STRESS REACTIVITY AND REGULATION IN YOUNG ADULTS AT VARIED RISK FOR DEPRESSION

By

MATTHEW C. MORRIS

Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

PSYCHOLOGY

August, 2011

Nashville, Tennessee

Approved:

Judy Garber

David Cole

Bruce E. Compas

Richard Shelton

Copyright © 2011 by Matthew C. Morris
All Rights Reserved

ACKNOWLEDGEMENTS

Matthew C. Morris was supported in part by a Ruth L. Kirschstein Individual National Research Service Award (1F31MH084425-01A1), an American Psychological Foundation Elizabeth Munsterberg Koppitz Graduate Student Fellowship, and a Vanderbilt Institute for Clinical and Translational Research Award (1 UL1 RR024975 from NCRR/NIH). I am especially grateful to my advisor, Dr. Judy Garber and my dissertation committee members, Drs. David Cole, Bruce E. Compas, and Richard Shelton, for their support and guidance throughout the design and implementation of this study and during the preparation of this manuscript. In addition, I am indebted to Dr. Lily Wang for her assistance with the data analysis plan.

TABLE OF CONTENTS

Page

ACKNOWLEDGEMENTS iii

LIST OF TABLES vi

LIST OF FIGURES vii

Chapter

I. INTRODUCTION 1

Features of the Cortisol Stress Response in Remitted Depression 5
Stressor Discrimination 7
Recent Stressful Life Events 8
Early Adversity 9
Stress Regulation 10
The Changing Role of Life Stress 12
The Current Study 13

II. METHODS 16

Participants 16
Measures 17
Procedures 20

III. RESULTS 25

Data Analytic Plan 25
Preliminary Analysis 26
Differences between Remitted and Never Depressed Individuals 29
Stressor Discrimination 34
Stressor Sensitization 35
Stress Regulation 37

IV. DISCUSSION 41

Differences between Remitted and Never Depressed Individuals 41
Stressor Discrimination 44
Stress Sensitization 45

Stress Regulation 46
Study Strengths and Limitations 49

REFERENCES 52

LIST OF TABLES

Table		Page
1.	Outline of study procedures	21
2.	Means and standard deviations of study variables for remitted depressed and never depressed participants	27
3.	Means, standard deviations, and correlations of covariates and dependent variables	28
4.	Means, standard deviations, and correlations between coping factors and dependent variables	30
5.	Means, standard deviations, and correlations between childhood trauma subscales and dependent variables	31
6.	Means, standard deviations, and correlations between coping factors and childhood trauma subscales	32

LIST OF FIGURES

Figure Page

1. Cortisol responses to HIGH-EVAL and NO-EVAL conditions of a standardized laboratory stressor (TSST) among remitted depressed (RD) and never-depressed (ND) individuals.....33

2. Mean scores (SEM) on change in cortisol output (AUCb) for RD and ND individuals in the NO-EVAL and HIGH-EVAL stressor conditions 35

3. Interaction of recent life stress and stressor condition predicting change in cortisol output (AUCb) 36

4. Interaction of primary control engagement coping and total recent stress level predicting cortisol reactivity 38

CHAPTER I.

INTRODUCTION

Major depressive disorder (MDD) is a very common (Kessler et al., 2005) and debilitating (Murray & Lopez, 1997) condition, with lifetime prevalence rates during adolescence reaching 12.94% for boys and 27.16% for girls (Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993). Risk for subsequent major depressive episodes (MDEs) increases as a function of the number of prior episodes. Risk of recurrence is 60% following an initial MDE, increases to 70% after a second MDE, and reaches 90% after a third (American Psychiatric Association, 2000; Solomon et al., 2000). Thus, individuals with a history of MDEs who are not currently depressed represent a group at increased risk for depression, but the mechanisms underlying this increased risk are not well understood.

Prior research has shown that stressful life events (SLEs) often precede MDEs (e.g., Brown & Harris, 1978; Daley, Hammen, & Rao, 2000; Kendler, Karkowski, & Prescott, 1999; Lewinsohn, Allen, Seeley, & Gotlib, 1999; Monroe & Simons, 1991) and are associated with the onset of depression in both children and adults (Grant, Compas, Thurm, McMarhon, & Gipson, 2004; Kendler et al., 1999). The etiological role of SLEs in relation to MDEs appears to change across successive recurrences (e.g., Lewinsohn et al., 1999). Alterations of the stress response are associated with early life stress (e.g., Heim et al., 2000), recent life stress (e.g., Rao, Hammen, & Poland, 2009), and the experience of depressive episodes themselves (e.g., Morris, Ciesla, & Garber, 2010).

These alterations, in turn, may confer increased risk for depression. One aim of the present study was to compare the stress response patterns of previously depressed individuals who have remitted (RD) with those who have never been depressed (ND) to identify factors that are present even during remission and possibly increase the likelihood of recurrence.

One important index of the stress response is activity of the hypothalamic-pituitary-adrenocortical (HPA; Stratakis & Chrousos, 1995) axis, a neurobiological system that promotes adaptation, or allostasis, by allowing organisms to accommodate to changing conditions in their environment (McEwen & Seeman, 1999). Exposure to stress triggers emotional responses, including activation in the limbic system, that initiate HPA-axis activity via connections with the hypothalamus. Neurons in the paraventricular nucleus of the hypothalamus then secrete corticotropin releasing hormone (CRH), which travels through the hypophyseal portal circulation and stimulates the anterior pituitary to release adrenocorticotropin hormone (ACTH). The ACTH signal, in turn, is carried through the peripheral circulation to the adrenal cortex where it triggers the production and release of cortisol, a glucocorticoid hormone responsible for a variety of regulatory functions in the central nervous system, metabolic system, and immune system (Sapolsky, Romero, & Munck, 2000). This entire process is referred to here as HPA-axis *stress reactivity*. Elevations in cortisol typically inhibit the HPA-axis via negative feedback mechanisms in the pituitary, hypothalamus, and hippocampus (Jacobson & Sapolsky, 1991; Munck, Guyre, & Holbrook, 1984; Sapolsky, Krey, & McEwen, 1986), which reflects HPA-axis *stress recovery*. Thus, the HPA axis is responsible for reactivity to stress as well as the maintenance of homeostasis (Sapolsky, 1992). Prolongation of the

stress response, through repeated activation or delayed recovery, can lead to adverse effects on the organism, or allostatic load (McEwen, 2003), which may increase vulnerability for depression via changes in the biological and cognitive determinants of the stress response.

The cortisol response to acute stress has three distinct features. Basal cortisol levels follow a diurnal rhythm, typically increasing in the early morning, peaking approximately 15-30 minutes after awakening (Schmidt-Reinwald et al., 1999), diminishing over the course of the day, and reaching a nadir at the end of the activity phase (Bailey & Heitkemper, 1991). *Stress reactivity* can be operationalized as the rate of change in cortisol levels following the onset of a biological or psychosocial challenge, and is constrained by pre-stress cortisol levels. *Stress recovery* can be indexed by the rate of decline in cortisol levels following the crest of the cortisol response to an acute stressor.

Psychosocial stress paradigms provide a critical contrast to biological challenge studies because the recruitment of suprahypothalamic structures involved in cognitive and affective processes allows a closer approximation of stress reactivity as it occurs in real-world contexts. Different types of laboratory stressors have been used to examine HPA-axis function, including emotion induction, noise exposure, public speaking/verbal interaction, and cognitive challenge. The present study utilized a modified version of the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), a combined public speaking/cognitive challenge task containing elements of motivated performance, uncontrollability, and social-evaluative threat that are related to robust and prolonged cortisol responses (Dickerson & Kemeny, 2004).

Currently depressed individuals show clear alterations of HPA-axis function (e.g., Carroll et al., 1981; Gold et al., 1986; Gold, Goodwin, & Chrousos, 1988a, 1988b; Holsboer et al., 1984; Nemeroff et al., 1984; Young et al., 1993). A meta-analysis of this literature concluded that depressed individuals have lower morning cortisol levels, higher afternoon cortisol levels, and blunted stress reactivity to and delayed recovery from psychosocial stressors as compared to healthy controls (Burke, Davis, Otte, & Mohr, 2005). The dysregulation hypothesis of depression suggests that alterations of the stress response persist beyond recovery from an MDE and increase vulnerability even in the absence of acute depressive symptoms (Siever & Davis, 1985). These markers may be latent, emerging only when the system is under stress.

Several lines of research support the dysregulation hypothesis. Alterations of HPA-axis function have been found to be heritable (Meikle, Stringham, Woodward, & Bishop, 1988) and associated with increased genetic or familial risk for developing depression among healthy, never-depressed individuals (Holsboer, Lauer, Schreiber, & Krieg, 1995; Mannie, Harmer, & Cowen, 2007; Vreeburg et al., 2010; Wichers et al., 2008). Moreover, HPA-axis alterations among formerly depressed individuals are associated with increased risk for recurrence (Applehof et al., 2006; Aubry et al., 2007; Halligan, Herbert, Goodyer, & Murray, 2007; Hatzinger et al., 2002; Rao et al., 2009; Zobel, Yassouridis, Frieboes, & Holsboer, 1999). Findings have been more mixed, however, with regard to changes in HPA-axis function following successful treatment. Whereas some studies have reported normalization of cortisol output after recovery (Holsboer, Liebl, & Hofschuster, 1982; Sachar, Hellman, Fukushima, & Gallagher, 1970; Steiger, von Bardeleben, Herth, & Holsboer, 1989), other studies have found no decline

in cortisol output (Deuschle et al., 2003), or even long-term HPA-axis dysregulation associated with subthreshold depressive symptoms (e.g., Deschauer, Grof, Alda, & Grof, 1999; Kathol, 1985). Thus, HPA-axis abnormalities may be pre-existing characteristics associated with risk for depression (*trait markers*) or consequences of MDEs (*scar markers*).

Features of the Cortisol Stress Response in Remitted Depression

The present study examined features of the cortisol response to a laboratory stressor that might serve as vulnerability markers in RD individuals, including pre-stress levels, cortisol reactivity, cortisol recovery, and aspects of total cortisol output. Results of studies examining basal cortisol levels in RD individuals have been inconsistent, with some studies reporting higher daily cortisol output in RD compared to ND individuals (Bos et al., 2005; Kathol, 1985) and no differences between basal levels in depressed and RD individuals (Amsterdam et al., 1988; Holsboer et al., 1985; Pintor et al., 2007), whereas others have found no differences between RD and ND individuals (Brown, 2001; Croes, Merz, & Netter, 1993; Trestman et al., 1991). We anticipated no significant differences in pre-stress cortisol levels between RD and ND individuals based on a previous study with a similar design and saliva sample collection procedures (Brown, 2001).

Five studies have examined cortisol reactivity in RD individuals using psychosocial laboratory stressors. Brown (2001) reported blunted average and peak cortisol responses to a combined public speaking and mental arithmetic task in RD versus ND women. Trestman and colleagues (1991) found a trend for a blunted cortisol response to a mental arithmetic task, corrected for basal cortisol differences, in RD as compared to

ND males. Using a sad mood induction, Chopra and colleagues (2008) reported a decrease in salivary cortisol levels among male and female depressed patients treated to full remission with either antidepressant medication or cognitive behavioral therapy. No ND controls were assessed, however, so these findings may reflect characteristics of the mood challenge protocol. A study of women in remission from recurrent MDD found an attenuated ACTH and cortisol response to psychosocial stress in the RD versus ND group (Ahrens et al., 2008). Finally, a recent study showed blunted cortisol reactivity to the TSST in RD versus ND women, but no differences in cortisol reactivity between RD and ND men (Bagley, Weaver, & Buchanan, 2011). Based on these findings, we anticipated blunted cortisol reactivity in RD versus ND individuals.

Most studies of cortisol recovery in RD individuals have used biological challenge paradigms, such as the dexamethasone suppression test (DST) and the combined DEX/CRH test, and generally have found that impaired HPA-axis negative feedback (causing prolonged cortisol secretion) persists in individuals in remission from MDEs (e.g., Holsboer et al., 1982). Such impaired HPA-axis feedback is associated with symptomatic relapse (Gurguis, Meador-Woodruff, Haskett, & Greden, 1990), number of prior MDEs and chronicity of depressive illness (Gurguis et al., 1990), and suicide and rehospitalization (Ribeiro, Tandon, Grunhaus, & Greden, 1993). Unfortunately, few psychosocial stress challenge studies have investigated HPA-axis stress recovery in RD versus ND individuals and none have examined the rate of decline in cortisol levels following peak levels. Based on evidence of blunted cortisol reactivity among RD versus ND individuals (e.g., Bagley et al., 2011), we hypothesized that RD individuals would exhibit slower decline in post-stressor cortisol levels due to lower crests.

Stressor Discrimination

Changes in the ability to appropriately discriminate between stressors of varying intensities as a function of number of prior MDEs has been proposed as one mechanism responsible for increased risk for future episodes (Monroe & Harkness, 2005), but empirical support for this hypothesis at the level of HPA-axis functioning is limited to currently depressed (CD) samples. Studies of cortisol responses to psychosocial stress tasks that manipulated factors thought to influence stress levels (e.g., success versus failure, control over an aversive stimulus, degree of difficulty of a cognitive task) have found impaired neuroendocrine discrimination in CD versus ND individuals (Croes et al., 1993; Netter, Croes, Merz, & Muller, 1991), greater cortisol output in a high stress condition in CD versus ND individuals, but no between-group differences in a low stress condition (Breier, 1989), and no differences between CD and ND individuals in cortisol responses to high versus low stress conditions (Ravindran, Griffiths, Merali, & Anisman, 1996). A study examining cortisol responses to different doses of synthetic ACTH revealed impaired neuroendocrine discrimination in melancholic depressed individuals compared to healthy controls (Amsterdam, Maislin, Gold, & Winokur, 1989).

The present study examined whether RD and ND individuals differed in their cortisol responses to stressors of different intensities. We modified an experimental paradigm (Gruenewald, Kemeny, Aziz, & Fahey, 2004) in which direct social-evaluative threat – a stressor dimension known to elicit significant cortisol responses (Dickerson & Kemeny, 2004) - was manipulated. Studies have shown that in healthy controls, cortisol reactivity differs between those in high versus low social-evaluative threat conditions (Balodis, Wynne-Edwards, & Olmstead, 2010; Gruenewald et al., 2004; Het, Rohleder,

Schoofs, Kirschbaum, & Wolf, 2009; Way & Taylor, 2010). These studies represent the most sophisticated tests of the stress discrimination hypothesis because they used control conditions that only differed from experimental conditions in the manipulation of social-evaluative threat and controllability. Other studies, (e.g., Nater et al., 2007; Rohleder, Wolf, Herpfer, Fiebich, Kirschbaum, & Lieb, 2006), however, have included control conditions that also differed in the physical and cognitive demands placed on participants which may have obscured the influence of social evaluation on cortisol responses. The present study included both traditional and 'placebo' (no social-evaluative threat) TSST conditions to examine differences in cortisol responses associated with social evaluation. We hypothesized that ND individuals would show greater cortisol responses to the high social evaluation condition (HIGH-EVAL) than the control condition (NO-EVAL), but that RD individuals would show similarly blunted cortisol responses to both conditions.

Recent Stressful Life Events

Although short-term physiological responses to acute stressors are considered adaptive, prolonged responses associated with chronic stress can lead to higher basal levels, blunted reactivity, and delayed recovery of stress responsive systems after acute stressors (Dienstbier, 1989). Meta-analytic evidence indicates that chronic stress is associated with lower morning cortisol levels, higher afternoon/evening cortisol levels, flatter diurnal cortisol rhythm, greater daily cortisol output, and enhanced suppression of cortisol following a DST (Miller, Chen, & Zhou, 2007). Whereas some studies suggest that recent life stress may be related to increased cortisol reactivity (e.g., Roy, Kirschbaum, & Steptoe, 2001) and delayed recovery (e.g., Pike et al., 1997) to a laboratory stressor, others have not found an association between chronic stress or daily

hassles and cortisol response to acute stress (e.g., van Eck, Nicolson, Berkhof, & Sulon, 1996; Roy, Steptoe, & Kirschbaum, 1998), or have found that severity of daily hassles in the past month is associated with decreased cortisol levels in response to a TSST (Heim et al., 2002). One study examining the impact of daily hassles on response to a psychosocial stress task among non-depressed individuals revealed that a higher number of daily hassles was associated with greater cortisol reactivity in the low effort condition and less reactivity in the high effort condition (e.g., Peters, Godaert, Ballieux, & Heijnen, 2003). In the present study, we anticipated that elevated levels of life stress in the 6 months preceding the laboratory stress task would be associated with a similar pattern of increased cortisol reactivity in the low stress condition and decreased reactivity in the high stress condition regardless of depression history.

Early Adversity

Early life stress is associated with increased risk for depression (Edwards, Holden, Felitti, & Anda, 2003; Espejo et al., 2006), particularly among females (MacMillan, Fleming, Streiner et al., 2001; Kaufman & Charney, 2001; Weiss, Longhurst, & Mazure, 1999), and may sensitize individuals to the depressogenic impact of minor stressors that occur later (Hammen, Henry, & Daley, 2000). Studies examining the impact of early adversity on the cortisol response to psychosocial stress tasks generally have reported blunted cortisol reactivity (e.g., Carpenter et al., 2007; De Bellis et al., 1994; Elzinga, Roelofs, Tollenaar, Bakvis, van Pelt, & Spinhoven, 2008; Luecken, Kraft, & Hagan, 2009; MacMillan et al., 2009), although some have found increased cortisol reactivity (e.g., Heim et al., 2000, 2001, 2002; Kaufman et al., 1997; Rao et al., 2008). These inconsistencies may be due to differences in the severity of depressive

symptoms at the time of assessment (Harkness, Stewart, & Wynne-Edwards, 2011) or to some studies focusing on the interaction of childhood adversity and recent life stress (Bevans, Cerbone, & Overstreet, 2008), which is associated with increased risk for depression (Espejo et al., 2006; Hammen et al., 2000; Harkness, Bruce, & Lumley, 2006; Kendler, Kuhn, & Prescott, 2004; McLaughlin, Conron, Koenen, & Gilman, 2010; Rudolph & Flynn, 2007). One study has shown that the cortisol response to a psychosocial stressor was greater among depressed adolescents with both a history of childhood adversity and high levels of recent chronic stress (Rao et al., 2008). In the present study, we expected that childhood trauma alone would be associated with blunted cortisol responses to the stress task, but would interact with recent life stress to predict increased cortisol reactivity.

Stress Regulation

Cortisol reactivity and recovery are likely influenced by both stressor features and response features. Coping has been defined as "conscious volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances" (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001, p. 89). The present study examined associations between individuals' reported responses to stress (i.e., volitional and involuntary) and cortisol responses to a psychosocial stress task. Volitional coping factors included primary control engagement (i.e., efforts to change the situation or emotional response, such as problem solving and emotional regulation), secondary control engagement (i.e., efforts to adapt to the situation, such as cognitive restructuring and acceptance), and disengagement coping (i.e., efforts to relinquish control over the situation, such as avoidance and denial).

Involuntary stress responses included involuntary engagement (e.g., rumination, physiological arousal) and involuntary disengagement (e.g., emotional numbing, escape). Laboratory-based studies have the advantage of standardizing stressor features so that variation in physiological responses can be attributed to individual differences in reported responses to stress rather than situation-specific factors (Connor-Smith & Compas, 2004).

Primary control coping strategies have been found to be associated with decreased internalizing problems (Connor-Smith et al., 2000; Wadsworth & Compas, 2002), lower levels of distress, better physical health outcomes (Pennebaker, 1997), and decreased cortisol output (e.g., Nicolson, 1992; O'Donnell, Badrick, Kumari, & Steptoe, 2008; Thorsteinsson & James, 1999). Secondary control coping has been associated with reduced severity and duration of depressed and anxious mood (Blagden & Craske, 1996; Nolen-Hoeksema, Morrow, & Fredickson, 1993) and higher cortisol levels (Nicolson, 1992). Greater use of disengagement coping appears to be associated with higher internalizing symptoms (Compas et al., 2001) and increased cortisol output (e.g., Knight et al., 1979; Sapolsky, 1992; Schulkin, Gold, & McEwen, 1998; Vaernes, Ursin, Daddagh, & Lambe, 1982). In the present study, we anticipated that RD individuals would report lower levels of primary and secondary control engagement coping and higher rates of disengagement coping. Moreover, we expected that primary control coping would be associated with decreased cortisol output and secondary control and disengagement coping would be associated with increased cortisol output.

Involuntary engagement and disengagement responses have been linked with increased physiological reactivity and emotional distress (e.g., Connor-Smith et al., 2000). The relation of rumination (one type of involuntary engagement response) and

HPA-axis function has received considerable attention. Rumination may affect cortisol levels by prolonging activation of negative emotional states through continuous reactivation of associative networks (Berkowitz, 1993); that is, rumination may serve to extend the stress response. Individual differences in perseverative cognitions are associated with cortisol reactivity and immune activity (see Brosschot, Gerin, & Thayer, 2006, for a review). Experimental studies indicate that rumination following a stressor is associated with increased cortisol output (e.g., Roger & Najarian, 1998; see Denson, Spanovic, & Miller, 2009, for a review). We hypothesized that involuntary engagement would be associated with increased cortisol output and slower cortisol recovery.

The Changing Role of Life Stress

"The neurobiology of affective disorder is a moving target and changes as a function of the longitudinal course of illness" (Post, 1992, p. 1005). Models attempting to explain changes in the role of life stress across depressive recurrences have posited either that depressive symptoms become progressively decoupled from stressors with each successive MDE (*stress autonomy*) or that stressors become increasingly capable of triggering depressive symptoms (*stress sensitization*) (Monroe & Harkness, 2005). Studies examining the influence of depression on the stress response (sometimes referred to as *episode sensitization*) generally have supported the stress sensitization model, with individuals becoming increasingly sensitized to less severe stressors as they experience more MDEs (e.g., Morris et al., 2010).

Research focusing on the role of early adversity provides a complementary perspective on stress autonomy and stress sensitization models by shifting emphasis from stress-related psychopathology to the experience of stress itself. According to this

perspective, early life stress can produce long-lasting changes in the stress response that moderate the relation of stress to depression later in life. Studies of early adversity have generally supported the stress sensitization model (e.g., Harkness et al., 2006; Rudolph & Flynn, 2007). The present study examined the relations of prior MDEs, early adversity, and recent life stress to the cortisol response to a psychosocial stress task. This represents an important step toward parsing the relative influence of depressive symptoms and life stress on stress sensitization processes.

The Current Study

The current study builds on existing research examining stress response features in young adults at varied risk for depression in the following ways. First, we utilized a remitted depression paradigm in order to help identify relatively stable vulnerability factors (as opposed to state-like concomitants) that are present after recovery from a depressive episode. Although behavioral high-risk designs generally have provided stronger support for depression vulnerability factors than remitted depression designs, we adopted design features recommended for optimizing the ability to detect clinically meaningful differences between RD and ND individuals (Haeffel et al., 2005). That is, participant selection was not based on receiving a therapeutic intervention (to minimize potential treatment effects) and we included priming procedures (i.e., TSST). Only one previous study (Bagley et al., 2011) has investigated features of the cortisol response to a psychosocial stress task in both men and women using a remitted depression design optimized to detect meaningful differences.

Second, we simultaneously tested predictions from several competing models of stress sensitization, including episode sensitization (i.e., previous MDEs), recent life

stress, and early adversity, using a laboratory-based stressor paradigm that permitted attributions of variation in cortisol responses to individual differences rather than situation-specific factors and stressor features (Connor-Smith & Compas, 2004). Psychosocial stress tasks have an advantage over studies examining basal cortisol levels or employing a biological challenge in that they activate suprahypothalamic structures and, hence, the endogenous response to stress (Rao et al., 2008). Fourth, we examined the relation of psychological factors to the cortisol response to a laboratory stressor using a well-validated self-report measure of coping and involuntary stress response features; this measure was designed to capture responses to social stressors and is, therefore, particularly well-suited for assessing relations between coping and cortisol responses to a stressor paradigm manipulating the degree of social-evaluative threat. Finally, this is the first study to compare RD and ND individuals in their cortisol responses to different levels of psychosocial stress using repeated salivary cortisol measurements.

The present study examined the following research questions and hypotheses. First, do remitted depressed (RD) and never depressed (ND) individuals differ in their report of depressive symptoms, total levels of recent stress, coping/involuntary stress responses in the previous 6 months, or their experience of childhood trauma? We hypothesized that RD participants would report higher levels of depressive symptoms and recent stress, less use of adaptive coping strategies (i.e., primary and secondary control engagement), greater use of maladaptive coping strategies (i.e., disengagement) and involuntary stress responses, and higher rates of childhood trauma. Second, do RD and ND participants differ in their cortisol responses to high versus low levels of social-evaluative threat? We hypothesized that ND participants would show greater cortisol

output in the HIGH-EVAL versus NO-EVAL conditions, whereas RD participants would not differ; that is, they would exhibit similarly blunted cortisol responses to both experimental conditions. Third, is the level of recent stressful life events related to individuals' cortisol responses to a laboratory stressor? We hypothesized that higher recent life stress would be associated with blunted cortisol reactivity, and that life stress would interact with stressor condition such that individuals with higher levels of recent life stress would show minimal change in cortisol output in each condition, whereas those with lower total stress levels would show greater cortisol output change in the high stress condition.

Fourth, does childhood trauma predict the cortisol response to a laboratory social stressor? We hypothesized that childhood trauma would be associated with blunted cortisol reactivity to the stress task, but would interact with recent life stress to predict increased cortisol reactivity. Fifth, do coping and involuntary stress response factors predict the cortisol response to a laboratory stressor? We hypothesized that greater use of primary control coping would be associated with decreased cortisol response and that higher rates of secondary control engagement, disengagement, and involuntary engagement would be related to increased cortisol response. We also explored whether coping and involuntary stress response variables interacted with total level of recent life stress to predict cortisol outcomes.

CHAPTER II.

METHOD

Participants

Participants were 102 individuals ages 18 to 31 years old (mean age = 22.97, *SD* = 3.87) recruited from the Vanderbilt University Medical Center research participant registry and from an undergraduate psychology subject pool at Vanderbilt University. Of these participants, 23 had experienced one prior MDE, 33 had experienced two or more MDEs, and 46 had never had an MDE. Volunteers were contacted by telephone, told about the study, asked if they are interested, and then screened. Exclusion criteria included current or past psychiatric disorders (i.e., Bipolar Disorder, Posttraumatic Stress Disorder) or health conditions (e.g., Cushing's Disease, Addison's Disease, hyperthyroidism, severe kidney or liver disease, pregnancy, hypoglycemia) known to exert unique influences on HPA axis activity, or use of prescription (e.g., corticosteroids, estrogen, amphetamines) and nonprescription (e.g., marijuana) drugs that might affect the cortisol measures assessed in this study. Participants using antidepressant medication or birth control were not excluded, however. Body mass index (BMI) – an indicator of human body fat - was calculated by dividing each participant's body weight by the square of their height. Participant's socioeconomic status was calculated using a four factor index (SES; Hollingshead, 1975).

Individuals meeting psychiatric inclusion criteria (i.e., without current or past Bipolar Disorder or PTSD) who screened for either (a) a history of MDD but not

currently in a depressive episode, or (b) no current or history of MDD were scheduled for the assessment interview and laboratory tasks. Inclusion in the RD group required a past diagnosis of MDD according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, text revision (*DSM-IV-TR*; American Psychiatric Association, 2000) as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1996). Full remission was defined as an absence of significant symptoms of depression for at least two months. Participants received course credit or $30 for participation in the study.

Measures

Depression. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1996) was administered to assess current and lifetime diagnoses of a subset of Axis I disorders (i.e., MDD, Bipolar Disorder, PTSD). Detailed information on all previous depressive experiences was obtained to determine the number of prior MDEs for each participant. History of depression was operationalized both as a dichotomous variable (i.e., yes or no) and as the number of prior MDEs. All interviews were audio-taped and a random 20% were re-rated for reliability by an independent evaluator who was unaware of the ratings of the primary interviewer. Inter-rater reliability for history of depression yielded a kappa of 1.00 for the dichotomous variable and a kappa of .80 for the number of previous MDEs.

The *Beck Depression Inventory-II* (BDI-II; Beck, Steer, & Brown, 1996) was used to assess participants' current level of depressive symptoms. The BDI-II is a 21-item, widely used, self-report inventory with good reliability and validity (Beck, Steer, Ball, & Ranieri, 1996). In this sample, coefficient alpha for the BDI-II was .85.

Recent life events. The short form (90 items) young adult version of the Perceived Events Scale (ES; Compas, Davis, Forsythe, & Wagner, 1987) was used to measure the number and severity of life events experienced by participants during the previous six months. Participants were asked to indicate whether each event occurred during this time, and to rate the valence of those events on a 9-point scale (-4 = Extremely Bad; 0 = Neither Good or Bad; +4 = Extremely Good). A total score for negative events occurring in the past 6 months was calculated by summing across all events rated -1 to -4 on desirability. Total recent stress level scores were multiplied by -1 so that higher scores indicated higher stress levels. Participants completed this measure online prior to their scheduled laboratory appointment.

Childhood Trauma. The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994) is a 28-item, self-report measure assessing the frequency of different types of abuse experienced as a child. Respondents rate each item on a 5-point scale from "never true" to "very often true." The CTQ has five subscales: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The neglect subscales (emotional and physical) were combined into a neglect composite score to reduce the number of variables analyzed. The CTQ has good reliability and validity (Bernstein et al., 1994); coefficient alphas for the subscales ranged from .70 to .91 in this sample.

Coping. The social stress young adult version of the Responses to Stress Questionnaire (RSQ; Connor-Smith, Compas, Wadsworth, Thomsen, & Saltzman, 2000) was used to assess coping/responses to stress. Participants completed the RSQ online prior to their scheduled laboratory appointment. The RSQ has good internal consistency (alphas from .73 to .85) and construct validity as evident in confirmatory factor analyses

(Connor-Smith et al., 2000). In this sample, coefficient alphas for the RSQ factors ranged from .64 to .90. The current study assessed the following factors: primary control engagement coping (problem solving, emotional modulation, emotional expression), secondary control engagement coping (positive thinking, cognitive restructuring, acceptance, distraction), disengagement coping (avoidance, denial, wishful thinking), involuntary engagement (rumination, intrusive thoughts, emotional arousal, physiological arousal, impulsive action), and involuntary disengagement (emotional numbing, inaction, escape, cognitive interference).

Psychosocial Stressor. A modified version of the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) was used to elicit a robust cortisol response. The task consisted of a 5-minute free-speech task and a 5-minute mental arithmetic task administered sequentially either in a high social evaluation condition (i.e., with the examiner in the room, participant connected to audio- and video-recording equipment and told that their performance would be evaluated and compared to other participants) or in a non social evaluation condition (i.e., participant alone in the examination room, told they were not being observed). The TSST is particularly appropriate for research on stress responses in participants at risk for depression due to its social-evaluative nature.

Cortisol. Salivary cortisol samples were collected using a saliva collection device (Salivette; Sarstedt Inc., Newton, NC). Participants were instructed to remove a cotton swab from the salivette, place it in their mouth, and to chew on it if necessary to stimulate salivation. Approximately 1 ml of saliva is required for duplicate determination. After about 1-2 minutes, participants were instructed to place the cotton swab back into the salivette and firmly replace the stopper. Following the experimental session, the salivettes

were taken to the Hormone Assay and Analytical Services Core at the Vanderbilt Clinical Research Center (CRC) where they were stored in a freezer at 4°C for 24 hours or at -10°C or lower for samples that were analyzed at a later date. Before analysis, specimens were thawed and centrifuged, with the supernatants collected and poured into freshly labeled tubes. Salivary cortisol levels were determined in duplicate using a commercially available enzyme immunoassay kit (Enzyme-Linked ImmunoSorbent Assay, ALPCO diagnostics, Salem, NH). The lower detection limit, or sensitivity, of this assay is 1.0ng/ml.

Procedures

Individuals meeting study criteria based on the telephone screen were invited to participate. The order of pre-screening and experimental procedures is presented in Table 1. Participants were instructed not to drink alcohol, smoke, use illegal drugs, engage in strenuous exercise, or visit the dentist within the 24 hours prior to their appointment, and to refrain from drinking (except water), eating, or brushing their teeth 1 hour before the session. Participants were screened for these behaviors at the beginning of the laboratory assessment period.

All laboratory sessions were conducted between the hours of 2:00 and 7:00 PM to control for diurnal variations in cortisol. After informed consent was obtained, the PI administered the Mood Disorder and PTSD sections of the SCID-I and participants completed the CTQ in room A of the laboratory suite. Following the SCID-I sections, participants completed the BDI-II, and then sat quietly for 10 minutes. Participants then were given the following instructions regarding the laboratory tasks:

Table 1. Procedures

Assessment	Procedures
Online	Events Scale (ES)
	Responses to Stress Questionnaire (RSQ)
Interview	Behavior screen
	Childhood Trauma Questionnaire (CTQ)
	SCID-I sections (MDD, Bipolar Disorder, PTSD)
Depressed Mood	Beck Depression Inventory (BDI-II)
Rest period (10 minutes)	
Pre-stress	TSST instructions
	TSST preparation (10 minutes)
	T1 (Pre-stress) cortisol [time = minute 0]
TSST	Speech task (5 minutes)
	T2 (Mid-task) cortisol [time = minute 7]
	Mental Arithmetic task (5 minutes)
Post-task	**T3 (Post-task) cortisol** [time = minute 15]
	Demographics Questionnaire
Recovery	**T4 (Recovery 1) cortisol** [time = minute 30]
	Rest period (10 minutes)
	T5 (Recovery 2) cortisol [time = minute 45]
Debriefing	

In the next phase of this experiment you will be asked to perform two challenging and demanding laboratory tasks, including a 5-minute free speech and a 5-minute arithmetic task. You will not be told the order of these tasks until you are about to begin.

For the speech, you will be asked to imagine that you are applying for an important position that you would very much like to have, with the task itself serving as an intensive, comprehensive interview. During your presentation, you should highlight personal attributes that would qualify you for this high level position, including what kind of a person you are, how you deal with responsibility, your problem solving skills, how you might manage a group of employees, and whatever else you deem important. You will not be given instructions for the mental arithmetic task until it is about to begin.

HIGH-EVAL condition:

When it is time for the tasks to begin, I will take you to the assessment room where your performance will be video-taped and audio recorded. A panel of 2 evaluators from our lab will be observing your recorded performance at a later date and judging the manner and contents of your speech. One of these evaluators is trained in behavioral observation methods and will be rating your nonverbal communication skills. I will be observing your speech directly in the room and taking additional notes on your performance that will be used in the final evaluation. However, I will not be able to answer any questions or provide feedback during the speech itself. You will be evaluated on the content of your presentation, how effectively you communicate, how you structure your ideas, how you respond to a challenging task with little preparation, and your personal style. It is important that you do your best because your performance will be rated in comparison with other participants in this study. Begin the speech task by introducing yourself and then addressing your qualifications for this position. It is important that you speak for the full 5 minutes.

For the mental arithmetic task, it is important that you perform as quickly and efficiently as possible because you will be rated in comparison to other participants in this study. As you may know, math aptitude is a good indicator of a number of important qualities. In particular, this task will assess your performance IQ.

You have 10 minutes to prepare your speech and make whatever notes you wish, but you will not be allowed to take these notes with you into the observation room. Once this preparation period is over I will inform you of the order of your tasks. Do you have any questions?

NO-EVAL condition:

When it is time for the tasks to begin, I will take you to the assessment room where you will complete them. Begin the speech task by facing the video camera and introducing yourself. Then address your qualifications for this

> position. Your speech will not be recorded. It is important that you speak for the full 5 minutes. You have 10 minutes to prepare your speech and make whatever notes you wish, but you will not be allowed to take these notes with you into the observation room. Once this preparation period is over I will inform you of the order of your tasks. Do you have any questions?

Participants provided their first (pre-stress) cortisol sample at the end of this 10 minute preparation period. This collection schedule allowed the maximum amount of time for participants to acclimate to the laboratory environment before the TSST began, as evidence suggests that novelty is associated with increases in cortisol levels (e.g., Shommer, Hellhammer, & Kirschbaum, 2003). They were shown into room B and asked to stand in front of a video camera while the microphone of an audiotape recorder was attached to their shirt. Half of the participants in each group (i.e., history of depression and healthy controls) were randomly assigned to the HIGH-EVAL and the other half to the NO-EVAL condition. This was determined by an algorithm based on the order in which their assessments were scheduled, their sex, and their history of depression to achieve approximately equal numbers in each condition. Similar to procedures outlined by Gruenewald et al. (2004), participants in the HIGH-EVAL condition were informed that their performance would be judged by a panel of evaluators, whereas those in the NO-EVAL condition were informed that they would perform the tasks while alone and unobserved in the room. The order of tasks was the same for all participants, with the 5 minute speech preceding the 5 minute mental arithmetic task. Instructions for the latter were the same in both conditions:

> For the arithmetic task you will stand where you are, facing the video camera, and subtract 13 from 2,097, stating this number aloud. From this number you will again subtract 13, stating this new number aloud, and so on. Work as quickly and efficiently as you can. Do you understand the task?

Participants provided their second (mid-task) cortisol sample between the speech

and arithmetic tasks. Immediately following the arithmetic task, participants returned to room A where they provided their third (post-task) cortisol sample. They then completed a demographics questionnaire and rested for 10 minutes. Participants then provided their fourth (recovery 1) cortisol sample, rested another 10 minutes, and provided their fifth (recovery 2) cortisol sample. At the end of the study, participants were fully debriefed regarding the nature of the experimental manipulation.

CHAPTER III.

RESULTS

Data Analytic Plan

Repeated measures cortisol data were expected to follow a systematic pattern of increase (stress reactivity) and decrease (stress recovery) following a laboratory stressor. To characterize trajectories for each individual, we fit a piece-wise linear regression model with one intercept (corresponding to the maximum cortisol level) and two slopes (corresponding to monotonic trends for cortisol reactivity and recovery). This was accomplished using procedure NLMIXED in SAS (9.2) Software. These parameters were used to capture the rate of increase in cortisol levels following initiation of the psychosocial stress task and the rate of decline in cortisol levels after each individual's maximum value. Pre-stress cortisol levels were entered as covariates into analyses predicting cortisol reactivity slopes because baseline values are known to constrain reactivity. Because peak cortisol levels may impact rate of decline, they were entered as covariates in analyses predicting recovery slopes.

Using procedures described by Pruessner and colleagues (2003), we calculated the area under the curve with respect to ground (AUCg) to characterize total cortisol output during the TSST, and the area under the curve with respect to baseline (AUCb) to capture change in cortisol levels over time. Whereas AUCg represents both basal cortisol output and stressor-induced change in cortisol levels, AUCb can be conceptualized as an

index of the sensitivity of the cortisol response to a stressor, and may be negative if levels decline below the baseline value.

We conducted two-way factorial analyses of covariance (ANCOVA) to test hypotheses regarding the interaction of categorical variables [history of depression X stressor condition]. The ANCOVA procedure used the Type III sum of squares to account for intercorrelations of independent variables. Main effects of one variable at different levels of the second variable were tested using simple main effects analyses. Hierarchical multiple regression analyses (Cohen & Cohen, 1983) were used to examine the association between independent variables [sex, age, SES, BMI, antidepressant medication use (ADM), depressive symptoms, history of depression, total level of recent stress, childhood trauma subscales, coping factors] and dependent variables, and to test interactions of childhood trauma, coping, and stress variables. Dependent variables were pre-stress cortisol levels, final recovery cortisol levels, slope parameters for cortisol reactivity and recovery, AUCg, and AUCb.

In the first block, covariates significantly associated with the dependent variable were entered in addition to predictor variables. The interactions of childhood trauma, coping, and stress variables were entered in the second block. All variables within each block were entered simultaneously; variables included in interactions were centered. Simple slope analyses were conducted on all significant interactions, per Aiken and West (1991).

Preliminary Analyses

Table 2 presents the means and standard deviations of all study variables. Table 3 presents correlations of covariates with dependent variables. Correlations between

Table 2. Demographic variables and self-report measures

	Remitted Depressed (n = 56)	Never Depressed (n = 46)	RD vs. ND
	M (*SD*)	*M* (*SD*)	X^2/t
Age (years)	23.2 (3.9)	22.6 (3.8)	-0.80
Body Mass Index (BMI)	24.0 (5.0)	23.9 (5.1)	-0.17
Education (years)	15.1 (2.7)	14.8 (2.6)	-0.58
Socioeconomic Status (SES)	54.3 (10.4)	55.7 (12.2)	0.64
Sleep			
Duration (hours)	7.34 (1.2)	7.13 (1.1)	-0.93
Wake time	8:20 a.m.	8:09 a.m.	-0.49
Mean wake time	7:56 a.m.	8:12 a.m.	0.97
	N (%)	*N* (%)	X^2/t
Sex			1.88
Male	17 (30.4)	20 (43.5)	
Female	39 (69.6)	26 (56.5)	
Stress condition			0.13
HIGH-EVALUATION	30 (53.6)	23 (50.0)	
NO-EVALUATION	26 (46.4)	23 (50.0)	
Race			2.68
Caucasian	44 (78.6)	38 (82.6)	
African American	6 (10.7)	3 (6.5)	
Asian	3 (5.4)	2 (4.3)	
Mixed	2 (3.6)	2 (4.3)	
American Indian	1 (1.8)	0 (0.0)	
No response	0 (0.0)	1 (2.2)	
Hispanic	4 (7.1)	3 (6.5)	0.02
Antidepressant use	13 (23.2)	2 (4.3)	7.17**
	M (*SD*)	*M* (*SD*)	F^a
Depressive symptoms	8.23 (5.9)	3.22 (3.3)	-5.11***
Total recent stress level	39.64 (17.8)	23.89 (13.0)	7.08**
Childhood trauma (total)	33.39 (9.6)	31.22 (6.4)	0.80
Emotional abuse	7.87 (4.0)	7.15 (2.1)	0.03
Physical abuse	6.38 (2.3)	5.59 (1.1)	5.18*
Sexual abuse	5.50 (1.6)	5.41 (2.2)	0.01
Neglect composite	13.58 (4.4)	13.07 (3.6)	0.31
Coping/Response to Stress			
Primary control	0.20 (0.04)	0.22 (0.04)	2.33
Secondary control	0.23 (0.06)	0.27 (0.04)	2.68
Disengagement	0.14 (0.03)	0.13 (0.02)	0.54
Involuntary Engagement	0.27 (0.05)	0.23 (0.04)	7.36**
Involuntary Disengagement	0.17 (0.03)	0.14 (0.03)	1.52

*p < .05; ** p < .01; ***p< .001; F^a = controlling for current depressive symptoms; RD = remitted depressed; ND = never depressed

Table 3. Means, Standard Deviations, and Correlations of Covariates and Dependent Variables

Variable	Mean	SD	1	2	3	4	5	6	7	8	9	10	11	12
1. Risk	0.55	0.50												
2. Sex	0.64	0.48	.14											
3. Age	22.97	3.87	.08	-.02										
4. SES	54.89	11.24	-.06	.13	-.21*									
5. BMI	23.94	5.00	.02	-.12	.43***	-.31**								
6. ADM	0.15	0.36	.27**	.14	.01	-.12	.08							
7. SC	0.52	0.50	.04	-.03	.00	-.22*	-.02	-.10						
8. C base	10.95	4.73	-.04	.07	-.31**	.02	-.22*	.07	.10					
9. C final	10.13	4.61	.02	.18	-.13	.07	-.03	.07	.11	-.04				
10. C react	0.18	0.27	-.24~	-.15	.10	-.05	.06	-.15	.20	.03	-.13			
11. C rec	-0.08	0.08	.14	.07	-.07	-.03	.06	.03	-.22*	-.13	.11	-.77***		
12. AUCg	481.52	215.23	-.14	-.09	-.16	-.09	-.12	-.03	.26**	.82***	-.11	.51***	-.45***	
13. AUCb	-11.23	128.08	-.18	-.27**	.24*	-.17	.16	-.16	.27**	-.28**	-.12	.89***	-.53***	.32**

~p <.06; *p < .05; ** p < .01; ***p< .001

Note: Risk (0 = never depressed; 1 = remitted depressed); SES = Socioeconomic Status; BMI = Body Mass Index; ADM = Antidepressant Medication; SC = Experimental condition (0 = low stress, 1 = high stress); C base = pre-stress cortisol level; C final = final cortisol recovery level; C react = cortisol reactivity slope; C rec = Cortisol recovery slope; AUCg = area under the curve with respect to ground; AUCb = area under the curve with respect to baseline.

dependent variables and coping factors and childhood trauma subscales are presented in Tables 4 and 5, respectively. Table 6 presents correlations between the childhood trauma subscales and coping factors. Figure 1 shows mean cortisol levels at each collection time point for RD and ND individuals in the HIGH-EVAL and NO-EVAL in response to the TSST.

All variables were examined for distributional properties and cases were screened for univariate and multivariate outliers. No significant differences were detected between RD and ND participants on demographic variables. Analyses revealed that randomization to stressor condition was successful, except for SES such that participants in the HIGH-EVAL condition reported lower SES. RD participants reported significantly higher levels of current depressive symptoms on the BDI than ND participants, although both groups were relatively low (see Table 2).

Significant correlations were observed between pre-stress cortisol levels and age (r = -.31, p = 002) and BMI (r = -.22, p = .029), between cortisol recovery and stressor condition (r = -.22, p = .033), between AUCg and stressor condition (r = .26, p = .008), and between AUCb and sex (r = -.27, p = .006), age (r = .24, p = .015), and stressor condition (r = .27, p = .006). Variables that were significantly associated with cortisol outcome variables were included as controls in subsequent analyses of those variables.

Differences between Remitted and Never Depressed Individuals

Do RD and ND participants differ in self-reported depressive symptoms, recent stress levels, childhood trauma, and coping/involuntary stress response factors?

Remitted depressed participants reported significantly higher levels of depressive symptoms at baseline than ND participants [t(100) = -5.11, p < .001]; therefore, BDI-II

Table 4. Means, Standard Deviations, and Correlations of Coping Factors and Dependent Variables

Variable	Mean	SD	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Risk	0.55	0.50													
2. Stress	32.47	17.61	.45***												
3. BDI-II	5.97	5.51	.46***	.56***											
4. RSQ PR	0.21	0.04	-.32**	-.44***	-.44***										
5. RSQ SC	0.25	0.05	-.39***	-.58***	-.59***	.36***									
6. RSQ DI	0.14	0.03	.07	.18	.29**	-.56***	-.26*								
7. RSQ IE	0.25	0.05	.43***	.57***	.50***	-.47***	-.84***	.02							
8. RSQ ID	0.16	0.03	.35***	.50***	.56***	-.70***	-.65***	.29**	.49***						
9. C base	10.95	4.73	-.04	.05	.03	.12	-.06	-.06	.07	-.11					
10. C final	10.13	4.61	.02	-.04	-.02	-.05	.02	.07	-.01	.00	-.04				
11. C reac	0.18	0.27	-.24~	-.29*	-.17	.21	.23	-.06	-.36**	-.07	.03	-.13			
12. C rec	-0.08	0.08	.14	.15	.10	-.04	-.02	.01	.07	-.02	-.13	.11	-.77***		
13. AUCg	481.52	215.23	-.14	.01	-.08	.19~	.01	-.01	-.07	-.14	.82***	-.11	.51***	-.45***	
14. AUCb	-11.23	128.08	-.18	-.06	-.19~	.13	.11	.08	-.24*	-.05	-.28**	-.12	.89***	-.53***	.32**

~$p < .06$; *$p < .05$; ** $p < .01$; ***$p < .001$

Note: Risk (0 = never depressed; 1 = remitted depressed); Stress = Total Stress Level 6 months prior to baseline; BDI-II = depressive symptoms; RSQ PR = Primary Control Coping; RSQ SC = Secondary Control Coping; RSQ DI = Disengagement Coping; RSQ IE= Involuntary Engagement; RSQ ID = Involuntary Disengagement; C base = pre-stress cortisol level; C final = final cortisol recovery level; C reac = cortisol reactivity slope; C rec = Cortisol recovery slope; AUCg = area under the curve with respect to ground; AUCb = area under the curve with respect to baseline.

Table 5. Means, Standard Deviations, and Correlations of Childhood Trauma Subscales and Dependent Variables

Variable	Mean	SD	1	2	3	4	5	6	7	8	9	10	11	12
1. Risk	0.55	0.50												
2. Stress	32.47	17.61	.45***											
3. BDI-II	5.97	5.51	.46***	.56***										
4. CTQ EA	7.54	3.31	.11	.18	.20*									
5. CTQ PA	6.02	1.88	.21*	.04	.03	.45***								
6. CTQ SA	5.46	1.89	.02	.18	.04	-.03	.13							
7. CTQ N	13.35	4.01	.06	.26*	.03	.63***	.55***	.20*						
8. C base	10.95	4.73	-.04	.05	.03	-.01	-.08	-.02	.05					
9. C final	10.13	4.61	.02	-.04	-.02	.03	.03	-.07	.01	-.04				
10. C reac	0.18	0.27	-.24~	-.29*	-.17	-.12	-.16	-.03	-.06	.03	-.13			
11. C rec	-0.08	0.08	.14	.15	.10	.05	.13	.08	.03	-.13	.11	-.77***		
12. AUCg	481.52	215.23	-.14	.01	-.08	-.05	-.14	-.05	.05	.82***	-.11	.51***	-.45***	
13. AUCb	-11.23	128.08	-.18	-.06	-.19~	-.07	-.11	-.04	-.01	-.28**	-.12	.89***	-.53***	.32**

~$p < .06$; *$p < .05$; ** $p < .01$; ***$p < .001$

Note: Risk (0 = never depressed; 1 = remitted depressed); Stress = Total Stress Level 6 months prior to baseline; BDI-II = depressive symptoms; CTQ EA = Emotional Abuse; CTQ PA = Physical Abuse; CTQ SA = Sexual Abuse; CTQ N= Neglect Composite (Emotional Neglect + Physical Neglect); C base = pre-stress cortisol level; C final = final cortisol recovery level; C reac = cortisol reactivity slope; C rec = Cortisol recovery slope; AUCg = area under the curve with respect to ground; AUCb = area under the curve with respect to baseline.

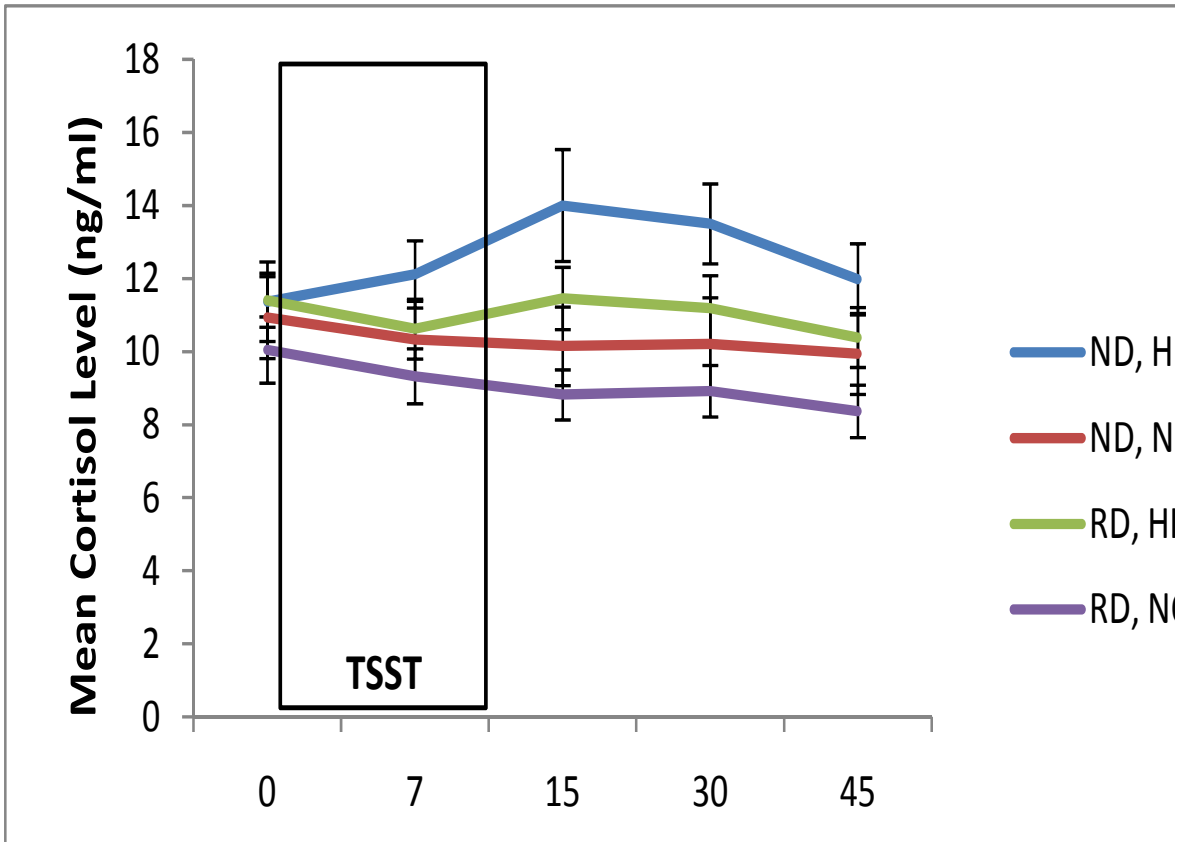
Table 6. Means, Standard Deviations, and Correlations between Coping Factors and Childhood Trauma Subscales

Variable	Mean	SD	1	2	3	4	5	6	7	8
1. RSQ PR	0.21	0.04								
2. RSQ SC	0.25	0.05	.36***							
3. RSQ DI	0.14	0.03	-.56***	-.26*						
4. RSQ IE	0.25	0.05	-.46***	-.84***	.02					
5. RSQ ID	0.16	0.03	-.70***	-.65***	.29**	.49***				
6. CTQ EA	7.54	3.31	-.03	-.26**	.19~	.14	.11			
7. CTQ PA	6.02	1.88	-.01	-.19~	.08	.16	.01	.45***		
8. CTQ SA	5.46	1.89	.12	-.07	-.13	.12	-.11	-.03	.13	
9. CTQ N	13.35	4.01	.09	-.20*	.08	.09	-.00	.63***	.55***	.20*

~$p < .06$; *$p < .05$; ** $p < .01$; ***$p < .001$

Note: RSQ PR = Primary Control Coping; RSQ SC = Secondary Control Coping; RSQ DI = Disengagement Coping; RSQ IE= Involuntary Engagement; RSQ ID = Involuntary Disengagement; CTQ EA = Emotional Abuse; CTQ PA = Physical Abuse; CTQ SA = Sexual Abuse; CTQ N= Neglect Composite (Emotional Neglect + Physical Neglect).

Figure 1.



scores were included as a covariate in subsequent analyses examining differences between RD and ND participants on recent stress levels, childhood trauma subscales, and coping factors.

The association between a history of depression and total level of recent stress was significant after controlling for current depressive symptoms [$F(1,98) = 7.08$, $p = .009$], such that RD participants reported greater total stress levels in the previous 6 months than ND participants. Of the childhood trauma subscales, physical abuse was significantly associated with history of depression, after controlling for current depressive symptoms [$F(1,98) = 5.18$, $p = .025$], indicating that RD participants reported greater levels of childhood physical abuse than ND individuals. Of the coping and involuntary

stress response factors, involuntary engagement was significantly associated with history of depression, after controlling for current depressive symptoms [$F(1,98) = 7.36$, $p = .008$], such that RD participants reported significantly greater rates of involuntary engagement than the ND group.

Stressor Discrimination

Does history of depression predict differences in cortisol response to high versus low social-evaluative threat? Stressor condition was significantly associated with cortisol recovery slopes (r = -.22, $p = .033$), AUCg (r = .26, $p = .008$), and AUCb (r = .27, $p = .006$). Individuals in the HIGH-EVAL condition had more rapid rates of decline in cortisol levels after peak values, higher overall cortisol output, and greater change in cortisol levels following T1 cortisol levels as compared to those in the NO-EVAL condition. That is, higher levels of social-evaluative threat resulted in a higher cortisol response to the psychosocial stress task, indicating that the experimental manipulation was successful.

Higher levels of current depressive symptoms were associated with blunted AUCb ($\beta = -.178$, $t = -1.98$, $p = .050$), controlling for sex, age, and stressor condition. History of depression did not directly predict the cortisol outcome variables. The interaction of stressor condition and depression history predicting change in cortisol output (AUCb) after baseline was not significant [$F(1, 96) = 2.46$, $p = .12$; see Figure 2]. However, exploratory simple main effects analyses revealed that the experimental manipulation was successful for ND participants who exhibited greater cortisol output in the HIGH-EVAL condition ($p = .002$) compared to those in the NO-EVAL condition. In contrast, for participants with a history of MDEs, level of cortisol output for those in the

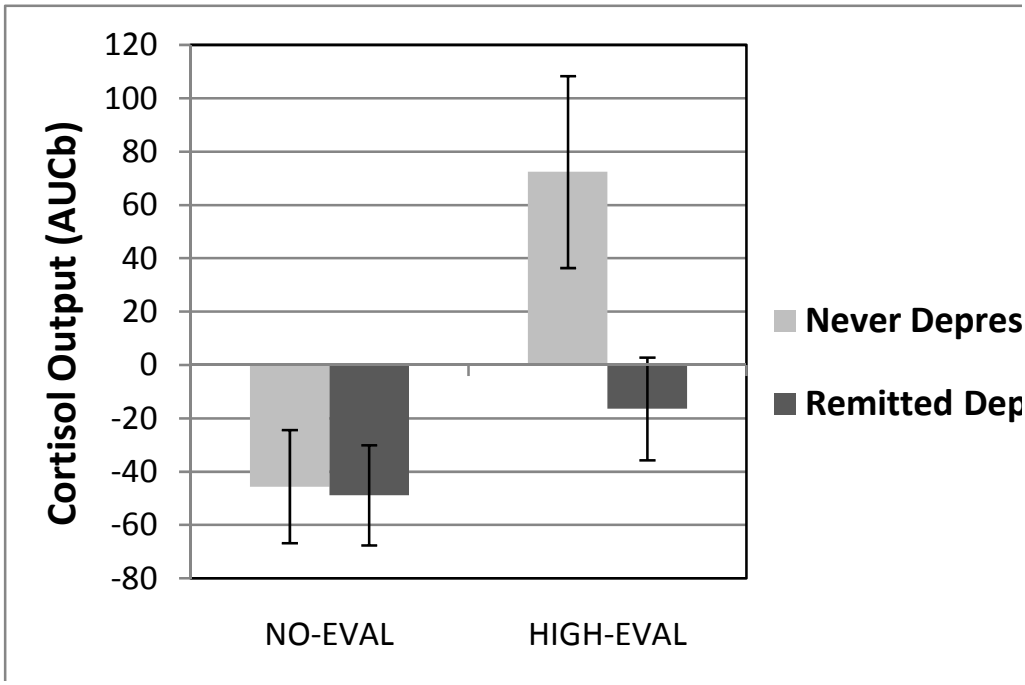
HIGH-EVAL condition was not significantly different from those in the NO-EVAL condition (p = .239). Thus, for participants with a history of depression, the stressor condition did not differentially affect their cortisol stress response.

Stress Sensitization

Does childhood trauma or recent life stress predict the stress response?

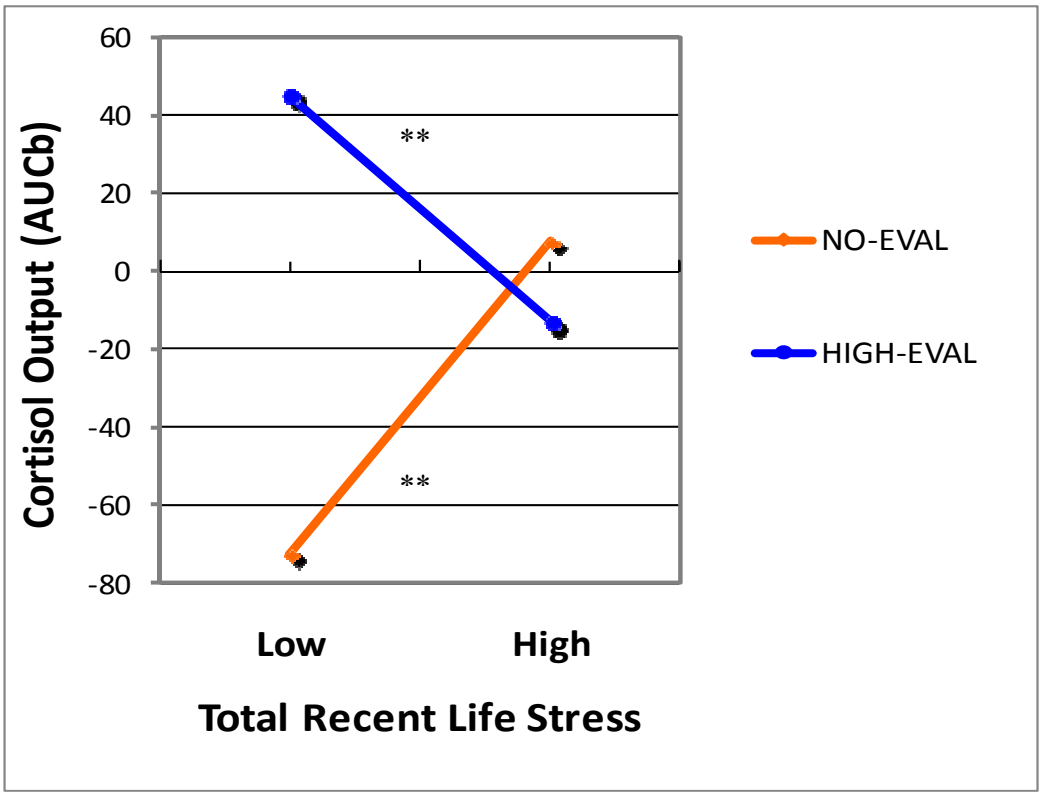
Childhood trauma subscales were not significantly related to any of the cortisol outcome variables, nor did they interact with recent life stress to predict cortisol responses. Greater total stress levels in the previous 6 months were associated with blunted cortisol reactivity to the TSST (r = -.29, p = .018), controlling for pre-stress cortisol levels (β = -.301, t = -2.46, p = .017), but were not related to the other cortisol outcome variables. In addition, the interaction of recent life stress and the experimentally manipulated stressor condition significantly predicted AUCb (β = -.266, t = -2.97, p = .004), controlling for

Figure 2.



age, sex, and current depressive symptoms (see Figure 3). Simple slope analyses revealed that among participants in the HIGH-EVAL condition, higher levels of recent stress were associated with lower AUCb (β = -4.476, t = -2.79, p = .006). The reverse pattern was observed among those in the NO-EVAL condition, such that higher levels of recent life stress were associated with higher AUCb (β = 5.009, t = 3.13, p = .002). Thus, at lower levels of recent life stress individuals showed the expected pattern of greater cortisol output in the social-evaluative threat condition; however, at higher levels of recent life stress individuals showed similarly blunted cortisol responses to both stressor conditions.

Figure 3.

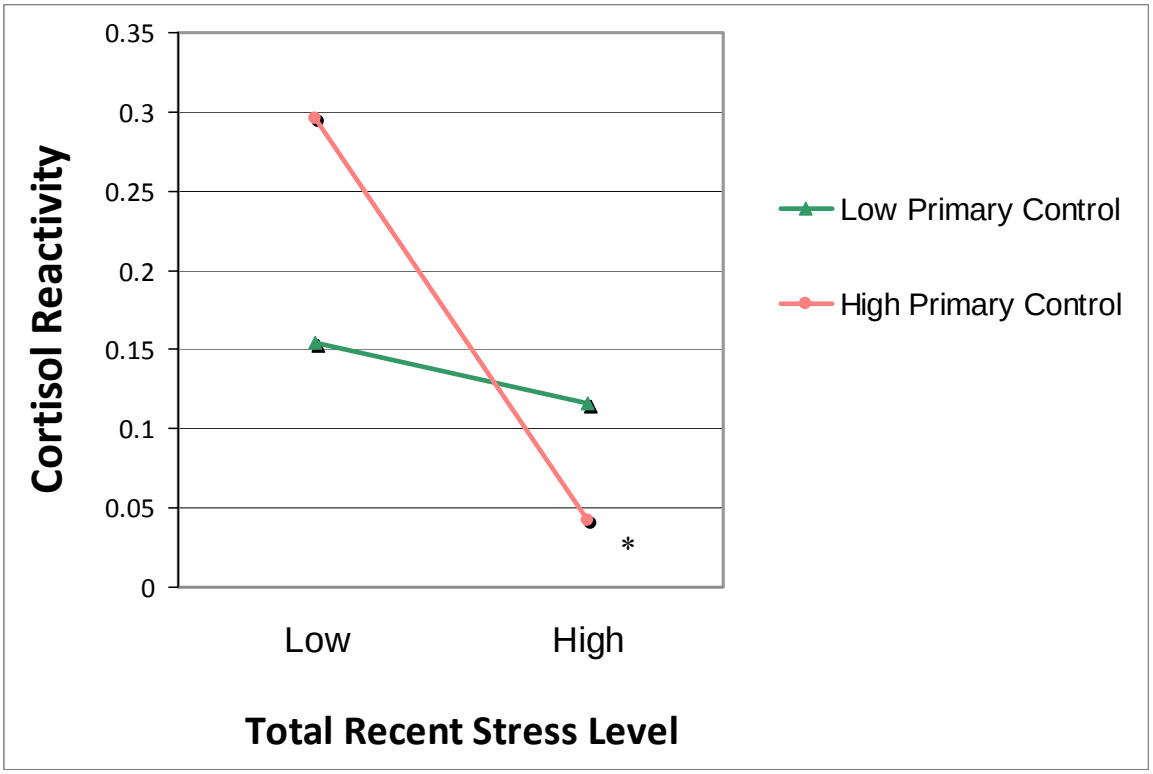


Stress Regulation

Do coping and involuntary stress response factors predict the cortisol response to a social evaluative stressor? Primary control coping. The relation of self-reported primary control coping to stressor-induced cortisol response was fairly consistent across outcome variables. Greater use of primary control coping predicted higher AUCg (β = .196, $t = 2.06$, $p = .042$), controlling for stressor condition, higher AUCb (β = .201, $t = 2.22$, $p = .029$), controlling for sex, age, and stressor condition, and greater cortisol reactivity at the level of a nonsignificant trend (β = .246, $t = 1.94$, $p = .057$), controlling for sex, age, and pre-stress cortisol levels. Moreover, primary control coping interacted with level of recent life stress to predict AUCb (β = -.221, $t = -2.49$, $p = .015$); simple slope analyses revealed that the relation of recent life stress to AUCb did not differ significantly from zero for individuals reporting high or low use of primary control coping. Primary control coping also interacted with recent life stress to predict cortisol reactivity at the level of a nonsignificant trend (β = -.238, $t = -1.99$, $p = .051$), controlling for pre-stress cortisol levels. Simple slope analyses revealed that among individuals reporting greater use of primary control coping, higher recent stress was associated with blunted cortisol reactivity (β = -.290, $t = -2.01$, $p = .049$); among individuals reporting lower use of primary control coping, stress levels were not associated with cortisol reactivity (see Figure 4). Taken together, these results suggest that greater self-reported use of primary control coping was associated with higher total cortisol output as well as greater change in cortisol output after baseline in response to a laboratory stressor; this pattern may differ for individuals reporting higher levels of recent stress, such that greater

use of primary control coping may be associated with blunted cortisol reactivity, regardless of stressor condition.

Figure 4.



Involuntary engagement. The relation of self-reported involuntary engagement to stressor-induced cortisol response was somewhat consistent across outcome variables. Greater involuntary engagement predicted blunted cortisol reactivity (β = -.356, t = -2.98, p = .004), controlling for sex, age, and pre-stress cortisol levels, and lower AUCb (β = -.205, t = -2.30, p = .024), controlling for sex, age, and stressor condition. Moreover, involuntary engagement interacted with stressor condition to predict AUCb (β = -.255, t = -2.89, p = .005), controlling for sex and age. Simple slope analyses revealed that among participants in the HIGH-EVAL condition, higher levels of involuntary engagement were

associated with lower AUCb (β = -.446, t = -3.72, p < .001); among participants in the NO-EVAL condition, higher levels of involuntary engagement were not significantly associated with AUCb. The interaction of involuntary engagement and stressor condition also predicted cortisol reactivity (β = -.253, t = -2.12, p = .038), controlling for sex, age, and pre-stress cortisol levels; simple slope analyses revealed that among individuals in the HIGH-EVAL condition, higher levels of involuntary engagement were associated with blunted cortisol reactivity (β = -.559, t = -3.44, p = .001); among participants in the NO-EVAL condition, higher levels of involuntary engagement were not significantly associated with cortisol reactivity. The interaction of involuntary engagement and level of recent life stress predicted cortisol reactivity (β = .303, t = 2.52, p = .015), controlling for sex, age, and pre-stress cortisol levels. At higher levels of recent life stress, involuntary engagement was positively associated with cortisol reactivity (β = 4.764, t = 2.37, p = .021; at lower levels of recent life stress, higher levels of involuntary engagement were negatively associated with cortisol reactivity (β = -5.350, t = -2.66, p = .010). In addition, the interaction of involuntary engagement with recent stress levels to predict AUCb showed a nonsignificant trend (β = .174, t = 1.87, p = .064); simple slope analyses indicated that the relation of involuntary engagement to AUCb was not significantly different from zero for individuals with high or low involuntary engagement, but they did differ from each other. Taken together, these results suggest that greater self-reported involuntary engagement was associated with decreased cortisol response to a laboratory stressor.

Involuntary disengagement. The interaction of involuntary disengagement with level of recent stress to predict AUCg showed a nonsignificant trend (β = .197, t = 1.96, p

= .053), controlling for stressor condition. Simple slope analyses showed that the relation of recent life stress to AUCg was not significantly different from zero for individuals with either high or low involuntary disengagement, although these slopes differed significantly from each other. Secondary control coping and disengagement coping were unrelated to cortisol outcome variables either alone, interacting with stressor condition, or interacting with recent stress levels.

CHAPTER IV.

DISCUSSION

The primary purpose of the present study was to determine whether remitted depressed (RD) individuals differed from never depressed (ND) individuals in their experience of recent life stress, early adversity, and use of coping strategies, and whether these stressor and coping features predicted cortisol responses to different intensities of a psychosocial stress task. In so doing, we hoped to identify potential trait markers that are present after remission from a depressive episode and may increase the likelihood of recurrence.

Differences between Remitted and Never Depressed Individuals

Consistent with our hypotheses, RD individuals reported higher levels of current depressive symptoms, greater number of recent stressful life events, higher rates of childhood physical abuse, and more involuntary engagement responses to stressors than ND individuals. RD and ND individuals, however, did not differ in their reported use of primary or secondary control engagement, disengagement coping, or involuntary disengagement, controlling for current depressive symptoms. Moreover, history of depression was not associated with reported emotional abuse, sexual abuse, or neglect.

Remitted depressed participants in the current study exhibited a blunted cortisol response to social-evaluative threat. Blunted cortisol responses to stress have been conceptualized as normative forms of dissociation or inhibition of the psychological experience of threat, providing a temporary means of attaining a sense of security and

control in stressful situations (Gunnar & Vazquez, 2001). Others have speculated that the ability to suppress one's affective, social-cognitive, or behavioral responses to threat may trigger decreases in reactivity of stress-response systems (Davies & Forman, 2002; Gold & Chrousos, 2002; Gunnar & Vazquez, 2001; Lopez, Vazquez, & Olson, 2004; Susman, 2006). The finding from the present study of a blunted cortisol response to a psychosocial stress task observed among RD individuals may be explained, in part, by higher rates of involuntary engagement and more recent life stress, which were both significantly correlated with a history of depression. Interestingly, decreased cortisol responsiveness to stress may result in hyperactivity of other physiological systems that could increase risk for immune-related disorders and chronic pain syndromes (Heim, Ehlert, & Hellhammer, 2000; Raison & Miller, 2003). Therefore, understanding the mechanisms that contribute to blunted HPA-axis stress reactivity may have implications for physical as well as mental health.

Recent stressful life events. Higher levels of recent life stress were associated with blunted cortisol reactivity. In addition, recent stress levels moderated the relation of stressor condition to change in cortisol output (AUCb), such that individuals with lower stress levels exhibited increased output in the HIGH-EVAL condition, whereas individuals with higher stress levels showed decreased output in the HIGH-EVAL condition. Explanations of the relation between chronic stress and the acute stress response have highlighted contextual, stressor, and temporal features. Regarding contextual factors, evolutionary-neurodevelopmental models (Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011) posit that elevated stress reactivity may lead to neutral or even positive outcomes under conditions of

support and protection, and negative health outcomes under conditions of chronic stress or adversity. Thus, decreased cortisol response in the HIGH-EVAL condition among individuals with greater recent stress exposure and the reverse pattern among individuals with less recent stress exposure may each represent adaptive calibrations of internal resources with environmental demands.

With regard to stressor features, Gump and Matthews (1999) suggested that "background stressors" influence acute stress responses. Tendencies for decreased reactivity (*habituation*) are observed with repeated exposures to similar stressors, and tendencies for increased reactivity (*sensitization*) are observed with single exposures to novel stressors. For example, one study examining serial exposure to the TSST among healthy men and women found evidence for habituation in the form of progressively reduced cortisol responses (Schommer et al., 2003).

Focusing on temporal features, a meta-analysis examining the influence of chronic stress on HPA-axis parameters found that cortisol secretion exhibited a time-dependent pattern, with "hypercortisolism" associated with more recent and ongoing stressors and "hypocortisolism" associated with more distant stressors (Miller et al., 2007). The present study examined recent life stress without distinguishing between stressor types or durations. Nevertheless, our findings suggest that prolonged or repeated exposure to stressors may lead to biological and/or cognitive adaptation, culminating in decreased cortisol reactivity (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Heim, Ehlert, & Hellhammer, 2000; McEwen, 1998).

Childhood trauma. Childhood trauma subscales were not directly related to cortisol outcomes and did not interact with recent stress levels to predict cortisol

responses. Reviews of the literature on the long-term neurobiological sequelae of childhood trauma exposure have noted considerable heterogeneity of findings, with some studies reporting increased HPA-axis activity and other studies reporting decreased activity (Tarullo & Gunnar, 2006). One factor thought to contribute to this variation is the time elapsed since the trauma. The 'attenuation hypothesis' proposes that sustained cortisol hypersecretion following trauma exposure will lead to an adaptive downregulation of cortisol secretion over time (Gunnar & Vazquez, 2001; Heim, Newport, Mletzko, Miller & Nemeroff, 2008; Susman, 2006). It is possible that the relation of childhood trauma to cortisol outcomes in the present study might have been clearer had we obtained more detailed information about the timing and chronicity of the traumatic events.

Stressor Discrimination

Analyses revealed that the laboratory stressor manipulation was successful, such that the HIGH-EVAL condition resulted in greater cortisol output than the NO-EVAL condition. This finding is consistent with evidence that degree of social-evaluative threat is positively associated with cortisol responses to psychosocial stress tasks (Dickerson & Kemeny, 2004). In addition, ND individuals showed the expected pattern of greater cortisol output in the HIGH-EVAL as compared to the NO-EVAL conditions. In contrast, RD individuals exhibited a relatively blunted cortisol response to both HIGH-EVAL and NO-EVAL conditions, thus indicating a lack of discrimination in their cortisol response to the two conditions. These results for remitted depressed individuals parallel findings for currently depressed individuals (Burke et al., 2005). Taken together, it seems that blunted cortisol response to stressors may represent a relatively stable and enduring

marker of risk for depression. Prospective longitudinal studies are needed, however, to determine if the cortisol stress response changes with successive MDEs, and whether alterations of HPA-axis activity function as biological mediators of stress sensitization.

Stress Sensitization

One aim of the present study was to examine the relations of depression and life stress to the cortisol response to a psychosocial stress task in order to better understand potential mechanisms of stress sensitization. Prior research has highlighted the role of previous depressive episodes (e.g., Morris et al., 2010), early adversity (e.g., Harkness et al., 2006), and recent life stress (e.g., Rao et al., 2009) in strengthening the link between life stress and depression. Overall, findings from the present study suggest that sensitization processes may be associated with reduced cortisol reactivity to stressors. Individuals with a history of depression exhibited blunted cortisol responses in the social-evaluative threat condition compared to ND participants. Among RD participants, however, the laboratory stressor condition did not differentially affect their cortisol stress response. We speculate that increasing HPA-axis sensitivity to relatively minor stressors among RD individuals may trigger an adaptive down-regulation of cortisol stress reactivity over time that could lead to the blunted cortisol responses observed in the present study.

Results also were consistent with the view that recent life stress may sensitize individuals to subsequent stressors. Individuals who reported higher stress levels in the 6 months prior to the laboratory stress task exhibited a pattern of blunted cortisol reactivity similar to those with a history of depression. Analyses did not reveal an association between childhood trauma and cortisol outcomes, however. Thus, both prior depressive

episodes and recent stressful life events were associated with alterations in HPA-axis activity, suggesting that stress sensitization processes may be linked to progressive blunting of cortisol responses. Future studies need to explore whether reduced cortisol reactivity represents a preexisting vulnerability factor for depression and to what extent it changes over time in response to depressive episodes and stressful life events.

Stress Regulation

Greater use of primary control coping was associated with increased cortisol output, and involuntary engagement was associated with decreased cortisol output. Given that primary control engagement coping is generally considered to be adaptive and involuntary engagement is generally considered to be maladaptive, how do we make sense of their differential impact on the cortisol response to a psychosocial stressor?

The characteristics of cortisol secretion in psychiatric disorders such as depression are well documented, yet their clinical relevance remains unclear. In the long-term, increased risk for physical and mental health problems are associated with both cortisol hyperactivity (e.g., Mason, 1991; McEwen, 2007) and hypoactivity (e.g., Raison & Miller, 2003). In the short-term, cortisol elevations in response to acute stressors are considered adaptive (Cicchetti & Rogosch, 2001). Animal studies suggest that corticosteroid hormones promote adaptive coping behaviors and cognitions (de Kloet, Oitzl, & Joels, 1999; Oitzl, Champagne, van der Veen, & de Kloet, 2010). Evidence from animal and human studies indicates that glucocorticoids enhance memory consolidation and temporarily impair retrieval and working memory. For example, the administration of glucocorticoids has been shown to reduce retrieval and enhance extinction of memories of emotionally arousing experiences (see Wolf, 2008; de Quervain, Aerni,

Schelling, & Roozendaal, 2009, for reviews). In addition, transient, moderate increases in cortisol levels have been associated with better performance on measures of executive function and self-regulation, with executive function mediating the relation of cortisol reactivity to self-regulation (Blair, Granger, & Razza, 2005). Thus, stressor-induced changes in cortisol levels appear related to memory processes, executive function, and self-regulation.

In a review examining the impact of single cortisol administrations on affective responses and early cognitive processing of affective information, Putnam and Roelofs (2011) proposed a framework for understanding the influence of cortisol secretion on effective coping with psychological stress. According to their cognitive processing hypothesis, stress-related increases in cortisol levels serve an adaptive function by restoring goal-directed processing of emotional information following a period of automatic and stimulus-driven processing. This perspective is consistent with evidence that the cortisol response to stress is slow-acting, reaches a peak approximately 20 minutes after stressor onset (Dickerson & Kemeny, 2004), and therefore, may be more involved in regulating, rather than facilitating, emotional responses to stress (Putnam & Roelof, 2011; Sapolsky et al., 2000). Among individuals with elevated anxiety, threat-biased attention is amplified and increased cortisol output may facilitate goal-directed behavior by promoting avoidance, whereas among healthy individuals, elevated cortisol may promote approach-related behavior (Bohnke, Bertsch, Kruk, Richter, & Naumann, 2010; Putnam, Antypa, Crysovergi, & van der Does, 2010; Van Peer, Roelofs, Rotteveel, van Dijk, Spinhoven, & Ridderinkhof, 2007). Thus, cortisol reactivity to stressors

facilitates goal-directed processing of emotional information, although the types of goal-directed behavior enacted may depend on individual characteristics.

Findings from the current study regarding the association of cortisol outcomes and coping factors fit nicely within this cognitive processing framework. Given that primary control engagement coping involves efforts to change the situation or the emotional response to it, we would expect that individuals who endorsed using these strategies more frequently would preferentially engage in goal-directed processing of threat-related information during the stress task, requiring elevated cortisol levels to inhibit more automatic and stimulus-driven processing. Consistent with this prediction, we found that individuals who reported greater use of primary control engagement coping showed increased cortisol reactivity to the TSST.

Interestingly, greater use of primary control coping among those with high recent stress levels was associated with blunted cortisol reactivity. According to evolutionary-neurodevelopmental models (Ellis et al., 2011), diminished cortisol responses may be adaptive in the context of high levels of stress to mitigate against the negative health outcomes associated with sustained or repeated cortisol elevations (Raison & Miller, 2003). We speculate that for those individuals who reported higher rates of primary control coping - strategies associated with greater cortisol reactivity – the impact of higher recent stress levels may have been amplified, resulting in an adaptive decrease in cortisol reactivity.

Involuntary engagement responses have been defined as temperamentally-based, conditioned reactions to stressors that may be outside of conscious awareness; although they are oriented toward the stressor or an individual's stress response, they are not goal-

directed (Connor-Smith et al., 2000). Based on the cognitive processing hypothesis (Putnam & Roelofs, 2011), we would expect individuals who endorsed higher rates of involuntary engagement to be less likely to engage in goal-directed processing during the stress task, more likely to engage in automatic stimulus-driven processing, and therefore more likely to exhibit reduced cortisol levels. Consistent with this prediction, results indicated that individuals who reported higher rates of involuntary engagement showed blunted cortisol reactivity to the TSST. Importantly, findings from the current study cannot determine whether engaging in coping strategies affects cortisol responses or if cortisol responses constrain the use of coping strategies. Future studies are needed to clarify the temporal ordering of these events.

Study Strengths and Limitations

The present study contributed to the literature on stress reactivity and regulation in depression in several ways. First, results were consistent with previous studies demonstrating blunted cortisol reactivity to psychosocial stress in remitted depressed individuals (Ahrens et al., 2008; Bagley et al., 2011; Brown, 2001; Chopra et al., 2008; Trestman et al., 1991) and extended these findings by examining the relation of early adversity and recent life stress in addition to history of depression to cortisol reactivity. We used a remitted depression design that optimized our ability to detect clinically meaningful differences between RD and ND individuals and allowed us to examine potential vulnerability factors that were present after recovery. Second, we examined the relation of self-reported coping and involuntary stress response features to cortisol reactivity to a laboratory stressor, thereby allowing us to attribute variation in these relations to individual differences rather than situation-specific factors (Connor-Smith &

Compas, 2004). An important clinical implication of these findings is that interventions aimed at relapse prevention among remitted depressed individuals should reduce reliance on involuntary engagement, increase the use of primary control engagement coping, and mitigate stress generation processes. Third, this is the first study to test the stressor discrimination hypothesis in RD and ND individuals using a psychosocial stress task that manipulated the degree of social-evaluative threat. The success of this manipulation suggests that this paradigm may be useful for future studies testing stress sensitization hypotheses regarding changes in the impact of stressors of varying intensities.

Limitations of the present study should be noted as they provide directions for future research. First, although the remitted depression design (and controlling for current depressive symptoms) allowed us to rule out the possibility that observed differences between RD and ND individuals were state markers, the cross-sectional design prevented us from determining whether these differences represented stable trait markers of risk for depression or scars triggered by prior MDEs that may or may not increase risk for depression. Second, the absence of findings for pre-stress cortisol levels and cortisol recovery slopes should be interpreted cautiously because it is possible that participants were not given sufficient time to acclimate to the laboratory space prior to the stress task or to return to basal levels following the stress task. Future studies should employ a cortisol sampling protocol that will allow for more rigorous testing of hypotheses regarding pre-stress and recovery cortisol levels (e.g., Rao et al., 2008). Third, null findings regarding the relation of childhood trauma to cortisol outcomes should be interpreted cautiously due to our reliance on a retrospective, self-report measure. Interview-based measures of early adversity are preferable in that they allow for more

precise assessment of the timing, severity, and chronicity of traumatic events. Fourth, the self-report measure of coping and involuntary stress responses captured the strategies participants endorsed using more or less frequently in the previous 6 months in dealing with social stressors. We can only make inferences, however, regarding the real-time strategies used by participants during the psychosocial stress task in the laboratory.

In conclusion, the present study provided evidence of blunted cortisol reactivity to a psychosocial stressor among young adults at risk for depression. History of depression, total level of recent stressful life events, and self-reported involuntary engagement responses to stress predicted decreased cortisol output. In contrast, greater use of primary control engagement coping predicted greater cortisol reactivity and output. Examining abnormalities in biological and cognitive factors both during and after recovery from a depressive episode may help clarify the processes that confer increased risk of recurrence. Remitted depression designs can be useful in identifying markers of risk, and can inform prospective studies that address whether these markers predict subsequent depressive episodes. Given that MDD is a highly prevalent, debilitating, and recurrent disorder, identifying mechanisms of risk can be used to guide the construction of targeted, practical, and efficacious treatment and prevention programs, and thus represents an extremely important public health goal.

REFERENCES

Ahrens, T., Deuschle, M., Krumm, B., van der Pompe, G., den Boer, J. A., & Lederbogen, F. (2008). Pituitary-adrenal and sympathetic nervous system responses to stress in women remitted from recurrent major depression. *Psychosomatic Medicine, 70,* 461-467.

Aiken, L.S., & West, S.G. (1991). *Multiple regression: Testing and interpreting interactions*. Newbury Park, CA; Sage.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Amsterdam, J.D., Maislin, G., Winokur, A., Berwish, N., Kling, Mitchell, & Gold, P. (1988). The o-CRH stimulation test before and after clinical recovery from depression. *Journal of Affective Disorders, 14,* 213-222.

Amsterdam, J.D., Maislin, G., Gold, P., & Winokur, A. (1989). The assessment of abnormalities in hormonal responsiveness at multiple levels of the hypothalamic-pituitary-adrenocortical axis in depressive illness. *Psychoneuroendocrinology, 14,* 43-62.

Appelhof, B.C., Huyser, J., Verweij, M., Brouwer, J.P., van Dyck, R., Fliers, E., Hoogendijk, W.J.G., Tijssen, J.G.P., Wiersinga, W.M., & Schene, A.H. (2006). Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). *Biological Psychiatry, 59,* 696-701.

Aubry, J.-M., Gervasoni, N., Osiek, C., Perret, G., Rossier, M.F., Bertschy, G., &

Bondolfi, G. (2007). The DEX/CRH neuroendocrine test and the prediction of depressive relapse in remitted depressed outpatients. *Journal of Psychiatric Research, 41,,* 290-294.

Bagley, S.L., Weaver, T.L., & Buchanan, T.W. Sex differences in physiological and affective responses to stress in remitted depression. (2011). *Physiology and Behavior,* doi: 10.1016/j.physbeh.2011.03.004.

Bailey, S.L., & Heitkemper, M.M. (1991). Morningness-eveningness and early-morning salivary cortisol levels. *Biological Psychology, 32,* 181-192.

Balodis, I.M., Wynne-Edwards, K.E., & Olmstead, M.C. (2010). The other side of the curve: Examining the relationship between pre-stressor physiological responses and stress reactivity. *Psychoneuroendocrinology, 35,* 1363-1373.

Beck, A.T., Steer, R.A., Ball, R., & Ranieri, W.F. (1996). Comparison of Beck Depression Inventories –IA and –II in psychiatric outpatients. *Journal of Personality Assessment, 67,* 588-597.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation.

Berkowitz, L. (1993).*Aggression: Its causes, consequences, and control.* New York, NY: McGraw-Hill.

Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Sapareto, E., & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child-abuse and neglect. *American Journal of Psychiatry, 151,* 1132-1136.

Bevans, K., Cerbone, A., & Overstreet, S. (2008). Relations between recurrent trauma

exposure and recent life stress and salivary cortisol among children. *Development and Psychopathology, 20,* 257-272.

Blagden, J.C., & Craske, M.G. (1996). Effects of active and passive rumination and distraction: A pilot replication with anxious mood. *Journal of Anxiety Disorders, 10,* 243-252.

Blair, C., Granger, D., & Razza, R.P. (2005). Cortisol reactivity is positively related to executive function in preschool children attending Head Start. *Child Development, 76,* 554-567.

Bohnke, R., Bertsch, K., Kruk, M.R., Richter, S., & Naumann, F. (2010). Exogenous cortisol enhances aggressive behavior in females, not in males. *Pschoneuroendocrinology, 35,* 1034-1044.

Bos, E.H. Bouhuys, A.L., Geerts, E., Van Os, T.W.D.P, Van der Spoel, I.D., Brouwer, W.H., & Ormel, J. (2005). Cognitive, physiological, and personality correlates of recurrence of depression. *Journal of Affective Disorders, 87,* 221-229.

Boyce, W.T., & Ellis, B.J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17,* 271-301.

Breier, A. (1989). Experimental approaches to human stress research: Assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. *Biological Psychiatry, 26,* 438-462.

Brosschot, J.F., Gerin, W., & Thayer, J.F. (2006). The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation, and health. *Journal of Psychosomatic Research, 60,* 113-124.

Brown, L.L. (2001). The cortisol response to psychosocial stress in women at risk for depression (Doctoral dissertation, Vanderbilt University). *Dissertation Abstracts International, 61*(11), 6125B.

Brown, G.W., & Harris, T.O. (1978). *Social origins of depression: A study of psychiatric disorder in women.* New York: Free Press.

Burke, H.M., Davis, M.C., Otte, C., & Mohr, D.C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology, 30,* 846-856.

Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., Wier, L.M., Mello, A.F., Mello, M.F., Anderson, G.M., Wilkinson, C.W., & Price, L.H. (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry, 62,* 1080-1087.

Carroll, B.J., Feinberg, M., Greden, J. F., Tarika, J., Albala, A., Haskett, R.F., James, N.M., Kronfol, Z., Lohr, N., de Vignr, J.P., & Young, E. (1981). A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. *Archives of General Psychiatry, 38,* 15-22.

Chopra, K.K., Segal, Z.V., Buis, T., Kennedy S.H., & Levitan, R.D. (2008). Investigating associations between cortisol and cognitive reactivity to sad mood provocation and the prediction of relapse in remitted major depression. *Asian Journal of Psychiatry, 1,* 33-36.

Cicchetti, D., & Rogosch, F.A. (2001). Diverse patterns of neuroendocrine activity in maltreated children. *Development and Psychopathology, 13,* 677-693.

Cohen, J., & Cohen, P. (1983). *Applied multiple regression/correlation analysis for the behavioural sciences* (2nd ed.). Hillsdale, NJ; Erlbaum.

Compas, B.E., Connor-Smith, J.K., Saltzman, H., Thomsen, A.H., & Wadsworth, M.E. (2001). Coping with stress during childhood and adolescence: Problems, progress, and potential in theory and research. *Psychological Bulletin, 127,* 87-127.

Compas, B.E., Davis, G.E., Forsythe, C.J., & Wagner, B.M. (1987). Assessment of major and daily stressful events during adolescence: The adolescent perceived events scale. *Journal of Consulting and Clinical Psychology, 55,* 534-541.

Connor-Smith, J.K., & Compas, B.E. (2004). Coping as a moderator of relations between reactivity to interpersonal stress, health status, and internalizing problems. *Cognitive Therapy and Research, 28,* 347-368.

Connor-Smith, J.K., Compas, B.E., Wadsworth, M.E., Thomsen, A.H., & Saltzman, H. (2000). Responses to stress in adolescence: Measurement of coping and involuntary stress responses. *Journal of Consulting and Clinical Psychology, 68,* 976-992.

Croes, S., Merz, P., & Netter, P. (1993). Cortisol reaction in success and failure condition in endogenous depressed patients and controls. *Psychoneuroendocrinology, 18,* 23-35.

Daley, S.E., Hammen, C., & Rao, U. (2000). Predictors of first onset and recurrence of major depression in young women during the 5 years following high school graduation. *Journal of Abnormal Psychology, 109,* 525-533.

Davies, P.T., & Forman, E.M. (2002). Children's patterns of preserving emotional security in the interparental subsytem. *Child Development, 73,* 1880-1903.

De Bellis, M.D., Chrousos, G.P., Dorn, L.D., Burke, L., Helmers, K., Kling, M.A., Trickett, P.K., & Putnam, F.W. (1994). Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *Journal of Clinical Endocrinology and Metabolism, 78,* 249-255.

de Kloet, R.E., Oitzl, M.S., & Joels, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neuroscience, 22,* 422-426.

Denson, T.F., Spanovic, M., & Miller, N. (2009). Cognitive appraisals and emotions predict cortisol and immune responses: A meta-analysis of acute laboratory social stressors and emotion inductions. *Psychological Bulletin, 135,* 823-853.

de Quervain, D.J., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology, 30,* 358-370.

de Quervain, D.J., & Margraf, J. (2008). Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: A novel therapeutic approach. *European Journal of Pharmacology, 583,* 365-371.

Deuschle, M., Hamann, N., Meichel, C., Krumm, B., Lederbogen, F., Kniest, A., Colla, M., & Heuser, I. (2003). Antidepressive treatment with amitriptyline and paroxetine: Effects on saliva cortisol concentrations. *Journal of Clinical Psychopharmacology, 23,* 201-205.

Dickerson, S.S., & Kemeny, M.E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130,* 355-391.

Dienstbier, R.A. (1989). Arousal and physiological toughness: Implications for mental

and physical health. *Psychological Review, 96,* 84-100.

Edwards, V.J., Holden, G.W., Felitti, V.J., & Anda, R.F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: Results from the Adverse Childhood Experiences Study. *American Journal of Psychiatry, 160,* 1453-1460.

Ellis, B.J., Boyce, W.T., Belsky, J., Bakermans-Kranenburg, M.J., & van Ijzendoorn, M.H. (2011). Differential susceptibility to the environment: An evolutionary-neurodevelopmental theory. *Development and Psychopathology, 23,* 7-28.

Elzinga, B.M., Roelofs, K., Tollenaar, M.S., Bakvis, P., van Pelt, J., & Spinhoven, P. (2008). Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: A study among healthy young subjects. *Psychoneuroendocrinology, 33,* 227-237.

Espejo, E.P., Hammen, C.L., Connolly, N.P, Brennan, P.A., Najman, J.M., & Bor, W. (2006). Stress sensitization and adolescent depressive severity as a function of childhood adversity: A link to anxiety disorders. *Journal of Abnormal Child Psychology, 35,* 287-299.

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1997). *User's guide for the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) - Clinician Version.* Washington, DC: American Psychiatric Press.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D.H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30,* 1010-1016.

Gold, P.W., Loriaux, D.L., Roy, A. Kling, M., Calabrese, J.R., Kellner, C.H., Nieman, L.K., Post, R.M., Pickar, D., Gallucci, N., Avergerinos, P., Paul, S., Oldsfield,

E.H., Cutler, G.B., & Chrousos, G.P. (1986). Response to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. *New England Journal of Medicine, 314,* 1329-1335.

Gold, P.W., Goodwin, F.K., & Chrousos, G.P. (1988a). Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress (Part 1 of 2). *New England Journal of Medicine, 319,* 348-353.

Gold, P.W., Goodwin, F.K., & Chrousos, G.P. (1988b). Clinical and biochemical manifestations of depression: Relation to the neurobiology of stress (Part 2 of 2). *New England Journal of Medicine, 319,* 413-420.

Gold, P.W., & Chrousos, G.P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High *vs* low CRH/NE states. *Molecular Psychiatry, 7,* 254-275.

Grant, K.E., Compas, B.E., Thurm, A.E., McMahon, S.D., & Gipson, P.Y. (2004). Stressors and child and adolescent psychopathology: Measurement issues and prospective effects. *Journal of Clinical Child and Adolescent Psychology, 33,* 412-425.

Gruenewald, T.L., Kemeny, M. E., Aziz, N., & Fahey, J.L. (2004). Acute threat to the social self: Shame, social self-esteem, and cortisol activity. *Psychosomatic Medicine, 66,* 915-924.

Gump, B.B., & Matthews, K.A. (1999). Do background stressors influence reactivity to and recovery from acute stressors? *Journal of Applied Social Psychology, 29,* 469-494.

Gunnar, M.R., & Vazquez, D.M. (2001). Low cortisol and a flattening of expected

daytime rhythm: Potential indices of risk in human development. *Development and Psychopathology, 13,* 515-538.

Gurguis, G.N., Meador-Woodruff, J.H., Haskett, R.F., & Greden, J.F. (1990). Multiplicity of depressive episodes: Phenomenological and neuroendocrine correlates. *Biological Psychiatry, 27,* 1156-1164.

Haeffel, G.J., Abramson, L.Y., Voelz, Z.R., Metalsky, G.I., Halberstadt, L., Dykman, B.M., Donovan, P., Hogan, M.E., Hankin, B.L., & Alloy, L.B. (2005). Negative cognitive styles, dysfunctional attitudes, and the remitted depression paradigm: A search for the elusive cognitive vulnerability to depression factor among remitted depressives. *Emotion, 5,* 343-348.

Halligan, S.L., Herbert, J., Goodyer, I., & Murray, L. (2007). Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biological Psychiatry, 62,* 40-46.

Hammen, C., Henry, R., & Daley, S.E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology, 68,* 782-787.

Harkness, K.L., Bruce, A.E., & Lumley, M.N. (2006). The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. *Journal of Abnormal Psychology, 115,* 730-741.

Harkness, K.L., Stewart, J.G., & Wynne-Edwards, K.E. (2011). Cortisol reactivity to social stress in adolescents: Role of depression severity and child maltreatment. *Psychoneuroendocrinology, 36,* 173-181.

Hatzinger, M., Hemmeter, U.M., Baumann, K., Brand, S., & Holsboer-Trachsler, E. (2002). The combined DEX-CRH test in treatment course and long-term outcome of major depression. *Journal of Psychiatric Research, 36,* 287-297.

Heim, C., Ehlert, U., & Hellhammer, D.H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology, 25,* 1-35.

Heim, C., Newport, D.J., Bonsall, R., Miller, A.H., & Nemeroff, C.B. (2001). Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry, 158,* 575-581.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., & Nemeroff, C.B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Journal of the American Medical Association, 284,* 592-597.

Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., & Nemeroff, C.B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33,* 693-710.

Heim, C., Newport, J., Wagner, D., Wilcox, M.M., Miller, A.H., & Nemeroff, C.B. (2002). The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: A multiple regression analysis. *Depression and Anxiety, 15,* 117-125.

Het, S., Rohleder, N., Schoofs, S., Kirschbaum, C., & Wolf, O.T. (2009). Neuroendocrine and psychometric evaluation of a placebo version of the 'Trier Social Stress Test.' *Psychoneuroendocrinology, 34,* 1075-1086.

Hollingshead, A.B. (1975). *Four factor index of social status.* Unpublished manuscript, Yale University.

Holsboer, F., Lauer, C.J., Schreiber, W., & Krieg, J.C. (1995). Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. *Neuroendocrinology, 62,* 340-347.

Holsboer, F., Liebl, R., & Hofschuster, E. (1982). Repeated dexamethasone suppression test during depressive illness. Normalization of test result compared with clinical improvement. *Journal of Affective Disorders, 4,* 93-101.

Holsboer, F., Haack, D., Gerken, A., & Vecsei, P. (1984). Plasma dexamethason concentrations and differential suppression response of cortisol and corticosterone in depressives and controls. *Biological Psychiatry, 19,* 281-291.

Holsboer, F., Gerken, A., Stalla, G. K., & Muller, O. A. (1985). ACTH, cortisol, and corticosterone output after ovine corticotropin-releasing factor challenge during depression and after recovery. *Biological Psychiatry, 20,* 276-286.

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews, 12,* 118-134.

Kathol, R. G. (1985). Persistent elevation of urinary free cortisol and loss of circannual periodicity in recovered depressive patients: A trait finding. *Journal of Affective Disorders, 8,* 137-145.

Kaufman, J., Birmaher, B., Perel, J., Dahl, R.E., Moreci, P., Nelson, B., Wells, W., & Ryan, N.D. (1997). The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. *Biological Psychiatry,*

42, 669-679.

Kaufman, J., & Charney, D. (2001). Effects of early stress on brain structure and function: Implications for understanding the relationship between child maltreatment and depression. *Development and Psychopathology, 13,* 451-471.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry, 156,* 837-848.

Kendler, K.S., Kuhn, J., & Prescott, C.A. (2004). The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry, 161,* 631-636.

Kessler, R.C., Berglund, P., Demier, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62,* 593-602.

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The Trier Social Stress Test: A tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychology, 28,* 76-81.

Knight, R. B., Atikins, A., Eagle, C. J., Evans, N., Finkelstein, J. W., Fukushima, D., Katz, J., & Weiner, H. (1979). Psychological stress, ego defenses, and cortisol production in children hospitalized for elective surgery. *Psychosomatic Medicine, 41,* 40-49.

Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R., & Andrews, J. A. (1993). Adolescent psychopathology : I. Prevalence and incidence of depression and other

DSM-II-R disorders in high school students. *Journal of Abnormal Psychology, 102,* 133-144.

Lewinsohn, P. M., Allen, N. B., Seeley, J. R., & Gotlib, I. H. (1999). First onset versus recurrence of depression : Differential processes of psychosocial risk. *Journal of Abnormal Psychology, 108,* 483-489.

Lopez, N. L., Vazquez, D. M., & Olson, S. L. (2004). An integrative approach to the neurophysiological substrates of social withdrawal and aggression. *Development and Psychopathology, 16,* 69-93.

Luecken, L.J., Kraft, A., & Hagan, M.J. (2009). Negative relationships in the family-of-origin predict attenuated cortisol in emerging adults. *Hormones and Behavior, 55,* 412-417.

MacMillan, H.L., Fleming, J.E., Streiner, D.L., Lin, E., Boyle, M.H., Jamieson, E., Duku, E.K., Walsh, C.A., Wong, M.Y., & Beardslee, W.R. (2001). Childhood abuse and lifetime psychopathology in a community sample. *American Journal of Psychiatry, 158,* 1878-1883.

MacMillan, H.L., Georgiades, K., Duku, E.K., Shea, A., Steiner, M., Niec, A., Tanaka, M., Gensey, S., Spree, S., Vella, E., Walsh, C.A., De Bellis, M.D., Van der Meulen, J., Boyle, M.H., & Schmidt, L.A. (2009). Cortisol response to stress in female youths exposed to childhood maltreatment: Results of the Youth Mood Project. *Biological Psychiatry, 66,* 62-68.

Mannie, Z.N., Harmer, C.J., & Cowen, P.J. (2007). Increased waking salivary cortisol levels in young people at familial risk of depression. *American Journal of Psychiatry, 164,* 617-621.

Mason, D. (1991). Genetic variation in the stress response: Susceptibility to experimental allergic encephalomyelitis and implications for human inflammatory disease. *Immunology Today, 12,* 57-60.

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine, 338,* 171-179.

McEwen, B. S. (2003). Mood disorders and allostatic load. *Biological Psychiatry, 54,* 200-207.

McEwen, B.S. (2007). Physiology and neurobiology of stress and adaptation. *Physiological Review, 87,* 873-904.

McEwen, B. S., & Seeman, T. (1999). Protective and damaging effects of mediators of stress: Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences, 896,* 30-47.

McLaughlin, K.A., Conron, K.J., Koenen, K.C., & Gilman, S.E. (2010). Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: A test of the stress sensitization hypothesis in a population-based sample of adults. *Psychological Medicine, 40,* 1647-1658.

Meikle, A.W., Stringham, J.D., Woodward, M.G., & Bishop, D.T. (1988). Heritability of variation of plasma cortisol levels. *Metabolism, 37,* 514-517.

Miller, G.E., Chen, E., & Zhou, E.S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin, 133,* 25-45.

Monroe, S. M. & Harkness, K. L. (2005). Life stress, the "kindling" hypothesis, and the recurrence of depression: Considerations from a life stress perspective.

Psychological Review, 112, 417-445.

Monroe, S. M. & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin, 110,* 406-425.

Morris, M.C., Ciesla, J.A., & Garber, J. (2010). A prospective study of stress autonomy versus stress sensitization in adolescents at varied risk for depression. *Journal of Abnormal Psychology, 119,* 341-354.

Munck, A., Guyre, P. M., & Holbrook, N. J. (1984). Physiological functions of glucocorticoids in stress and their pharmacological actions. *Endocrine Reviews, 5,* 25-44.

Murray, C. L. & Lopez, A. D. (1997). Global mortality, disability, and the contribution of risk factors: Global burden of disease study. *Lancet, 349,* 1436-1442.

Nater, U.M., Moor, C., Ukere, U., Stallkamp, R., Martin, M., Ehlert, U., & Kliegel, M. (2007). Performance on a declarative memory task is better in high than low cortisol responders to psychosocial stress. *Psychoneuroendocrinology, 32,* 758-763.

Nemeroff, C. B., Widerlov, E., Bissette, G., Walleus, H., Karlsson, I., Eklund, K., Kilts, C. D., Loosen, P. T., & Vale, E. (1984). Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science, 226,* 1342-1344.

Netter, P., Croes, S., Merz, P., & Muller, M. (1991). Emotional and cortisol response to uncontrollable stress. *Stress and Anxiety, 13,* Eds: Spielberger, C. D., Sarason, I. G., Strelau, J., & Brebner, J. M. T. New York: Hemisphere Publishing

Corporation.

Nicolson, N.A. (1992). Stress, coping and cortisol dynamics in daily life. In de Vries, M.W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in their Natural Settings.* Cambridge University Press, New York, pp. 219-232.

Nolen-Hoeksema, S., Morrow, J., & Fredrickson, B.L. (1993). Response styles and the duration of episodes of depressed mood. *Journal of Abnormal Psychology, 102,* 20-28.

O'Donnell, K., Badrick, E., Kumari, M., & Steptoe, A. (2008). Psychological coping styles and cortisol over the day in healthy older adults. *Psychoneuroendocrinology, 33,* 601-611.

Oitzl, M.S., Champagne, D.L., van der Veen, R., & de Kloet, E.R. (2010). Brain development under stress: Hypotheses of glucocorticoid actions revisited. *Neuroscience and Biobehavioral Reviews, 34,* 853-866.

Pennebaker, J.W. (1997). Writing about emotional experiences as a therapeutic process. *Psychological Science, 8,* 162-166.

Peters, M.L., Godaert, G.L.R., Ballieux, R.E., & Heijnen, C.J. (2003). Moderation of physiological stress responses by personality traits and daily hassles: less flexibility of immune system responses. *Biological Psychology, 65*, 21-48.

Pike, J.L., Smith, T.L., Hauger, R.L., Nicassio, P.M., Patterson, T.L., McClintick, J., Costlow, C., & Irwin, M.R. (1997). Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. *Psychosomatic Medicine, 59*, 447-459.

Pintor, L., Torres, X., Navarro, V., de Osaba, M. J. M., Matrai, S., & Gasto, C. (2007).

Corticotropin-releasing factor test in melancholic patients in depressed state versus recovery: A comparative study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 31,* 1027-1033.

Post, R.M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry, 149,* 999-1010.

Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D.H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28,* 916-931.

Putnam, P., Antypa, N., Crysovergi, P., & van der Does, A.J. (2010). Exogenous cortisol acutely influences motivated decision-making in healthy young men. *Psychopharmacology, 208,* 257-263.

Putnam, P., & Roelofs, K. (2011). Effects of single cortisol administrations on human affect reviewed: Coping with stress through adaptive regulation of automatic cognitive processing. *Psychoneuroendocrinology, 36,* 439-448.

Raison, C. L. & Miller, A. H. (2003). When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *American Journal of Psychiatry, 160,* 1554-1565.

Rao, U., Hammen, C., Ortiz, L.R., Chen, L.-A., & Poland, R.E. (2008). Effects of early and recent adverse experiences on adrenal response to psychosocial stress in depressed adolescents. *Biological Psychiatry, 64,* 521-526.

Rao, U., Hammen, C.L., & Poland, R.E. (2009). Longitudinal course of adolescent depression: Neuroendocrine and psychosocial predictors. *Journal of the American*

Academy of Child & Adolescent Psychiatry, 49, 141-151.

Ravindran, A. V., Griffiths, J., Merali, Z., & Anisman, H. (1996). Variations of lymphocyte subsets associated with stress in depressive populations. *Psychoneuroendocrinology, 21,* 659-671.

Ribeiro, S. C., Tandon, R., Grunhaus, L., & Greden, J. F. (1993). The DST as a predictor of outcome in depression: A meta-analysis. *American Journal of Psychiatry, 150,* 1618-1629.

Roger, D., & Najarian, B. (1998). The relationship between emotional rumination and cortisol secretion under stress. *Personality and Individual Differences, 24,* 531-538.

Rohleder, N., Wolf, J.M., Herpfer, I., Fiebich, B.L., Kirschbaum, C., & Lieb, K. (2006). No response of plasma substance P, but delayed increase of interleukin-1 receptor antagonist to acute psychosocial stress. *Life Sciences, 78,* 3082-3089.

Roy, M.P., Kirschbaum, C., & Steptoe, A. (2001). Psychological, cardiovascular, and metabolic correlates of individual differences in cortisol stress recovery in young men. *Psychoneuroendocrinology, 26,* 375-391.

Roy, M.P., Steptoe, A., & Kirschbaum, C. (1998). Life events and social support as moderators of individual differences in cardiovascular and cortisol reactivity. *Journal of Personality and Social Psychology, 75,* 1273-1281.

Rudolph, K.D., & Flynn, M. (2007). Childhood adversity and youth depression: Influence of gender and pubertal status. *Development and Psychopathology, 19,* 497-521.

Sachar, E.J., Hellman, L., Fukushima, D.K., & Gallagher, T.F. (1970). Cortisol production in depressive illness: A clinical and biochemical clarification. *Archives*

of General Psychiatry, 23, 289-298.

Sapolsky, R. M. (1992). *Stress, the Aging Brain, and the Mechanisms of Neuron Death.* Cambridge; London: MIT Press.

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The adrenocortical axis in the aged rat: Impaired sensitivity to both fast and delayed feedback inhibition. *Neurobiology of Aging, 7,* 331-335.

Sapolsky, R.M., Romero, L.M., & Munck, A.U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21,* 55-89.

SAS Institute, Inc. (2002). *SAS/STAT software: Version 9.0 [Computer software]*. Cary, NC: Author.

Schmidt-Reinwald, A., Pruessner, J.C., Hellhammer, D.H., Federenko, I.., Rohleder, N., Schurmeyer, T.H., & Kirschbaum, C. (1999). The cortisol response to awakening in relation to different challenge tests and a 12-hour cortisol rhythm. *Life Sciences, 64,* 1653-1660.

Schommer, N.C., Hellhammer, D.H., & Kirschbaum, C. (2003). Dissociation between reactivity of the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenal-medullary system to repeated psychosocial stress. *Psychosomatic Medicine, 65,* 450-460.

Schulkin, J., Gold, P., & McEwen, B.S. (1998). Induction of corticotropin-releasing hormone gene expression by glucocorticoids: Implication for understanding the states of fear and anxiety and allostatic load. *Psychoneuroendocrinology, 23,* 219-243.

Siever, L. J. & Davis, K. L. (1985). Overview: Toward a dysregulation hypothesis of depression. *American Journal of Psychiatry, 142,* 1017-1031.

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Lavori, P. W., Shea, M. T., Coryell, W., Warshaw, M., Turvey, C., Maser, J. D., & Endicott, J. (2000). Multiple recurrences of major depressive disorder. *American Journal of Psychiatry, 157,* 229-233.

Steiger, A., von Bardeleben, U., Herth, T., & Holsboer, F. (1989). Sleep EEG and nocturnal secretion of cortisol and growth hormone in male patients with endogenous depression before and after treatment and after recovery. *Journal of Affective Disorders, 16,* 189-195.

Stratakis, C. A. & Chrousos, G. P. (1995). Neuroendocrinology and pathophysiology of the stress system. *Annals of the New York Academy of Sciences, 771,* 1-18.

Susman, E. J. (2006). Psychobiology of persistent antisocial behavior: Stress, early vulnerabilities and the attenuation hypothesis. *Neuroscience and Biobehavioral Reviews, 30,* 376-389.

Tarullo, A.R., & Gunnar, M.R. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior, 50,* 632-639.

Thorsteinsson, E.B., & James, J.E. (1999). A meta-analysis of the effects of experimental manipulations of social support during laboratory stress. *Psychology & Health, 14,* 869-886.

Trestman, R. L., Coccaro, E. F., Berstein, D., Lawrence, T., Gabriel, S. M., Horvath, T. B., & Siever, L. J. (1991). Cortisol responses to mental arithmetic in acute and remitted depression. *Biological Psychiatry, 29,* 1051-1054.

Vaernes, R., Ursin, H., Darragh, A., & Lambe, R. (1982). Endocrine response patterns and psychological correlates. *Journal of Psychosomatic Research, 26,* 123-131.

van Eck, M.M., Nicolson, N.A., Berkhof, H., & Sulon, J. (1996). Individual differences in cortisol responses to a laboratory speech task and their relationship to responses to stressful daily events. *Biological Psychology, 43,* 69-84.

Van Peer, J.M., Roelofs, K., Rotteveel, M., van Dijk, J.G., Spinhoven, P., & Ridderinkhof, R. (2007). The effects of cortisol administration on approach-avoidance behavior: An event-related potential study. *Biological Psychology, 76,* 135-146.

Vreeburg, S.A., Hartman, C.A., Hoogendijk, W.J.G., van Dyck, R., Zitman, F.G., Ormel, J., Penninx, B.W.J.H. (2010). Parental history of depression or anxiety and the cortisol awakening response. *British Journal of Psychiatry, 197,* 180-185.

Wadsworth, M.E., & Compas, B.E. (2002). Coping with family conflict and economic strain: The adolescent perspective. *Journal of Research on Adolescence, 12,* 243-274.

Way, B.M., & Taylor, S.E. (2010). The serotonin transporter promoter polymorphism is associated with cortisol response to psychosocial stress. *Biological Psychiatry, 67,* 487-492.

Weiss, E.L., Longhurst, J.G., & Mazure, C.M. (1999). Childhood sexual abuse as a risk factor for depression in women: Psychosocial and neurobiological correlates. *American Journal of Psychiatry, 156,* 816-828.

Wichers, M., Myin-Germeys., I., Jacobs, N., Kenis, G., Derom, C., Vlietinck, R., Delespaul, P., Mengelers, R., Peeters, F., Nicolson, N., & van Os, J. (2008).

Susceptibility to depression expressed as alterations in cortisol day curve: A cross-twin, cross-trait study. *Psychosomatic Medicine, 70,* 314-318.

Wolf, O.T. (2008). The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychologica, 127,* 513-531.

Young, E. A., Kotun, J., Haskett, R. F., Grunhaus, L., Greden, J. F., Watson, S. J., & Akil, H. (1993). Dissociation between pituitary and adrenal suppression to dexamethasone in depression. *Archives of General Psychiatry, 50,* 395-403.

Zobel, A. W., Yassouridis, A., Frieboes, R-M, & Holsboer, F. (1999). Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. *The American Journal of Psychiatry, 156,* 949-951.