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Liana Meffert April 12, 2016

The Role of Emotional Dysregulation in Perceived Distress and Cortisol Response During Acute Psychosocial Stress

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

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Adverse physical and mental health outcomes are known to be associated with one's social environment and stressful life experiences. Emotional dysregulation (ED) is a potential mediator of the adverse health outcomes associated with life stress, trauma, and psychopathology. The current study explores associations between ED, subjective emotional distress, and plasma cortisol response to a standardized social-evaluative stressor, the Trier Social Stress Test (TSST).

The study demographic consists of African-American women with Type 2 Diabetes Mellitus (T2DM) and high rates of major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) from a low socioeconomic (SES) inner-city population. ED was measured using the Difficulties in Emotional Dysregulation measure while subjective distress was measured using the Profile of Mood States (POMS). Current symptoms of MDD and PTSD were measured and controlled for using the Beck Depression Inventory (BDI) and the Clinician-Administered PTSD Scale (CAPS).

A significant association was found between high ED and increased subjective distress immediately following the TSST, suggesting that ED may contribute to the relationship between social-evaluative stressors and psychological stress. Critically, the effect remained significant when controlling for the presence of current MDD and PTSD symptoms. Total changes in plasma cortisol were measured using an area under the curve analysis. We found that there was trend for association between ED and total plasma cortisol output.

In sum, ED may increase subjective distress and HPA-axis dysregulation, ultimately leading to whole-body adverse outcomes in high-risk populations. Our data suggest that ED may be a potential therapeutic target for at-risk populations.

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Table of Contents

The Role of Emotional Dysregulation in Perceived Distress and Cortisol Response during Acute Psychosocial Stress

Introduction

Adverse physical and mental health outcomes are known to be associated with one's social environment and stressful life experiences. Among the most potent of these risk factors are low socioeconomic status (SES) and childhood trauma (Alim et al., 2006; Gillespie et al., 2009; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Saydah, Imperatore, & Beckles, 2013). The mechanisms mediating these associations between environmental factors are multidimensional and complex, but their understanding can provide better insights into psychopathological processes and guide the implementation of preventive and therapeutic interventions.

Emotional dysregulation (ED) is a potential mediator of the adverse behavioral health outcomes associated with life stress, trauma, and psychopathology (Bradley, DeFife, et al., 2011; Michopoulos et al., 2015). ED can be defined as deficits in acceptance and awareness of emotions and lack of emotional regulation strategies (J. J. Gross & Thompson, 2007). Previous studies have found associations between early childhood trauma exposure and ED. ED has also been implicated as both a risk factor and predictor of major depressive disorder (MDD) and post-traumatic stress disorder (PTSD), which are both involved in the hypothalamic-pituitary-adrenal-axis (HPA-axis)

dysregulation. The current study explores the role of ED in the psychological and physiological response to an acute social-evaluative stressor.

Background

Childhood Trauma Exposure & ED

High rates of trauma exposure are associated with increased risk for adverse physical and mental health problems, including diabetes, obesity (Jin et al., 2009; Weiss et al., 2011), MDD and PTSD (Alim et al., 2006; Gillespie et al., 2009). Individuals living in low SES communities are at greater risk for trauma exposure, including early childhood trauma (Gillespie et al., 2009). High childhood trauma exposure, particularly in the form of interpersonal violence, increases the risk of developing MDD and PTSD (Alim et al., 2006; Gillespie et al., 2009).

Childhood stress and trauma disrupt an individual's ability to appropriately respond and cope with stressors (Lanius, Vermetten, et al., 2010; Pollak, 2008). One dysregulated response is the cognitive appraisal of stressful stimuli. What would be considered successful neurocognitive adaptations to an abusive home environment, such as a decreased sensory threshold for threatening stimuli, becomes maladaptive in normative settings, with inappropriate attendance to negative stimuli (Pollak, 2008). Examples of adaptive emotional regulation include approaches such as problem solving and reappraisal, whereas strategies such as suppression and avoidance illustrate maladaptive emotional regulation (Aldao, Nolen-Hoeksema, & Schweizer, 2010).

Early childhood trauma exposure is predictive of increased ED (Lanius, Frewen, Vermetten, & Yehuda, 2010; Michopoulos et al., 2015). The inability to regulate emotions has been proposed as a potential risk factor for psychopathology. To that end, several studies have found ED to be both predictive of and a risk factor for MDD and PTSD (Powers, Stevens, Fani, & Bradley, 2015). Certain emotional regulation strategies, such as rumination, avoidance, and suppression, are associated with higher prevalence of psychopathology (Aldao, Nolen-Hoeksema, & Schweizer, 2010), which suggests that not only establishing emotional regulation, but also employing efficacious emotional regulation strategies is important for therapeutic intervention. Low SES communities are at increased risk for childhood trauma exposure and violence, environmental risk factors that increase their odds of developing adult psychiatric and non-psychiatric illnesses (Gillespie et al., 2009). Therefore, ED may be a particularly effective therapeutic target for mediating psychological and, ultimately, physiological pathologies in low SES communities with high trauma loads.

Psychopathology and ED

PTSD is identified by characteristic symptoms that emerge following exposure to one or more clinically significant traumatic experiences, defined as physical threat of injury or death to oneself or others and the inability to exert control or the situation. Emotional reactions to traumatic events vary widely between individuals: common reactions include fear-based re-experiencing of the experience in the form of repetitive, involuntary, and intrusive thoughts or recurrent dreams, negative cognition states, psychological dissociation, or, conversely, hyperarousal and high emotional reactivity. In

a recent national survey, the lifetime prevalence of PTSD in the general population was nearly 7% (Kessler, Chiu, Demler, & Walters, 2005). However, rates as high as 46.2% have been described in urban, low-income, predominantly African-American populations (Gillespie et al., 2009) wherein approximately 89% of study participants report clinically significant lifetime trauma exposure. Of those individuals with PTSD, 72% also had comorbid psychiatric disorders such as Major Depressive Disorder (MDD) (Gillespie et al., 2009).

ED is associated with lower positive affect and poorer coping mechanisms; a similar failure to regulate emotions has been observed in individuals with PTSD (Powers, Stevens, Fani, & Bradley, 2015). Aspects of ED in PTSD include emotional over-modulation and emotional under-modulation (Lanius, Vermetten, et al., 2010). The dissociative subtype in PTSD is characterized by emotional over-modulation, such as disassociation and numbing, which can lead to emotional disengagement from traumatic memories and fearful situations (Lanius, Vermetten, et al., 2010). The second subtype of ED in PTSD is emotional under-modulation, exemplified by states of hyperarousal and re-experiencing of trauma. Proposed pathways for ED in PTSD include a generalized, or increased sensitivity, of the fear response and early life vulnerabilities that interrupt the development of physiological and emotional regulation in response to stressor exposure (Lanius, Vermetten, et al., 2010).

In contrast to PTSD, MDD is characterized by the presence of depressed mood and/or reduction in the capacity to experience pleasure for a period of at least two weeks (American Psychiatric Association, 2013). Other symptoms of MDD may include disrupted ability to concentrate, reduced or excessive sleep, appetite disturbance,

feelings of worthlessness, and thoughts of death or suicide (American Psychiatric Association, 2013). Depressed individuals often exhibit disengagement and lower levels of emotional reactivity. MDD is positively correlated with emotional regulation strategies such as rumination, avoidance and suppression, and negatively correlated with problem solving and reappraisal (Aldao et al., 2010). Recent estimates for the 12 month and lifetime prevalence of MDD in women are 6.87% and 17.10%, respectively, though higher 12 month (18%) and lifetime (39.8%) prevalence of MDD has been described in urban, low income, predominantly African-American populations (Gillespie et al., 2009).

The implications for research on mental illness in African-American women, an underserved population, cannot be undervalued considering the extreme sociological and economic consequences of mental illness and the dearth of literature on this population. Comorbid PTSD and MDD are associated with increased distress, symptom severity and lower functioning (Shalev, 1998). The employee healthcare costs for individuals with PTSD or MDD are significantly higher than that of employees without a mental illness and the effect is compounded when mental disorders are comorbid with adverse physical health outcomes, such as diabetes (Berndt, Bailit, Keller, Verner, & Finkelstein, 2000).

Disease Comorbidity & Implications for ED

Comorbid PTSD and MDD are associated with increased distress, symptom severity and lower functioning (Shalev, 1998). The employee healthcare costs for individuals with PTSD or MDD are significantly higher than that of employees without a mental illness and the effect is compounded when mental disorders are comorbid with

adverse physical health outcomes, such as diabetes (Berndt et al., 2000). Comorbidity between psychiatric disorders and type 2 diabetes mellitus (T2DM) has been observed in schizophrenia, anxiety disorders, and major depression (Prince et al., 2007). It could be argued that one facet of disease comorbidity in the presence of psychiatric illness is caused by declining rates of treatment adherence, which exacerbate pre-existing medical conditions (Delahanty, Bogart, & Figler, 2004).

African-Americans have increased odds of developing T2DM, primarily predicted by low socioeconomic status (SES) (Link & Mckinlay, 2009; Saydah et al., 2013). In a predominantly African-American urban population, 88.1% endorsed a mean monthly income of less than $2,000 (N=1356) while 27% reports a mean monthly income of less than $250 (N=421) (Gillespie et al., 2009). Collectively, both low SES and mental disorders predict worse outcomes for diabetics (Prince et al., 2007). Alternatively, there is the less explored interaction between T2DM and mental illness. Individuals with T2DM have a twofold risk for depression compared to non-diabetics. The reverse is also true: individuals with depression are 60% more likely to develop T2DM (CDC, 2011). While the underlying etiology surrounding the co-morbidity of diabetes with psychopathology remains unclear, one common cognitive construct that might increase risk for both physical and adverse mental health outcomes is ED.

ED as a Mediator of Physiological Response during the TSST

It is clear that psychological factors influence the activity of the HPA-axis, which is involved in regulating the release of several hormones, including cortisol, in response to stress exposure. In this study, The Trier Social Stress Test (TSST) represents the

stress exposure. The TSST induces a perceived social-evaluative threat and reduced locus of control, both of which predict a heightened cortisol response (Dickerson & Kemeny, 2004; Stansbury & Gunnar, 1994). A social-evaluative threat can be described as the potential to be negatively characterized or perceived by others. With respect to the TSST, the social-evaluative threat is characterized by the presence of an audience “trained in behavioral analysis” and a video recorder (Dickerson & Kemeny, 2004). The TSST consistently produces an increase in negative affect, fear, and confusion (Hellhammer & Schubert, 2012; Kelly, Tyrka, Anderson, Price, & Carpenter, 2008). One review of the psychobiological efficacy of the TSST found that the TSST reliably produces a 2 to 4-fold increase in cortisol levels (Kirschbaum, Pirke, & Hellhammer, 1993). Thus, the TSST is frequently used to determine how HPA-axis and function is perturbed under different mental health conditions.

Studies suggest that one’s approach to emotional regulation influences sympathetic response (J. J. Gross, 2002). The emotional regulatory strategy of suppression during high emotion-eliciting tasks has been consistently linked to increased sympathetic response (J. J. Gross & Levenson, 1993) and predictive of a heightened cortisol response from baseline following social-evaluative speech tasks (Lam, Dickerson, Zoccola, & Zaldivar, 2009). Larger cortisol responses have also been implicated in perceived lack of control (Stansbury & Gunnar, 1994). For individuals who struggle with emotional regulation, stressful stimuli would likely produce a diminished perception of control over the situation, thus leading us to expect an exaggerated cortisol response. In contrast, effective emotional regulation may terminate the

physiological stress response through appropriate reappraisal (Stansbury & Gunnar, 1994).

Considering the dearth of literature on the influence of ED on HPA-axis reactivity, predictions are based on research concerning HPA-axis reactivity and PTSD, MDD, and childhood trauma. As discussed earlier, there are high rates of co-occurrence between psychological distress and ED, providing a proximal link for HPA-axis response in individuals with high ED. Physical abuse and severe maltreatment during early childhood has been associated with lower cortisol response across time points during TSST and blunted adrenocorticotropic hormone (ACTH) response during the TSST (Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011). Critically, none of the subjects met DSM-IV criteria for MDD or PTSD at the time of the study.

In response to exogenous ACTH stimulation, women with a history of childhood abuse and current MDD demonstrated a significantly greater cortisol response than those with a history of childhood abuse and no current MDD (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). Similar trends have been demonstrated with respect to the TSST in which abused women with current MDD had higher cortisol response 30 and 60 minutes following the TSST and higher maximal cortisol concentrations than women with a history of abuse and without current MDD (Heim et al., 2000). Therefore, it is possible that in the absence of current MDD, a history of severe childhood maltreatment alone would independently predict a blunted HPA-axis response during the TSST. Lastly, PTSD is also associated with hypo-cortisolism, in part due to increased sensitivity to negative feedback inhibition, also known as “super-suppression” of cortisol (Heim, Ehlert, & Hellhammer, 1999; Raison & Miller, 2003). The presence of enhanced

negative feedback inhibition would predict a blunted cortisol response in response to an acute stressor.

Conversely, prevailing literature suggests MDD is associated with state-dependent cortisol hypersecretion, possibly due to corticotrophin-releasing factor (CRF) hypersecretion, (Gillespie & Nemeroff, 2005) and greater variation in cortisol circadian rhythms (Yehuda, Teicher, Trestman, Levengood, & SIever, 1996). Therefore, it follows that we would expect to see more extreme HPA-axis responses in women with MDD. As discussed earlier, ED is a risk factor for MDD (Powers et al., 2015) and the two cognitive states share many significant environmental risk factors that include early childhood trauma.

Thus, the presence of MDD, high rates of early childhood trauma, and comorbid stress disorders, such as PTSD, confound the possibility of predicting a directional HPA-axis response during the TSST. While the contradictory nature of the variables most associated with high rates of ED do not delineate a clear directional response in women with ED, they do suggest the presence of dysregulated plasma cortisol output during the TSST.

ED as a Mediator of Psychological Distress to the TSST

In their book on the conceptual foundations of emotional regulation, Dr. James Gross and Dr. Ross Thompson describe the emotional regulation process as the "valuation of valuation"(J. J. Gross & Thompson, 2007), an emotional regulation strategy employed, consciously or not, in response to a formerly generated emotion. Failure to emotionally regulate may be reflective of a lack of emotional awareness or

sense of self-efficacy, in this instance, one's ability to effectively influence the trajectory of the initial emotion (J. J. Gross & Thompson, 2007).

The Profile of Mood States (POMS) provides a measure of subjective distress during the TSST. A study examining the effects of meditation found that mindful meditation focused on generating feelings of compassion reduced POMS distress scores during the TSST (Pace et al., 2009). If we consider meditation as advancing an individual's ability to focus and regulate emotions, we would predict that decreased emotional regulation would produce higher POMS distress scores with respect to the TSST. In contrast to the POMS, which assesses subjective perception of emotions at a specific time-point, the DERS is a measure of overall emotional regulation, including dimensions critical in reducing psychological distress during the TSST. If, in general, an individual struggles to mediate their emotional responses to given stimuli, we would expect to see higher levels of distress at any given time-point during the TSST, as measured by the POMS.

The purpose of this study is to explore the association between ED, POMS scores and plasma cortisol. In consideration of the psychological and physiological aspects of ED, we hypothesize that individuals with ED will have a different psychological and physiological response as measured by plasma cortisol to an acute stressor (TSST). Since ED predicts an individual's diminished ability to regulate emotions, we hypothesize that there is a significant association between greater ED and heightened psychological distress following the TSST.

Methods

Parent Project & Participant Demographics

The current Stress and Diabetes (SAD) Study (R01MH099211; PI-Gillespie) utilizes the recruiting and assessment infrastructure established as part of its parent project titled “Genetic and Trauma-Related Risk Factors for PTSD” (R01MH071537; PI-Ressler). As of December 1, 2015 the parent project had recruited over 9,000 participants and published a number of papers concerning trauma exposure and the interaction between genetics, environment, emotional regulation, and psychopathology in a population of county hospital patients in Atlanta, Georgia (Bradley, DeFife, et al., 2011; Bradley, Westen, et al., 2011; Gillespie et al., 2009; Michopoulos et al., 2015; Weiss et al., 2011). Participants were recruited from Grady Memorial Hospital in the Diabetes Care Clinic, Primary Care Clinic, and Obstetrics-Gynecology Clinic. Grady is a not-for-profit healthcare system that serves the low SES population of downtown Atlanta, a city of over 4 million people. The study sample consisted of primarily African-American women (93.4%) from low SES backgrounds (89.2% have a household monthly income of < $2000) found in the Grady Memorial Hospital primary care clinics (Gillespie et al., 2009). Based on samples taken from the Grady Hospital population, current prevalence of MDD in female subjects was 18% and lifetime prevalence of MDD was 39.8% (Gillespie et al., 2009). The same study found that in large sample of females (n=993), 86.1% had experienced a significant trauma with the most frequent causes of trauma exposure being a serious accident or injury, sexual contact at or before the age of 13 and physical attack by an intimate partner (Gillespie et al., 2009).

Measures

Childhood Trauma Questionnaire (CTQ)

The CTQ is a 28-item measure that assesses rates of childhood trauma exposure in the form of neglect, emotional, physical and sexual abuse. The questionnaire uses a 5 point self-report scale ranging from *never true* to *always true* with a positive correlation between high scores and high rates of childhood abuse (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997).

Traumatic Events Inventory (TEI)

A 14-item version of the TEI was used to assess for lifetime trauma history. The TEI probes for different categories of trauma including natural disasters, car accidents, sudden life-threatening illnesses, time spent in war zones, and physical and sexual abuse . The TEI also records frequencies of trauma occurence, including whether the trauma was experienced or witnessed. Scores were summed to measure cumulative adult truama exposure (Gillespie et al., 2009; Schwartz et al., 2006).

Beck Depression Inventory-II (BDI)

The BDI-II is a 21-item self-report measure for depressive symptoms with high internal consistency (alpha=0.91) (Beck, Steer, Ball, & Ranieri, 1996). The measure probes for depression symptom severeity within the past two weeks.

Difficulties in Emotional Regulation Scale (DERS)

The DERS measure is a 36-item self-report scale that measures an individual's ability to emotionally regulate by targeting specific dimensions of emotional regulation. These dimensions include 1) emotional awareness 2) emotional acceptance 3) the ability to regulate impulsive behavior and 4) one's ability to vary emotional response with respect to the environment (Gratz & Roemer, 2004).The DERS has high internal consistency and construct validity (Gratz & Roemer, 2004).

Responses are graded on a scale from 1-5 with 1 being *almost never* and 5 being *almost always*, and a score range of 36-180 (Gratz & Roemer, 2004). DERS can also be broken into 6 subscales of ED including emotional non-acceptance (e.g. "When I'm upset, I feel guilty for feeling that way"), difficulties with being goal-directed (e.g. "When I'm upset, I have difficulty concentrating"), impulsive behavioral control (e.g. "When I'm upset, I become out of control") emotional awareness (e.g. "I am attentive to my feelings"), availability of emotional regulation strategies to the individual (e.g. "When I'm upset, I believe that I will remain that way for a long time") and emotional insight (e.g. "I know exactly how I am feeling").

Clinician-Administered PTSD Scale (CAPS)

The CAPS is a valid diagnostic measure for PTSD based on DSM-IV criteria (Weathers, Keane, & Davidson, 2001). The measure assesses for 17 symptoms of PTSD within three symptom clusters (re-experiencing, avoidance/numbing, and arousal) (Dudley et al., 1995). The CAPS yields a dichotomous and continuous measure, allowing for assessment of the presence/absence of PTSD and a measurement of symptom severity(Dudley et al., 1995).

Mini International Neuropsychiatric Interview (MINI)

The MINI is a diagnostic tool for current MDD based on DSM-IV criteria with high inter-rater reliability and specificity (Lecrubier et al., 1997). The mean duration time of clinical interview is 21 minutes.

Structured Clinical Interview for DSM-IV (SCID)

The SCID-DSMIV was developed for psychiatric diagnosis in research (Ventura, Liberman, Green, Shaner, & Mintz, 1998) and used in combination with the MINI to confirm the presence or absence of MDD.

Profile of Mood States (POMS)

The POMS is a subjective ranking of mood with a 5-point Likert scale and high internal consistency (Curran, Andrykowski, & Studts, 1995). The measure is designed to assess acute changes in mood state (Pace et al., 2009). POMS is a 30-item measure which can be broken into six subscales of tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment and vigor-activity. The total POMS score is calculated by summating the first five subscales and subtracting the vigor-activity subscale scores.

Participant Recruitment

Initial Assessment

Initial subject recruitment took place during regular clinical hours. Subjects who agreed to participate completed a number of self-report measures including a demographic form, which assesses subject age, self-identified race, marital status, education, income, employment, disability status, and measures detailed above (Initial Assessment Measures). Measures completed during the initial interview included the Childhood Trauma Questionnaire (CTQ) (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997), Traumatic Events Inventory (TEI) (Schwartz et al., 2006) and Beck Depression Inventory (BDI) (Beck, Steer, Ball, & Ranieri, 1996). Completion of all measures took between 45-90 minutes. Upon completion, participants were paid $15 for their time and invited to participate in the second phase of the study.

Secondary Phase

The secondary phase involved completion of self-report measures, including the DERS, and structured clinical interviews, including the CAPS to test for presence or absence of PTSD. The MINI and SCID DSM-IV were also given to test for presence or absence of MDD. Participants were paid $60 dollars for participation in the secondary phase of the study.

Inclusion Criteria for S&D study:

1.) Ability to provide informed consent 2.) African-American 3.) Female 4.) Literate 5.) Willingness to participate in study 6.) History of childhood or adult trauma exposure 7.) Diagnosis of Type 2 diabetes mellitus established historically

Exclusion Criteria for S&D study:

1.) Current treatment for autoimmune disorder 2.) Current treatment with non-steroidal anti-inflammatory, glucocorticoid, antidepressant, antipsychotic, anticonvulsant, or benzodiazepine medications 3.) Chart diagnosis of mental retardation, bipolar, or psychotic disorder 4.) Pregnancy.

Participants met all inclusion/exclusion criteria for the S&D study. All protocols and procedures were approved by the Emory Institutional Review Board and the Grady Hospital Research Oversight Committee.

Procedures

Study Day 1 and Study Day 2 took place within two weeks of each other and within two weeks of initial assessment with CAPS and MINI completed by parent project.

Study Day 1 – Baseline measures

Subjects were admitted to Atlanta Clinical and Translational Science Institute (CTSI) at Grady Memorial Hospital. We obtained basic measurements of height, weight, BMI, heart rate, blood measurements and samples. Participants were paid $75 dollars for participation in Study Day 1.

Study Day 2 – TSST

Subjects were admitted to the CTSI to perform the TSST. Subjects were asked to abstain from over-the-counter non-steroidal anti-inflammatory agents or aspirin within 72 hours of the TSST. Smoking was allowed the morning of the TSST, but prohibited from admittance to CTSI until discharge. Subjects were allowed the caffeine equivalent of one cup of coffee and told to refrain from alcohol the day prior to the TSST. Lastly, pre-menopausal females were scheduled during the follicular phase of their menstrual cycle (Childs, Dlugos, & De Wit, 2010).

The TSST took place in the early afternoon, between 1:10 pm and 1:34 pm, as indicated elsewhere (Kirschbaum et al., 1993). The test was broken up into two parts following a seven-minute “anticipatory” period in which subjects were instructed to begin preparing their speech. The first task consisted of an impromptu 5-minute speech and the second involved a 5-minute arithmetic task in which subjects were asked to count down from a given number by a predetermined amount. Subjects performed in front of a panel of three judges that they were told were experts in behavioral analysis. The judges were instructed not to give the subject any positive or negative verbal or nonverbal cues. The TSST was standardized across participants to take 15 minutes to complete (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Pace et al., 2009).

POMS measures were given at pre-determined time points before and after the TSST (Table 1). Baseline blood samples (B1, B2) were taken by trained research nurses before the TSST. Following the TSST, 9 blood samples (T1-T9) were taken at pre-determined intervals (Table 1). Changes in POMS scores were calculated as the difference between post-POMS and pre-POMS (Pace et al., 2009) and baseline cortisol

levels (B1, B2) were averaged. Plasma cortisol was measured by mass spectrometry and ACTH was measured by radioimmunoassay. Assays were completed on 22 participants at the time of the current analysis. Assays were performed by the Biomarkers Core Laboratory of Yerkes National Primate Center at Emory University. Subject reimbursement for Study Day 2 was $225.

-15	-10	-5	0	4	5	12	24	25	30
B1	Pre-POMS	B2	Ant. Period	Ant. Period	T1	TSST	TSST	T2	Post-POMS
40	55	70	85	90	145	205	265	270	--
T3	T4	T5	T6	3rd-POMS	T7	T8	T9	Final POMS	

Table 1. Timing of TSST Blood Samples and POMS scores on Study Day 2. Time points are in minutes with respect to anticipatory period (time=0). For the purposes of this study, the anticipatory period is considered a component of the TSST, thus total time for the TSST is 24 minutes.

Statistical Analysis

A one-way repeated measures ANOVA (analysis of variance) was used to compare mean POMS scores across time points during the TSST. The DERS was converted to a categorical variable with delineations of “low” and “high” ED using a median split at 72.5 and added as a covariate in the one-way repeated measures ANOVA. A one-way ANOVA was used to compare the independent variable, the median-split DERS, to the dependent variable of changes in POMS scores from

baseline. POMS subscales were obtained for a total of 39 participants with the actual number varying based on which variables were controlled for. A one-way ANOVA was also used to establish which POMS subscales were driving the relationship seen between DERS and changes in total POMS scores from baseline. A univariate ANOVA was used to repeat the analysis for changes in POMS scores from baseline and changes in the POMS subscale of depression-dejection from baseline, controlling for current PTSD and MDD symptoms. Lastly, a linear regression model was used to look at the relationship between POMS and DERS as a continuous variable, controlling for current symptoms of depression and PTSD.

A one-way repeated measures ANOVA was used to compare plasma cortisol levels across all TSST time points. At the time of data analysis, the sample size for plasma cortisol assays was 22. Changes in plasma cortisol levels were analyzed using the area under the curve with respect to increase (AUCi) and area under the curve with respect to ground (AUCg). AUCi and AUCg were calculated as described in the Pruessner, et al. paper (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). While AUCg is the total area under the curve, AUCi is the area above baseline (AUCg) subtracted from the net decrease below baseline (Fekedulegn et al., 2007).

A linear regression model was used to look at the predictive relationship between DERS total score and changes in plasma cortisol. The dependent variables were cortisol AUCg and cortisol AUCi while DERS, as a continuous measure, was the predictive variable. This linear regression model was repeated again, controlling for current symptoms of depression and PTSD. The test was then repeated with the median-split DERS using a univariate ANOVA. The univariate ANOVA was done for

both plasma cortisol AUCg and AUCi, controlling for current MDD and PTSD symptoms. Statistical analysis was done using IBM SPSS version 23 with statistical significance at the $p<0.05$ level.

Results

Aim 1: ED as a mediator of psychological distress response to the TSST

Total POMS scores varied significantly by time (F=7.62, p=0.001) (Figure 1). Total POMS scores were significantly greater 30 minutes after the TSST compared to all other time points (Figure 1).

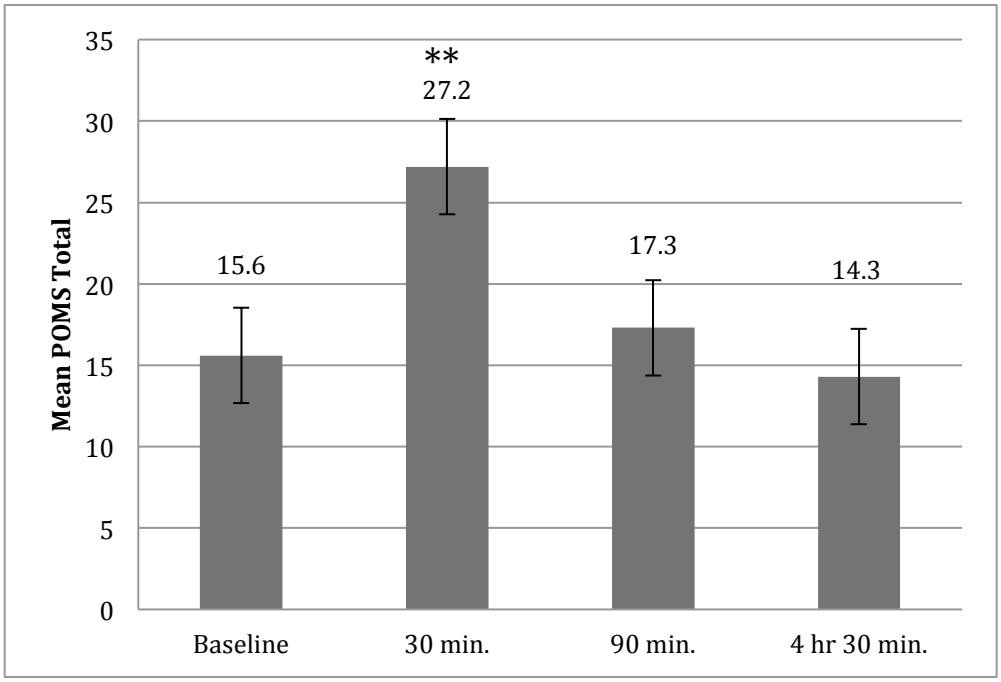

Figure 1. Mean (±*SEM)* POMS scores varied significantly by time with respect to the TSST. The subjective distress reported 30 minutes following the TSST was significantly elevated. ***p*<.01

A one-way ANOVA was used to compare differences in subjective distress between low and high ED groups. High ED was significantly associated with larger changes in POMS scores, calculated as the difference from baseline to 30 minutes following the TSST ($p=0.020$, Figure 2; Table 2). The effect was still significant ($p<0.05$) when controlling for current MDD and PTSD symptoms. Furthermore, for those with high ED, the mean total POMS scores immediately following the TSST (30 minute time point) were significantly higher than those in the lower ED group ($F=5.84$, $p=0.020$, Figure 2).

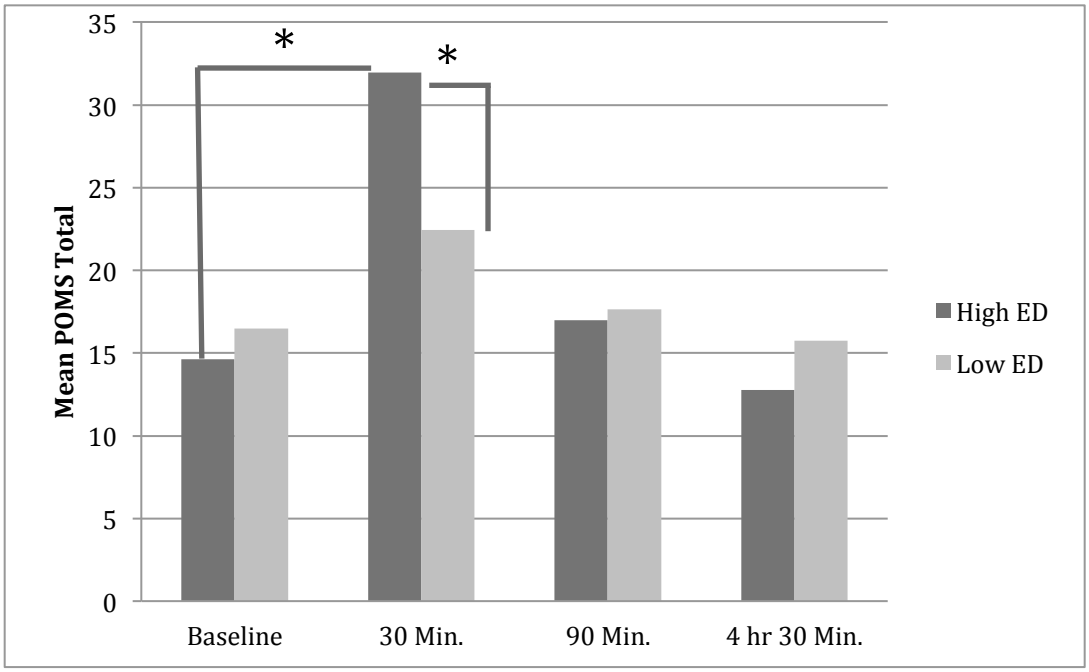

Figure 2. High ED is associated with both greater mean total POMS scores 30 minutes following TSST and greater changes from baseline.*$p<.05$

Changes in the POMS subscales were also analyzed using one-way ANOVA showing that the increases in the POMS subscales of depression-dejection and tension-anxiety were significantly associated with high ED (Table 2). When a univariate analysis was done with DERS as the independent variable and the depression-dejection subscale as the dependent variable, controlling for current MDD and PTSD symptoms, the effect remained significant (F=5.12, p=0.030). Neither MDD (p=0.953) or PTSD (p=0.494) symptom severity were predictive of increased depression-rejection endorsement on the POMS 30 minutes following the TSST.

Analyses were repeated for the tension-anxiety subscale; differences between the high ED and low ED groups were no longer significant when controlling for current MDD and PTSD symptoms.

POMS Scores Change	High ED	Low ED	F Value	P Value
POMS Total	18.1±5.14	4.42±2.01	5.90	0.02*
Tension-Anxiety	5.25±1.21	2.19±0.81	4.49	0.04*
Depression-Dejection	3.00±0.87	0.571±0.20	7.72	p<.01**
Anger-Hostility	3.95±1.29	2.05±0.77	1.60	0.21
Vigor-Activity	0.050 ±0.98	-1.45±0.89	1.29	0.26
Fatigue-Inertia	2.50±1.28	-0.81±1.10	3.85	0.06
Confusion-Bewilderment	3.85±1.09	2.05±0.65	2.07	0.16

Table 2. Mean values for changes in subscales 30 minutes after TSST ± the standard error (SE). A one-way ANOVA demonstrates that DERS is significantly associated with changes in POMS scores 30 minutes following the TSST. The POMS subscales of depression-dejection

and tension-anxiety appear to be driving the effect of total change in POMS scores from baseline. *p<.05, **p<.01

Aim 2: ED as a mediator of physiological change in the HPA-axis

Repeated measures ANOVA demonstrated a significant effect of time for plasma cortisol levels during the TSST (F=36.13, p=0.000) with a maximal cortisol response 40 minutes after initiation of the TSST (Figure 3). There was a significant difference between the maximal plasma cortisol response at 40 minutes and mean plasma cortisol levels at 5 minutes following the initiation of the TSST (Figure 3).

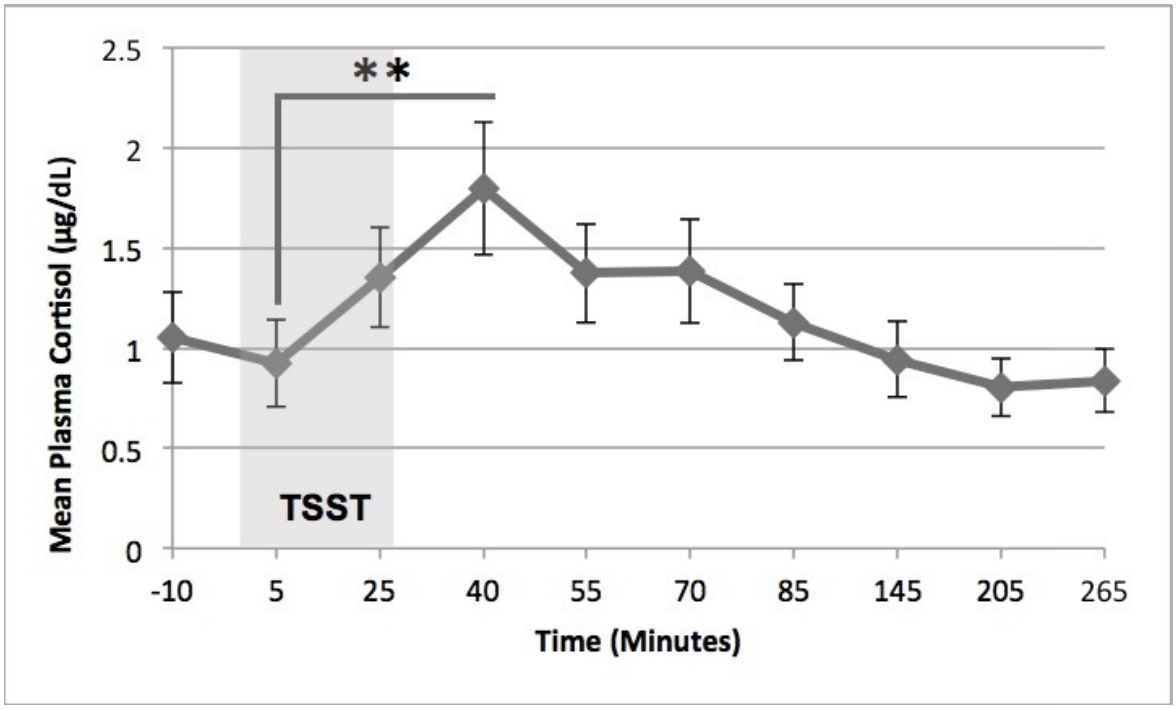

Figure 3. Mean plasma cortisol levels ± SE. There was a significant effect of time on mean plasma cortisol levels (ug/dL) during the TSST. An asterisk denotes the significant difference between the plasma cortisol levels 5 minutes and 40 minutes following initiation of the TSST (0.833±0.29). The time outlined as TSST includes the anticipatory period, with minutes denoted

with respect to TSST. The first plasma cortisol data point is an average of baseline plasma cortisol values taken 15 minutes and 5 minutes prior to the TSST. ***p*<.01

A univariate ANOVA was used to examine associations between DERS and plasma cortisol output. While there was no significant effects of DERS on plasma cortisol AUCi, there was a trend for association between high DERs and increased plasma cortisol AUCg, when controlling for current MDD and PTSD symptoms (Figure 4). Furthermore, MDD symptom severity was significantly associated with plasma cortisol AUCg (F=4.85, p=0.044), though PTSD symptom severity was not, in this analysis.

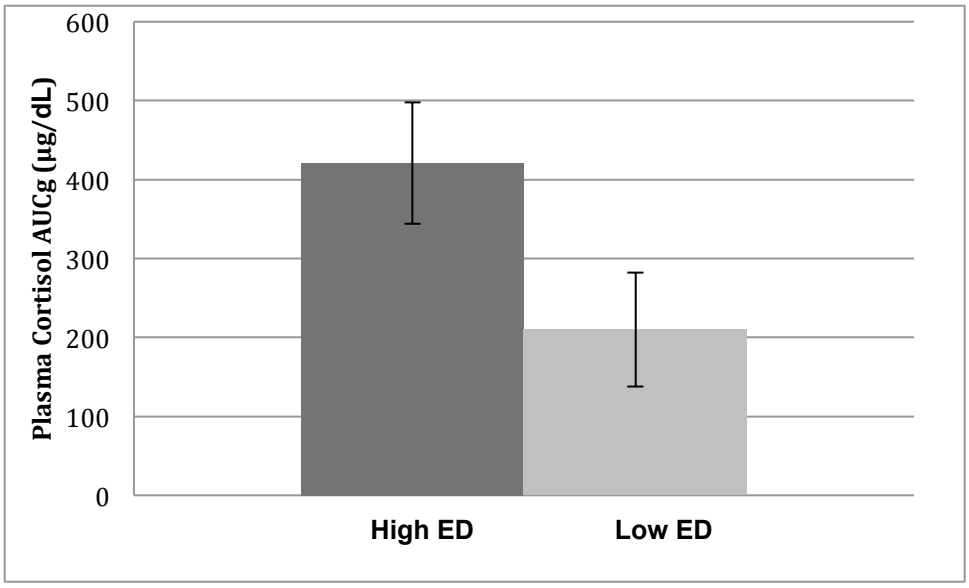

Figure 4. Plasma cortisol AUCg delineated by high and low ED. There was a trend for increased AUCg in women with high ED (p=0.084).

Discussion

Psychological Response

To our knowledge, the current study is the only study to date that has examined the influence of ED on psychological and physiological response to a social-evaluative stressor in T2DM women. Our first aim was to explore the association between ED and subjective distress following the TSST. The results from the current study are critical for increasing our understanding of how ED influences an individual's psychological response to acute social stress.

Importantly, the increase in total POMS from baseline in response to the TSST confirms that the TSST is a potent psychological stressor. Similar changes in POMS scores have been seen previously in experiments using POMS and the TSST to measure changes in subjective stress (Pace et al., 2009). Furthermore, the significant association between high ED and increased subjective distress immediately following the TSST suggests that ED may contribute to the relationship between social-evaluative stressors and psychological stress. Critically, the effect remained significant when controlling for the presence of current MDD and PTSD symptoms. The POMS subscale of depression-dejection appeared to be driving the effect, with increased endorsement of feelings of sadness, unworthiness, discouragement, loneliness and gloominess following the social-evaluative stressor. The significance of the POMS subscale of depression-dejection indicates that the heightened psychological distress resulting from ED is primarily expressed in terms of increased negative self-appraisal. Endorsement of the POMS subscale of tension-anxiety was also significant, with increased endorsement of feelings of tenseness, shakiness, uneasiness, nervousness and anxiousness. The

significance of the depression-dejection and tension-anxiety subscales suggests that ED is associated with an increase in specific elements of emotional distress following the TSST.

A recent study found that ED plays an analogous role in mediating the relationship between childhood maltreatment and emotional eating (Michopoulos et al., 2015). More specifically, increased frequency of emotional eating may reflect a compensatory emotional regulation strategy meant to cope with higher rates of subjective distress. Emotional eating is not only reflective of the need to self-regulate, but also the lack of access to other emotional regulation strategies and ability to vary emotional regulation strategies, which are dimensions of ED measured by the DERS. Emotional eating is one example of a maladaptive coping strategy that might have a detrimental influence on health and preexisting conditions, such as T2DM, due to its association with a higher BMI (Delahanty, Meigs, Hayden, Williamson, & Nathan, 2002). Thus, improvement in emotional regulation could potentially influence subjective distress and emotional eating, simultaneously facilitating both psychological and physical outcomes.

Understanding that the TSST not only increases subjective distress in individuals with high ED, but also specifically increases feelings of unworthiness and dejection, illuminates specific emotional vulnerabilities in low SES women. In a population such as ours, with high rates of trauma exposure (Table 3) and T2DM, feelings of depression and dejection provoked intermittingly by social-evaluative stressors could have a damaging impact on individuals' sense of self-worth, and, thus, self-care and willingness to seek the constant medical attention needed to manage T2DM.

Vulnerability to enhanced subjective distress in the face of social-evaluative stressors may also contribute to less satisfactory relationships, and thus the efficacy of social support systems. A study of adult women with T2DM suggested that women had more success managing their diabetes (demonstrated by blood glucose levels) when they were satisfied with their social support system (Kaplan & Hartwell, 1987). The potential for social support as a buffer against stress and negative health outcomes may be reduced for individuals with social anxiety provoked by greater elevated distress during social evaluation.

Furthermore, given that ED is related to a range of psychiatric conditions, it follows that individuals who scored high on the DERS would demonstrate general deficits in emotional regulation arenas such as reappraisal, problem solving, and acceptance, the absence of which could clearly contribute to increased anxiety and depression following any range of social stressors (Aldao et al., 2010). A study on social approval by others found a relationship between cognitive vulnerability, defined by predisposition and vulnerability to depression, and reaction to social appraisal (Whittal & Dobson, 1991). More specifically, higher rates of cognitive vulnerability predicted increased subjective reports of depression, anxiety, and hostility post-social-evaluative interaction (Whittal & Dobson, 1991).

A similar relationship between specific areas of emotional vulnerability and negative social-interaction outcomes was made between social concerns (e.g. the need for social approval) and avoidance/detachment symptoms of PTSD in crack/cocaine users (McDermott, Tull, Gratz, Daughters, & Lejuez, 2009). In this study, emotional regulation strategies measured using the DERS reliably predicted the probability of a

PTSD diagnosis, above and beyond anxiety symptom severity (McDermott et al., 2009). Although there are clearly other important contributing factors in the development of PTSD and MDD, such as symptoms of anxiety and depression, it is plausible ED plays a trans-diagnostic role in exacerbating existing conditions.

The lack of effective internal emotional regulation strategies may lead an individual to be more dependent on external sources of approval and valuation of self. Thus, the ability to buffer negative social interactions is limited, and often leads to negative emotional responses. In conclusion, ED can be viewed as a trans-diagnostic cognitive vulnerability predictive of worse emotional outcomes in response to social-evaluative stressors. Further research is needed to specifically identify what aspects of ED are most predictive of negative outcomes, and thus present the best targets for therapeutic intervention. Analysis of the DERS subscales, including specific dimensions of emotional awareness, or inability to vary emotional regulation strategies by context, may increase understanding of specific ED deficits and their relative influence on emotional distress.

Physiological Response

It is well established that emotions can influence physiological functioning (Lam et al., 2009). Our second aim was to determine whether ED was associated with a change in plasma cortisol response to the TSST. Our plasma cortisol outcome measure, AUC, provides a measure of collective cortisol response across time-points (Fekedulegn et al., 2007). Specifically, AUCg is a measure of total hormonal production

over time, while AUCi reflects the sensitivity of the stress axis in response to a stressor (Fekedulegn et al., 2007). Our results suggest that 1) the TSST successfully produced a physiological stress response, as seen in repeated measures of plasma cortisol across time points and that 2) ED shows a trend for association with increased total glucocorticoid output in response to the TSST. Since AUCg is a summation of total hormonal output during the TSST, it is a measure of both elevated baseline levels and increased intensity, or distance, between each data point. The combination of elevated hormonal output and increased intensity suggests a possible dysregulation in the HPA-axis in women with high ED.

Another possible explanation for the association between ED and increased plasma cortisol output is the relationship between the efficacy of the emotional regulation strategies and physiological response to stress. As established in the introduction, cognitive appraisal and interpretation of a stressor can ultimately influence an individual's physiological response. Previous studies have sited reappraisal as an effective coping mechanism in the face of stressful events that may ultimately lead to decreased autonomic arousal (James J. Gross & John, 2003). A study on attention regulation in preschoolers that had been physically abused demonstrated increased and prolonged autonomic measures of heart rate and skin conductance in response to two adults fighting, as compared to the non-abused control group. While the control group showed initial arousal, the ability to reevaluate the event (i.e. realize that the situation was not relevant to themselves) led to a decrease in autonomic arousal (Pollak, 2008). One element of ED measured in the DERS, access to emotional regulation strategies, may be a relevant dimension of ED in children, and ultimately adults, with a history of

trauma. This current study suggests that access to a range of emotional regulation strategies may be influential in truncating heightened physiological responses to stressful events (Stansbury & Gunnar, 1994).

Given the established relationship between MDD and hypercortisolemia (Gillespie & Nemeroff, 2005), it follows that MDD symptoms would be significantly associated with increased AUCg. Higher plasma cortisol output reflects an insufficient or dysregulated negative feedback system. Under normal homeostatic conditions, increased cortisol production in response to a stressor should induce negative feedback via the hypothalamus and anterior pituitary gland. The trend towards significance between the DERS and AUCg, when controlling for current symptoms of MDD and PTSD, suggests that ED may contribute, or exacerbate, the problem of HPA-axis dysregulation above and beyond the presence of MDD and PTSD symptoms. However, future studies are necessary to determine whether this is indeed the case, as our study was likely underpowered due to lack of available data from the larger dataset.

The dexamethasone suppression test (DST) demonstrates differing glucocorticoid responsiveness in the HPA-axis between MDD and PTSD. Dexamethasone is an orally administered synthetic glucocorticoid that acts on the anterior pituitary to reduce secretion of ACTH, and ultimately secretion of cortisol from the adrenal cortex. The presence of MDD is often associated with a failure to suppress plasma cortisol levels, termed DST “nonsupression,” that is indicative of dysregulation in the negative feedback system (Gillespie & Nemeroff, 2005). Conversely, PTSD is associated with “supersupression,” an increased responsiveness in the HPA-axis that results in dramatically decreased cortisol levels in response to the DST (Yehuda et al.,

2000). Given that PTSD is associated with enhanced cortisol suppression (Heim et al., 1999; Yehuda et al., 2000), it is possible that the contribution of PTSD to the overall effect of AUCg was minimized by the small sample size we had of PTSD-only participants in the current study. Furthermore, the trend towards elevated AUCg in the high ED, comorbid diagnosis group, suggests that PTSD may have less of an influence on HPA-axis dysregulation via plasma cortisol “supersupression” when comorbid with MDD.

The association between high ED and HPA-axis dysregulation is particularly relevant for groups with high rates of metabolic syndrome (MetS) and T2DM. HPA-axis dysregulation has potential to adversely impact glucocorticoid regulation, and consequently blood sugar levels, exacerbating existing T2DM and metabolic irregularities. Emerging data suggests that MetS includes a cluster of abnormalities, specifically, and most pertinently, hyperglycemia, hypercortisolemia, and reduced insulin secretion (Anagnostis, Athyros, Tziomalos, Karagiannis, & Mikhailidis, 2009). While the precise relationship between these metabolic abnormalities is complicated, it is clear that the presence of HPA-axis dysregulation and its association with symptoms of MetS would exacerbate the presence of T2DM. In sum, ED may increase subjective distress and HPA-axis dysregulation, ultimately leading to whole body adverse outcomes in high-risk populations (Table 3).

Limitations & Future Directions

Limitations of the current study include the subjective nature of the psychiatric measures used, which include the DERS (the primary dependent variable) and the POMS (one of the outcome variables for this study). The cross-sectional nature of the study design also prevented us from assessing causation; significant findings in this study are based on associations. Furthermore, the current study was underpowered to assess differences in cortisol responses to the TSST. A larger sample of plasma cortisol assays will be needed to confirm whether the trends seen in this smaller sample are significant. While outside the scope of this study, future studies might explore the role of comorbid psychiatric disorders in HPA-axis dysregulation. The small sample size in this study demonstrates trends of elevated plasma cortisol levels for comorbid groups. To our knowledge, no other work has been done on HPA-axis dysregulation and comorbid MDD and PTSD.

The homogenous sample of African American women with T2DM is both a strength and a weakness. While the specificity of the participant sample may make it harder to generalize results, these results are highly applicable and translatable to a high-risk, underserved population. Due to high rates of trauma exposure, psychiatric conditions, and relative risk of T2DM and MetS in this population, the current finding that ED is a significant predictor of psychological distress to an acute stressor and increased HPA-axis dysregulation is relevant to this group of women (Table 3). While these findings are highly pertinent and useful for understanding this vulnerable population, further studies will be needed to assess the efficacy of ED as a therapeutic target in other populations.

		High ED	Low ED	P-Value
		n=24	n=24	
Employment				
	Currently Employed	5 (20.8%)	7 (29.2%)	0.74
	On Disability	11 (45.8%)	7 (29.2%)	0.37
Education				0.61
	<12th Grade	5 (20.8%)	5 (20.8%)	
	12th or high school Graduate	8 (33.3%)	4 (16.7%)	
	GED	1 (4.17%)	1 (4.17%)	
	some college or tech school	7 (29.2%)	9 (37.5%)	
	tech school grad	0	2 (8.33%)	
	college grad	3 (12.5%)	3 (12.5%)	
Monthly Income				0.43
	$0-249	3 (12.5%)	4 (16.7%)	
	$250-499	0	3 (12.5%)	
	$500-999	7 (29.2%)	5 (20.8%)	
	$1000-1999	9 (37.5%)	7 (29.2%)	
	$2000 or more	4 (16.7%)	5 (20.8%)	
Physiological				
	Current Tobacco Use	1 (4.17%)	3 (12.5%)	1.00
	Currently on Birthcontrol	2 (8.33%)	3 (12.5%)	0.52

Current Psychological Diangnosis				
	PTSD Diagnosis (CAPS)	3 (12.5%)	2 (8.33%)	1.00
	MDD Diagnosis (SCID/MINI)	3 (12.5%)	2 (8.33%)	1.00
	Comorbid PTSD/MDD	7 (29.2%)	3 (12.5%)	0.29
	None	11 (45.8%)	15 (62.5%)	0.37
Mean±SEM				
	Age	51.25±1.38	52.38±1.65	0.61
	BMI	37.604±2.147	35.02±1.68	0.35
	PTSD Symptoms (CAPS)	20.27±2.80	12.61±2.14	0.04*
	MDD Symptoms (BDI)	19.02±2.35	11.83±1.702	0.02*
	Childhood Trauma (CTQ)	42.17±3.99	32.71±2.17	.04*
	Adult Trauma (TEI)	3.04±.464	3.17±.445	0.85

Table 3. Demographic table for study sample. In some instances, information was unavailable, or participants did not endorse on the measure, thus not all categories add up to n=24. *p<.05.

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