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Cortisol Responses to Psychosocial Stress: The Role of Childhood Maltreatment and Depression

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Abstract: **This study examined cortisol reactivity to repeated psychosocial stressors in 35 adolescents and young adults aged 12 to 26 years. Participants were divided into three study groups: controls with no history of major depressive disorder (MDD) or childhood maltreatment (n = 18); a diagnosis of MDD at Time 1 but no history of maltreatment (MDD-only; n = 10); and both MDD and maltreatment (MDD+MALTX; n = 7). Participants with MDD recovered from their depressive episode prior to the second psychosocial stress task. The MDD-only group had higher cortisol responses at Time 1 relative to other groups. No between-group differences were observed in cortisol responses at Time 2. Depressed individuals with maltreatment did not differ from controls in their cortisol responses at Time 1 or Time 2. Findings suggest that elevated cortisol stress reactivity is a state-dependent correlate of depression in youth with no history of maltreatment.**

Keywords: **Hypothalamic-pituitary-adrenal axis; depression; maltreatment; recovery; cortisol; stress**

I INTRODUCTION

Childhood maltreatment (MALTX), including emotional, physical and sexual abuse as well as emotional and physical neglect, is a preventable major public health problem world-wide [1, 2]. MALTX induces a cascade of neurobiological changes which, in turn, increase the risk for psychiatric disorders, including major depressive disorder (MDD). Some scientists have argued for the presence of distinct neurobiological subtypes of depression based on MALTX [3, 4].

Disrupted hypothalamic-pituitary-adrenal (HPA) function often characterizes individuals with MALTX and MDD [3, 5]. There is limited research on the impact of MALTX on HPA reactivity in youth. The few studies employing psychosocial stress tasks in youth reported decreased adrenocorticotropic hormone and cortisol reactivity in adolescents with MALTX history [6, 7]. A third study found increased cortisol reactivity and delayed cortisol recovery among adolescents with MALTX history and mild-to-moderate depression, but decreased cortisol reactivity in those with moderate-to-severe

depression [8]. Finally, early life-adversity (which also included MALTX) moderated the effect of MDD on cortisol responses to the stressor, by increasing cortisol responses only in depressed adolescents who also had early-life adversity [9]. The current study extended these findings by assessing cortisol reactivity in youth with either MDD only or MDD and MALTX both during the depressive episode and after recovery.

II METHOD

Participants

Participants were 35 youth divided into three groups: individuals with neither MALTX nor MDD (Controls; n = 18); MDD but no history of MALTX (MDD-only; n = 10); and both MDD and MALTX (MDD+MALTX; n = 7). Both depressed groups met criteria for MDD for a minimum duration of 4 weeks. Participants with a lifetime history of mania, hypomania, schizophrenia, schizoaffective disorder or autism, or with a family history of bipolar disorder, were excluded from the study. Controls had no evidence of lifetime psychopathology in the self or in any first-degree relative. Participants were medically healthy and free from psychotropic medication (for a minimum of 8 weeks; most participants were medication-naive), alcohol and illicit drug use.

Measures

Depression: The diagnosis of MDD and other psychiatric disorders was based on semi-structured interviews: the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [10]. The K-SADS-PL was administered to the participant and parent, and summary scores were tabulated. Self-reported depressive symptoms were assessed with the Beck Depression Inventory (BDI) [11].

Family History of Psychopathology: History of psychiatric disorders in the first-degree relatives was determined by a semi-structured interview, the Family History-Research Diagnostic Criteria (FH-RDC) [12], with the parent as the informant.

Maltreatment: Information on early-life adversity was obtained from the youth and parent with a semi-structured interview, the Childhood Adversity Interview [13]. This interview assessed seven types of adversity including separation/loss, life-threatening illness/injury, physical neglect, emotional abuse/assault, physical abuse/assault, witnessing domestic violence, and sexual abuse/assault before the age of 10 years. Summary scores were tabulated for each domain, using ratings (1 = none, 5 = most severe) from both informants. The presence of MALTX was determined by a score of three or greater on the following subscales: physical abuse/assault, sexual abuse/assault, and/or witnessing domestic violence domains prior to age 10 years.

Psychosocial Stressor: A standardized psychosocial stress protocol, the Trier Social Stress Test (TSST), was used to induce HPA response [14]. It involved a 5-minute public speaking task (following a 5-minute preparation period), and a 5-minute mental arithmetic task, performed in front of an audience [9]. Instructions for the speech task and the starting number for the serial subtraction task were altered for the second assessment to avoid the possibility that participants would give a rehearsed speech or memorize the correct sequence of numbers. Baseline saliva samples were collected at 30-minute intervals for 2 hours prior to the stress task (five samples)

following a 30-minute acclimation to the laboratory. Post-stress saliva samples were collected immediately after the task and at 10-minute intervals for 60 minutes (seven samples). The stress protocols were conducted in the late afternoon/early evening to control for delayed circadian phase in adolescents [15]. The second TSST was administered at the first 6-month follow-up visit when the depressed participants met criteria for recovery (i.e., 12 weeks with no clinically significant symptoms). Age- and duration-matched controls were then selected for the repeated TSST. Following the first TSST, an experimenter informed participants in a neutral manner that they performed well on the task, given the circumstances. Participants were fully debriefed regarding the experimental deception after the second TSST.

Cortisol: Cortisol levels were determined in duplicate using a commercially available enzyme immunoassay kit (Enzyme-Linked ImmunoSorbent Assay, ALPCO diagnostics, Salem, NH). Pre-stress cortisol was computed as the mean of the fourth and fifth baseline samples. Following the procedures described by Pruessner and colleagues [16], area under the curve with respect to ground (AUCg), which represents both basal (pre-stress) cortisol output and stressor-induced change in cortisol levels, was calculated.

Longitudinal Follow-up: The KSADS-PL and Longitudinal Interval Follow-up Evaluation (LIFE) [17] were administered at 6-month intervals. Recovery from the depressive episode was determined by a rating of ≤2 on the Psychiatric Status Rating component of the LIFE and a Hamilton Depression Rating Scale [18] score of <6 for a minimum duration of 3 months prior to the follow-up TSST. Age- and sex-matched controls were selected at follow-up for each depressed individual in recovery.

Data Analytic Plan

Cortisol data were log-transformed to reduce skewness. We first conducted analysis of covariance (ANCOVA) with repeated measures (with Greenhouse-Geisser correction) to test the 2-way interaction of time by group (Controls, MDD-only, MDD+MALTX), predicting changes in mean cortisol levels from baseline (mean of pre-stress samples 4 and 5) to the final recovery sample (post-stress sample 7) at Time 1 (current MDD) and Time 2 (recovered MDD). Significant group X time interactions were further probed by planned pairwise comparisons between groups at each post-stress time point. Next, we conducted ANCOVAs to test the main effect of group predicting AUCg cortisol responses at Time 1 and Time 2. All analyses included age, sex and current depressive symptoms as covariates. Effect sizes ($\eta 2$) are reported for all ANCOVAs and describe the ratio of variance explained in cortisol measures by predictors after controlling for covariates; 0.0099, 0.0588, and 0.1379 represent small, medium, and large effect sizes, respectively [19]. Finally, we examined differences between Time 1 (current depression) and Time 2 (recovery) AUCg cortisol responses within groups (MDD-only, MDD+MALTX).

III RESULTS

Table 1 presents the means and standard deviations of all study variables. The groups did not differ significantly on demographic variables. As expected, MDD+MALTX group had a higher MALTX score (derived from the Childhood Adversity Interview)

than Controls and MDD-only groups. Both depressed groups had significantly higher scores on BDI during the depressive episode (T1) compared to controls. Confirming full recovery of depression by the second TSST, there were no group differences in BDI scores at T2. The groups did not differ significantly on baseline cortisol levels at Time 1 or Time 2.

Responses to Psychosocial Stress: Post-task Cortisol Levels

Pre- and post-stress serial cortisol secretory patterns at Time 1 are depicted in Figure 1, Panel A. Repeated measures ANCOVA revealed a significant group X time interaction [$F(8.3, 120.4) = 2.50$, $p = .01$, $\eta^2 = .15$]. Planned pairwise comparisons at each post-stress time point revealed significantly higher cortisol levels for the MDD-only group relative to Controls at 10 minutes ($t(26) = 2.56$, $p = .02$), 30 minutes ($t(26) = 2.91$, $p = .008$), 40 minutes ($t(26) = 2.35$, $p = .03$), and 50 minutes ($t(26) = 2.35$, $p = .03$) after the stress task was completed. MDD-only group also had significantly higher cortisol levels relative to the MDD+MALTX group at 0 minutes ($t(15) = 2.17$, $p = .05$), 10 minutes ($t(15) = 2.52$, $p = .02$), 20 minutes ($t(15) = 3.09$, $p = .008$), 30 minutes ($t(15) = 3.72$, $p = .002$), and 40 minutes ($t(15) = 3.25$, $p = .005$) after the stress task was completed. No significant differences were observed between Controls and MDD+MALTX.

Pre- and post-stress serial cortisol secretory patterns at Time 2 are depicted in Figure 1, Panel B. Repeated measures ANCOVA revealed a non-significant trend for the group X time interaction [$F(5.8, 71.9) = 2.10$, $p = .07$, $\eta^2 = .14$].

Responses to Psychosocial Stress: AUCg Cortisol

There was a significant main effect for group predicting AUCg cortisol at T1 [$F(2, 29) = 3.48$, $p = .04$, $\eta^2 = .19$], controlling for age, sex and current depressive symptoms. Consistent with the results for repeated measures ANCOVA, MDD-only group showed the highest AUCg cortisol responses, whereas MDD+MALTX group showed the lowest values (Figure 2). Planned pairwise comparisons revealed that the MDD-only group had significantly greater T1 AUCg cortisol responses than Controls [$t(26) = 2.24$, $p = .03$] and the MDD+MALTX group [$t(15) = 3.46$, $p = .003$]; however, the MDD+MALTX group did not differ from controls in their T1 AUCg cortisol responses [$t(23) = .48$, $p = .63$]. There was no significant main effect for group predicting AUCg cortisol at T2 [$F(2, 25) = .76$, $p = .48$, $\eta^2 = .06$], controlling for age, sex and current depressive symptoms.

Comparison of Cortisol Responses to the Stressor during the Depressive Episode and Remission

Analyses revealed a non-significant trend for lower AUCg cortisol responses during remission in the MDD-only group ($t(9) = 2.15$, $p = .06$) (Figure 2). For the MDD+MALTX group, AUCg cortisol responses did not change significantly ($t(6) = 1.19$, $p = .28$).

IV DISCUSSION

In this pilot study, cortisol responses to a psychosocial stressor were elevated among youth with current depression but no history of MALTX relative to both normal controls and individuals with both depression and MALTX. When these youth were reassessed after recovering from their depressive episode, they no longer exhibited higher cortisol responses, suggesting that cortisol reactivity

to a psychosocial stressor may be state-dependent [20-22].

No significant change in cortisol responses was observed for depressed individuals with MALTX history. Some scientists postulated that the impact of early adversity on stress response systems changes over time, reflecting a transition from early hyperactivity to later hypoactivity [3, 23, 24]. Consistent with this hypothesis, meta-analyses revealed that chronic stress is associated with decreasing daily cortisol output over time [25], and that daily cortisol output among individuals with posttraumatic stress disorder with or without comorbid MDD was lower for samples in which more time had elapsed since the focal trauma [26]. Moreover, a prospective study following sexually-abused females from childhood into adulthood demonstrated within-person changes from higher-to-lower morning (non-stress) cortisol levels over time, with a shift from high-to-low occurring at approximately age 16 years [27]. To our knowledge, there are no reports on how cortisol reactivity to psychosocial stress changes over time in MALTX victims, nor whether the transition from HPA hyper- to hypo-activity applies to both circulating, non-stress cortisol levels and cortisol reactivity to a psychosocial or pharmacological challenge. The present findings suggest that a history of MALTX may counteract the enhanced cortisol reactivity observed in currently depressed youth. Future prospective studies with larger samples are needed to examine the possible mechanisms for this dampening effect, including the developmental timing of MALTX and/or the duration of chronic stress.

In conclusion, the present findings, albeit in modest sample sizes, suggest that higher cortisol reactivity to psychosocial stress is primarily a state-dependent correlate of 'pure' depression. That this particular HPA alteration did not characterize youth with both depression and MALTX is consistent with the perspective that distinct neurobiological subtypes of depression exist based on a history of MALTX [3, 4]. Considering the unique effects of depression and MALTX on HPA function in addition to the timing, frequency and duration of MALTX-exposure will be critical for elucidating developmentally-sensitive, neurobiological models of MALTX-related and non-MALTX-related psychopathology. A critical avenue for future research remains to determine the implications of HPA hyper- versus hypo-reactivity for depression-risk and response to psychotherapeutic and/or pharmacologic treatments.

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DECLARATION OF CONFLICTS

The authors report no conflicts of interest.

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Table 1. Means and standard deviations of study variables in Controls, MDD-only and MDD+MALTX Groups

	Controls (n = 18)	MDD-only (n = 10)	MDD + Maltreatment (n = 7)	
	M (SD)	*M (SD)*	*M (SD)*	*F(p)*
T1 Age (years)	21.3 (3.2)	19.3 (5.4)	18.4 (3.9)	1.54 (.23)
Days elapsed from T1 to T2	85.4 (18.3)	92.1 (25.4)	102.4 (44.4)	2.96 (.07)
Maltreatment score*	3.5 $(0.6)_a$	4.4 $(2.4)_a$	7.6 $(2.4)_b$	12.49 (<.001)
T1 BDI score*	3.2 $(4.7)_a$	14.2 $(12.3)_b$	16.7 $(9.0)_b$	9.30 (.001)
T2 BDI score	0.3 (0.8)	3.5 (6.4)	3.7 (3.9)	2.49 (.10)
T1 Baseline cortisol (µg/dL)	0.08 (0.05)	0.09 (0.04)	0.09 (0.04)	0.95 (.40)
T2 Baseline cortisol (µg/dL)	0.09 (0.09)	0.06 (0.02)	0.08 (0.05)	0.31 (.74)
T1 AUCg cortisol*	6.3 $(3.3)_a$	9.7 $(4.2)_b$	5.3 $(2.5)_a$	3.70 (.036)
T2 AUCg cortisol	7.0 (7.5)	7.8 (3.8)	6.4 (4.9)	0.75 (.48)
	N (%)	*N (%)*	*N (%)*	*F(p)*
Sex				0.24 (.79)
Male	8 (44.4)	4 (40.0)	4 (57.1)	
Female	10 (55.6)	6 (60.0)	3 (42.9)	
Race				2.78 (.08)
Caucasian	17 (94.4)	6 (60.0)	5 (71.4)	
Non-Caucasian	1 (5.6)	4 (40.0)	2 (28.6)	

MDD = major depressive disorder at T1; Maltreatment score = Sum of physical abuse/assault, sexual abuse/assault, and witnessing violence domains of the Childhood Adversity Interview; BDI = Beck Depression Inventory; Baseline cortisol = mean of pre-stress samples 4 and 5; µg/dL = micrograms per deciliter; AUCg = area under the curve with respect to ground (computed from raw data); Note: ANOVA tests on AUCg cortisol were based on log-transformed data.

*Different alphabetical subscripts denote significant differences between the groups.

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FIGURE CAPTIONS

Figure 1. Mean cortisol levels (± standard error of the mean) to a standardized laboratory stressor (TSST) at Time 1 (during the depressive episode; Panel A) and Time 2 (after recovery; Panel B) among Controls, MDD-only and MDD+MALTX.

Figure 2. Mean AUCg cortisol responses (± standard error of the mean) to a standardized psychosocial stressor (TSST) at Time 1 (during the depressive episode) and Time 2 (after recovery) among Controls, MDD-only and MDD+MALTX.

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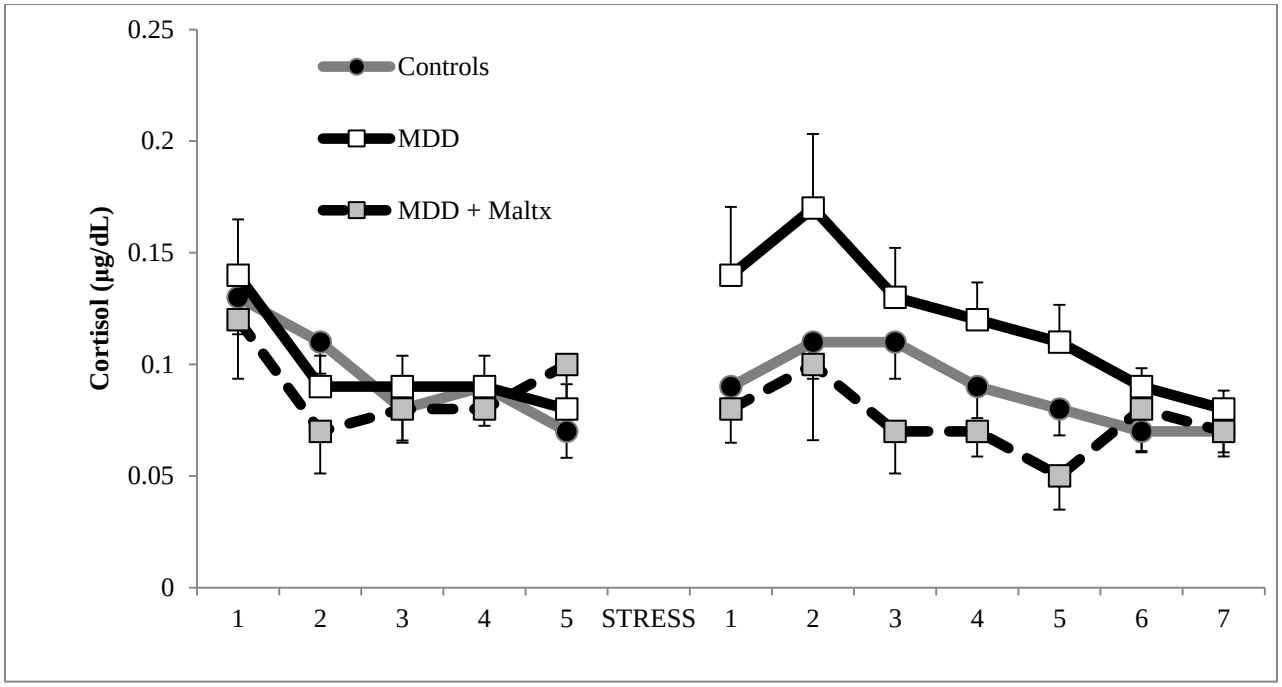
Figure 1.

(Panel A)



(Panel B)

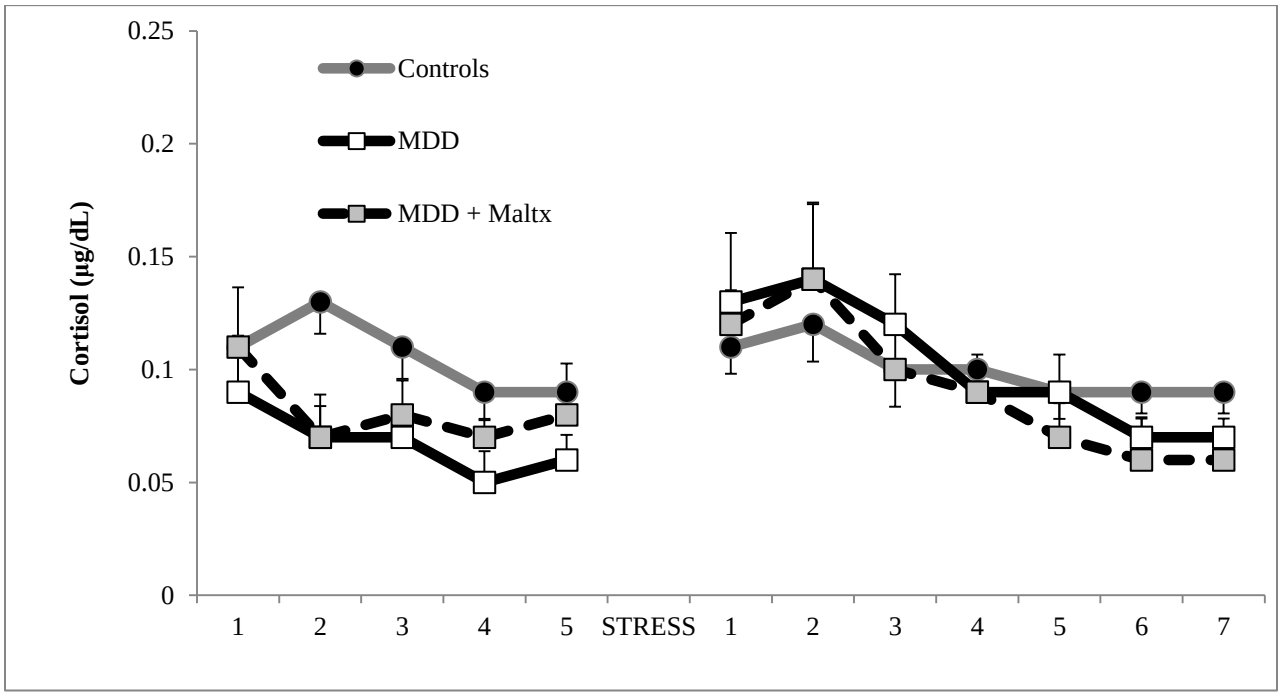


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Figure 2.