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Cortisol reactivity to experimentally-manipulated psychosocial stress in young adults at varied risk for depression

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Abstract

This study examined cortisol and affective reactivity to a psychosocial stress task in 102 young adults who varied in risk for depression (56 remitted-depressed, 46 never-depressed). Participants were randomly assigned to either a stress (i.e., social-evaluative threat) or control (i.e., no social-evaluative threat) condition. For never-depressed individuals, cortisol responses were significantly greater in the stress compared to the control condition. Moreover, cortisol responses were significantly greater for never-depressed than remitted-depressed individuals in the stress condition. For individuals with a history of depression, cortisol responses did not differ significantly between the stress and control conditions. Negative affective reactivity also was higher for never-depressed, but not remitted-depressed, individuals in the stress compared to the control condition. Moreover, cortisol responses were inversely related to negative affect during the recovery phase in both stress and control conditions. Findings indicate the lack of a robust cortisol response to social evaluation stress among remitted-depressed individuals as compared to that of never depressed controls. Future studies should investigate unique and interactive links between these hypothalamic-pituitary-adrenal and affective reactivity alterations and risk for subsequent depressive episodes.

Keywords

Stress; depression; remission; cortisol; negative affect

Individuals with a history of major depressive episodes (MDEs) who are not currently depressed represent a group at increased risk for recurrent MDEs. The mechanisms underlying this increased risk, however, are not well understood. Research has shown that stressful life events often precede MDEs^[1]. The relation of stressful life events to MDEs appears to change across successive episodes^[2]. Alterations of the stress response are associated with early life stress^[3,4], recent life stress^[4], and the experience of MDEs themselves^[5]. These alterations in the stress response, in turn, may confer increased risk for depression^[6,7,8,9]. One aim of the present study was to determine whether alterations in stress pathways characterize formerly depressed individuals even during remission.

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HPA Function in Remitted Depression

The hypothalamic-pituitary-adrenocortical (HPA) axis is a major effector pathway of the stress system, mediating its adaptive functions^[10]. The present study assessed cortisol responses to a laboratory stressor -- a modified version of the Trier Social Stress Test (TSST^[11]). The TSST contains elements of motivated performance, uncontrollability and social-evaluative threat, and produces robust cortisol responses^[12].

Current depression is clearly linked with alterations of HPA function^[13,14], including elevated basal cortisol levels and impaired negative feedback inhibition^[15]. Research examining cortisol responses to psychosocial challenge has been inconsistent, with some studies reporting less robust cortisol responses associated with depression in older individuals^[16], and others showing elevated and prolonged cortisol responses in adolescents^[4]. Alterations of the stress response may persist beyond recovery from an MDE and increase vulnerability to subsequent episodes^[6,7,8,9,17]. These HPA vulnerability markers may be latent, emerging only when the system is under stress. Findings from remitted-depressed samples have been inconsistent, with some studies reporting a return to normal from the observed decreased cortisol suppression in response to dexamethasone during MDE (relative to healthy controls) after recovery^[18], and others reporting persistent HPA dysregulation^[19,20].

Stress Reactivity

Research involving healthy controls has shown that cortisol reactivity differs between high versus low social-evaluative threat conditions^[21,22,23]. One mechanism proposed to underlie risk for future depressive episodes is heightened sensitivity to more commonly experienced minor stressors as a function of number of prior MDEs^[24]. Empirical support for this hypothesis at the level of HPA function, however, is limited to studies of currently depressed samples^[25,26,27]. The present study assessed cortisol responses to traditional (high social-evaluative threat) and control (no social-evaluative threat) conditions of the TSST among remitted- and never-depressed individuals. Primary analyses examined the interaction of depression history and stressor condition predicting cortisol reactivity after controlling for the effects of recent life stress, due to well-established associations of stress with both depression and HPA response^[4,28]. Secondary analyses tested these interactive models after further controlling for current depressive symptoms.

Finally, we examined affective reactivity models of whether the interaction of depression history and stressor condition predicted changes in positive and negative affect. We tested two temporal hypotheses integrating cortisol and affective reactivity. First, based on evidence of a positive relation between negative affect and cortisol levels immediately before and after a stress task^[29], we expected that initial cortisol responses would be linked to increased negative affective reactivity. Second, based on the previous finding of an inverse relation between post-task negative affect and cortisol responses to the TSST^[30], we tested a “mood-buffering” hypothesis that cortisol reactivity would be associated with decreased negative affect during the recovery phase.

Method

Participants

Participants were 102 individuals (56 remitted-depressed and 46 never-depressed), ages 18 to 31 years (mean age = 22.97, *SD* = 3.87). Among remitted-depressed participants, 22 had experienced one prior MDE, 22 had experienced two episodes, and 12 had experienced three or more prior MDEs. Inclusion in the remitted-depressed group required a past diagnosis of

MDD as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I^[31]). Full remission was defined as an absence of significant symptoms of depression for at least two months^[32]. The never-depressed group had no lifetime history of a depressive disorder. Participants were screened and excluded for current or past bipolar disorder or posttraumatic stress disorder (PTSD), health conditions known to influence HPA function, or use of prescription or non-prescription drugs (e.g., benzodiazepines) that might affect the HPA system. Neither remitted-depressed nor never-depressed participants were excluded for having a current or lifetime anxiety disorder other than PTSD. Participants using antidepressant medication ($n = 13$ in remitted-depressed group; $n = 2$ in never-depressed group) or birth control ($n = 40$) were not excluded. Participants were recruited primarily from Vanderbilt University (students and employees) through online research participant registries; they received course credit or \$30 for participation in the study. All procedures were approved by the Vanderbilt University Institutional Review Board.

Measures

Participants completed a demographics questionnaire regarding household income, occupation, highest level of education, and current height and weight (to compute body mass index). Socioeconomic status (SES) was calculated using a four-factor index^[33], which is based on occupation and education level.

Depression—The SCID-I^[31] was used to assess current and lifetime diagnoses of MDD, bipolar disorder, and PTSD. Detailed information on all previous depressive experiences was obtained to determine the number of prior MDEs. Depression history 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. Interrater 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^[34]) was used to assess participants' current level of depressive symptoms. The BDI-II is a 21-item, widely used, self-report measure with good reliability and validity^[35]. In this sample, coefficient alpha for the BDI-II was .85.

The short form of the *Positive and Negative Affect Schedule* (PANAS^[36]) is a 10-item mood scale consisting of 5 items assessing positive affect (e.g., "inspired," "enthusiastic") and 5 items assessing negative affect (e.g., "distressed," "nervous"). It was administered six times, once after each saliva sample. The PANAS has adequate psychometric properties that are robust to age and sex differences^[37]. In this sample, coefficient alphas ranged from .78 to .89 for positive and from .63 to .90 for negative affect. Affective reactivity was computed as the maximum value from anticipatory stress (T1) to the final recovery sample (T5) minus the baseline (T0) value.

Recent life events—The young adult version of the Perceived Events Scale (PES^[38]) 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 of the 90 events occurred during this time, and to rate the valence of the endorsed events on a 9-point scale ($-4 = \text{Extremely Bad}$; $0 = \text{Neither Good or Bad}$; $+4 = \text{Extremely Good}$). A total score for negative events occurring in the past 6 months was calculated by summing across all events rated as -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 laboratory appointment.

Psychosocial Stressor—The TSST consisted of a 5-minute free-speech task and a 5-minute mental arithmetic task administered sequentially. In the current study, participants were randomly assigned to either a social evaluation (stress) condition or to a no social evaluation (control) condition. Similar to procedures outlined by Gruenewald and colleagues^[21], participants in the stress condition were informed that the examiner would be in the room and their performance would be audio- and videotaped and then evaluated and compared to other participants by a panel of judges. Participants randomized to the control condition were informed that they would perform the tasks alone in the room and they would not be observed, recorded, or evaluated.

Cortisol—Salivary cortisol samples were collected using a saliva collection device (Salivette; Sarstedt Inc., Newton, NC). 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. Participants were instructed not to drink alcohol, smoke, use nonprescription 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; none required rescheduling. All laboratory sessions were conducted between 2:00 and 7:00 p.m. to control for diurnal variations in cortisol.

After written informed consent was obtained, participants were administered the Mood Disorders and PTSD sections of the SCID-I by a trained Masters level graduate student (MCM) supervised by an expert clinician (JG). They then completed the BDI-II and sat quietly for 10 minutes. Following this rest period, participants provided their first cortisol sample (T0: baseline). Then they were randomly assigned to the stress or control condition, informed about their laboratory task assignment, and they provided the second cortisol sample at the end of the 10-minute preparation period (T1: anticipatory stress, 10 minutes after T0). Participants then were escorted to another room where they performed the tasks. For all participants, the speech task preceded the mental arithmetic task. Participants provided their third (T2: mid-task, 17 minutes after T0) cortisol sample between the speech and arithmetic tasks and their fourth (T3: post-task, 25 minutes after T0) cortisol sample immediately following the arithmetic task. They then completed a demographics questionnaire, rested for 10 minutes, provided their fifth (T4: recovery 1, 40 minutes after T0) cortisol sample, rested another 10 minutes, and then provided their sixth (T5: recovery 2, 55 minutes after T0) and final, cortisol sample. At the end of the study, participants were fully debriefed regarding the nature of the experimental manipulation.

Data Analytic Plan

All variables were examined for distributional properties, and cases were screened for univariate (± 3 SD from the mean) and multivariate outliers; three outliers were excluded during screening from analyses of positive and negative affect reactivity. Cortisol data were log-transformed to reduce skewness. Following procedures described by Pruessner and colleagues^[39], we calculated area under the curve with respect to ground (AUC_G) and with respect to baseline (AUC_I) to determine whether these two measures provided unique information regarding HPA function in remitted depression. Consistent with prior work with this sample^[40], AUC values were computed using the T1 to T5 samples, which reflect the cortisol response to the TSST; the T0 sample was included as a covariate rather than in the

computation of AUC, because T0 levels were elevated and likely influenced by stress on arrival to the laboratory^[41]. Whereas AUCg represents both basal cortisol output and stressor-induced change in cortisol levels (T1 cortisol levels plus changes from T1 to T5), AUCi can be conceptualized as an index of the sensitivity of the cortisol response to a stressor (changes from T1 to T5 minus T1 cortisol levels), and may be negative if levels decline below the T1 value. That AUCi can capture changes in the sign and magnitude of cortisol responses is particularly useful for studies of remitted-depressed individuals, given findings that cortisol levels may either fail to increase or may decrease following a psychosocial challenge^[42]. A previous study conducting principal components analyses demonstrated that AUCg and AUCi assess distinct aspects of the cortisol response; whereas AUCg is associated with measures of total hormonal secretion, AUCi is associated with measures of pattern or rate of change in hormone levels over time^[43]. We first conducted analysis of covariance (ANCOVA) with repeated measures (with Greenhouse-Geisser correction) to test the main and interaction effects of depression history and stress condition predicting changes in mean cortisol levels and positive/negative affect from T1 to T5. Next, we conducted two-way ANCOVAs to test the interaction of depression history and stress condition predicting AUCi and AUCg cortisol responses and positive/negative affective reactivity. Affective reactivity was computed as the maximum value from T1 to T5 minus the baseline (T0) value. Primary analyses examining cortisol responses included T0 baseline (log-transformed) cortisol as a covariate and all analyses included recent life stress as a covariate. Secondary analyses tested models including current depressive symptoms as an additional covariate.

The hypothesis that initial cortisol responses would be linked to increased negative affective reactivity was examined using the baseline (T0), anticipatory stress (T1), and mid-task cortisol (T2) samples. The hypothesis that cortisol reactivity would be linked to decreased negative affect during the recovery phase was examined using AUCg and AUCi cortisol and recovery negative affect (T4, T5). Effect sizes (η^2) are reported for all two-way ANCOVAs and describe the ratio of variance explained in cortisol measures (AUCi, AUCg) or positive/negative affective reactivity by predictors after controlling for covariates; 0.0099, 0.0588, and 0.1379 represent small, medium, and large effect sizes, respectively^[44].

Results

Table 1 presents the means and standard deviations of all study variables. The groups did not differ significantly on any demographic variable. The remitted-depressed group had more severe depressive symptoms currently than the never-depressed group; however, the mean values were within the non-clinical range. Recent stress levels were significantly higher in remitted-depressed individuals and were linked to increased negative affective reactivity. Baseline cortisol and AUCg cortisol levels did not differ between remitted-depressed and never-depressed groups in either the stress or control conditions. However, in the stress condition, AUCi cortisol was significantly lower in the remitted-depressed group (Table 1). Table 2 presents correlations among the study variables. Baseline cortisol levels were negatively correlated with AUCi cortisol and positively correlated with AUCg cortisol. Of note, AUCi and AUCg cortisol were not significantly correlated ($r_s = .07$). Cortisol output (AUCi, AUCg) did not differ significantly according to antidepressant medication or oral contraceptive use. AUCi (but not AUCg) cortisol levels were greater for males than females [$t(99) = 2.57, p = .01$]. Age was significantly correlated with both AUCi [$r_s = .27, p < .01$] and AUCg [$r_s = -.20, p = .04$] cortisol. However, because the remitted- and never-depressed groups did not differ on these demographic variables we did not include them in models testing the depression history X stress condition interactions.

Effect of Stress Condition on Cortisol Response and Affective Reactivity in Remitted-Depressed and Never-Depressed Participants

Figure 1 shows mean cortisol levels at each collection point for remitted-depressed and never-depressed groups in the stress and control conditions in response to the TSST. A significant condition X time interaction [$F(3.00, 278.76) = 5.15, p < .01, \eta^2 = .05$] indicated that cortisol levels differed significantly between time points based on stress condition. The interaction of group and time showed a nonsignificant trend [$F(3.00, 278.76) = 2.45, p = .06, \eta^2 = .03$]. The 3-way interaction of group, stress condition, and time was not significant [$F(1.47, 278.76) = 1.47, p = .22, \eta^2 = .02$]. The 3-way interactions of group, stress condition, and time did not significantly predict positive affect [$F(2.51, 230.77) = .22, p = .85, \eta^2 = .00$] or negative affect [$F(2.82, 262.28) = 1.25, p = .29, \eta^2 = .01$].

Stress Reactivity

The interaction of stress condition X depression history significantly predicted AUCi cortisol, controlling for baseline cortisol and recent life stress levels [$F(1, 93) = 3.93, p = .05, \eta^2 = .04$]. Follow-up ANCOVA analyses revealed that AUCi cortisol responses among never-depressed individuals were significantly higher in the stress than in the control condition [$F(1, 41) = 14.10, p < .01, \eta^2 = .26$]. Moreover, AUCi cortisol responses in the stress condition were significantly greater for never-depressed than for remitted-depressed individuals [$F(1, 49) = 4.96, p = .03, \eta^2 = .09$]. The pattern of results was similar when current depressive symptoms were controlled, albeit a statistically non-significant trend was found due to limited power [$F(1, 92) = 3.36, p = .07, \eta^2 = .04$]. The interaction of stress condition X depression history did not significantly predict AUCg cortisol after controlling for baseline cortisol and recent life stress levels [$F(1, 93) = 1.07, p = .31, \eta^2 = .01$]. The pattern of results for AUCg cortisol was similar when current depressive symptoms were included [$F(1, 92) = 0.94, p = .34, \eta^2 = .01$]. Post-hoc analyses using Spearman's rank order correlations revealed that AUCi cortisol was not significantly associated with the total duration of past MDEs ($r_s = .15, p = .28$) or number of past MDEs ($r_s = .04, p = .76$) in the remitted-depressed group. However, AUCi cortisol was negatively correlated with current depressive symptoms ($r_s = -.29, p < .01$) in the overall sample.

The interaction of stress condition X depression history significantly predicted negative affective reactivity, controlling for recent life stress levels [$F(1, 92) = 4.19, p = .04, \eta^2 = .04$]. Follow-up ANCOVA analyses revealed higher negative affective reactivity levels among never-depressed individuals in the stress than in the control condition [$F(1, 41) = 7.90, p < .01, \eta^2 = .16$]; negative affective reactivity levels did not differ between the stress and control conditions for remitted-depressed individuals [$F(1, 50) = .18, p = .68, \eta^2 = .004$]. With regard to the comparison between groups, negative affective reactivity did not differ significantly between remitted- and never-depressed individuals in the stress condition [$F(1, 48) = .64, p = .43, \eta^2 = .01$], whereas there was a non-significant trend for remitted-depressed individuals to show greater negative affective reactivity than never-depressed individuals in the control condition [$F(1, 43) = 3.86, p = .06, \eta^2 = .08$]. The pattern of results for the interaction of stress condition and depression history predicting negative affective reactivity was similar when current depressive symptoms were included [$F(1, 91) = 3.97, p < .05, \eta^2 = .04$]. Regarding positive affective reactivity, the interaction of stress condition X depression history was not significant, controlling for recent life stress levels only [$F(1, 91) = .26, p = .61, \eta^2 = .003$], or both stress levels and depressive symptoms [$F(1, 90) = .39, p = .53, \eta^2 = .004$].

Integrating Cortisol and Affective Reactivity

The association between increased negative affective reactivity and increased baseline (T0) cortisol showed a non-significant trend ($r = .20, p < .06$). Negative reactivity was not

significantly associated with anticipatory stress ($r = .09, p = .36$) or mid-task cortisol levels ($r = .10, p = .32$). Positive affective reactivity was not significantly associated with baseline ($r = -.02, p = .86$), anticipatory stress ($r = .02, p = .85$), or mid-task cortisol levels ($r = -.04, p = .73$). Spearman's rank order correlations revealed that AUCi cortisol was negatively associated with negative affect levels at recovery (T4: $r_s = -.26, p < .01$; T5: $r_s = -.20, p < .05$), but not positive affect levels at recovery (T4: $r_s = -.14, p = .17$; T5: $r_s = -.16, p = .12$). AUCg cortisol was associated with neither negative affect levels at recovery (T4: $r_s = .16, p = .11$; T5: $r_s = .07, p = .52$) nor positive affect levels at recovery (T4: $r_s = .03, p = .75$; T5: $r_s = .01, p = .90$).

Discussion

The goal of the present study was to determine whether individuals with a history of MDD, but currently in remission, differed significantly from individuals who had never had a depressive episode regarding their cortisol responses to an experimentally-manipulated psychosocial stress task. Cortisol responses were significantly greater for never-depressed than remitted-depressed participants in the stress condition; history of depression explained 9% of the variance in AUCi cortisol over and above baseline cortisol and recent life stress, which is considered a medium-to-large effect size^[44]. Finding elevated TSST cortisol responses among the never-depressed group was consistent with other research demonstrating that social-evaluative threat is associated with robust cortisol responses to psychosocial stress tasks^[8]. Moreover, we found that stressor condition explained 26% of the variance in AUCi cortisol among never-depressed individuals, over and above baseline cortisol and recent life stress, which is considered a large effect size. Whereas never-depressed individuals showed greater cortisol responses in the stress as compared to the control condition, remitted-depressed participants did not. Additionally, stress condition did not interact with depression history to predict AUCg cortisol responses, controlling for baseline cortisol levels and recent stress levels.

Similar to the findings on cortisol responses, negative affective reactivity [i.e., the maximum value from T1 to T5 minus the baseline (T0) value] among never-depressed individuals was significantly higher in the stress condition compared to the control condition, but was not significantly different between conditions for remitted-depressed individuals. Interestingly, there was a non-significant trend for remitted-depressed individuals to show greater negative affective reactivity compared to never-depressed individuals in the control condition. Stressor condition did not interact with history of depression to predict positive affective reactivity. Finally, evidence consistent with the cortisol mood-buffering hypothesis was found: higher AUCi cortisol responses to the TSST were associated with lower negative affect (but not positive affect) at both recovery time points.

What may account for the absence of a robust cortisol response to social evaluation stress in remitted-depressed individuals? Researchers examining determinants of cortisol responses to psychosocial stressors have interpreted diminished (or “blunted”) cortisol reactivity to be a possible marker of resilience, a cognitive and/or biological adaptation to previous stress exposure (i.e., ‘stress inoculation’), a marker of vulnerability, or a result of situation-specific coping strategies. For example, higher trait depressive rumination has been found to be associated with lower cortisol reactivity to a social-evaluative stressor in a sample of healthy young adults^[23] and could be a reflection of increased depression vulnerability. Alternately, low cortisol reactivity to acute stressors could represent a normative form 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^[45]. Individuals with a history of depression may be primed for reduced cortisol reactivity when confronted with social-evaluative threat due to increased exposure to, and more negative appraisal of, stressful life

events. Interestingly, higher current depressive symptoms were associated with both a history of depression and reduced cortisol reactivity (lower AUCi cortisol); moreover, depressive symptoms were negatively associated with AUCi cortisol when included in the statistical model testing the interaction of depression history and stressor condition. These findings complement prior research showing that sub-clinical depressive symptoms predict relapse and recurrence^[46] by demonstrating that higher levels of depressive symptoms also were linked to lower cortisol responses to psychosocial stress.

Prior studies have demonstrated that both major and minor stressors become increasingly capable of triggering depressive symptoms as individuals experience more MDEs^[5]. Heightened sensitivity to more commonly experienced minor stressors has been proposed as a risk factor for recurrence of depressive episodes^[24]. The present study examined individual differences in cortisol reactivity to determine whether increased responses to both stress and control conditions would be observed at the level of HPA function for remitted-depressed individuals. Interestingly, results indicated that AUCi cortisol responses among remitted-depressed individuals were not significantly different in the stress as compared to the control condition. Analyses of affective reactivity complemented these cortisol findings by demonstrating that remitted-depressed individuals showed similarly high degrees of negative affective reactivity in the stress and control conditions; there also was a trend for greater negative reactivity in the control condition for remitted-depressed as compared to never-depressed individuals. A study of remitted and never-depressed men and women similarly found higher levels of negative affect in remitted-depressed individuals both before and immediately after a TSST compared to never-depressed controls^[47]. The present study showed that negative affect during recovery was inversely correlated with AUCi cortisol. Thus, higher cortisol responses to psychosocial stressors may attenuate negative affective responses during the recovery phase^[30], and lower AUCi cortisol responses to stress in remitted-depressed individuals may lead to enhanced negative affective reactivity. Future studies should explore whether there is a link between heightened sensitivity to the depressogenic effects of minor stressful life events and reduced HPA reactivity to experimentally-manipulated stress.

Studies examining cortisol responses to psychosocial stressors in remitted-depressed individuals have yielded somewhat inconsistent results. Brown^[48] found blunted TSST cortisol reactivity (i.e., lower average, maximum, and AUC cortisol response) in remitted-depressed versus never-depressed women, although the groups did not differ significantly in recent self-reported life stress. Brown^[48] also found that cortisol reactivity to the TSST among remitted-depressed women taking antidepressant medications was robust and did not differ significantly from never-depressed women⁴⁸. However, they did not include a control condition to assess differences in cortisol reactivity due to social-evaluative threat.

Trestman and colleagues^[49] reported a trend for a blunted cortisol response to a mental arithmetic task in remitted-depressed compared to never-depressed males. Using a sad mood induction technique, Chopra and colleagues^[42] reported a decrease in salivary cortisol levels among both male and female depressed patients treated to full remission. Never-depressed controls were not 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 cortisol response to psychosocial stress in the remitted-depressed versus never-depressed group^[50]. Finally, a recent study showed blunted cortisol reactivity to the TSST in remitted-depressed versus never-depressed women, but not in men^[47]. Comparisons across these studies are difficult due to differences in sample characteristics (e.g., inclusion of males and/or females, mean

age), psychosocial stress tasks (i.e., mood induction, cognitive, social-evaluative) and statistical approaches (i.e., indices of cortisol reactivity).

The current study showed significant interactions between depression history and stress condition predicting AUCi, but not AUCg, cortisol, which has important implications for future research. First, these results indicate that AUCi and AUCg cortisol reflect distinct aspects of the HPA response to psychosocial stress in a sample of remitted-and never-depressed individuals. Second, whereas AUCg cortisol was strongly and positively correlated with baseline cortisol, AUCi cortisol was moderately and negatively correlated with baseline cortisol. This suggests that these measures could offer distinct temporal windows into HPA function, with AUCg being more closely related to long-term basal cortisol secretion and AUCi being a better reflection of short-term stress reactivity. For example, in a subset of the current sample reassessed after 6 months, AUCg cortisol interacted with previous depressive episodes to predict depressive symptom trajectories, such that more rapid increases in depressive symptoms were observed for individuals with higher AUCg cortisol and more previous depressive episodes^[40].

Study Strengths and Limitations

The present study contributed to the literature on stress reactivity in remitted depression by investigating stress reactivity using a psychosocial stress task that manipulated the degree of social-evaluative threat. This experimental paradigm may be useful in future studies testing stress sensitization hypotheses regarding changes in the impact of stressors of varying intensities. Using a remitted depression design permitted examination of relatively stable HPA alterations that were present following recovery from an MDE.

Limitations of the present study provide directions for future research. First, due to the cross-sectional design, we cannot determine whether differences between remitted-depressed and never-depressed groups reflect preexisting ‘trait markers’ of risk for depression or ‘scar markers’ resulting from prior MDEs that may or may not increase risk for depression. Second, the impact of psychiatric comorbidity on the results is unclear because remitted-depressed and never-depressed participants were not assessed for psychiatric disorders other than current or past MDD, bipolar disorder, or PTSD. Nevertheless, evidence of differences in cortisol responses between remitted- and never-depressed participants despite this methodological shortcoming argues for the robustness of the findings. Third, the baseline cortisol sample was obtained within one hour of participants’ arrival to the laboratory and may reflect HPA activation due to a combination of novelty of the environment, anticipatory anxiety, and/or the psychiatric assessments administered prior to the TSST eliciting information about psychiatric symptoms and lifetime trauma. Future studies should adopt more stringent procedures designed to obtain “true” baseline values^[4]. Fourth, the modified TSST may have triggered lower cortisol responses relative to the traditional TSST^[7] due to the absence of an actual evaluating committee (only the experimenter remained in the room during the stress condition), although participants were told they were being videotaped to be evaluated by a committee later. Fifth, findings may not generalize to clinical populations or to individuals from lower SES backgrounds. Finally, although psychotropic medications did not influence cortisol measures in the current study, antidepressant medication use has been previously linked to HPA function^[48].

In conclusion, the present study demonstrated reduced cortisol reactivity to social-evaluative threat in young adults with a history of depression. Examining abnormalities in biological factors both during and after recovery from an MDE 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 examining whether these markers

predict subsequent MDEs. Given that MDD is a highly prevalent, debilitating, and recurrent disorder, a better understanding of the mechanisms of risk is needed to inform the construction of targeted, practical, and efficacious interventions, and thus represents an important public health goal.

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Figure 1.

Mean cortisol levels ($\pm$ standard error of the mean) to stress and control conditions of a standardized laboratory stressor (TSST) among remitted-depressed (RD) and never-depressed (ND) individuals.

Figure 2. Mean AUCi cortisol responses (± standard error of the mean) for remitted-depressed and never-depressed individuals in the stress and control conditions.

Table 1

Means and standard deviations of study variables for remitted-depressed and never-depressed participants

	Remitted Depressed (<i>n</i> = 56)	Never Depressed (<i>n</i> = 46)	RD vs. ND
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	χ^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
	<i>N</i> (%)	<i>N</i> (%)	χ^2/t
Sex			1.88
Male	17 (30.4)	20 (43.5)	
Female	39 (69.6)	26 (56.5)	
Race			0.26
Caucasian	44 (78.6)	38 (82.6)	
Non-Caucasian	12 (21.4)	8 (17.4)	
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>t</i>
Depressive symptoms (BDI-II)	8.23 (5.9)	3.22 (3.3)	5.11***
Recent life stress (PES)	39.64 (17.84)	23.89 (13.02)	4.98****
Affective reactivity			
Control condition			
Negative affect reactivity	.88 (.73)	.40 (.49)	-1.97~
Positive affect reactivity	.82 (.98)	.61 (.58)	-.95
Stress condition			
Negative affect reactivity	.75 (.68)	.86 (.63)	-.22
Positive affect reactivity	.88 (.78)	.63 (.67)	-.60
Cortisol			
Control condition			
Baseline (ng/ml)	10.46 (4.19)	11.72 (6.09)	0.65
AUCi	-48.83 (95.48)	-45.61 (101.68)	0.30
AUCg	403.25 (158.00)	446.85 (244.90)	0.94
Stress condition			
Baseline (ng/ml)	11.56 (3.92)	13.13 (7.58)	0.64
AUCi	-16.40 (105.38)	72.38 (172.42)	2.77**
AUCg	497.20 (195.68)	584.21 (232.36)	1.60

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

****
 $p < .0001$;

RD = remitted depressed; ND = never depressed; BDI-II = Beck Depression Inventory, second edition; PES = Perceived Events Scale; Affective reactivity = maximum value from T1 to T5 minus the baseline (T0) value; Baseline = T0 cortisol; AUCi = area under the curve with respect to increase; AUCg = AUC with respect to ground; ng/ml = nanograms per milliliter. Note: *t* tests on cortisol outcomes were based on log-transformed data.

Table 2

Correlations of Depression, Stress, and Cortisol Measures

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Age	--										
2. Sex	-.02	--									
3. ADM use	.01	.14	--								
4. Prior MDE	.07	.10	.21*	--							
5. MDE duration	-.07	.10	.16	.43***	--						
6. Depressive symptoms (BDI-II)	-.08	.07	.21*	.49***	.19~	--					
7. Recent stress level (PES)	-.03	.06	.35***	.42***	.18	.56***	--				
8. NA reactivity	.08	.08	.13	.13	.05	.12	.26**	--			
9. PA reactivity	.11	-.08	-.04	.05	-.02	.17	.05	-.03	--		
10. Baseline cortisol	-.25*	.08	.05	-.09	-.04	-.01	.07	.20~	-.02	--	
11. AUCi cortisol	.27**	-.25*	-.16	-.16	.08	-.24*	-.07	.04	-.06	-.33**	--
12. AUCg cortisol	-.20*	-.07	-.05	-.15	-.05	-.06	.03	.13	-.02	.81***	.07

~ $p < .06$;

* $p < .05$;

** $p < .01$;

*** $p < .001$.

Note: Sex (0 = male, 1 = female); ADM use = Antidepressant medication use (0 = no use); Prior MDE (0, 1, 2, 3 or more); MDE = Major Depressive Episode; MDE duration = total months depressed; BDI-II = Beck Depression Inventory, second edition; PES = Perceived Events Scale; NA = negative affect; PA = positive affect; Baseline cortisol = T0 cortisol (log-transformed); AUCi cortisol = area under the curve with respect to increase (log-transformed); AUCg = AUC with respect to ground (log-transformed).