaffected relative of a person with schizophrenia, and healthy controls (Kring & Moran, 2008). Furthermore, these findings are consistent with a meta-analysis of 26 laboratory-based studies of emotional experience in schizophrenia which found that patients report higher levels of aversion in response to both positive and negative stimuli (Cohen & Minor, 2011).

The evidence for difference in both appraisal and experience of social situations in schizophrenia suggests the need for better understanding of the experience of the TSST in schizophrenia. Jones and Fernyhough (2007) pointed out that the diathesis-stress model proposed by Walker & Diforio (1997) did not address how the subjective experience of a stressor impacts physiological response. The authors were particularly interested to know if the literature based on healthy controls (or the importance of social threat and uncontrollability) will extend to the schizophrenia population.

## **Hypotheses**

Hypothesis I: Based on previous research, it is hypothesized that individuals with schizophrenia will exhibit small increases in cortisol relative to healthy controls. Conversely, group differences are not expected in heart rate and rating of negative emotions on the VAS. Task appraisal differences are expected to emerge when examining the PASA; it is hypothesized that the SZ group will have a higher primary appraisal and lower secondary appraisal of the TSST.

Hypothesis II: It is hypothesized that people with schizophrenia who have better social cognition will have a greater cortisol response to the psychosocial stressor, while healthy controls with better social cognition will have a smaller cortisol response.

Similarly, it is hypothesized that better performance on a test of everyday skills will be positively related to cortisol response for the SZ group, and the opposite relationship will be observed in the HC group.

Hypothesis III: It is also hypothesized that the prevalence of childhood adversity would be greater in the schizophrenia group than among the healthy controls. Lastly, it is hypothesized that individuals who report more childhood adversity will respond with lower levels of cortisol to the social stress test across the sample. It is also hypothesized that childhood sexual abuse will account for a greater portion of variance in the cortisol released than other forms of abuse sustained during childhood.

## CHAPTER 3

### METHODS

#### **Participants**

Thirty-six participants enrolled in the study. Three healthy controls were excluded from the study. One healthy control gave minimal effort as was determined by poor performance, another healthy control reported that he was recently diagnosed with adrenal fatigue, and the third healthy control was uncooperative. These participants were paid for the time they spent working in the laboratory and dismissed from further participation. Thirty-three men between the ages of 18 and 65 were included in the present study. Sixteen people were diagnosed with schizophrenia or schizoaffective disorder, and seventeen people were healthy controls. The sample consisted of only males because previous findings indicate that females have a distinct hormonal response to stressors (Kirschbaum et al., 1999) and a different relationship between hormonal response and social cognition than males (Wadiwalla, et al., 2010; Smeets et al., 2009; Andrews et al., 2007). Together these findings suggest that generalizability between the genders is limited; therefore, the current study focused on investigating the response found in males to reduce variability in the data.

Study exclusion criteria consisted of: history of traumatic brain injury, history of electro-shock therapy, inability to provide informed consent, English is not the primary language, inability to comprehend the current testing battery, history of substance abuse or dependence in the past six months, or were unable to participate due to sensory impairments. Individuals with medical illness known to affect functioning of the central nervous system or conditions that are known to cause disturbances in HPA axis functioning were also excluded. Additionally, healthy

controls were excluded if they had a family history positive for one or more first-degree relatives with schizophrenia or bipolar disorder.

## **Measures**

Several domains of functioning were measured including: clinical symptoms, social cognition, functional capacity, estimated intelligence and cognitive functioning, and self-report measures that examine stress response and history of trauma. Additionally, there were several outcome measures used to assess stress response associated with the Trier Social Stress Test (TSST).

**Clinical Symptom Measures.** These instruments were used to confirm study eligibility and measure current symptom levels.

**Structured Clinical Interview for DSM-IV.** Individuals with schizophrenia were diagnosed with schizophrenia by their treating clinician. Clinical diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID; First, Gibbon, Spitzer, & Williams, 2002). The SCID was also used to ensure that the healthy controls did not meet criteria for any mental health diagnosis in the last year or a lifetime diagnosis of schizophrenia or bipolar disorder. The SCID is designed to identify clinical symptoms and determine diagnoses that meet criteria for psychopathology. Criteria from the DSM 5 (American Psychiatric Association, 2013) were also consulted.

**Brief Psychiatric Rating Scale.** The Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) consists of 18 clinician rated items designed to measure several aspects of psychopathology including mood, disorganization, anxiety, and positive and negative psychotic symptoms. The ratings were made based on answers to a semi-structured interview that asked about the previous two weeks' worth of functioning, and behavioral observations made during



interview. Each item is rated on a scale of 1 to 7 (absent to extremely severe). A total score is derived by summing up all of the items.

***Scale of Assessment of Positive Symptoms.*** The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) is a 34-item clinician rated scale that assesses positive symptoms including, hallucinations, delusions, thought disorder, bizarre behavior, and formal thought disorder on a scale of 0 to 5 (absent to severe). Global ratings for each domain evaluate the overall severity of the symptom. The scores are based on the participant's report of presence of the symptom in the past two weeks and behavioral observations during the interview. Adding the 34 items produces a total score reflecting an overall level of positive symptoms.

***Scale of Assessment of Negative Symptoms.*** The Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983) is a 30 item clinician-rated scale designed to measure negative symptoms across the following domains: affective flattening, alogia, avolition-asociality, anhedonia, and attentional impairment. Global ratings are made to assess the overall severity of each of the domains, a total sum of all of the items administered indicating overall severity.

***Estimated Intelligence and other Measures of Cognition.*** Three subtests from the Wechsler Adult Intelligence Scale, third edition (WAIS-III; Wechsler, 1997) were used to calculate an estimated current intelligence. Those three subtests are: Block Design (BD), Vocabulary (VO), and Matrix Reasoning (MR). The regression equation used to estimate current full scale IQ is  $(VO \text{ Scaled Score} \times 2.727) + (BD \text{ Scaled Score} \times 2.727) + 42.535$  (Schoenberg, Scott, Duff, & Adams, 2010).

***WAIS-III Block Design Subtest.*** The Block Design subtest (Wechsler, 1997) is a test of perceptual reasoning. This subtest asks the respondent to assemble red and white blocks to match

images of increasing complexity within a time limit. This is a test of perceptual reasoning. Points were awarded for correct completions within the time limit and the points are summed to obtain a total raw score. Raw scores are then converted to age-corrected scaled scores.

***WAIS-III Vocabulary Subtest.*** The Vocabulary subtest (Wechsler, 1997) assesses the crystallized ability of vocabulary knowledge. This test asks respondents to define increasingly complex words and awards points for correct responses. Total points earned are summed together and converted to age-corrected scaled scores.

***WAIS-III Matrix Reasoning Subtest.*** The Matrix Reasoning subtest (Wechsler, 1997) assesses perceptual reasoning by asking respondents to solve visual puzzles by selecting the missing piece from a set of potential responses. Raw scores are converted to age-corrected scaled scores.

**Social Cognition.** Measures were used to assess various aspects of social cognition and functioning.

***Reading of the Mind in the Eyes Test.*** The Eyes Test (Baron-Cohen et al., 2001) is a test of one's ability to accurately determine the expression communicated by a set of eyes. The participant was asked to select one adjective from four options that most closely matches the emotion communicated by a narrowly cropped eye region. The participant is awarded a point for the correct response and does not receive feedback about the accuracy of the selection made. The total number of items answered correctly was used as the outcome variable for the current study.

***Hinting Task.*** The Hinting Task (Corcoran et al., 1995) consists of ten social scenarios that are read aloud and requires that participants to infer the implied intention of a character in a social scenario. The participant is read a scenario where one of the characters states a need indirectly and is then asked to explicitly state what the implied intent is. If the respondent gets a

question either fully or partially wrong, designated prompts are provided that allow the participant an opportunity to earn additional credit. This assessment does not have a discontinue criteria therefore all items were administered.

***WAIS-III Picture Arrangement.*** The WAIS-III Picture Arrangement (PA) subset consists of pictures of characters in ten social scenarios. Participants are asked to find the logical order for each set of cards that would convey a coherent story. Each set of cards is increasingly more difficulty than the previous set of cards and participants receive credit for only correctly arranged sets. PA is sensitive to social cognition deficits in schizophrenia and bipolar disorder (Thaler et al., 2013). Raw score of correctly arranged sets were used.

**Functional Capacity.** Functional capacity, or ability to attend to day-to-day responsibilities, was assessed using.

***UCSD Performance Based Skills Assessment.*** The UCSD Performance Based Skills Assessment (UPSA; Patterson, Goldman, McKibbin, Hughs, & Jeste, 2001) is a laboratory measure of day-to-day functioning. This measure assesses functioning across five domains: planning recreational activities, finance, communication, transportation, and house hold chores. Each of the subscales yields a raw score, which was transformed into a percentage and then multiplied by 20 to contribute proportionally to a total score. The five scores are then added together to yield a total score ranging from 0-100.

This instrument was developed to for assessment of psychiatric populations. Impaired performance has been reported among people with schizophrenia (Vogel, 2015).

**Self-Report Questionnaires.** Self-report questionnaires were used to examine trauma history, stress reactivity, and defeatist beliefs.

***Childhood Trauma Questionnaire.*** The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) is a 28-item self-report questionnaire that assesses childhood trauma, including emotional, physical, and sexual abuse, and emotional and physical neglect. Additionally, three questions assess potential Minimization/Denial. The scale consists of five items per abuse type that are rated on a 5 point Likert scale ranging from 0 to 4 (never true to very often true). The total score per trauma type was used in further analysis. Studies have demonstrated comparable reliability of report of childhood abuse for individuals with psychiatric diagnosis and healthy controls (Read et al., 2005).

***Life Events Checklist.*** The Life Events Checklist (LEC; Gray, Litz, Hsu, & Lombardo, 2004) has a list of 16 different and potentially traumatic life events that are often associated with PTSD. The LEC was used to identify potentially traumatic events experienced by the participant during his lifetime, allowing for the comparison of overall traumatic events that one has been subjected to personally, witnessed, or learned about. Additional options of “not sure” and “doesn’t apply” are also included. Total number of items endorsed per category was included in analyses.

***Defeatist Performance Beliefs from the Dysfunctional Attitudes Scale.*** The Defeatist Performance Beliefs (DPB) is a subscale of the Dysfunctional Attitudes Scale (DAS; Weissman, 1978). This measure consists of 15 mal-adaptive beliefs (e.g., “It is difficult to be happy unless one is good looking, intelligent, rich, and creative.”) and asks participants to rate to what extent they agree with each item on a scale of 1 (Agree Totally) to 7 (Totally Disagree). The items are reverse scored, therefore lower scores on the DPB correspond with lower rates of defeatist beliefs, and the sum of all of the responses is the total score.

***Perceived Stress Reactivity Scale.*** Perceived response to common and potentially stressful situations was measured by the Perceived Stress Reactivity Scale (PSRS; Schlotz, et al., 2011). This questionnaire presents a stressful scenario (e.g., “When others criticize me...”) and asks respondents to select the response that most closely resembles their reaction to stress from three options. Higher scores correspond to higher perceived stress reactivity. The PSRS measures Perceived Reactivity to Work Overload (WO), Perceived Reactivity to Social Conflicts (SC), Perceived Reactivity to Failure (FA), Perceived Reactivity to Social Evaluation (SE), and Prolonged Reactivity (Pro).

***Toronto Alexithymia Scale-20.*** Alexithymia, or the inability to understand and/or articulate one’s own emotional experience, was assessed using the Toronto Alexithymia Scale-20 (TAS-20; Bagby, Parker, & Taylor, 1994). The TAS-20 is a self-report questionnaire consisting of 20 items that answered on a scale of 1 to 5 (ranging from Strongly Disagree to Strongly Agree). The items assess three dimensions: 1) Difficulty Identifying Feelings (DIFF) for example, “I am often confused about the emotion I am feeling” 2) Difficulty Describing Feelings (DEF) for example, “It is difficult for me to find the right words for my feelings”; and 3) Externally Oriented Thinking (EOT) for example, “I find examination of my feelings useful in solving personal problems.” Five of the items on this scale were reverse scored. Scores contributing to each dimension were added together.

With respect to background and applicability, this version of the scale was created to address the psychometric shortcomings of a previous version. The revision was based on the responses of 965 individuals and yielded a measure with good internal consistency, test-re-test reliability, and a factor structure consistent with the construct of alexithymia. Stable factor structure was reported for healthy controls and psychiatric outpatients (Loas et al., 2001; Bagby,

Parker, & Taylor, 1994); however, at least one discrepant factor structure was reported for a sample of 76 outpatients with schizophrenia (Maggini & Raballo, 2004). Additionally, the TAS-20 has been used to investigate schizophrenia and has been found to be associated with symptom severity and verbal abilities (Cedro et al., 2000; Stanghellini, G., & Ricca, V., 1995).

**Measures used to Evaluate Response to Experimental Stressor.** Procedures used to evaluate response to the Trier Social Stress Test included evaluations of emotion using a visual analogue scale, measurement of heart rate, and the Primary Appraisal Secondary Appraisal Scale.

**Visual Analogue Scale (VAS).** Participants were provided a page with 5 emotions (Nervous, Scared, Calm, Excited, Happy) with corresponding 15-centimeter lines where they were asked to indicate the intensity of each emotion ranging from “Not at all” to “Extremely.” The VAS scale can be found in the Appendix. Because cortisol is main outcome variable and time point 9 was only collected for participants who had additional measures to complete in the laboratory, heart rate and VAS scales were not administered at time point 9.

**Primary Appraisal Secondary Appraisal Scale.** The Primary Appraisal Secondary Appraisal Scale (PASA; Gaab et al., 2005) is a 16 item self-report measure based on the transaction stress theory, which is used to assess the cognitive appraisal of the TSST. This measure examines primary appraisal, or one’s impression of a given task’s demands, and secondary appraisal, or the perception of one’s resources and abilities to meet the demands of the task. The PASA was administered after the TSST was explained. Participants were asked to make their ratings on a six point Likert scale with ranging from 1, or Completely Disagree, to 6, or Complete Agree. These indices were found to have good internal consistency (Gaab et al., 2005).

The PASA has four primary scales: Perceived Threat (e.g., “I do not feel threatened by the situation”), Challenge (e.g., “The situation is important to me”), Self-Efficacy (e.g., “In this situation I know what I can do”); and Expectation of Control (e.g., “It mainly depends on me whether the experts judge me positively”). Additionally the secondary scales of Primary Appraisal (PA), or the sum of Perceived Threat and Challenge indices, and Secondary Appraisal (SA), or the sum of Self-Efficacy and Expectation of Control, can be calculated. Lastly, Tertiary Scale termed the Stress Index (SI) can be determined. The SI uses the following formula:  $PA - SA$ .

The primary appraisal scales of the PASA were found to account for significant portions of the cortisol stress response for a sample of physically and psychiatrically healthy male university students. Interestingly, secondary appraisal indices were not found to be significant (Gaab et al., 2005).

**Salivary sampling.** Saliva samples were collected before the TSST and at designated time points during the TSST. Study participants were asked to keep a SalivaBio Oral Swab (SOS) under their tongues for 90-120 seconds, a time frame recommended for saturation of the SOS. The participants were then instructed to place the SOS into a swab storage tube, which was then placed in a sample container bag. The samples were refrigerated until the end the experiment, at which point all of the samples were transported and stored at  $-20^{\circ}\text{C}$  until they were processed. The samples were assayed using Salimetrics cortisol enzyme immunoassay (Salimetrics LLC, State College, PA) per the instructions provided by the manufacturer that can be found here: <https://www.salimetrics.com/assets/documents/1-3002n.pdf>.

Samples stored in  $-20\text{C}$  were thawed at room temperature, vortexed, and then centrifuged at  $1500\times g$  for 15 minutes. Each plate included 25 uL of standards, controls, and saliva in their

respective wells and all were run in duplicate. Additionally, non-specific binding (NSB) wells were included on each plate to serve as the blank when calculating cortisol concentration from the optical density values. 200 uL of Enzyme Conjugate was added to each well and then mixed on a plate rotator for five minutes at 500 rpm followed by 55 minutes of room temperature incubation without shaking. Each plate was then washed four times with a 1X wash buffer and thoroughly tamped between each wash. Following the washes, 200 µL of Substrate Solution was added to each well and mixed on a rotator for five minutes at 500 rpm and then incubated in the dark at room temperature for an additional 25 minutes. Finally, 50 µL of Stop Solution was added to each well and mixed at 500 rpm for three minutes. Plates were read at 450 nm within 10 minutes of adding the Stop Solution. To calculate the cortisol concentrations, the NSB wells were subtracted from the average optical density for all duplicate wells and then interpolated on a standard curve utilizing a 4-parameter non-linear regression curve fit.

Several precautions were taken to increase the accuracy and reliability of the cortisol sample readings. Individuals processing the samples were kept blind to the study design and study hypothesis. To obtain a robust measure of the cortisol concentration, each sample was processed in duplicate and the mean cortisol concentration of the two samples was used as the final outcome. Finally, the samples were run on a plates composed of 90 wells. The samples were distributed equally among the plates with respect to group.

**Other.** Participants were asked their height and weight and their self-reported parameters were used to determine their Body Mass Index (BMI). Participants were also asked whether they currently smoked or not. If participants reported that they did smoke, they were asked standardized questions to quantify their daily tobacco use. Age of illness onset was obtained from SCID interview and subtracted from current age to obtain the variable of illness duration.



## Procedures

***Recruitment and Informed Consent.*** Participants were recruited through advertising, including flyers posted in the community and Internet advertising. The majority of the clinical sample was recruited through a local community outpatient clinic.

The UNLV Institutional Review Board (IRB) approved all of the research procedures. Interested participants were provided with a brief study description, informed about the associated risks and benefits, and were given an opportunity to ask questions. Those who stated they would like to participate were asked to provide verbal consent to undergo a phone screening and were asked a number of questions to establish study eligibility. Those who appeared to meet the study criteria were scheduled to present for an in-person study at the laboratory. On campus parking passes were provided for research participants. For those who are unable to secure transportation, Taxi services were arranged and paid for. Participants were compensated at a rate of \$5.00 for every 30 minutes of study participation paid upon completion and were provided with a lunch of their choice. Whenever possible, all study procedures were completed within the same testing session.

Written informed consent was obtained from study participants prior to engaging in any of the study procedures. After consent was obtained, participants completed the diagnostic and screening procedures. Demographic information was obtained and participants completed the SCID-5 interview to assess for DSM-IV classified Axis I psychiatric disorders. Psychiatric interview was used to assess current symptomology. If participants were found to be eligible, the remainder of the battery was completed. Trained doctoral level graduate students in conducted the testing in quiet, private rooms. Breaks were provided when asked for by participants.

**Collection of Stress Response Measures.** In order to evaluate stress response to the TSST, saliva, heart rate, the VAS and PASA were administered at specified time points throughout the evaluation. These time points were selected to allow for baseline estimates of stress, stress response to the TSST, and resolution of stress following the TSST. Time points are indicated in Table 1.

Table 1

*Time Points for Collection of Stress Response Measures*

Time Point	Stress Response Measure			
	Saliva	VAS	Heart Rate	PASA
1. Clinical Interview	X	X	X	
2. Cognitive Testing	X	X	X	
3. Relaxation	X	X	X	
4. Anticipation	X	X	X	X
5. Immediately after TSST	X	X	X	
6. 15 minutes after the TSST	X	X	X	
7. 30 minutes after the TSST	X	X	X	
8. 45 minutes after the TSST	X	X	X	
9. Social Cognitive Testing	X			

*Note.* VAS = emotion visual analogue scale; PASA = Primary Appraisal Secondary Appraisal Scale.

As can be seen from Table 1, saliva was collected at 9 time points throughout the study. The first saliva sample was collected one hour after participants arrived to complete the study; participants were told that they were not allowed to eat, smoke, or drink liquids other than water

one hour prior to sample collection and were therefore asked to collaborate with the assessors to coordinate timing for when these samples could be collected (e.g., inform the administrator if they would like a smoke break in to smoke immediately after the first sample is collected to time an ensure that an hour passes before the second sample is collected). The second sample was collected approximately one hour following the first one. This procedure ensured that participants did not eat, smoke, or drink anything other than water one hour prior to sample collection. Subsequent samples were timed to ensure that no samples were collected within an hour of any of these activities. Collection of samples 3-8 occurred during the TSST. Finally, sample 9 was taken 45-60 minutes after sample 8. The sample was collected for participants who had measures to complete following the TSST; however, participants were not asked to stay to submit this sample if they had completed all of the other study procedures. More detail regarding these samples is provided later in the procedures section.

Heart rate and VAS were collected at 8 time points (see Table 1). The first two time points corresponded to clinical interviews and time points 3-8 were during the TSST. Heart rate was measured by the study administrators who used their index and middle fingers to locate participants' pulse on their inner wrist. Once the pulse was located the number of beats detected in a 15 second time period was multiplied by 4 to calculate the beats per minute. At this point, participants were asked to complete a VAS.

The PASA was administered at time point 4, or the anticipation stage of the TSST, to measure the participants' appraisal of the task and their personal resources to meet the challenge.

**Trier Social Stress Test.** The Trier Social Stress Test (TSST) is a laboratory social stress test designed to invoke a brief stress response. For the current study, a modified version of the TSST was utilized. As stated previously, a meta-analysis of 208 laboratory studies found that the

tasks that were most effective at eliciting a physiological response were unpredictable and included social-evaluative threat (Dickerson & Kemeny, 2004). Studies that included a cognitive task in addition to the aforementioned components were found to have the most robust response; so cognitive tasks were also used in the current protocol. The Trier Social Stress Test was completed between the hours of 13:00 and 16:00 to take advantage of the naturally occurring dip in cortisol levels in the afternoon (Smythe et al., 1997).

The start of the TSST is marked by a relaxation phase. The participants were instructed to relax alone in the same room they were assessed and were provided with neutral reading materials (e.g., magazines about cooking and travel) during this time to reduce boredom. After ten minutes of relaxation, the third salivary sample was collected. Participants were asked to fill out a visual analog scale (VAS) asking them to tick the level of each emotion they were experiencing in the moment, including nervous, scared, calm, excited, and happy. Responses were measured in centimeters ranging from “Not at All” on the left to “Extremely” on the right and ranged from 0-15 cm. (see appendix for copy of the scale). Next, participants’ heart rate was measured.

The second phase is the anticipatory anxiety phase. Participants were informed that they will be explaining to a panel of experts why they are suitable candidates for a job they would like. Participants were led into another room where they were shown two confederates sitting behind a desk in a room with a video camera and microphone. Participants were provided with a pad of paper and a writing instrument for notes and were given 10 minutes to compose their speech; however, they were not told how much time they would have. After ten minutes planning, the fourth saliva sample was collected. At this point the participants were asked to

complete the PASA and the mood VAS, and their heart rate was measured. Participants were asked to leave their notes in the room where the speech was composed.

The performance phase was next. Participants were led into a room where they were asked to deliver a speech in front of two trained judges explaining why they are the best candidates for a job they desired. If subjects were silent for 20 seconds one of the confederates would prompt, “You still have some time left. Please continue.” This prompt was only to be used twice for each participant. In the event that a participant needed another prompt, as indicated by 20 seconds of silence, the confederates would ask the following questions one at a time: “What are your challenges you think you might encounter on this job?”; “What are some qualities that would make you good at this job?”; “Tell us about a time you resolved a conflict you are proud of.” After the public speaking portion, the participants were asked to perform mental calculations. They were asked to start at 1,793 and count backwards by subtracting 13’s. One of the confederates corrected participants if they made an error and instructed them to restart at 1,793. Participants were to perform calculations for two minutes. After this phase, participants were escorted back into the testing room.

The next phase is the resolution phase. Once they returned to the testing room, participants submitted the fifth saliva sample, completed the VAS and had their heart rate measured. Participants were then debriefed. Participants were informed that this task was designed to be stressful and that they were not being evaluated or recorded. Participants were asked the following questions: 1) How do you think you did?; 2) What went well?; 3) What was difficult?; 4) Did you try anything to make it less difficult? Did it work?; 5) How would you describe the raters?; 6) Do you have any thoughts about what the raters thought of you? Once the interview was completed the confederates came into the testing room to inform the participants

that they did well and thank them for their participation. Participants were then left alone to relax and the sixth, seventh, and eighth salivary samples were collected 15, 30, and 45 minutes after completing the social stressor, respectively. These samples were used to determine the resolution of the stress response. When these samples were collected, participants also completed the VAS and their heart rate was measured. A ninth salivary sample was collected approximately one hour after participants completed the TSST if there were additional study procedures that needed to be completed. Participants were not kept specifically to collect this salivary sample if they did not have any other reason to stay in the lab.

## **Analyses**

### **Evaluating Hypothesis I:**

Hypothesis I: Based on previous research, it is hypothesized that individuals with schizophrenia will demonstrate a smaller increase in cortisol in response to the TSST relative to healthy controls. No group differences in heart rate, and ratings of negative emotions during the TSST are expected. Previous research indicates that a greater cortisol response to a psychosocial stressor tends to correspond with more subjective stress. It is hypothesized this relationship would be reversed in schizophrenia so that individuals with greater cortisol response will report less anxiety.

Differences in cortisol levels were evaluated using repeated measures ANOVA with group (control vs. schizophrenia) as the between factor and time as the within factor. A significant group effect would confirm the hypothesis.

Area under the curve (AUC) was calculated to obtain single measures of cortisol release using the formulas recommended by Pruessner and colleagues (2003). The use of AUC formulas is recommended as a means of reducing the number of comparisons when data across multiple

time points is examined. There are two formulas: AUC with respect to ground (AUC<sub>G</sub>) and AUC with respect to overall increase (AUC<sub>I</sub>). The AUC<sub>G</sub> is a measure that is related to “total hormonal output,” while AUC<sub>I</sub> is thought to be more representative of responsivity or sensitivity of the hormonal system to produce changes over time. The formulas are presented below:

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2}$$

$$AUC_I = AUC_G - m_1 \cdot \sum_{i=1}^{n-1} t_i$$

Where  $n$  is the number of samples,  $i$  is the initial sample,  $m$  is the measure (of cortisol in this case), and  $t$  is time between samples (e.g.,  $t_2$  is the time between sample 2 and sample 3). For the current study, the AUC<sub>G</sub> will be calculated for time points 3-8 as response to TSST is of primary interest. For AUC<sub>I</sub>, time point 3 will be used as the baseline time point,  $m_1$ , as it immediately follows a resting period prior the TSST and participants are expected to be related during this time. Similar to AUC<sub>G</sub>, time points 3-8 will be used for current analyses. ANOVA will be used to examine differences in cortisol production between the groups.

Additionally, repeated measures ANOVA was used to determine if the two groups differ significantly in cortisol production with respect to each of the time points. Repeated measures ANOVA was also used to examine differences in VAS ratings.

Pearson correlations were used to examine the relationship between overall cortisol released during the TSST and Primary Appraisal and Secondary Appraisal Scales from the PASA, total score on the Defeatist Attitude Beliefs Scale, total score of the Perceived Stress Reactivity Scale, and total score from the Toronto Alexithymia Scale-20.

### **Evaluating Hypothesis II:**

Hypothesis II: Similarly, it is hypothesized that people with schizophrenia who have better social cognition and perform better on a test of everyday functioning will have a greater cortisol response to the psychosocial stressor, while healthy controls with better social cognition will have a smaller cortisol response. Repeated measures ANOVAs were used to examine group differences in performance on social cognitive measures and assessment of skills of everyday functioning. Pearson correlations were used to examine the relationship between the social cognition measures and AUC.

### **Evaluating Hypothesis III:**

Hypothesis III: It is also hypothesized that the prevalence of childhood adversity would be greater in the schizophrenia group than among the healthy controls. Lastly, it is hypothesized that childhood sexual abuse will account for more of the variance in AUC than other forms of abuse. Pearson correlations were used to examine group differences in associations of cortisol and levels of childhood abuse endorsed.



## CHAPTER 4

### RESULTS

#### **Data Screening**

*Accuracy of data file.* Initially, data was screened and evaluated to ensure accurate of data entry. Data was scored and entered twice. An excel program was used to detect discrepancies between the two entries to ensure accuracy of data entry. Additionally, range and frequency statistics were examined to identify data that is outside of an acceptable range and missing data. Data was also examined to make sure that assumptions of parametric tests were met.

*Outliers.* Outliers were identified using box plots. Outliers were considered scores that were outside 1.5 times the interquartile range. These scores were converted to the next highest score in the distribution so that they would continue to maintain their extreme position in the distribution, but have decreased influence on measures of central tendency and variability (Tabachnick & Fidell, 2013). This procedure was utilized for one score on the Sexual Abuse and Physical Abuse subscales of the Childhood Trauma Questionnaire. Additional outliers in the cortisol data were identified using this methodology and will be discussed below.

**Missing Data.** A healthy control was missing a Transportation subtest score of the UPSA; this participant did not complete this subtest due to examiner error. This score was replaced by the mean performance of the healthy control group on this scale. A total of five items from the PASA were left blank by the participants (two items by the HC group and three by the SZ group). These values were replaced by the average of the rest of the rest of the subscale from which they were missing. Two of the participants from the SZ groups did not complete the Hinting Task and Picture Arrangement due to scheduling conflicts and those scores were replaced with group means. Additional information about missing data and outliers with respect to cortisol is discussed below.

### **Preliminary Analysis**

Demographic information for the participants is summarized in Table 2. The schizophrenia (SZ) group completed significantly fewer mean years of education and had significantly lower mean IQ estimates than the healthy control (HC) group. The differences observed in IQ and education were expected based on research that has established cognitive deficits to be a core feature of schizophrenia (Aylward, Walker, & Bettes, 1984), which negatively impacts IQ and contributes to lower academic achievement among people with schizophrenia (e.g., Green, 1996). Because these observations are believed to be reflective of the underlying psychopathology associated with schizophrenia, covariance procedures were not used to correct their influence because doing so would essentially control for the independent variable of interest (i.e., diagnosis). Groups did not differ significantly on age or ethnicity.

No significant differences in body mass index (BMI) were found, which is notable for the current study because higher BMI has been found to be associated with higher cortisol production (Fraser et al., 1999). With respect to nicotine use, one participant reported daily

electric-cigarette (e-cigarette) use, and estimated that he uses one cartridge per day. According to a review published in the American Journal of American Medicine summarizing findings from 687 articles, there is great variability in the doses of nicotine absorbed from E-cigarette use (Glasser et al., 2016), therefore this participant is indicated separately in Table 2. Tobacco use data for one HC participant was not available. Overall, no significant group differences were found in smoking when examining categories of nicotine use. Nevertheless, it appears that the SZ group uses more nicotine than the HC group. Analyses examining the relationship with smoking and cortisol levels will be presented under hypothesis 1.

Table 2

*Demographic Information by Group*

Variable	Group		F	p
	Control Mean (SD)	Schizophrenia Mean (SD)		
Age	37.1 (10.0)	43.9 (10.3)	3.66	.07
Education	14.5 (2.3)	11.7 (2.3)	12.59	<.001
Estimated IQ	110.0 (18.0)	84.4 (4.3)	14.03	<.01
Body Mass Index	27.9 (4.5)	30.9 (5.3)	3.11	.09
Age of Illness Onset	--	20.9 (3.6)	--	--
Illness Duration	--	23.0 (11.0)	--	--
			$\chi^2$	p
Ethnicity (%)			1.78	.78
Caucasian	58.8	37.5		
African American	17.7	25.0		
Hispanic/Latino	5.9	12.5		
Biracial	11.8	12.5		
Other	5.9	12.5		
Smoking (cigarettes/day; %)				
0	82.4	50.0	8.61	.07
1-10	11.8	12.5		
11-20	0.0	25.0		
20+	0.0	12.5		
E-Cigarettes	5.9	0.0		

Table 3 summarizes measures reflecting symptomatic functioning. As anticipated, the SZ group had significantly higher levels of psychopathology across all measures including the BPRS, SAPS and SANS.

Table 3

*Symptoms Ratings by Group*

Variable	Group		F	p
	Control Mean (SD)	Schizophrenia Mean (SD)		
BPRS	20.7 (2.8)	37.2 (9.5)	47.35	<.001
SAPS Total	0.8 (2.2)	21.3 (13.7)	36.87	<.001
Hallucinations	0.0 (0.0)	1.8 (1.6)	20.75	<.001
Delusions	0.0 (0.0)	1.9 (1.6)	24.63	<.001
Bizarre Behavior	0.0 (0.0)	0.4 (0.7)	6.16	.02
Thought Disorder	0.1 (0.3)	1.5 (1.4)	15.37	<.001

*Note.* BPRS = Brief Psychiatric Rating Scale; SAPS = Scale for Assessment of Positive Symptoms; SANS = Scale for assessment of Negative Symptoms

Fourteen (87.50%) of the people in the SZ group were diagnosed with schizophrenia and two (12.50%) were diagnosed with schizoaffective disorder. Ten (62.50%) of the people in the SZ group were prescribed atypical antipsychotic medication, three (18.75%) were prescribed a typical antipsychotic medication, one (6.25%) was prescribed an anti-depressant, and two (12.50%) reported that they were not taking medication.

The results of self-report measures are presented in Table 4. The SZ group endorsed significantly higher levels of alexithymia, as evidenced by a higher overall score on the Toronto Alexithymia Scale-20 (TAS-20) and the three contributing factor scores, including Difficulty Identifying Feelings, Difficulty Describing Feelings, and Externally Oriented Thinking. Significant group differences were also observed in the total score of the Perceived Stress Reactivity Scale, with the SZ group reporting higher levels of stress reactivity. However, not all subtests were significantly different; only Work Overload and Social Evaluation subscales

yielded significant group differences with the SZ group reporting higher levels of subjective reactivity in these areas of functioning. Finally, a significant group difference was found in Defeatist Performance Beliefs in the expected direction with the schizophrenia group endorsing a greater degree of defeatist beliefs.

Table 4

*Self-Report Measures by Group*

Measure	Group		<i>F</i>	<i>p</i>
	Control Mean ( <i>SD</i> )	Schizophrenia Mean ( <i>SD</i> )		
TAS-20 Total	38.4 (7.1)	55.0 (10.1)	30.36	<.001
Difficulty Identifying Feelings	9.7 (3.1)	18.0 (6.9)	20.45	<.001
Difficulty Describing Feelings	10.7 (3.2)	15.4 (3.8)	15.13	<.01
Externally Oriented Thinking	18.0 (3.4)	21.6 (4.5)	6.91	<.01
PSRS Total	11.3 (7.0)	19.3 (8.5)	8.80	<.01
Work Overload	1.3 (1.6)	3.9 (2.2)	14.76	<.001
Social Conflict	3.1 (2.1)	4.6 (2.3)	3.61	.07
Failure	2.8 (1.7)	3.6 (1.7)	1.51	.23
Social Evaluation	2.2 (1.7)	4.3 (2.6)	8.10	<.01
Prolonged Reactivity	1.9(1.6)	3.0 (1.9)	3.33	.08
Defeatist Performance Beliefs	39.9 (9.0)	62.3 (17.3)	22.08	<.001

*Note.* TAS-20 = Toronto Alexithymia Scale-20; PSRS = Perceived Stress Reactivity Scale

### Evaluating Hypothesis 1

Whenever possible, the cortisol samples were processed in duplicate and the average concentration was used in the analyses. For samples that did not contain enough saliva to run in duplicate, the concentration of the single sample obtained and processed was used. Five samples in total did not have enough saliva to run in duplicate: three from one subject in the SZ group and two samples from two different participants in the HC group. The inter-assay coefficient variable was calculated to be 10.62%, which is below the Salimetrix cut off of 15%. Therefore, the single samples are considered sufficiently reliable and no corrective measures were taken.

Samples were collected at approximately the same time for both of the groups. For the SZ group

the average time of collection was 3:51 p.m. ( $sd=41$  minutes), while for the HC group, the average time of collection was 3:21 p.m. ( $sd = 35$  minutes). When each of the times was converted to minutes past noon (e.g., 3:15 p.m = 195 minutes) a two-sample revealed that the differences were non-significant ( $F=0.005, p=0.94$ ). Therefore, it seems that time of collection is comparable for the two groups.

Eight participants (6 HC and 2 SZ) were missing cortisol data for time point 9. This occurred because sample 9 was only collected if participants were completing other evaluation procedures. These missing values were replaced with the average of the group to which they belonged. Cortisol data for five samples was also missing for 4 participants (one HC participant was missing 2 samples) at different time points throughout the study for two people from the healthy control group and 2 people from the schizophrenia group. These data were missing because four of the samples did not contain enough saliva to run (2 samples from HC and 2 samples from SZ) and one sample (S1) was not collected because the HC participant took a sip of a beverage other than water before the sample was to be collected. These data were also replaced with group means for each respective time point.

Outliers in cortisol concentrations were identified with respect to each group. Therefore, means and standard deviations were calculated for the SZ and HC groups separately. No outliers were identified in the schizophrenia group. There were nine outliers in the HC group (five of these were generated by the same participant for time points 1-5) and three outliers in the SZ group in the data, as indicated by inspection of a boxplot for values greater than 1.5 times the interquartile range. These scores were converted to the next highest score in the distribution so that they would continue to maintain their extreme position in the distribution, but have

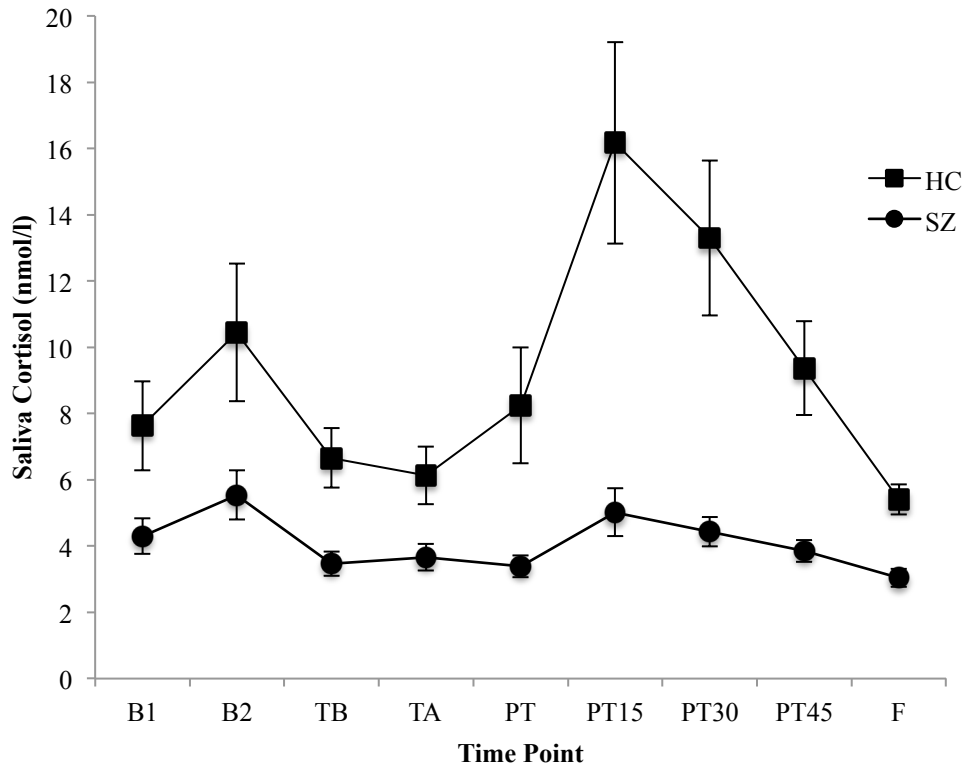
decreased influence on measures of central tendency and variability (Tabachnick & Fidell, 2013).

Correction of the outliers improved the skewedness and kurtosis of the group of the data. The primary analyses were run with the corrected data and no changes in the results were observed; therefore, the analyses presented below are for the original data.

Results of the cortisol analyses are presented in Figure 2 and Table 5. To examine group differences in cortisol production, a 2x9 mixed model analysis of variance (ANOVA) was used in which group served as the between-subjects variable and cortisol samples across the nine time points were the repeated measure. Mauchly's test indicated that assumptions of sphericity were violated,  $W = 0.00$ ,  $\chi^2(35) = 222.70$ ,  $p < 0.001$ . Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates to interpret main and interaction effects. Results of the ANOVA indicated significant main effects for group,  $F(1, 31) = 14.84$ ,  $p < .001$ ,  $\eta^2 = .324$ , and for cortisol levels,  $F(2.66, 46.94) = 9.23$ ,  $p < .0001$ ,  $\eta^2 = .229$ , as well as a significant group by cortisol level interaction effect,  $F(2.66, 82.42) = 4.76$ ,  $p = 0.005$ ,  $\eta^2 = .133$ . To examine whether replacement of means for cortisol sample 9 affected the main and interaction effects, comparable analyses were conducted for time points 1 – 8. The main and interaction effects remained significant with a significant main effect for group,  $F(1, 31) = 13.63$ ,  $p < .001$ ,  $\eta^2 = .305$ , and for cortisol levels,  $F(2.49, 77.12) = 8.58$ ,  $p < .0001$ ,  $\eta^2 = .217$ , as well as a significant group by cortisol level interaction effect,  $F(2.49, 77.12) = 4.81$ ,  $p = 0.01$ ,  $\eta^2 = .134$ . Figure 2 shows the group by cortisol level interaction effect. Post hoc analyses indicated that the interaction effect was accounted for primarily by the group differences in cortisol time points 5 – 9, where the HC group evidence a relatively larger increase in cortisol levels from time points 5 – 6, and a steeper rate of cortisol decline from time points 6 – 9 compared to the SZ group.

Figure 2

*Cortisol Concentrations by Time Point for Schizophrenia (SZ) and Healthy Controls (HC)*



*Note.*

HC = Healthy Control; SZ = Schizophrenia; B1 = Baseline 1; B2 = Baseline 2; TB = TSST Baseline; TA = TSST Anticipation; PT = Post TSST; PT15 = 15 minutes Post TSST; PT30 = 30 minutes Post TSST; PT45 = 45 minutes Post TSST; F = Final.

The salivary free cortisol response with respect to ground (AUC<sub>g</sub>) and with respect to increase (AUC<sub>i</sub>) were also calculated for the TSST (time points 3-8) to examine the time points collected during the afternoon and those collected during the TSST. As stated previously, time point 3, collected at the end of the relaxation phase, was used as the “ground” time point for AUC<sub>g</sub>. Analyses revealed significant differences between the two groups for both AUC<sub>i</sub>  $F(1,31) = 14.15, p < .005, \eta^2 = .313$ , and AUC<sub>g</sub>  $F(1,31) = 7.55, p < .05, \eta^2 = .196$ . This indicates that the HC group produced significantly more cortisol both when baseline level of cortisol is accounted



for and when it is not. The SZ group had lower baseline levels of cortisol and responded with less cortisol at the times cortisol was sampled.

Pearson correlations were used to further examine relationships between cortisol production and demographic factors, including smoking and duration of illness. The correlation between number of cigarettes smoked per day and AUCI for the overall sample was  $r = -.25$  ( $p = .17$ ) and the correlation between number of cigarettes smoked per day and AUCg was  $r = -.13$  ( $p = .48$ ), both of these relationships fall in the small effect size range (Cohen, 1992). Illness duration was calculated as age at assessment minus age of onset of psychiatric illness. For three participants the age of illness onset was unavailable; therefore, illness duration could not be calculated for them. To examine the relationship between illness duration is related to AUCg Pearson correlation was used. The correlation between cortisol AUCg and illness duration was calculated to be non-significant ( $r = -.06$ ,  $p = .85$ ).

To further examine the relationship between nicotine use, group, and cortisol production, a 2 X 2 X 8 repeated measures ANOVA was used in which group (SZ vs. HC) and smoking status (current smoker vs. non-smoker) served as between subjects variables, and time point served as within subjects variables. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated,  $W = 0.01$ ,  $\chi^2(27) = 166.16$ ,  $p < .001$ , therefore Greenhouse-Geisser correction was applied to correct the degrees of freedom. The results of the analysis indicated significant main effect for time point,  $F(2.55, 71.51) = 7.80$ ,  $p < .001$ ,  $\eta^2 = .218$  and a significant interaction effect between time point and group,  $F(2.55, 71.51) = 4.51$ ,  $p = .01$ ,  $\eta^2 = .139$ . The two-way interaction of time point by smoking status was not significant  $F(2.55, 71.51) = 0.63$ ,  $p = .57$ ,  $\eta^2 = .022$ . Additionally, the three-way interaction between time point, group, and smoking

status was also non-significant [ $F(2.55, 71.51) = 0.16, p = .90, \eta^2 = .006$ ]. Overall, these findings suggest that smoking status does not impact cortisol production in a detectable manner.

Table 5

*Cortisol Concentrations by Time Point for Each Group*

Time Point	Corresponding Event	Group		F	p
		Control Mean (SD)	Schizophrenia Mean (SD)		
1	Clinical Interview	7.6 (5.6)	4.3 (2.1)	5.07	<.05
2	Cognitive Testing	10.5 (8.6)	5.5 (3.0)	4.72	<.05
3	Relaxation	6.6 (3.7)	3.5 (1.5)	10.43	<.01
4	Anticipation	6.1 (3.6)	3.7 (1.6)	6.40	<.05
5	Post TSST	8.3 (7.2)	3.4 (1.3)	7.02	<.05
6	TSST + 15 mins.	16.2 (12.5)	5.0 (2.9)	12.03	<.01
7	TSST + 30 mins.	13.3 (9.6)	4.4 (1.8)	13.11	<.01
8	TSST + 45 mins.	9.4 (5.8)	3.9 (1.3)	13.69	<.01
9	Cognitive Testing	5.4 (1.9)	3.0 (1.1)	19.49	<.01

Note. TSST = Trier Social Stress Test.

Results of the heart rate analyses are presented in Figure 3 and Table 6. A 2 x 8 mixed model ANOVA was used to examine heart rate across the time points. Group served as the between subjects variable and heart rate time point was the repeated measure. Mauchly's test indicated that assumptions of sphericity were violated,  $W = .19, \chi^2(27) = 47.99, p < .01$ . Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates to interpret main and interaction effects. The main effect for heart rate was significant,  $F(4.85, 150.30) = 16.74, p < .001, \eta^2 = .351$ , although the main effect for group was not significant,  $F(1,31) = 3.37, p = .08, \eta^2 = .098$ , nor was the interaction effect,  $F(4.85, 150.30) = .50, p = .77, \eta^2 = .016$ . Post hoc analyses revealed significant differences between groups on time points 2 and 3 (see Table 6). There were also significant differences in heart rate between time points 1 and 5,  $F(1,31) = 54.50, p < .001, \eta^2 = .637$  and time points 5 and 8,  $F(1,31) = 38.08, p < .001, \eta^2 = .551$ ,

indicating significant increase in heart rate in response to the TSST and significant decrease in heart rate following the TSST.

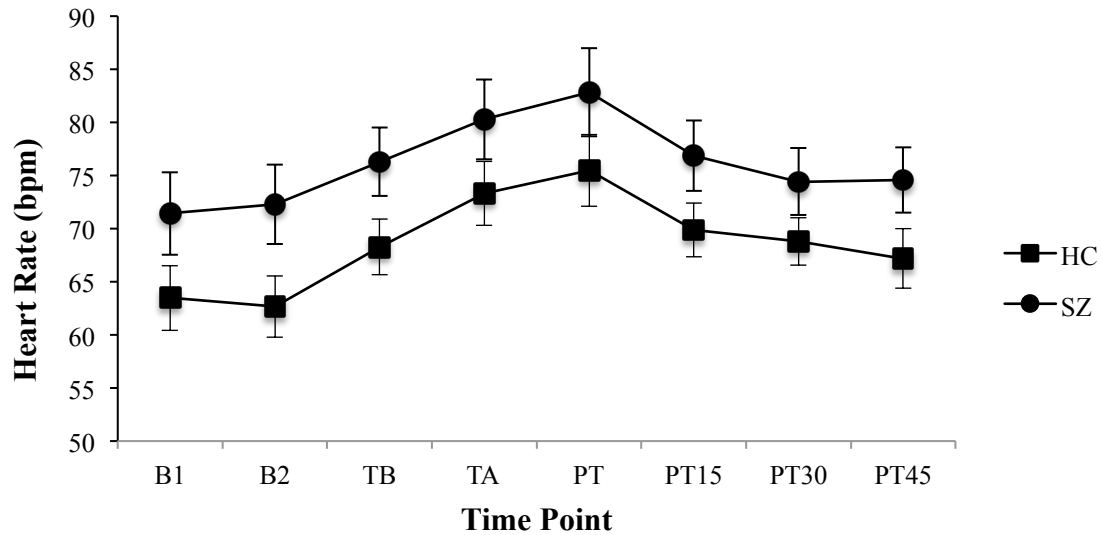
Table 6

*Heart Rate by Time Point for Schizophrenia and Control Groups*

Time Point	Corresponding Event	Group		<i>F</i>	<i>p</i>
		Control Mean ( <i>SD</i> )	Schizophrenia Mean ( <i>SD</i> )		
1	Clinical Interviews	62.8 (11.2)	70.0 (14.1)	2.64	.11
2	Cognitive Testing	61.9 (10.8)	71.8 (13.4)	5.45	.03
3	Pre-TSST Relaxation	67.5 (10.0)	75.3 (11.6)	4.21	.05
4	Anticipation Stage	72.9 (11.2)	79.3 (13.7)	1.57	.22
5	Post TSST	74.8 (12.9)	81.0 (15.4)	1.57	.22
6	TSST + 15 mins.	68.9 (9.8)	75.5 (12.3)	2.90	.10
7	TSST + 30 mins.	67.5 (8.9)	72.9 (11.8)	2.18	.15
8	TSST + 45 min	66.1 (10.9)	72.0 (13.3)	1.94	.17

*Note.* TP = Time Point; TSST = Trier Social Stress Test

Figure 3. Heart Rate by Time Point for Schizophrenia (SZ) and Healthy Controls (HC)



*Note.* HC = Healthy Control; SZ = Schizophrenia; B1 = Baseline 1; B2 = Baseline 2; TB = TSST Baseline; TA = TSST Anticipation; PT = Post TSST; PT15 = 15 minutes Post TSST; PT30 = 30 minutes Post TSST; PT45 = 45 minutes Post TSST.

The Visual Analog Scales (VAS) were examined next. Because several of the study participants expressed confusion about how the variable “Calm” was to be interpreted and some people even reported that they coded it incorrectly for the majority of the study, calm was excluded from the analyses. One participant in the SZ group was missing two emotions for time point 8 (nervous and excited). Because there was no manipulation between time point 7 and 8, time point 7 was carried forward to fill in the missing scores for time point 8.

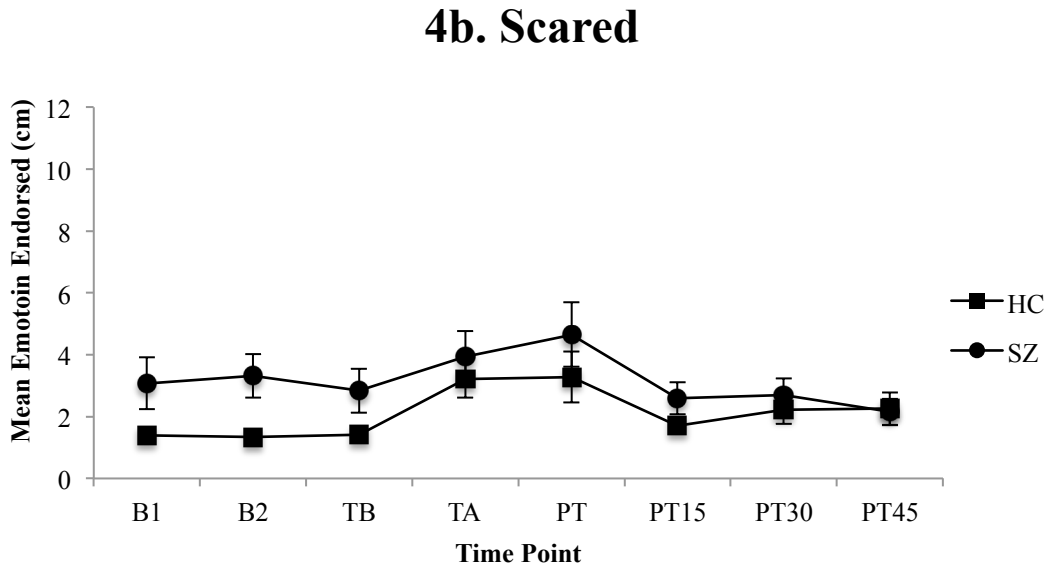
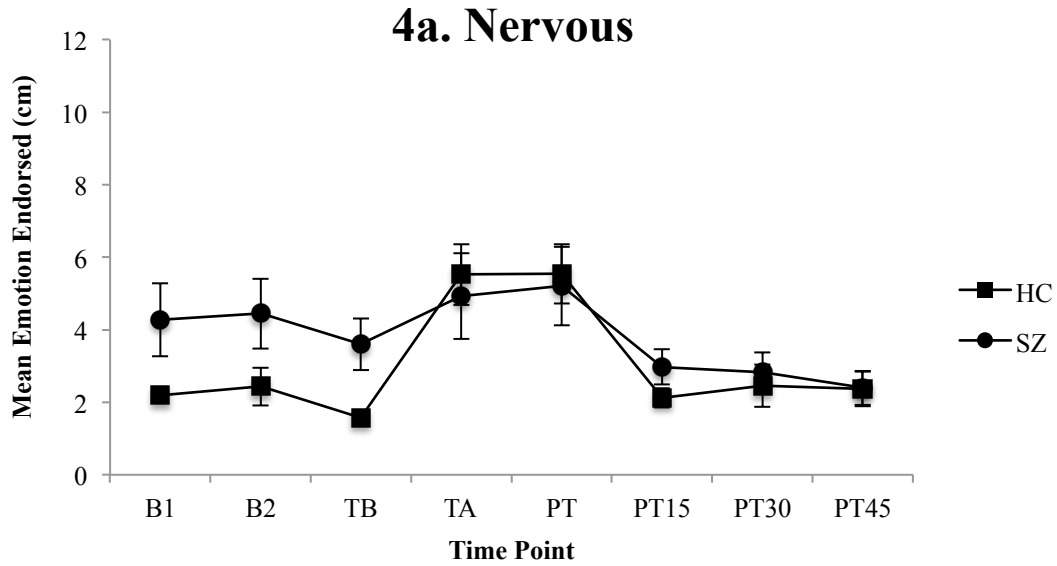
To examine VAS results, a 2 X 4 X 8 mixed model ANOVA was used in which group served as a between subjects variable, and emotion (Nervous, Scared, Excited, Happy) and time point served as within subjects variables. Mauchly's test of sphericity indicated that the assumption of sphericity had been violated,  $W = 0.00$ ,  $\chi^2(230) = 614.56$ ,  $p < .001$ , so Greenhouse-Geisser correction was applied to correct the degrees of freedom. The results of the analysis indicated significant main effects for VAS emotion,  $F(1.48, 45.74) = 68.05$ ,  $p < .001$ ,  $\eta^2$

= .687, and for VAS time point,  $F(4.66, 144.30) = 6.27, p < .001, \eta^2 = .168$ , although the main effect for group was not significant,  $F(1,31) = 1.88, p = .18, \eta^2 = .057$ . There was a significant two way interaction effect for VAS time point by VAS emotion,  $F(8.84, 274.04) = 4.68, p < .001, \eta^2 = .131$ , although the two way interaction effects were not significant for VAS time point by group,  $F(4.66, 144.30) = 0.86, p = .50, \eta^2 = .027$ , or VAS emotion by group,  $F(1.48, 45.74) = 0.57, p = .52, \eta^2 = .018$ . Finally, the three-way group by VAS emotion by VAS time point interaction effect was significant,  $F(8.84, 274.04) = 3.20, p < .001, \eta^2 = .131$ . This three way interaction effect is presented in Figures 4a-d.

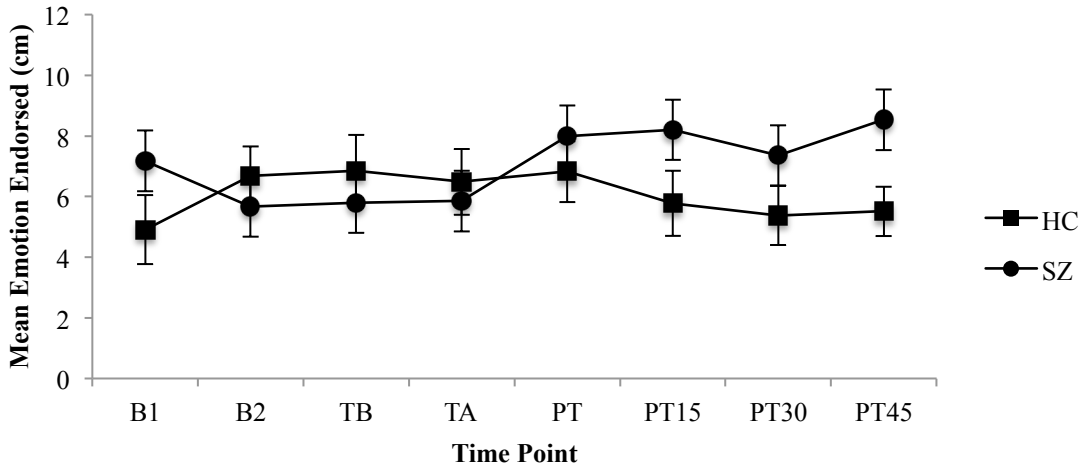
As can be seen from the figures, the interaction effect is accounted for by group differences in the intensity of VAS emotions reported during the study that vary by VAS time point. Post-hoc analyses were conducted to further examine the three-way interaction effect. Results of these analyses indicated that compared to controls, during the baseline phase as indexed from time points 1 to 3, the schizophrenia group indicated significantly higher VAS Nervous,  $F(1,31) = 9.50, p < .005, \eta^2 = .235$ , and VAS Scared,  $F(1,31) = 7.07, p < .05, \eta^2 = .186$ , although no such differences were present for VAS Excited or Happy ( $p$ 's  $> .05$ ). During the TSST, as indexed by time points 4 and 5, no significant differences were present between the groups on any of the VAS emotions ( $p$ 's  $> .05$ ). In the resolution phase, the schizophrenia group had higher VAS excitement compared to controls,  $F(1,31) = 5.37, p < .05, \eta^2 = .148$ , although there were no other significant differences between groups for any of the other VAS emotions ( $p$ 's  $> .05$ ). Based on these findings, the SZ group indicated significantly higher overall negative emotions during the baseline phase, the control group exhibited a greater increase in negative emotions during the TSST phase, and the schizophrenia group demonstrated increased excitement in the resolution phase.

Figures 4a-d.

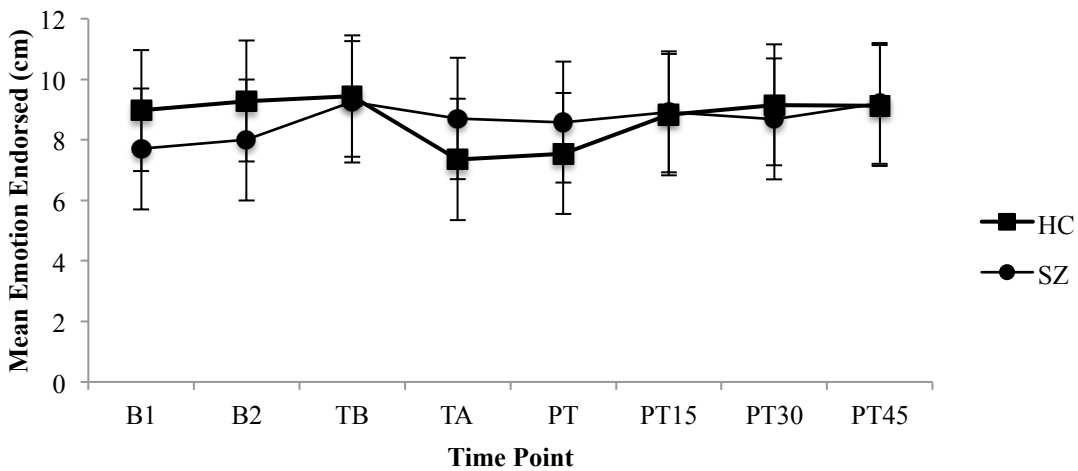
*Ratings of Nervousness, Fear, Excitement, and Happiness by Time Point for Schizophrenia (SZ) and Healthy Control (HC) Groups*



### 4c. Excited



### 4d. Happy



*Note.* HC = Healthy Control; SZ = Schizophrenia; B1 = Baseline 1; B2 = Baseline 2; TB = TSST Baseline; TA = TSST Anticipation; PT = Post TSST; PT15 = 15 minutes Post TSST; PT30 = 30 minutes Post TSST; PT45 = 45 minutes Post TSST.

Evaluations were present for VAS negative emotions at times 4 and 5 corresponding with the anticipations stages and completions of the TSST, while cortisol increases were present at time points 6 and 7, 15 and 30 minutes after the TSST, respectively. The lag in the rise of

cortisol concentrations is expected as unbound levels of cortisol continue to increase 15-20 minutes after a stressor's cessation (Kirschbaum & Hellhammer, 2000). In contrast, the increase in VAS negative emotions corresponds with heart rate data, which also peak at time points 4 and 6. This finding is expected given that, like the VAS ratings, heart rate is a more temporally proximate measure of stress response compared to cortisol.

Task appraisal differences were examined on the Primary Appraisal and Secondary Appraisal (PASA) scale. A 2 x 4 mixed model ANOVA was used to examine differences between groups on the four PASA primary scales. Group served as the between subjects variable and PASA primary scale scores were the repeated measure. Mauchly's test indicated that assumptions of sphericity were violated,  $W = .336$ ,  $\chi^2(5) = 32.43$ ,  $p < .001$ . Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates to interpret main and interaction effects. The main effect for PASA score was significant,  $F(1.79, 53.60) = 7.59$ ,  $p < .005$ ,  $\eta^2 = .197$ , although the main effect for group was not significant,  $F(1,31) = 0.03$ ,  $p = .86$ ,  $\eta^2 = .001$ , nor was the interaction effect,  $F(1.79, 53.60) = .08$ ,  $p = .90$ ,  $\eta^2 = .003$ . Similarly, no significant group differences were present for the secondary scales, which are summary scores for the primary scale, or on the stress index (see Table 7). Results indicate that the groups' primary and secondary appraisals, or evaluation of threat and personal resources to cope with the threat were similar as measured by the PASA. Results of analyses presented in Table 7.



Table 7

*Primary Appraisal Secondary Appraisal Scale Scores (PASA) by Group*

PASA	Group		<i>F</i>	<i>p</i>
	Control Mean ( <i>SD</i> )	Schizophrenia Mean ( <i>SD</i> )		
<b>Primary Scales</b>				
Threat	12.7 (5.2)	13.1 (3.9)	.05	.83
Challenge	16.1 (3.0)	16.4 (3.8)	.05	.83
Self-Efficacy	16.9 (3.6)	16.4 (4.4)	.10	.75
Control Expectancy	16.7 (4.0)	17.1 (3.9)	.07	.80
<b>Secondary Scales</b>				
Primary Appraisal	28.8 (6.7)	29.4 (6.5)	.07	.79
Secondary Appraisal	33.6 (6.5)	33.5 (7.4)	.001	.97
Stress Index	-4.8 (10.3)	-4.1 (11.0)	.04	.85

Pearson correlations were used to examine relationships between the variables for each of the groups. Results indicate that the only significant correlation for either of the groups is between AUCg and DPB due to small sample size. Effect sizes indicated by the correlations (Cohen, 1992) reveal medium effect sizes were present between the AUCg and the PASA primary and secondary appraisal scale score, and between the AUCi and the PASA secondary appraisal score. A large effect size was present between AUCg and the DPB scale score for the SZ group only. This data is presented in Table 8.

Table 8

*Correlations among Demographic Variables and Self-Report Measures with AUC Measures per Group*

Variable	Control		Schizophrenia	
	AUCi	AUCg	AUCi	AUCg
P.A.	-.04	-.04	.05	-.25
S.A.	.11	.09	.23	-.35
TAS	-.09	.05	.01	-.18
PSRS	-.17	-.16	-.12	-.01
DPB	-.08	-.08	-.19	<b>-.50*</b>

*Note.* \*  $p < .05$ ; AUCi = Area Under the Curve overall increase; AUCg = Area Under the Curve with respect to ground; P.A. = PASA's Primary Appraisal scale; S.A. = PASA's Secondary Appraisal scale; DPB = Defeatist Performance Beliefs; PSRS = Perceived Stress Reactivity Scale

Participants' free response answers to the questions asked after the TSST were reviewed. There were several differences between the responses of the HC and SZ groups. For example, the HC group was more likely to evaluate their performance in neutral or favorable terms ("pretty good"; "could be better"); while the SZ group was more likely to use negatively charged terms like "terrible" to describe their performance. Additionally, the SZ group was more likely to describe the raters in negative terms compared to the HC group. Interestingly, the SZ group more often reported being perceived in a negative manner and more frequently reported feeling judged by the raters for based on race, low education, or having a mental illness. The interested reader is directed to the appendix to examine the raw responses.

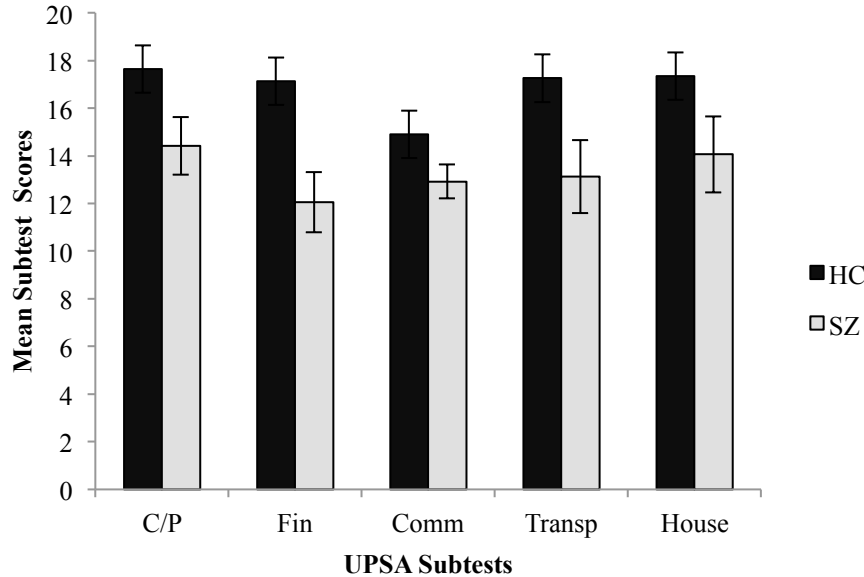
## Hypothesis 2

Results of the social cognitive measures and functional outcome measure are presented in Table 9. To examine group differences in functioning, UPSA scores were examined in a 2x5 mixed model analysis of variance (ANOVA) which group served as the between-subjects

variable and UPSA scaled scores were the measure. Mauchly's test indicated that assumptions of sphericity were violated  $W= 0.44, \chi^2 (9) = 23.89, p < 0.01$ . Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates to interpret main and interaction effects. Results of the ANOVA indicate that there was a significant main effect for group,  $F (1,31) = 10.95, p < .005, \eta^2 = .261$ , and for UPSA subtest score,  $F (2.73,84.58) = 2.97, p < .05, \eta^2 = .087$ , although the interaction effect between the UPSA subscales and the group was not significant,  $F (2.72,84.58) = 1.35, p = .26, \eta^2 = .042$ . Post-hoc analyses revealed that group differences were primarily driven by difference between Planning, Finance and Communication subtests. See Figure 5 for plots of group means.

Figure 5

*UPSA Subtests Scores for Schizophrenia (SZ) and Healthy Controls (HC)*



*Note.* HC = Healthy Control; SZ = Schizophrenia; UPSA = UCSD Performance-Based Skills Assessment; C/P = Comprehension/Planning; Fin = Finance; Comm = Communication; Transp = Transportation; House = Household.

A 2x3 mixed model ANOVA was used to evaluate differences between the groups' performances on social cognitive tests. In this analysis, group was the between subjects variable and total scores from the Eyes Test, Hinting Test, and Picture Arrangement were the within subjects variable. Assumptions of Mauchley's test of sphericity were met,  $W = 0.90$ ,  $\chi^2(2) = 3.33$ ,  $p = 0.19$ , therefore, no corrections were applied. Results indicated that the main effect for social cognitive test was significant,  $F(2,62) = 194.54$ ,  $p < .001$ ,  $\eta^2 = .863$ , as was the main effect for group,  $F(1,31) = 21.83$ ,  $p < .001$ ,  $\eta^2 = .413$ . The interaction between the tests of social cognition and group was also significant  $F(2,62) = 3.44$ ,  $p < .05$ ,  $\eta^2 = .100$ . See Table 9 for group means.

Given that scores from the social cognitive measures are not standardized which obscures meaningful interpretation of the main effect for social cognitive test and the interaction effect, standard scores ( $z$ ) were computed for each social cognitive measure using the mean and standard deviation of the control group for each test. These standard scores were used in the post hoc analysis. The interaction effect is presented in Figure 6. Post hoc analysis comparing the groups indicated the schizophrenia group performed significantly worse than controls on all social cognitive measures, as reported in Table 9. Repeated measures ANOVA that included the social cognition standard scores for the schizophrenia group indicated a significant overall effect,  $F(2,30) = 3.67, p < .05, \eta^2 = .196$ . Contrasts indicated significant differences between scores for the Eyes Test and Picture Arrangement,  $F(1,15) = 5.19, p < .05, \eta^2 = .257$ , but no significant difference between Picture Arrangement and the Hinting Test,  $F(1,15) = 0.01, p = .97, \eta^2 = .001$ .

Table 9

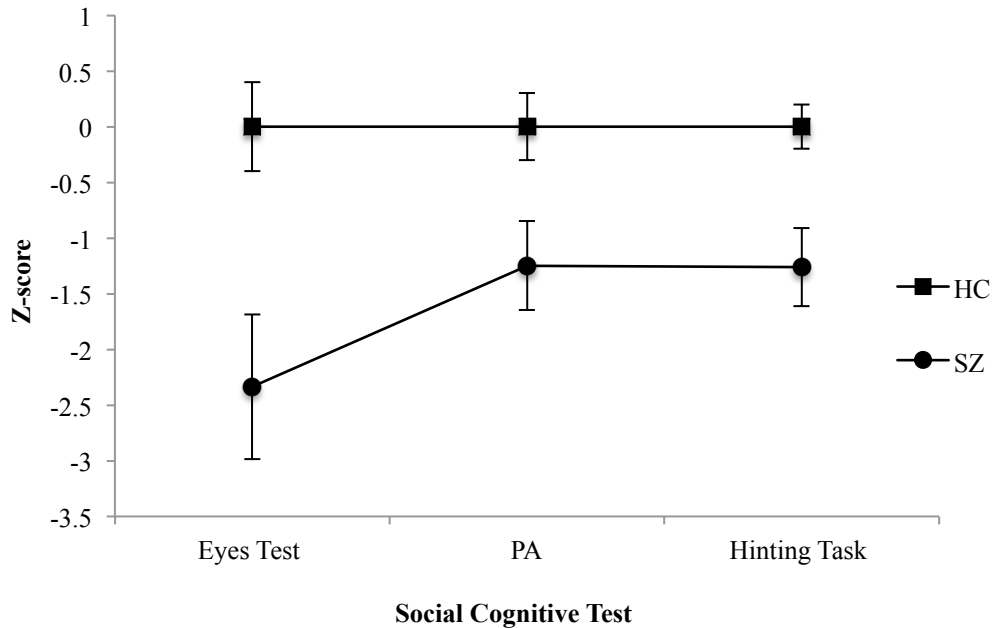
*Measures of Social Cognition by Group*

Measure	Group		<i>F</i>	<i>p</i>
	Control Mean ( <i>SD</i> )	Schizophrenia Mean ( <i>SD</i> )		
Eyes Test (Total)	28.1 (3.1)	20.8 (7.1)	14.70	<.005
Hinting Task (Total)	14.5 (3.0)	10.5 (3.3)	12.82	<.005
Picture Arrangement (SS)	10.8 (2.6)	7.6 (3.1)	10.54	<.005
UPSA Total	83.8 (8.5)	69.7 (16.7)	3.61	<.005
Activities/Planning	17.6 (1.8)	14.4 (4.9)	6.57	<.05
Finance	17.1 (1.7)	12.1 (5.1)	15.48	<.001
Communication	14.9 (1.9)	12.9 (2.8)	5.64	<.05
Transportation	17.3 (2.8)	13.1 (6.1)	6.28	<.05
Household	17.4 (3.1)	14.1 (6.4)	3.61	.07

*Note.* UPSA = UCSD Performance-Based Skills Assessment.

Figure 6

*Interaction Effect for Social Cognitive Test Scores*



*Note.* HC = Healthy Control; SZ = Schizophrenia; PA = Picture Arrangement.

Pearson correlations were used to examine the associations between these measures and cortisol production for the schizophrenia and control groups. No significant correlations were found when groups were examined individually due to small sample size. Effect sizes indicated by the correlations (Cohen, 1992) indicate medium effect sizes were present between AUCg and Hinting Task, and AUCi and Picture arrangement for the SZ group. In both instances the relationship was negative suggesting that better performance on tests of social cognition is inversely related to AUC. No correlations of this magnitude were found in the healthy control group. Results of the correlation analyses are presented in Table 10.

Table 10

*Correlations among Social Cognitive Variables with AUC Measures per Group*

Measure	Control		Schizophrenia	
	AUCi	AUCg	AUCi	AUCg
Eyes Test	.24	.13	-.25	-.08
Hinting Task	-.02	.01	-.12	<b>-.42</b>
Picture Arr.	-.16	-.18	<b>-.40</b>	-.13
UPSA	.26	.23	.21	.09

*Note.* Picture Arr. = Picture Arrangement scaled score; UPSA = UCSD Performance Based Skills Assessment; Small correlations are italicized (.1-.29); Medium correlations are in bold (.3-.49)

### Evaluating Hypothesis 3

Exposure to traumatic events between the two groups was examined. Mixed model ANOVA revealed that the interaction effect between group and the number of traumatic events endorsed as witnessed or experienced endorsed on the LEC was not statistically significant,  $F(1,31) = 0.15$ ,  $p = .71$ ,  $\eta^2 = .005$ , or the subscale scores. These findings are in line with other research indicating that people with schizophrenia do not endorse a greater number of traumatic life events overall.

Conversely, there was a statistically significant interaction effect between group and the levels childhood trauma endorsed on the CTQ,  $F(1,31) = 31.36$ ,  $p < .001$ ,  $\eta^2 = .503$ . The interaction effect is driven by greater levels of childhood trauma found in the schizophrenia group. This difference was also present for all CTQ categories of childhood abuse and neglect (see Table 11).

Table 11

*Ratings of Trauma by Group*

Measure	Group		<i>F</i>	<i>p</i>
	Control Mean ( <i>SD</i> )	Schizophrenia Mean ( <i>SD</i> )		
CTQ Total	7.5 (7.6)	32.3 (16.5)	31.36	<.001
Emotional Abuse	1.4 (2.4)	7.9 (4.2)	30.65	<.001
Physical Abuse	1.5 (2.0)	5.9 (5.8)	8.82	<.01
Sexual Abuse	0.5 (2.2)	2.5 (3.4)	4.03	<.05
Emotional Neglect	2.9 (1.2)	10.0 (5.1)	20.31	<.001
Physical Neglect	1.2 (1.5)	6.9 (4.4)	25.44	<.001
LEC	10.4 (9.4)	9.4 (7.1)	0.15	.71
Happened to me	3.4 (2.4)	4.9 (3.5)	2.13	.15
Witnessed it	3.0 (3.1)	1.5 (1.8)	2.88	.10
Learned about it	4.0 (4.0)	3.0 (4.6)	0.44	.51

*Note.* CTQ= Childhood Trauma Questionnaire; LEC = Life Events Checklist.

Hierarchical multiple regression was used to determine if the addition of childhood abuse and neglect improved the prediction of AUCi over childhood sexual abuse (CSA) alone. AUCi was selected for this analysis because it better adjusts for lower baseline levels of cortisol in the SZ group and is a better measure of HPA axis responsivity. Sexual abuse was designated as the first step based on previous research that indicates that presence of CSA predicts conversion to psychosis and schizotypal personality disorder beyond other types of childhood abuse and neglect (Bechdolf et al., 2010; Afifi et al., 2011; Thompson et al., 2014). Levels of childhood trauma were entered into the regression, with sexual abuse added as the first step, followed by abuse (physical and emotional) and neglect (physical and emotional).

See Table 12 for details on each regression model. As can be seen, none of the models run reached statistical significance; therefore, associations between AUC and childhood abuse were examined using correlations.



Table 12

*Results of Hierarchical Multiple Regression*

	AUCi					
	Model 1		Model 2		Model 3	
	B	$\beta$	B	$\beta$	B	$\beta$
Constant	554.97		640.44		638.27	
Sex Abuse	-47.00	-.27	-21.04	-.12	-10.70	-.06
Emot Abuse			-12.55	-.10	-15.41	-.13
Phys Abuse			-17.59	.21	-16.38	-.19
Emot Neg					-17.16	-.18
Phys Neg					9.38	-.13
$R^2$	.04		.04		-.01	
$F$	2.47		1.45		0.92	
$\Delta R^2$	.07		.06		.01	
$\Delta F$	2.47		.95		.23	

*Notes.* Sex Abuse = Sexual Abuse on CTQ; Emot Abuse = Emotional Abuse on CTQ; Phys Abuse = Physical Abuse on CTQ; Emot Neg = Emotional Neglect on CTQ; Phys Neg = Physical Neglect on CTQ.

Pearson Correlations were used to examine associations between childhood trauma and AUCi and AUCg; results of this analysis can be found in Table 13. Small to medium associations between sub-scales of the CTQ and area under the curve for the SZ and HC groups were found. Interestingly, total CTQ scores were positively correlated with AUCi for the HC group while a negative association was found for the SZ group.

Table 13

*Correlations Among CTQ and AUC per Group*

Measure	Group			
	Control		Schizophrenia	
	AUCi	AUCg	AUCi	AUCg
CTQ Total	<b>.31</b>	<i>.15</i>	<i>-.17</i>	<i>.04</i>
Emotional Abuse	<b>.33</b>	<i>.16</i>	<i>-.26</i>	<i>-.13</i>
Physical Abuse	<i>.01</i>	<i>.02</i>	<b>-.40</b>	<i>-.17</i>
Sexual Abuse	<i>-.14</i>	<i>-.15</i>	<i>.03</i>	<i>.05</i>
Emotional Neglect	<b>.36</b>	<i>.19</i>	<i>-.23</i>	<b>.33</b>
Physical Neglect	<i>.24</i>	<i>.18</i>	<i>.11</i>	<i>.29</i>

*Note.* Small correlations are italicized ( $r = .1-.29$ ); Medium correlations are in bold ( $r = .3-.49$ ); CTQ = Childhood Trauma Questionnaire.

## CHAPTER 5

### DISCUSSION

The current study contributes to the growing field of work investigating abnormal physiological response to psychosocial stress in schizophrenia. Present results are in line with previous studies that have found an attenuated cortisol response to psychosocial stressors in schizophrenia at various stages of illness including inpatient, clinically stable outpatient, first episode, chronic, and those at clinically high risk for developing schizophrenia (Ciufolini, Dazzan, Kempton, Pariante, & Mondelli, 2014; Pruessner et al., 2013; van Venrooij et al., 2012; Jansen, Gispen-de Wied, & Kahn, 2000; Jansen et al., 1998). Results from the present study confirm the finding of attenuated stress response in schizophrenia relative to the healthy controls, both in overall cortisol production (AUC<sub>g</sub>) and with respect to baseline cortisol levels (AUC<sub>i</sub>) during the TSST.

The groups were comparable on smoking behaviors and body mass index (BMI), suggesting that these results are not better accounted for by other factors impacting physiological functioning. The control group, recruited through Internet advertising, represented a group of individuals who were likely to differ from the SZ group solely on the variable of interest, which is the diagnosis itself. This procedure selected for individuals without a psychiatric diagnosis that would ensure internal consistency of the experiment itself, as the results of this sample would likely model relationships between variable of interest that exist in people who are similar on all variables except for the presence of schizophrenia. This procedure accounts for discrepancies in the exclusion rates between the two groups, as referring clinicians aware of exclusion criteria, which eliminated a greater portion of inappropriate candidates. This may contribute to some problems with interpretation, such as the gap in IQ between the two groups; however, to this

author's knowledge there have been no reported findings examining the relationship between stress response to the TSST and IQ.

Similar to the findings reported by Pruessner and colleagues (2013), baseline cortisol levels were lower for the clinical group than healthy controls. This finding is true for the relaxation time point of the TSST and the two time points prior to the start of the TSST. Lower cortisol production in SZ is contrary to finding from Walker & Diforno (1997) who reported that levels of cortisol are higher among people with schizophrenia. It may be feasible that discrepancies in baseline cortisol levels in current study may be due to differences in subjective experiences that are not reflected by the VAS. Overall, this baseline difference is not well understood.

Nevertheless, the present findings of diminished cortisol response in the SZ group are consistent with the compelling accumulation of evidence suggesting that early trauma exposure is associated with an increased risk for psychiatric disorders in adulthood. Patterns of cortisol stress response have been observed to vary across disorders. For example, women with a positive history of childhood abuse and current diagnoses of depression and PTSD have exhibited a pattern of increase cortisol response to psychosocial stressors (Heim et al., 2002). Similarly, differences in reactivity have been observed between patients with schizophrenia and depression (Ciufolini et al., 2014) suggesting that the HPA axis may be uniquely involved in various forms of psychopathology. Thus, further research accounting for factors such as lifetime trauma exposure, gender, and other variable of interest is warranted.

Another potential explanatory mechanism could be an enhanced feedback resulting from a down regulation of CRF receptors with an addition of increased negative glucocorticoid feedback. Interestingly, differences found in current study parallel the diminished cortisol

production in response to a psychosocial stressor in males with a history of adverse childhood events reported by Elzinga and colleagues (2008).

Despite the group differences found in current work, the use of cortisol as a biomarker has been discouraged due to multiplicity of factors that trigger HPA axis activation. For example, Hellhammer and colleagues (2009) point out dissociations between salivary cortisol levels and adrenocorticotrophic hormone, corticotrophin releasing factor, arginine vasopressin (AVP), and cortisol levels in blood and urine. The authors list several factors psychological and physiological factors that impact associations (Kudielka, Hellhammer, & Wüst, 2009). While the pattern of hypo-responsivity has been largely consistent in the group of studies examining the TSST in schizophrenia, a solid case for clinical utility of a biomarker has yet to be made as no studies have examined the normalization of the cortisol stress response following treatment. Additionally, there is little agreement about the etiology of this presentation, including teasing apart whether the blunted response is a predisposing/vulnerability factor or a condition that is the result of ineffective coping with trauma or other stressors. Overall, future research is warranted to bolster the case for using the stress response as a biomarker.

Current work provides additional support for the increased negative feedback of glucocorticoid receptors in response to chronic stress. The lack of variation in the cortisol response observed in the SZ sample appears to be tied to hypo-cortisolism as reported by King & Hegadoren, 2002. Further support can be observed among healthy individuals who live in stressful conditions for long periods of time. However, in the present study the relationship between duration of illness and cortisol production was not found to be significant; this may potentially be due to lack of variability in the cortisol data or, as previously mentioned, the multitude of factors that impact cortisol production.

The present findings provide convergent evidence of impaired activation of the HPA axis in response to social stressors. This may offer at least a partial explanation of the social cognitive deficits reported for people with schizophrenia (Green et al., 2012; Fett et al., 2011) as it is possible that abnormal reactivity is due to aberrant functioning in key brain regions, particularly within the limbic system. Structural abnormalities in key limbic regions have been widely reported in individuals with schizophrenia (e.g., Tamminga et al., 1992; Bogerts et al., 1990). Elevations in cortisol production have been demonstrated to increase corticotropin-releasing hormone (CRH) mRNA expression in the amygdala, which resulted in exaggerations in the fear response (Schulkin et al., 1998).

Results from the current study suggest that there may be associations between social cognition and cortisol response for people with schizophrenia. It is possible that better social cognitive abilities may leave one with a better sense of control in social situations. One potential explanatory mechanism is that people with naturally higher social cognition tend to experience interacting with others as more positive and are therefore less stressed in anticipation of social encounters. Further research examining this relationship is warranted.

It is also interesting that cortisol levels at time point 2, sampled three hours after the participants had been in the laboratory, was one of the highest cortisol levels for the SZ group. Time point 2 occurred during the diagnostic and symptom assessments. This may suggest that the clinical group found the diagnostic and symptom assessments and neuropsychological testing more stressful than the healthy controls; however, this is not reflected in the VAS appraisals of nervousness. Additionally, visual inspection indicates that time point 2 is higher for the SZ than time point 1, which would argue against a failure to habituate to the laboratory environment.

Finally, a similar cortisol increase was present for the controls, suggesting that the effect was not specific to the schizophrenia group.

To this author's knowledge, this is the first study to conduct a modified version of the Trier Social Stress Testing using live confederates with people with schizophrenia. The published studies using laboratory psychosocial stress tasks employ an imagined panel (e.g., leading the participant to believe that they are being evaluated by someone behind two-way glass) or inform the subjects that they are being recorded. Some evidence exists in support of the idea that a live panel produces a greater cortisol response relative to an imagined panel (Kelly et al., 2007). The present task was effective at eliciting a physiological response as indicated by greater levels of anxiety endorsed during the TSST relative to baseline measures and increased heart rate in both groups. While the participants in the current study reported finding the task stressful, no adverse effects were reported or observed, which may have positive implications for future research considering employing this paradigm. Additionally, most studies have not utilized a topic related to professional experience because it has been reasoned that patients may have less experience with interviews and would therefore experience the TSST differently from healthy controls (e.g., Brenner, et al., 2011). The current work suggests that despite potentially less interviewing experience, the manipulation was successful and experienced in a similar manner by the groups.

The current study did not find evidence to support the claim that the schizophrenia group found the task less stressful than the healthy control group based on the visual analog scales where similar levels of negative emotions were reported by both groups during the TSST. Nor were differences found on participants' appraisal of threat (primary appraisal) or their perception of their ability to meet the perceived challenge (secondary appraisal) of the TSST. Similarly, the

schizophrenia group exhibited comparable increases in heart rate to the healthy controls, indicating that the schizophrenia group found the task stressful and that other facets of physiological responding were intact. These findings may suggest that there is significant overlap in the way that the groups perceived the TSST. Previous study of the PASA revealed a positive correlation between magnitude of cortisol response and perceived threat of the TSST among healthy college aged men (Gaab et al., 2005). For the current study, the correlation between PASA and the AUC<sub>i</sub> and AUC<sub>g</sub> scores for the total sample were  $r = -.06$  and  $r = -.07$ , respectively, which is inconsistent with these prior findings due to lack of significance. Interestingly, no group differences in task appraisal on the PASA were found in the current study. Also, neither primary nor secondary appraisal was related to levels of cortisol. This appears align with other groups that report similar evaluations of laboratory stressors by people with schizophrenia and healthy controls. For example, van Venrooij et al. (2010) found that male patients and healthy controls endorsed similar levels of nervousness and experience of control on visual analog scales while preparing for a public speaking task. The similarities in tasks appraisal are somewhat unexpected given that several studies have reported an increased prevalence of negative emotion for those diagnosed with schizophrenia, people at ultra high risk for schizophrenia, first-degree relatives of people with schizophrenia and people with schizotypal disorder (Palmier-Claus et al., 2011; Phillips et al., 2011; Tessner et al., 2011; Myin-Germeys et al., 2001).

To this writer's knowledge, the only other study to use the PASA with people diagnosed with schizophrenia found that the SZ group appraised a role-play as more threatening than unaffected first degree relatives of people with schizophrenia and healthy controls (Delawalla, 2010); however, no group differences in threat were found for appraisal of a mathematic test of



working memory. It is possible that the group difference was found due to healthy controls' lower appraisal of the Role Play condition, as it appears that the schizophrenia group rated both the calculation and role play conditions similarly. The similarities in reported subjective experience could be due to other factors. For example, is possible that these differences are due to a lack of more nuanced vocabulary as indicated by the difference in IQ observed between the groups. It is also feasible that higher levels of Alexithymia in the SZ group may impair accurate reporting of emotional state.

The free response portion of the study revealed that there were some differences in how the two groups described their experience of the TSST. For example, those with schizophrenia were more likely to use extreme language to describe the confederates (e.g., “evil” or “soulless”). Overall, the schizophrenia group described their performance more negatively, and often cited the difficulty of the subtraction component. People in the SZ group were also more likely to deny trying anything to make the task easier, which may speak to the lower prevalence of adaptive coping strategies among individuals with schizophrenia (Brenner, 2011). Conversely, people in the control group were more likely to describe the task in neutral terms and identified specific examples of things that they did well. Interestingly, some participants in the SZ group indicated that they experienced the task as surreal (e.g., comparing it to the “twilight zone.”). This may suggest that measures including stress-induced dissociation may be sensitive to finding differences in the subjective experience of TSST. Finally, it is notable that those diagnosed with schizophrenia were more likely to articulate concerns that they were disliked based on aspects of their identity or achievement. For example, one participant stated that the confederates “hated” him because of his race, another participant reported that he perceived that the confederates

perceived him as uneducated or a “street person,” while another participant stated that the confederates expected him to do badly because of his diagnosis.

The findings pertaining to the second two questions in the current work were somewhat preliminary due to the relatively modest sample sizes, and should therefore be interpreted with caution. Small to medium correlations were found between measures of social cognition and cortisol response. Overall, the majority of the relationships for both the schizophrenia and healthy control group were negative; indicating that poorer performance on social cognitive tasks is associated with greater cortisol response. Interestingly, the relationships between a measure of everyday skills and cortisol response were positive, suggesting the higher cortisol levels were associated with better functioning. There is insufficient research to venture an interpretation of these relationships presently; it is recommended that future studies examine these relationships to determine if the findings are generalizable and address factors that might better elucidate underlying mechanisms that account for these correlations.

The current regression analysis findings suggest that history of childhood abuse did not account for the variance in overall cortisol response. The non-significant findings may be in part accounted for by the relatively small sample size included in this study. Correlational analyses did reveal a medium sized relationship between AUC<sub>i</sub> and total childhood trauma endorsed, emotional abuse and neglect. This is somewhat unexpected, as childhood abuse has been found to be associated with decreased stress response in healthy controls (Carpenter et al., 2007). For the schizophrenia group, physical abuse was negatively associated with AUC<sub>i</sub> supporting the prior findings regarding impact of abuse on cortisol. As expected, the current study found greater prevalence of childhood trauma among people with schizophrenia. Trauma history has been reported to contribute to the probability of developing adulthood psychosis apparently

independent of genetics (Husted, Ahmed, Chow, Brzustowicz, & Bassett, 2010). Zubin and Spring's (1977) stress vulnerability model proposes that people have a biological vulnerability to psychosis that provides a certain resilience to developing psychosis allowing some to tolerate higher levels of stress without resulting in emergence of psychotic symptoms. Theoretically, surpassing the threshold results in greater probability of developing psychosis. Therefore, the experience of trauma leads to increased vulnerability of developing psychosis. Similarly, the stress-sensitization model (Harkness, Hayden, & Lopez-Duran, 2015) posits that a person may develop psychosis following a major stressor in the context of a biological vulnerability. After the initial emergence of psychotic symptoms a person's vulnerability theoretically increases and the person may require less stress in the future to develop future problems. Therefore, the experience of childhood trauma may result in increased biological vulnerability for psychosis to stressors experienced later in life. Interestingly, in line with the stress sensitization model, the clinical sample endorsed higher sensitivity to work overload and social evaluation on the PSRS.

Future studies may help expand generalizability of current work by including a broader population of participants, including women. Studies including women may benefit from taking into account hormonal factors (e.g., phase of menstrual cycle, use of oral contraceptives). The addition of other control groups, such as first-degree relatives of people with schizophrenia may help elucidate the role of genetics. Additionally, clinical control groups (e.g., people with depression or anxiety disorders, or PTSD) may help evaluate the specificity of the attenuated cortisol response.

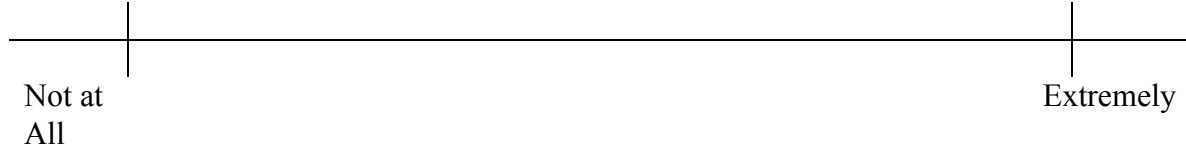
One of the limitations in current study is the relatively modest sample size. Given that the sample size in the current study may have limited ability to detect significant effects for some of the analyses. Future studies may help expand generalizability of current work by recruiting a

larger sample of participants. Future studies may help expand generalizability of current findings by including women. Finally, variability in heart rate data precluded identification of heart rate differences between the groups, even though there were apparent differences between the groups that reflected changes observed in the cortisol data. More precise measurement of heart rate in future studies might allow for significant differences to be observed by minimizing variance.

APPENDIX A

Right now I feel:

**Nervous**



**Scared**



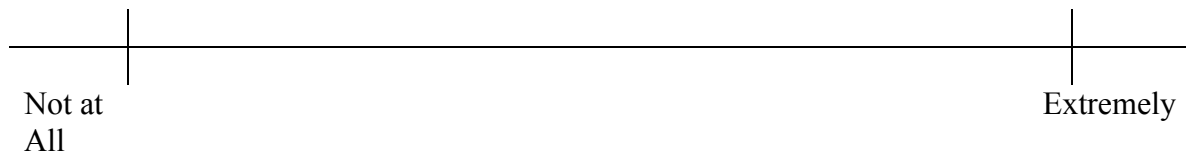
**Calm**



**Excited**



**Happy**



## APPENDIX B

### Trier Social Stress Test Appraisal Interview Responses

Table 14

*HC Question 1: How Do You Think You Did?*

Participant	Response
01	“Terrible;” “Unprepared”
02	“Could be better”
03	“Horrible. Hard to fill the time;” “Their eyes kept looking at me and they were very serious;” “I felt I was doing something wrong”
04	“Different than expected;” “I thought they’d ask questions”
05	“Pretty well”
06	“Considering the little time to prepare - pretty good”
07	“Not enough time to prepare speech;” “I repeated things;” “I stopped a few times because I thought time went faster;” “6.5/10”
08	“I’m not sure how to interview”
09	“Alright. Not a typical interview I’ve done because I typically cook during an interview”
10	“Alright until I stopped then I needed to come up with more stuff.”
11	“Quite thrown without the notes. I finished my speech and they didn’t respond;” “Did pretty badly because there wasn’t enough time to prepare and my thoughts didn’t come out right”
12	“Mediocre. Covered good points but I was far too nervous;” “I had several awkward pauses and didn’t make enough eye contact;” “I said ‘umm’ too much”
13	“The interview went well. I like talking to people”
14	“Covered most of the points but had trouble remembering them in order;” “Not as fluid as I would like”
15	“Could have done better;” “I didn’t feel too muddled;” “I didn’t stutter but there wasn’t much content”
16	“Pretty good.”
17	“It was fine, just the number part was difficult. I didn’t expect to go backwards. I’m not good with numbers.”

*Note.* HC = Healthy Control.

Table 15

*HC Question 2: What Went Well?*

Participant	Response
01	“When I was describing/presenting myself for the position; explaining why I was qualified.”
02	“Started off well getting out what I prepared but I didn’t have time to prepare enough to fill the time and improvising is more difficult.”
03	“Nothing. Especially not the math.”
04	“Filling the time;” “The was <i>not</i> my favorite;” “I made good eye contact with the people.”
05	“Nothing.”
06	“I got my ideas out. Highlighted my experience and explained ability to contribute to company.”
07	“Initial introduction went well. I got my goals set but didn’t elaborate much;” “Organized at first but then came apart.”
08	“I made strong points”
09	“Everything was alright.”
10	“The fact that I recovered.”
11	“I stayed relaxed and didn’t show that I was flustered;” “I tried to cover my nervousness.”
12	“D minus;” “Almost failed;” “The numbers threw off my concentration.”
13	“Had a decent game plan;” “When I was under time I felt like I kept my composure.”
14	“Getting thoughts across;” “I sold myself.”
15	“Counting backwards;” “I was surprised at my ability to stretch out the information in my mind;” “Vamping”
16	“Continuing talking non-stop for five minutes’
17	“Nothing.”

*Note.* HC = Healthy Control.

Table 16

*HC Question 3: What Was Difficult?*

Participant	Response
01	“Very little time to prepare;” “I don’t have much experience interviewing;” “Speaking was hard.”
02	“Improvising was difficult;” “Little time to plan what to say.”
03	“Counting.”
04	“The people were not responding;” “The math was hard;” “I made no eye contact.”
05	“I tried to get the interviewers to respond and it was hard when they didn’t;” “I come off cold”
06	“Blank faces;” “No communication back and forth.”
07	“Coming up with a scenario. Thinking of something to say.”
08	“Gauging how long I should talk for;” “I didn’t get a response;” “Number part was hard.”
09	“They seemed a little off putting because they didn’t respond”
10	“The counting was difficult;” “They didn’t respond.”
11	“No interaction so it was very one-sided;” “No follow up questions;” “I felt put on the spot.”
12	“The math part was difficult;” “Being recorded”
13	“Talking about myself is difficult;” “Interviewers didn’t ask questions, interact and stared.”
14	“Keeping my thoughts in order;” “Taking up five minutes.”
15	“Not having materials and not being prepared;” “I had little content and no aides.”
16	“Continuing talking non-stop for five minutes.”
17	“I didn’t expect to be asked to count backwards. It wasn’t difficult, just surprising.”

*Note.* HC = Healthy Control.



Table 17

*HC Question 4: Did You Try Anything to Make it Less Difficult? Did it Work?*

Participant	Response
01	"I tried slowing down my breathing but I didn't help;" "Open body language"
02	"I don't know"
03	"Picturing the numbers"
04	"I told myself to 'keep going,' it can't go on forever. This made the speech easier but not the math."
05	"I kept in mind that it's not a real interview;" "This helped."
06	"I told myself that as long as I share the best "me" everything will be OK."
07	"I said 'Umm' a lot;" "It helped to look at something else in the room because it gave me time to come up with something else to say."
08	"Preparing the speech; this is a practiced pitch;" "I tried to look at them both equally."
09	"I tried to figure out what they wanted but it didn't work;" "Kept up eye contact."
10	"I tried to keep it fun and light hearted."
11	"Preparing. Having a rough plan helped."
12	"No"
13	"Avoiding eye contact made me feel more comfortable but I was aware that I should have made more eye contact;" "I tried to slow myself down;" "Took deeper breaths."
14	"I remembered my notes and it was helpful."
15	"When I felt a stutter coming on I looked above them or looked at the floor to regain composure."
16	"I tried to remember things concisely and speak clearly. Yes, it worked."
17	"Starting over again gave me a chance to get it again."

*Note.* HC = Healthy Control.

Table 18

*HC Question 5: How Would You Describe the Raters? (If No Response: Likeable? Hostile?)*

Participant	Response
01	"I think they're OK;" "Likable"
02	"Stern;" "Not friendly."
03	"Very serious;" "Intense;" "Pre-established feeling that they won't hire me and I couldn't change their negative impression;" "It was hard to read them."
04	"I assumed they're professionals;" "They seemed very different from normal people;" "They were abnormally neutral."
05	"They kept an impassive attitude."
06	"They were down-to-business, serious about the right candidate;" "Direct;" "They had no emotion"
07	"Neural – almost robotic;" "Attractive."
08	"They were unresponsive;" "The woman was slouching more and the guy maybe more friendly;" "The woman seemed a little more skeptical."
09	"They were impersonal;" "Felt awkward."
10	"Stone cold;" "Seemed like they hated me."
11	"They were cold;" "Nothing coming back."
12	"They were stone faced – very good at not responding. They didn't laugh."
13	"Very distant and very neutral"
14	"They were not typical;" "There was no back-and-forth"; "It was difficult to read their response."
15	"Stoic;" "Firm;" "Business-like;" "Not likeable but not hostile;" "Their eye contact was intense."
16	"Stoic. Not likable."
17	"They were nice. They were quiet. There's not a lot to describe."

*Note.* HC = Healthy Control.

Table 19

*HC Question 6: Do You Have Any Thoughts About What the Raters Thought of You?*

Participant	Response
01	“Not a good candidate.”
02	“I couldn’t tell. They probably thought I was somewhat qualified.”
03	“No.”
04	“Maybe that I know how to give good speeches;” “Probably thought that I was comfortable but don’t know how to subtract.”
05	“No – there was no body language until the end”.
06	“Not really.”
07	“Not really.”
08	“No.”
09	“Not really.”
10	“Not at all.”
11	“Hopefully fairly confident.”
12	“They thought I was stupid because of the math;” “Other parts went were pretty good.”
13	“Geez. Very nervous. That’s it.”
14	“No. They didn’t ask questions. No feedback.”
15	“Average public speaker, but probably thought I was unprepared due to the huge gaps of silence.”
16	“I didn’t think they cared. Irate maybe?”
17	“They saw that I didn’t have an answer and that I wasn’t getting it.”

*Note.* HC = Healthy Control.

Table 20

*HC Question 7: Do You Have Any Relevant Experience?*

Participant	Response
01	“None.”
02	N/A
03	“Course instructor”
04	“Took speech and debate in high school.”
05	“Some experience studying and practicing public speaking.”
06	“Had to do a lot of pitches for work.”
07	“Not any interviews.”
08	N/A
09	N/A
10	N/A
11	“No interviews in 14 years, but do have casual “job chats.” Speak in front of people on a daily basis for job.
12	“Spoke at many funerals.”
13	“Took speech class and taught for a bit in college;”
14	“I hired a lot of people.”
15	“Public speaking class in high school;” “I had to train people in at [work];” “I worked [in customer service] and had to speak in front of ten to fifteen people.”
16	“Job interviews, training people.”
17	“I’ve had lots of job interviews and I try to be myself.”

*Note.* HC = Healthy Control; N/A = Not Available; [ ] = details were generalized to protect confidentiality.

Table 21

*SZ Question 1: How Do You Think You Did?*

Participant	Response
01	"I don't know;" "For most jobs I just give them a resume;" "I'm surprised they didn't have questions."
02	"Terrible on the math;" "I don't know how on the interview."
03	"Not good. I didn't know what to say;" "I said 'umm' a lot;" "I had trouble making eye contact with the woman;" "Low confidence."
04	"It was kind of scary;" "Felt like the twilight zone;" "I think I passed but didn't do too well;" "I felt shocked."
05	"It was challenging. I don't think I did too well."
06	"Not very well. Seems like you're in the twilight zone."
07	"I think I did OK. It was frustrating because before the schizophrenia I was more impressive."
08	"I don't know. Pretty good."
09	"I kind of fell apart but I did a good job."
10	"I ran out of speech time in 30 seconds. That was probably not good;" "Lots of pauses and 'umms.'"
11	"It was embarrassing. I think the next guy can do it but I can't do it;" "He kept saying start at 1022;" "They were silent."
12	"I felt nervous; the questions made me nervous and counting backwards was hard. I think I did poorly. I can't count backwards, but the interview was OK."
13	"Pretty good."
14	"It didn't come out how I wanted it to. I didn't show the confidence that I wanted to."
15	"Terrible. I had nothing to say."
16	"OK. I wanted to get a job inventing things. I did OK with my speech."

*Note.* SZ = Schizophrenia.

Table 22

*SZ Question 2: What Went Well?*

Participant	Response
01	"I didn't like the math part, but the interview was OK."
02	"Nothing."
03	"Nothing really. I felt intimidated;" "I felt put on the spot like a victim."
04	"The voices went away;" "I didn't feel scared but kind of weird."
05	"They listened to me talk about my job and why I was qualified;" "I got a lot of information out."
06	"I wasn't upset or nervous."
07	"I picked a good topic;" "No problems filling the time;"
08	"I knew the subject and knew what to say."
09	"It ended."
10	"Nothing, really."
11	"My speech went alright. I expressed myself and the way I feel;" "I was comfortable – it was a nice room. I thought the camera was on and didn't mind."
12	"I don't know. Probably the questions;" "Maybe I did well. Spoke pretty good."
13	"Posture. What I said."
14	"My effort. Kept smiling through the whole thing. It was uncomfortable but I stuck it out."
15	"That it was short. I had a sense of humor."
16	"I brought my point across pretty well."

*Note.* SZ = Schizophrenia.

Table 23

*SZ Question 3: What Was Difficult?*

Participant	Response
01	"They didn't ask about my training or questions;" "Not much."
02	"Counting."
03	"Seeing the camera and mike;" "The serious look on their faces... I felt put on the spot;" "I felt like a victim."
04	"The math was hard. I couldn't subtract the numbers;" "It was like the twilight zone."
05	"They weren't smiling."
06	"They were stone-faced. Not smiling or reacting;" "I asked them questions and they didn't respond."
07	"I had trouble with the math;" "I felt thrown off by task."
08	"The number thing. I did really bad on that;" "I had extra time;"
09	"I went blank in there and it was hard to answer questions;" "They had blank faces."
10	"I've gone through interviews and they're always stressful;" "I ran out of material."
11	"They were silent and not talking at all;" "It wasn't quick, it took ten minutes because what I said wasn't enough."
12	"Counting backwards."
13	"I shake a lot. It was very hard for me not to show them fear. That's the hardest part. Also, counting backwards."
14	"Got nervous and forgot what to say. Hard to speak in clear, coherent sentences."
15	"I was thinking about if I would have consequences for this; they didn't hide the way they were looking at me."
16	"Trying to make the speech longer."

*Note.* SZ = Schizophrenia.

Table 24

*SZ Question 4: Did You Try Anything to Make it Less Difficult? Did it Work?*

Participant	Response
01	"I relaxed and tried to breathe. It worked"; "I used humor to make it better."
02	"No."
03	"I didn't look at their faces. It kind of helpful."
04	"No."
05	"No."
06	"I kept talking and that was helpful."
07	"Having schizophrenia you get a lot of road blocks. I felt paranoid and nervous;" "I hit a wall. Felt like something was wrong."
08	"I had notes and everything;" "Kept in mind that it's not real."
09	"Not let it get to me because it's fake."
10	"I came up with something to say."
11	"I cooperated and did by best;" "I'm sure the adding was slow."
12	"I tried to calm myself down by breathing in and out. It was helpful;"
13	"Deep breathing, relaxing, and clearing my mind worked."
14	"Smiling helped. Familiar examples, asking interviewers questions to make it more comfortable."
15	"I tried not looking straight in their face, I tried looking around the room."
16	"No."

*Note.* SZ = Schizophrenia.



Table 25

*SZ Question 5: How Would You Describe the Raters? (If No Response: Likable? Hostile?)*

Participant	Response
01	"They're regular people who want answers."
02	"They were professional;" "Nice."
03	"They were mean;" "Serious;" "Cold;" "Hostile;" "Their eyes sent messages of fear." "They didn't smile."
04	"Evil."
05	"I can't say. Maybe sad;" "They listened to what I had to say."
06	"Stone faced and robotic;" "They were morbid and had no souls."
07	"They weren't judging me;" "They were OK. They didn't do much;" "I didn't notice them."
08	"Usually interviewers respond more. I didn't know how to adjust to them. Usually I adjust to people;" "They were flat. I couldn't read them;" "They were kind of mean;" "Unfriendly."
09	"They were serious;" "I thought about cursing them out;" "Nothing can be said to satisfy them;" "Disciplinarians;" "Cold."
10	"They wanted to shoot me;" "They had a mean look on their faces;" "Kind of angry."
11	"They were quiet. Sort of like hosts themselves;" "They were just doing their job."
12	"They're nice. Seemed professional."
13	"Good, likable. All interview people are not likable."
14	"Cold and stern. Not interested."
15	"Very serious, like robots."
16	"They were OK."

*Note.* SZ = Schizophrenia.

Table 26

*SZ Question 6: Do You Have Any Thoughts About What the Raters Thought of You?*

Participant	Response
01	"They liked me."
02	"They thought I can't count."
03	"Not really."
04	"They hated me because I'm black."
05	"No idea."
06	"I wonder if they thought I was mentally ill and needed help;" "They were testing my patience."
07	"No."
08	"No. As you get older you see all types of people."
09	"No."
10	"I don't know."
11	"I don't have the slightest idea;" "They knew I wasn't that educated and that I was more of a 'street person' not a 'school person'."
12	"No. I don't know;" "I kept getting those numbers wrong. Maybe they thought I did good."
13	"No."
14	"I thought they were aware of immature impulse to leave... Reflecting on it now it seems like they didn't like me."
15	"No, I don't know."
16	"They thought I was OK. It was an OK speech."

*Note.* SZ = Schizophrenia.

Table 27

*SZ Question 7: Do you Have Any Relevant Experience?*

Participant	Response
01	"I worked a lot of jobs and have done lots of interviews."
02	N/A
03	"Never really been in an interview. I've had one group interview and one one-on-one interview;" "I don't have public speaking experience;" "I'm not good at knowing my own strengths."
04	"I do some public speaking in church;" "I took some classes on how to interview."
05	"I've had some interviews and passed some interviews."
06	"I've had lots of different jobs and had lots of interviews. I used to be on a debate team."
07	"In high school I [was in a club]. We practiced making speeches and played impromptu games."
08	"I have been through interviews before and know what owners are interested in;" "I took some classes about job interviews."
09	"I spoke at [meeting] podium and interviewed for peer groups."
10	"I'm more hands on and not good at interviews;" "I'm horrible at public speaking and failed in college so I took [language class] instead."
11	"No."
12	"I've had some job interviews but not in the last ten years;" "I don't have public speaking experience."
13	"Interview at a fast food restaurant as a teenager."
14	"Spoke in front of advisory board in [mental health center]. Teaching English in [foreign country]."
15	"Took a class in middle school or high school."
16	"Job interviews, a little bit of public speaking 'in the streets' (e.g., at the bus station or restaurants)"

*Note.* SZ = Schizophrenia; N/A = Not Available; [ ] = details were generalized to protect confidentiality.

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## CURRICULUM VITAE

**Mary Vertinski**

Email: [mvertinski@gmail.com](mailto:mvertinski@gmail.com)

### EDUCATION

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- Jan 2015 – Present     Doctor of Philosophy, Clinical Psychology  
*University of Nevada, Las Vegas, NV (UNLV), Las Vegas, NV*  
Major Advisor: Daniel Allen, Ph.D.  
Dissertation Title: “Understanding Stress Reactivity in Schizophrenia”
- Dec 2014                 Master of Arts, Clinical Psychology  
*University of Nevada, Las Vegas (UNLV), Las Vegas, NV*  
Major Advisor: Daniel Allen, Ph.D.  
Thesis Title: “Factor Structure of the CPT-II”
- May 2007                 Bachelor of Arts, Psychology  
*University Of California, San Diego (UCSD), La Jolla, CA*  
Provost’s Honors awarded 2005- 2007

### INTERNSHIP APPOINTMENT

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- Aug 2016- Aug 2017     Richard L. Roudebush Veterans Affairs Medical Center  
Program: Serious Mental Illness/Recovery

### CLINICAL TRAINING AND EXPERIENCE

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#### Pre-doctoral Practicum Training

#### VA Southern Nevada Healthcare System (VASNHS)

#### Psychosocial Rehabilitation and Recovery Center

Las Vegas, Nevada

Jul 2015- May 2016

Supervisor: Jeffrey Gilliland, Psy.D.

- **Doctoral Practicum Student:** Providing individual therapy to combat and non-combat veterans with a wide array of diagnoses including PTSD, schizophrenia, bipolar disorder, anxiety, mood disorders, substance abuse, and personality disorders. Psychotherapy provided from an integrative approach drawing from CBT, DBT, interpersonal, and existential therapies. Individual therapy provided for nine weekly clients, diverse with respect to age, ethnicity, and service era including Vietnam, Gulf War, and OEF/OIF. Conducting diagnostic evaluations and writing accompanying treatment plans. Co-facilitating Seeking Safety Group for clients with comorbid PTSD and substance use disorders. Independently developed and implemented a psychotherapy group based on DBT principles of emotion regulation and interpersonal effectiveness. Collaborating with psychiatrists and social workers to maintain up-to-date care.

- **Supervision and Didactics:** Receiving 2-3 hours of weekly individual supervision consisting of case and note review, case conceptualization, modeling, and live observation. Trained in efficient use of CPRS. Attending weekly case conference meetings.

**The PRACTICE: A UNLV Community Mental Health Training Clinic**  
Las Vegas, Nevada

Aug 2014- Aug 2015  
Supervisors: Noelle Lefforge, Ph.D.  
Michelle Paul, Ph.D.

- **Doctoral Practicum Student:** Provided individual, group and couple therapy to diverse clients with respect to age, gender, ethnicity, sexual orientation, and clinical presentation. Co-facilitated DBT groups for adults. Collaborated with other mental health professionals to coordinate client care. Therapy was provided from an integrative perspective. Incorporated use of psychometric assessment when appropriate.
- **Graduate Assistant:** Responsible for general administrative procedures, including regular front desk duties, informal clinical consultation for junior students, and overseeing adherence to protocols to ensure safety and ethical practice. Provided support for group treatments and couples' counseling. Updated consent forms and clinic policy manuals to optimize logistical procedures, and created procedures to increase integration of research and clinical practice. Conducted research to inform ethical and up-to-date practice.
- **Supervision and Didactics:** Supervision consisted of weekly individual and group meetings to maintain client welfare and further clinical skill development. Modalities included: tape review, session report, note and treatment plan review, and live observation. Participated in co-therapy with a licensed psychologist of a long-term client with refractory personality pathology. Sought out specialized training in couples' counseling with additional weekly group supervision. Attended weekly staff consultation meetings.

**Southern Nevada Adult Mental Health Services**  
**Rawson-Neal State Psychiatric Inpatient Hospital**  
Las Vegas, Nevada

Aug 2014-May 2015  
Supervisor: Paula Squitieri, Ph.D.

- **Doctoral Practicum Student:** Provided psychodiagnostic assessment, individual and group therapy, and consultation services for a diverse population of adults hospitalized for psychiatric care in a state hospital. The majority of the patients served were low SES, lacking insurance, and diagnosed with SMI. Assessment opportunities included differential diagnosis, assessment of intelligence, behavioral analysis, risk assessment, neuropsychological screening, malingering, and evaluation of social and emotional functioning. Treatment modalities used include CBT, DBT, existential, and interpersonal approaches. Compiled a standardized manual for administration of DBT on an inpatient psychiatric unit that will be utilized by future clinicians with an accompanying instructional presentation. Composed an orientation presentation for future interns to provide education about legal holds, available state resources, and the role of the psychologist on the psychiatric inpatient unit.
- **Supervision and Didactics:** Received a minimum of one hour of weekly supervision consisting of session and note review, and case conceptualization. Received live observation during group facilitation, and received feedback to hone group facilitation skills. Worked on a multidisciplinary treatment team consisting of psychiatrists, social workers, nurses, and



psychologists to coordinate client care. Exposed to the process of legal holds and commitment to a psychiatric hospital.

**Innovative Psychological Solutions**

Las Vegas, Nevada

Jul 2013-Dec 2013

Supervisor: Danielle Bello, Ph.D.

- **Doctoral Practicum Student:** Conducted neuropsychological assessments with children, adolescents, adults, and elderly adults in an outpatient setting using a flexible neuropsychology battery. Cases were typically psychiatric, medical, and academic with referral sources generally including medical doctors, psychiatrists, school counselors, and social service agencies (e.g., CPS). Responsible for test administration, scoring and interpretation, assisting in clinical interviews, and report writing. Commonly presented patient diagnoses included learning disorders, ADHD, adjustment disorders, affective disorders, cognitive impairment secondary to medical conditions, traumatic brain injury, dementia, substance abuse, personality disorders, and pervasive developmental disorders.
- **Supervision and Didactics:** Supervision consisted of weekly individual meetings, and in vivo co-assessment.

**The PRACTICE: A UNLV Community Mental Health Training Clinic**

Las Vegas, Nevada

May 2013-Aug 2013

Supervisor: Noelle Lefforge, Ph.D.

- **Doctoral Practicum Student:** Provided individual therapy to a caseload of 4-7 clients. Worked with adults diagnosed with affective disorders, adjustment disorders, autism spectrum disorders, and serious mental illness. Primary theoretical approach used was integrative therapy.
- **Supervision and Didactics:** Supervision was comprised of weekly individual meetings utilizing case discussion and review of session video recordings. Attended a weekly practicum seminar, which included didactic instruction and clinical case conferences.

**Center for Applied Neuroscience**

Las Vegas, Nevada

Jun 2012-Aug 2013

Supervisor: Sharon Jones-Forrester, Ph.D.

- **Doctoral Practicum Student:** Conducted neuropsychological assessments with children, adolescents, adults, and elderly adults in an outpatient setting using a flexible neuropsychology battery. Cases were typically psychiatric, medical, and academic with referral sources generally including medical doctors, psychiatrists, school counselors, and the military. Responsibilities included test scoring and interpretation, assisting in clinical interviews, and report writing. Commonly presented patient diagnoses included learning disorders, ADHD, adjustment disorders, affective disorders, cognitive impairment secondary to medical conditions, stroke, traumatic brain injury, dementia, epilepsy, substance abuse, and pervasive developmental disorders.
- **Supervision and Didactics:** Supervision consisted of weekly individual and group meetings and in vivo co-assessment.

**Private Practice, Lisa Linning Ph.D.**

January 2012-October 2012

Las Vegas, Nevada

Supervisor: Lisa Linning, Ph.D.

- **Doctoral Practicum Student:** Co-led two 18-week adolescent Dialectical Behavior Therapy groups comprised of adolescents with serious emotional dysregulation. Common presenting problems included self-harm, suicidal attempts, substance abuse, and psychiatric hospitalization. Co-facilitated group discussion, assisted with managing group dynamics, created handouts, led mindfulness activities, and wrote treatment notes. Provided complementary psychoeducation for parents. Conducted adjunct individual therapy with one adolescent, which resulted in occasional opportunity for observation of family therapy.
- **Supervision and Didactics:** Supervision consisted of weekly individual and group meetings and in vivo co-facilitation of group therapy.

**Center for Individual, Couple, and Family Counseling**  
Las Vegas, Nevada

Aug 2011-Aug 2012  
Supervisor: Noelle Lefforge, Ph.D.

- **Doctoral Practicum Student:** Provided long-term individual therapy for a caseload of 7-8 clients. Client diagnoses included personality, affective, and adjustment disorders, bipolar disorder, and schizophrenia. Primary theoretical approach used was eclectic, drawing heavily from psychodynamic, behavioral, and interpersonal orientations.
- **Graduate Assistant:** Responsibilities included performing front-desk duties, such as scheduling, furnishing clients with information, informal orientation and support for incoming students, and ensuring regular access to clinic facilities for staff and clients.
- **Supervision and Didactics:** Supervision was comprised of weekly individual and small-group meetings utilizing case discussion and videotape review. Attended weekly practicum seminar, which included didactic and clinical case conferences.

**UNLV Psychological Testing and Assessment Clinic**  
Las Vegas, Nevada

Aug 2011-Aug 2012  
Supervisors: Michelle Paul, Ph.D.  
Noelle Lefforge, Ph.D.

- **Doctoral Practicum Student:** Conducted intakes, psychodiagnostic assessments, written reports, and feedback sessions for adults and children presenting with learning and psychiatric disorders. Diagnoses included personality disorders, affective disorders, adjustment disorders, pervasive developmental disorders, ADHD, and learning disabilities.
- **Supervision and Didactics:** Individual meetings and in vivo co-assessment.

### Other Related Clinical Experience

**Harmony Health Care**  
Las Vegas, Nevada

Nov 2011-Aug 2012  
Supervisor: Michelle Humm, Ph.D.

- **Psychological Test Administrator:** Administered neuropsychological assessments for clients ages 6-83, including intellectual, emotional, and cognitive assessments.

**Rape Trauma Services**

Apr 2008-Apr 2009

San Bruno, California

Supervisor: Sarah Jarvis

- **Sexual Assault Counselor:** Provided on-call assistance for crisis line callers and survivors of sexual assault during post-assault medical exams and forensic interview. Received specialized training in sexual assault counseling and became familiar with community resources.

**Behavioral Crisis Unit, SFPD**  
San Francisco CA

Jun 2006-Sep 2006  
Supervisor: Officer Kelly Dunn

- **Student Intern:** Shadowed the Psychiatric Liaison of the San Francisco Police Department to work with clients with legal and mental health problems.

**Healthy Within**  
La Jolla, California

Apr 2006-Jun 2006  
Supervisor: Divya Kakaiya, Ph.D.

- **Student Intern:** Interviewed physical education instructors at elementary and middle schools and attended eating disorder support groups.

## **SUPERVISION EXPERIENCE**

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**The PRACTICE: A UNLV Community Mental Health Training Clinic**  
Las Vegas, Nevada

May 2014-Aug 2015  
Supervisors: Michelle Paul, Ph.D.  
Noelle Lefforge, Ph.D.

- **Supervisor in Training:** Supervised two junior clinical psychology doctoral students and one master's student in clinical mental health as they provided individual psychotherapy for a caseload of 5-6 clients. Supervisees provided in-person and tele-counseling therapy. Identified stagnating clients for co-therapy to facilitate clinical progress and model nuanced therapeutic techniques for supervisees. Supervision philosophy was developmental. Supervision consisted of weekly meetings to review session, build conceptualization skills, write treatment plans, and maintain up-to-date session notes. Additionally, I provided support during group supervision with junior students in the clinical psychology program. Prepared and led presentations on relevant topics including selecting clinically relevant readings, clinic procedures, and refining administrative skills. Reviewed supervisees' session video recordings and provided feedback aimed to strengthen clinical skills, broadening use of therapeutic techniques, and building client conceptualization skills.
- **Supervision and Didactics:** Training in supervision consisted of a course dedicated to learning supervision models, techniques, and supervision related research. Received weekly supervision of supervision consisting of recording review and case conceptualization of my supervisee's developmental level and needs. Attended weekly and later bi-weekly group supervision meetings.

## **RESEARCH EXPERIENCE**

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**Neuropsychology Research Program**

Aug 2010-Aug 2017

University of Nevada, Las Vegas

Supervisor: Daniel Allen, Ph.D.

Study (Dissertation): Understanding Cortisol Stress Response in Schizophrenia

Designed a study to investigate the impact of subjective experience and prior experiences of trauma on salivary cortisol levels in response to a psychosocial laboratory stressor. Submitted IRB approval. Ran participants, analyzed the data, and wrote up the results.

Study: Wechsler Intelligence Scale for Children, Fifth Edition, Standardization Study

Was trained and approved in the administration of the WISC-V standardized test. Tested one child without diagnoses and one child with psychopathology.

Study: Social Cognition in Bipolar Disorder With and Without Psychosis

Screened and scheduled potential study participants, including individuals diagnosed with bipolar disorder and healthy controls. Observed administration of testing battery. Assisted with contacting community clinicians to facilitate recruitment.

**Auditory Cognitive Neuroscience Laboratory**

University of Nevada, Las Vegas

Aug 2011-Jun 2012

Supervisors: Joel Snyder, Ph.D.

Daniel Allen, Ph.D.

Study: Neural Mechanisms of Perceptual Processing in Schizophrenia and Bipolar Disorder

Assessed individuals with and without psychiatric diagnoses, to ensure that the participant met eligibility criteria. Administered standardized assessment instruments. Conducted phone screens, scheduled study participants and arranged for transportation.

**Veterans Administration**

San Francisco, CA

Sep 2007-May 2010

Supervisors: Sophia Vinogradov, M.D.

Melissa Fisher, Ph.D.

Study: Computerized Cognitive Rehabilitation in Schizophrenia

Conducted neurocognitive and symptom assessments for stable, outpatients with schizophrenia and healthy comparison controls. Ran magnetoencephalography scans and assisted with fMRI's for study participants.

**University of California, San Francisco**

San Francisco, CA

Sep 2007-May 2010

Supervisor: Rachel Loewy, Ph.D.

Study: Computerized Cognitive Rehabilitation in Early Psychosis

Administered neuropsychological assessments for people at ultra-high risk for developing psychotic disorders and those who have recently been diagnosed with schizophrenia. Scored recordings of emotion induction for degree and frequency of negative and positive emotions.

**Veterans Administration**

San Francisco, CA

Sep 2008- May 2010

Supervisors: Dieter Meyerhoff, Ph.D.

Timothy Durazzo, Ph.D.

Study: Neurological Recovery of Abstinent Individuals With Alcohol Use Disorders

Screened potential study participants to ensure they meet study criteria. Coordinated with treatment day centers to facilitate timely neuropsychological and neuroimaging appointments.

**Veterans Administration**  
San Diego, CA

Sep 2006- May 2007  
Supervisor: Elizabeth Twamley, Ph.D.

Study: Neurocognition in Hospice Patients

Assessed cognitive deficits in hospice patients across several domains including executive functioning, reasoning, verbal memory, and mental status. Assisted with poster and manuscript preparation.

**University of California, San Diego**  
San Diego, CA

Sep 2006- May 2007  
Supervisor: Tracy Love, Ph.D.

Study: Long-term Recovery Following Neurological Insult

Became familiar with language testing for aphasia patients. Assisted with processing MRI images using AFNI software

**Veterans Administration**  
San Diego, CA

Sep 2005- May 2006  
Supervisor: Dean Delis, Ph.D.

Study: Longitudinal Study of Cognition in Older Adults

Administered comprehensive neurocognitive batteries to older adults

**PEER REVIEWED PUBLICATIONS**

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Strauss, G., **Vertinski, M.**, Vogel, S.J., Ringdahl, E.N., Allen, D.N. (2016). Psychometric properties of the Brief Negative Symptom Scale in bipolar disorder and schizophrenia. *Schizophrenia Research*, 170(2-3), 285-289.

Ramage, E.M., Klimas, N., Vogel, S.J., **Vertinski, M.**, Yerkes, B.D., Flores, A., Sutton, G.P., Ringdahl, E.N., Allen, D.N., Snyder, J.S. (2017). Concurrent sound segregation impairments in schizophrenia: The contribution of auditory-specific and general cognitive factors. *Schizophrenia Research*, 170(1), 95-101.

Thaler, N.S., Allen, D.N., Sutton, G.P., **Vertinski, M.**, & Ringdahl, E.N. (2013). Differential impairment of social cognition factors in bipolar disorder with and without psychotic features and schizophrenia. *Journal of Psychiatric Research*, 47(12), 2004-2010.

Thaler, N. S., Strauss, G. P., Sutton, G. P., **Vertinski, M.**, Ringdahl, E. N., Snyder, J. S., & Allen, D. N. (2013). Emotion perception abnormalities across sensory modalities in bipolar disorder with psychotic features and schizophrenia. *Schizophrenia Research*, 147(2), 287-292.

Allen, D.N., Strauss, G.P., Barchard, K.A., **Vertinski, M.**, Carpenter, W.T., & Buchanan, R.W. (2013). Differences in developmental changes in academic and social premorbid

adjustment between males and females with schizophrenia. *Schizophrenia Research*, 146(1), 132-137.

Allen, D.N., Thaler, N.S., Barchard, K.A., **Vertinski, M.**, & Mayfield, J. (2012). Factor structure of the Comprehensive Trail Making Test in children and adolescents with brain dysfunction. *Psychological Assessment*, 24(4), 964-972.

Durazzo, T.C., Fryer, S.L., Rothlind, J.C., **Vertinski, M.**, Gazdzinski, S., Mon, A., & Meyerhoff, D.J. (2010). Measures of learning, memory and processing speed accurately predict smoking status in short-term abstinent treatment-seeking alcohol-dependent individuals. *Alcohol and Alcoholism*, 45(6), 507-513.

Dale, C.L., Findlay, A.M., Adcock, R.A., **Vertinski, M.**, Fisher, M., Genevsky, A., Aldebot, S., Subramaniam, K., Luks, T.L., Simpson, G.V., Nagarajan, S.S., & Vinogradov, S. (2010). Timing is everything: Neural response dynamics during syllable processing and its relationship in schizophrenia and healthy comparison subjects. *International Journal of Psychophysiology*, 75(2), 183-193.

Twamley, E.W., Woods, S.P., Zurhellen, C.H., **Vertinski, M.**, Narvaes, J.M., Mausbach, B.T., Patterson, T.L., & Jeste, D.V. (2008). Neuropsychological substrates and everyday functioning implications of prospective memory impairment in schizophrenia. *Schizophrenia Research*, 106(1), 42-49.

## **PROFESSIONAL PRESENTATIONS & PUBLISHED ABSTRACTS**

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\* Denotes presentation has a corresponding published abstract.

\***Vertinski, M.**, Allen, D.N., & Mayfield, J. (2014, November). Factor Structure of the CPT-II. Poster Session Presentation at the 34th Annual Convention of the National Academy of Neuropsychology, Fajardo, PR.

Call, E.T., **Vertinski, M.**, Thaler, N.T., Sutton, G.P., Bello, D.T., & Allen, D.N. (2014, May). Associations between quality of life and everyday life skills in severe mental illness. Poster session presented at the Annual Convention of the Nevada Psychological Association, Reno, NV.

\***Vertinski, M.**, Allen, D.N., & Mayfield, J. (2013, April). Factor structure of the CPT-II in a pediatric TBI sample. Poster session presented at the 33<sup>rd</sup> Annual Scientific Meeting of the National Academy of Neuropsychology; 2013 October 16-19; San Diego, CA. Also presented in April of 2013 at the Annual UNLV Graduate and Professional Student Association Research Conference, Las Vegas, NV.

**Vertinski, M.** (2012, November). Factor analysis of the Premorbid Adjustment Scale (PAS) and its potential for predicting long-term outcome in schizophrenia. Platform session presented at the 32<sup>nd</sup> Annual Scientific Meeting of the National Academy of



Neuropsychology; Nashville, TN. Also presented in May of 2012 at the Annual Convention of the Nevada Psychological Association, Las Vegas, NV.

- \***Vertinski, M.**, Allen, D.N., Strauss, G.P., Thaler, N.S., & Buchanan, R. (2012, November). Relations between memory abilities and premorbid adjustment abnormalities in patients with schizophrenia. Poster session presented at the 32<sup>nd</sup> Annual Convention of the National Academy of Neuropsychology, Nashville, TN. Also
- \*Ringdahl, E.N., Thaler, N.S., Sutton, G.P., **Vertinski, M.**, & Allen, D.N. (2012, November). Selective impairments in recognizing emotions are present in bipolar disorder with psychotic features. Poster session presented at the 32<sup>nd</sup> Annual Convention of the National Academy of Neuropsychology, Nashville, TN.
- Lee, B.G., Barney, S.J., Catalano, L.T., Ringdahl, E.N., **Vertinski, M.**, Adams, J.L., Shugarman, Y.Y., Snyder, J.S., Allen, D.N., & Strauss, G.P. (2012, October). Anhedonia is associated with impaired long-term memory for positive emotional stimuli in individuals with schizophrenia. Poster presented at the 26<sup>th</sup> Annual Convention of the Society for Research in Psychopathology, Ann Arbor, MI.
- Stuart, B.K., Ford, D., **Vertinski, M.**, McPherson, M., Vinogradov, S., & Loewy, R.L. (2012, October). The discrepancy between the experience and expression of emotion as a risk marker for conversion to psychotic disorder. Poster session presented at the 8<sup>th</sup> Annual International Convention on Early Psychosis, San Francisco, CA.
- \*Ramage, E.M., Barney, S.J., Flores, A., Klimas, N., **Vertinski, M.**, Ringdahl, E.N., Sutton, G.P., Allen, D.N., & Snyder, J.S. (2012, May). Concurrent sound segregation impairment in schizophrenia. Poster session presented at the 67<sup>th</sup> Annual Convention of the Society of Biological Psychiatry, Philadelphia, PA.
- \*Ringdahl, E.N., Thaler, N.S., Sutton, G.P., **Vertinski, M.**, & Allen, D.N. (2012, March) Deficits in functional capacity are associated with psychotic symptoms in bipolar disorder. Poster session presented at the 4th Annual Convention of the American College of Professional Neuropsychology, Las Vegas, NV.
- \*Ringdahl, E.N., Thaler, N.S., **Vertinski, M.**, & Allen, D.N. (2012, March). Is the WAIS-III picture arrangement subtest sensitive to psychosis? Poster session presented at the 4th Annual Convention of the American College of Professional Neuropsychology, Las Vegas, NV.
- \*Verbiest, R., Thaler, N.S., Ringdahl, E.N., **Vertinski, M.**, & Allen, D.N. (2012, March). Tone discrimination impairment is uniquely linked to bipolar disorder with psychotic features. Poster session presented at the 4th Annual Convention of the American College of Professional Neuropsychology, Las Vegas, NV.
- \*Hart, J.S., Thaler, N.S., **Vertinski, M.**, Baldock, D., & Allen, D.N. (2012, March). Facial discrimination uniquely predicts visual affect recognition in bipolar disorder with

psychotic features. Poster session presented at the 4th Annual Convention of the American College of Professional Neuropsychology, Las Vegas, NV.

\*Thaler, N.S., **Vertinski, M.**, Ringdahl, E.N., Woolery, H., & Allen, D.N. (2012, March). Affect identification impairments in bipolar disorder with and without psychotic features. Poster session presented at 4th Annual Convention of the American College of Professional Neuropsychology, Las Vegas, NV.

\***Vertinski, M.**, Allen, D.N., Thaler, N.S., Heisler, D., Park, B., & Barney, S.J. (2011, November). Construct validity of the search identification task. Poster session presented at the 31<sup>st</sup> Annual Scientific Convention of the National Academy Neuropsychology, Marco Island, FL. Also presented at the UNLV Graduate Student Research Fare, Las Vegas, NV.

\***Vertinski, M.**, Terranova, J., Mayfield, J., & Allen, D.N. (2011, March). Factor structure of the Connor's test of Continuous Performance-II in children with TBI. Poster session presented at the 3<sup>rd</sup> Annual Convention of the American Board of Professional Neuropsychology, Las Vegas, NV.

\***Vertinski, M.**, Smith, L., Thaler, N.S., Mayfield, J., & Allen, D.N. Criterion validity of the TOMAL in pediatric TBI. (2010, October). Poster session presented at the 30<sup>th</sup> Annual Convention of the National Academy of Neuropsychology, Vancouver, Canada.

Gazdzinski, S., **Vertinski, M.**, Durazzo, T.C., Mon, A., & Meyerhoff, D.J. (2010, June). The role of nutrition and physical activity in alcohol-associated brain injury. Poster session presented at the 33<sup>rd</sup> Annual Scientific Meeting of the 33<sup>rd</sup> Annual Convention of the Research Society on Alcoholism, San Antonio, TX.

\***Vertinski, M.**, Hadland, C., Thaler, N.S., Strauss, G.P., & Allen, D.N. (2010, March). The relationship between long-term smoking and memory and motor skills in clinical populations. Poster session presented at the 3<sup>rd</sup> Annual Convention of the American Board of Professional Neuropsychology, Las Vegas, NV.

Dale, C.L., Findlay, A.M., Adcock, R.A., Genevsky, A., **Vertinski, M.**, Luks, T.L., Simpson, G.V., Nagarajan, S.S., & Vinogradov, S. (2009, June). Perceptual interference exacerbates voice onset time-dependent syllable discrimination and alters performance-related MEG response dynamics in patients with schizophrenia. Poster session presented at 15<sup>th</sup> Annual Convention of the Organization for Human Brain Mapping, San Francisco, CA.

Hinkley, L.B.N., Guggisberg, A.G., Findlay, A.M., **Vertinski, M.**, Fisher, M., Adcock, R.A., Vinogradov, S., & Nagarajan, S.S. (2009, June). Alpha band resting-state functional connectivity maps in patients with schizophrenia. Poster session presented at 15<sup>th</sup> Annual Convention of the Organization for Human Brain Mapping, San Francisco, CA.



Herman, A.B., Nagarajan, S.S., Findlay, A., **Vertinski, M.**, & Vinogradov, S. (2009, June). Neural correlates of phoneme production preparation in schizophrenic patients and healthy controls. Poster session presented at 15<sup>th</sup> Annual Convention of the Organization for Human Brain Mapping, San Francisco, CA.

\*Khatibi, K., Findlay, A.M., Adcock, R.A., Subramaniam, K., Aldebot, S., Hearst, A., **Vertinski, M.**, Marco, E.J., Nagarajan, S.S., & Vinogradov, S. (2008, April). Neuroplasticity-based cognitive training in schizophrenia normalizes magnetoencephalography auditory duration mismatch responses in cortex. Poster presented at the 15<sup>th</sup> Annual Convention of the Cognitive Neuroscience Society, San Francisco, CA.

Twamley, E.W., Woods, S.P., Zurhellen, C.H., **Vertinski, M.**, Narvaez, J.M., Mausbach, B.T., Patterson, T.L., & Jeste, D.V. (2008, February). Prospective memory impairment and everyday functioning in schizophrenia. Poster session presented at the 37<sup>th</sup> Annual International Neuropsychological Society, Atlanta, GA.

## **AWARDS AND HONORS**

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May 2013      Poster Presentation Award, Second Place, Nevada Psychological Association  
2013 Annual Conference, \$100

Nov 2012      Invited Student Presenter, National Academy of Neuropsychology

Nov 2012      Student Travel Award, UNLV Graduate & Professional Student Association,  
\$300

Nov 2012      Sponsorship Winner of the Women in Leadership Committee, National Academy  
of Neuropsychology

May 2012      Patricia J. Sastaunak Scholarship, \$2,500

Mar 2012      Theodore Blau Student Poster Award, First Place, American College of  
Professional Psychology Conference, \$150

Mar 2012      Outstanding Presentation Award, Second Place, UNLV Graduate & Professional  
Student Association Poster Conference, \$100

Oct 2011      Student Travel Award, UNLV Graduate & Professional Student Association,  
\$500

Feb 2002      Elected Member, *Psi Chi* Honor Society

## **TEACHING AND MENTORING EXPERIENCE**

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Jan 2016-May 2016 &      **Introductory Psychology (PSY 101)**  
Aug 2013- May 2014      Instructor of Record  
University of Nevada, Las Vegas

Independently taught two lower division psychology courses per semester aimed at providing a basic overview of the history of psychology as a field, research methods, and currently important topics in psychology. Designed lectures, activities, discussions, exams, and quizzes.

Aug 2015-Dec 2015                    **Psychology of Learning and Memory (PSY 420)**  
Instructor of Record  
University of Nevada, Las Vegas

Independently taught two upper division psychology courses per semester aimed at understanding the neurobiological, cognitive, and social aspects of learning and memory. Created lectures, activities, discussions, exams, and quizzes. Additional assignments include a research paper and presentation of a relevant peer reviewed article.

Aug 2010-Aug 2016                    **Graduate Student Mentor**  
Undergraduate Outreach Mentorship Program  
University of Nevada, Las Vegas

Volunteer mentor in OUMP, designed to recruit and retain undergraduates from under-represented groups to pursue graduate training in psychology or other mental health care fields.

Mar 2007-Jun2007                    **Developmental Psychology (PSY 106)**  
Instructional Assistant  
University of California, San Diego

Mar 2004-Jun 2006                    **Conversation Leader**  
English Language Institute, La Jolla, CA

### **AD HOC REVIEWER**

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Journal of Child and Adolescent Substance Abuse, 09/2014, Supervised by Daniel Allen, Ph.D.

Journal of Child and Adolescent Substance Abuse, 08/2013, Supervised by Daniel Allen, Ph.D.

Journal of Child and Adolescent Substance Abuse, 03/2013, Supervised by Daniel Allen, Ph.D.

### **PROFESSIONAL AND SERVICE ACTIVITIES**

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2014-2015                    Diversity Committee Co-Chair, Nevada Psychological Association  
2015                         Graduate Student Interviewer, Clinical Psychology Department  
   Admissions Interviews, UNLV  
2014                         Workshop Volunteer Nevada Psychological Association  
2013-2015                    Cohort Representative, Clinical Student Committee, Psychology  
   Department, UNLV  
2013-2014                    UNLV Student Representative, Nevada Psychological Association  
2013-2014                    UNLV Student Representative, Consortium Committee of Nevada  
   Psychological Association  
2013                         Guest Panelist, UNLV Psi Chi Chapter Meeting  
2012-2014                    Student Volunteer at Workshop, Nevada Psychological Association:

- 2011 May 2012; May 2013, Sep 2013, Sept 2013, Apr 2014,  
Member, Nevada Psychological Association Diversity Committee
- 2011 Student Volunteer at Annual Conference, National Academy of  
Neuropsychology
- 2011 New Graduate Student Mentor, UNLV
- 2010 Student Volunteer at Annual Conference, National Academy of  
Neuropsychology
- 2010 Volunteer, High School Suicide Prevention Outreach, Nevada Parents  
Encouraging Parents (PEP)

## **CLINICAL TRAININGS AND WORKSHOPS**

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- Jun 2014 Spirit of Motivational Interviewing  
Featuring: Toni Chance  
One-day workshop, Nevada Partnership for Training
- Apr 2014 Dialectical Behavioral Therapy with Parents, Couples, and Families  
Featuring: Allen Fruzzetti, Ph.D.  
Two day workshop, Nevada Psychological Association
- Oct 2013 Partnership in Action: Providing Tools to Enhance Our Response to Human  
Trafficking  
One-day workshop, Southern Nevada Human Trafficking Task Force
- Sep 2013 Diagnosing Autism and Related PDD's, Pediatric Bipolar Disorder, ADHD, and  
Applications of BASC-2 in Behavioral RTI: An Advanced Training on the  
BASC-2  
Featuring: Cecil Reynolds, Ph.D.  
One day workshop, Nevada Psychological Association
- Sep 2013 Adventures on the Electronic Frontier: Ethics and Risk Management of the  
Digital Era  
Featuring: Jeffery Yunggren, Ph.D.  
One day workshop, Nevada Psychological Association
- Jul 2013 DSM-V: What You Need to Know  
Featuring: Dodge Slagle, Ph.D. & Barry Cole, M.D., DFAPA  
One day workshop, Nevada Psychiatric Association & Nevada Psychological  
Association
- May 2013 Navigating the Changing Landscape of Psychology  
Featuring: Katherine Nordal, Ph.D., David Antonuccio, Ph.D., &  
Stacey Tovino, J.D., Ph.D.  
One day workshop, Nevada Psychological Association
- 2012-2013 Comprehensive Training in Dialectical Behavioral Therapy  
Featuring: Alan Fruzzetti, Ph.D.  
Eight day workshop, Nevada Psychological Association
- Nov 2012 Ethics and Decision Making for Nevada Psychologists  
Featuring: Stephen Behnke, J.D., Ph.D.  
One day workshop, Nevada Psychological Association
- Jan 2012 Everything Clinicians Should Know About Brain Development, Gambling, Eating  
and Related Process Addictions with Young Adults

Featuring: Ken Winters, Ph.D., Larry Ashley, Ed.S., Cortney Warren, Ph.D., & Cynthia Briggs, Ph.D.

One day workshop, UNLV Counseling Program and State of Nevada Association of Addiction Professionals

Nov 2011 Eating Disorders and Obesity: Outpatient Assessment and Treatment

Featuring: Lindsey Ricciardi, Ph.D.

One day workshop, Nevada Psychological Association

Oct 2011 Working with Challenging Couples

Featuring: John Friel, Ph.D.

One day workshop, Nevada Psychological Association

Apr 2011 Psychopharmacology: Integration of Medical and Psychological Treatments

Featuring: Morgan Sammons, Ph.D., & Steven Tulkin, Ph.D., M.S.

One day workshop, Nevada Psychological Association