Cortisol reactivity to social stress in adolescents: Role of depression severity and child maltreatment

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1. Introduction

Forty years of research has consistently documented dysregulation of hypothalamic-pituitary-adrenal (HPA) axis functioning in the pathophysiology of adult major depressive disorder (MDD) (Carroll et al., 1981; Holsboer, 2000). Furthermore, a recent meta-analysis of HPA axis function in 41 studies employing primarily adolescent samples reported that adolescents with MDD show greater cortisol production (or less suppression) after the dexamethasone suppression test (DST; d = .57), as well as higher basal cortisol levels (d = .20), in comparison to non-depressed groups (Lopez-Duran et al., 2009).

However, the DST and basal cortisol have been criticized as indices of HPA axis functioning because they fail to assess the endogenous response of the HPA axis to psychological stress (Rao et al., 2008). Therefore, more recently investigators have used psychological challenge paradigms such as the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993). The TSST is one of the few available stress protocols that...
combines elements of uncontrollability and high levels of social-evaluative threat. Stress tasks containing these two components are associated with the largest HPA axis stress responses and the longest recovery times (Dickerson and Kemeny, 2004).

Meta-analytic results in adults have indicated that depressed individuals show blunted cortisol reactivity in response to psychological challenge, particularly in older and more severely depressed individuals (Burke et al., 2005). Only one study to our knowledge has compared depressed versus non-depressed adolescents using the TSST (Rao et al., 2008), and it found elevated and prolonged cortisol secretion in response to the TSST in depressed adolescents. In younger children, studies have found blunted cortisol reactivity in depressed children relative to controls (Luby et al., 2003, 2004). Several investigators have argued, however, that a distinction needs to be made between child and adolescent MDD, particularly with respect to HPA axis function (Kaufman and Charney, 2003; Kaufman et al., 2001). Therefore, results across these two sets of studies may not be comparable. Nevertheless, what is consistent across most studies using challenge paradigms in adult and pediatric MDD is a much larger variability in cortisol response within the depressed group versus the non-depressed individuals (Lopez-Duran et al., 2009). It is this heterogeneity within MDD that may help to account for inconsistencies in results across studies.

Two important sources of individual variability that have consequences for the HPA axis system are (a) a history of childhood maltreatment, and (b) individual differences in depression severity. On the one hand, research in both adult and child/adolescent samples has found that childhood maltreatment is associated with increased cortisol reactivity in response to biological (e.g., corticotropin-releasing hormone [CRH]) and psychological stress challenge (De Bellis et al., 1994; Helm et al., 2000, 2001, 2002; Kaufman et al., 1997; Rao et al., 2008). On the other hand, there is a literature in adults linking severe depression to blunted cortisol reactivity response to stress challenge (Burke et al., 2005). Severe melancholic depression, in particular, has been linked to biological markers in the HPA axis (e.g., nonsuppression on the DST), and HPA axis parameters appear to be among the strongest discriminators of melancholic versus non-melancholic depression (Akil et al., 1993; Carroll et al., 1980; Dinan and Scott, 2005; Tsigos and Chrousos, 2002; Zimmerman et al., 1985).

It is noteworthy that these two lines of research reveal an opposing pattern of HPA function; that is, childhood maltreatment is associated with heightened reactivity, and high depression severity is associated with blunted reactivity. Childhood maltreatment and depression severity are, themselves, highly correlated (Harkness and Monroe, 2002). Therefore, it is possible that failure to take both of these sources of heterogeneity into account in research on the HPA axis in MDD may at least in part explain inconsistencies in findings across studies. To date, however, there have been no studies examining the relation of individual differences in depression severity to cortisol reactivity in adolescents, nor have there been any studies in either adults or adolescents examining the interaction of childhood maltreatment and depression severity on HPA axis function.

The goal of the present study was to examine the relation of childhood maltreatment, depression severity, and their interaction, to cortisol reactivity and total cortisol exposure in response to the TSST. We hypothesized that (a) consistent with the adult literature, adolescents with MDD will show blunted cortisol reactivity and lower total cortisol output in response to the TSST than non-depressed controls, particularly among those with a severe depression; (b) again, consistent with previous literature, adolescents with a history of childhood maltreatment will show greater cortisol reactivity and total cortisol exposure in response to the TSST than those without; and (c) depression severity will fully moderate the relation of childhood maltreatment to cortisol reactivity: heightened cortisol reactivity to the TSST in those with a history of child maltreatment will only be seen in the less severely depressed adolescents, whereas blunted cortisol reactivity will be seen in those with a history of child maltreatment in the context of severe depression. The latter hypothesis is tentative given the lack of previous research examining the relation of childhood maltreatment to HPA axis function moderated by depression severity.

2. Methods and materials

2.1. Participants

Participants were 71 individuals (48 females) ages 12—21 years (M = 15.39, SD = 2.11) recruited from a mid-sized community in Ontario, Canada. The ethnic diversity of our sample was consistent with that of the community (89% European ancestry). Our depressed sample was drawn from community mental health agencies and community advertisements seeking adolescents with depression. Our non-depressed sample was recruited from local high schools and community advertisements seeking healthy adolescents. Adolescents whom we identified as depressed from the self-referrals were referred for mental health treatment.

The depressed adolescents all met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) criteria for a current non-bipolar, non-psychotic mood disorder. Exclusion criteria included the presence of a psychotic disorder, bipolar disorder, substance dependence, conduct disorder, developmental disability, or medical disorder that could cause depression. Adolescents in the non-depressed group were free of all current or past psychiatric diagnosis.

Our initial sample included 92 adolescents. Of this group, 12 were excluded because they met criteria for one of the exclusionary diagnoses, and 9 either did not complete the childhood maltreatment interview, or were missing more than one cortisol sample. The resulting sample of 71 did not differ from excluded participants in terms of age, sex, ethnicity, or parental occupation status (all ps > .44). Of the 21 adolescents who were excluded, 52% (n = 11) had been recruited from community mental health sites, and 48% (n = 10) were from advertisements or local high schools (p > .90).

2.2. Assessment measures

The present study was conducted in compliance with our University’s Health Sciences Research Ethics Board.
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Written informed consent was obtained from all adolescents, and from a parent or guardian for adolescents under 18. Interviews and questionnaires were administered by one of three graduate students in clinical psychology. Adolescents participated in two sessions separated by one week to reduce participant burden. Both sessions were conducted at the same time of day. Session 1 included the diagnostic interview and questionnaires. Session 2 included the TSST and childhood maltreatment interview. The childhood maltreatment interview was conducted a full 2 h following the TSST.

### 2.2.1. Diagnostic measure
All adolescents received the full child and adolescent version of the Schedule of Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 2000) to evaluate the presence of current and/or past DSM-IV Axis I diagnoses. Interviews were conducted by senior graduate students in clinical psychology who were trained to gold-standard reliability status (Grove et al., 1981). This interview began with the collection of basic demographic information, including parental occupation. Occupations were subsequently rated by two independent judges on a 1- to 7-point scale according to the Hollingshead Index of Social Position (Hollingshead, 1975). Discrepancies between raters were resolved by consensus, and the consensus rating was used in analyses. Parent report of adolescent symptoms was not gathered based on evidence documenting that parent reports of adolescent internalizing disorders produce a high level of false negatives (Klein et al., 2005).

Thirty-eight (54%) adolescents met criteria for a current depressive disorder (n = 24 major depressive disorder, n = 10 depressive disorder not otherwise specified, n = 4 dysthymia). Of these, 20 (53%) adolescents met criteria for at least one comorbid Axis I disorder (see Table 1).

### 2.2.2. Depression symptoms
Participants completed the BDI-II (Beck et al., 1996), a 21-item questionnaire assessing the severity of depressive symptoms over the past two weeks. We compared three depression severity groups based on BDI-II scores: minimal depression (BDI-II 0–13; n = 30), mild/moderate depression (BDI-II 14–25; n = 16), and moderate/severe depression (BDI-II 26–49; n = 25). The group labels are consistent with those employed by Beck et al. (1996).3

<table>
<thead>
<tr>
<th>Depression Group</th>
<th>No/mild depression (n = 30)</th>
<th>Moderate depression (n = 16)</th>
<th>Severe depression (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>SD</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Sex (female)</td>
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<td>20</td>
<td>67</td>
</tr>
<tr>
<td>Age</td>
<td>14.73</td>
<td>2.30</td>
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</tr>
<tr>
<td>Tanner</td>
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<td>.82</td>
<td></td>
</tr>
<tr>
<td>Parental occupation</td>
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<td>1.63</td>
<td></td>
</tr>
<tr>
<td>Age at first onset</td>
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<tr>
<td>Treatment (yes)</td>
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<td></td>
</tr>
<tr>
<td>Comorbidity (yes)</td>
<td>6</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

### 2.2.3. Pubertal status
Pubertal status was assessed using the Tanner stages of sexual maturation (Tanner, 1962). Self-report was based on a choice between five illustrations of breast (females) and pubic hair (males and females) development, as validated against physician assessment for this age group (Taylor et al., 2001). Scores could range from 1 to 5, with higher scores representing later stages. It should be noted that none of the adolescent girls were pregnant at the time of the study.

### 2.2.4. Childhood maltreatment
Participants were interviewed using the Childhood Experience of Care and Abuse contextual semi-structured interview and rating system (CECA) (Bifulco et al., 1994). The CECA interviews were conducted 2 h following the TSST, thus allowing for full recovery of cortisol function before querying about this emotionally charged information. The following scales were assessed: (1) antipathy — hostility or coldness toward the child (e.g., harsh criticism or name-calling); (2) indifference — neglect of the child’s physical and/or emotional needs (e.g., not providing adequate food or clothing; not comforting the child when upset); (3) physical abuse — violence toward the child (e.g., punching, hitting with an object, or threatening with a knife); and (4) sexual abuse — non-consensual sexual contact by any perpetrator (e.g., fondling, oral sex, and/or penetration). All interviews were audiotaped.

The above scales were rated for severity (1-marked, 2-moderate, 3-some, 4-little/none) by raters who were unaware of the participants’ depression status. Ratings were anchored to the CECA manual, which includes hundreds of examples and rating rules. CECA interviewers and raters received extensive training and ongoing supervision in the

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3 Beck et al. (1996) suggest the following cutoffs: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. We did not use the exact same groupings as Beck et al. because we did not have sufficient sample size to divide our sample into four groupings. Therefore, we chose three groupings that cut the moderate group in half, putting the lower half with the mild/moderate group and the upper half with the moderate/severe group.
Bedford College procedures for rating the CECA by the first author. Inter-rater reliabilities ranged from $k = .86-1.0$ (Harkness et al., 2006). The severity ratings of maltreatment using the CECA were very negatively skewed (i.e., the majority of participants had ratings of 4—little/none). Therefore, we created a composite variable — “childhood maltreatment,” representing the presence versus absence of at least some (level ‘3’) antipathy and/or indifference and/or physical abuse and/or sexual abuse.

2.3. Cortisol collection and Trier Social Stress Task

Participants were asked to refrain from eating and drinking for 1 h prior to their arrival at the lab. All saliva was collected in previously labeled 5 ml polypropylene vials (PGC Scientifics Corporation, MD) by passive drool (Shirtcliff et al., 2001) between the hours of 3 pm and 5 pm because this is a period of low cortisol relative to the morning (Grosch et al., 2003). All participants were medically healthy and had not experienced an acute injury in the preceding 24 h.4

We followed precisely the procedure outlined by Krischbaum, Pirke, and Hellhammer (1993) in defining the time points for saliva sample collection during the TSST. The TSST protocol began with a 10-min rest period to allow the participant to adjust to the research setting. Participants then provided a baseline saliva sample (sample a). They were then led into the experimental room and introduced to two research assistants who the participants were told were members of a selection committee from a human resources department. Participants were told that they were to prepare a 5-min speech that would serve as a “job interview,” and that they would give their speech to the selection committee. They were told that their speech would be videotaped. This point in time served as the onset of the stressor. Participants were then led back into the experimental room and given 10 min to prepare, after which we collected a second sample (sample b). Participants were then led back into the experimental room where they delivered their speech and performed an arithmetic test, which consisted of serially subtracting by 13, starting from 1022, as quickly as possible without making any mistakes. This phase of the TSST took approximately 20 min, after which we collected a third sample (sample c). Therefore, sample c was collected 30 min after the onset of the stressor, the time point of peak cortisol reactivity. A fourth sample was collected 1 h later (sample d), and a fifth and final sample was collected another hour later (sample e). Following the TSST, participants were fully debriefed regarding the purpose of the TSST and the nature of the deception.

2.3.1. Hormone determinations

All saliva samples were immediately placed in a freezer for short-term storage and eventually transported, on ice, to a secure frozen storage (−20 °C). Resulting supernatant were assayed for cortisol using an enzyme-linked immunosassay designed specifically for saliva (1-0102/1-0112; Salimetrics LLC, State College, PA). All samples from one individual were placed on the same plate so that inter-assay variability did not contribute to quantification error. Each sample was quantified in duplicate at 25 μL, and triplicate high and low controls (4-COO1) were distributed across each plate to track precision and accuracy. Samples that had a coefficient of variation ≥15% were repeated on another plate (Berg and Wynne-Edwards, 2001). Repetition was used to reject one of the original duplicates but was not used in analyses. Salivary cortisol measured by this method is highly correlated with serum cortisol ($r = .96$; Salimetrics validation). In all, 24 assay runs, in four batches, were conducted. The high control, measured at 1.1 μg/dL, had an intra-assay coefficient of variation of 4.2% and an inter-assay coefficient of variation of 5.8%. The low control, measured at .1 μg/dL had an intra-assay coefficient of variation of 6.9% and an inter-assay coefficient of variation of 11.1%.

2.3.2. Cortisol parameters for analyses

We used sample a ("rest phase") as participants’ baseline against which to gauge differences across depression severity and history of childhood maltreatment in: (a) raw baseline cortisol concentration in μg/dL ($M = .12$, $SD = .08$, range = .04—.49, Skew = 2.20), (b) ‘cortisol reactivity,’ defined as peak cortisol concentration (sample c) minus baseline (sample a) divided by baseline ($M = .27$, $SD = .71$, range = $.68 – 3.44$, Skew = 2.14), and (c) area under the curve (AUC) relative to self ($M = -.07$, $SD = 8.65$, range = $– .24.25–25.63$, Skew = .26). AUC is a measure of the total cortisol output over the TSST calculated as the sum of the area of the four trapezoids bounded by the baseline value and framed by the cortisol concentration in the five saliva samples from the session. Square-root transformations were applied to baseline cortisol and cortisol reactivity to normalize these variables (transformed skew values < 1.5). The untransformed estimated marginal means are presented in the figures for ease of interpretability.

3. Results

3.1. Participant characteristics

Demographic and clinical characteristics of the three depression severity groups are presented in Table 1. There were no significant relations of depression severity group to sex ($p = .42$) or Tanner score ($p = .19$). However, groups differed in age, at a trend, $F(2, 68) = 2.80$, $p = .07$, $\eta^2 = .08$, and parental Hollingshead index, $F(2, 68) = 7.00$, $p < .005$, $\eta^2 = .17$. Among those with a diagnosis of a depressive disorder, there were no significant differences between those of moderate and severe BDI-II scores in percentage of those on a recurrence, age at first onset, percentage of those with a comorbid disorder, or percentage of those receiving treatment (all $p s > .15$). Of those receiving treatment, 8 were on an antidepressant medication. These 8 adolescents were not

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4 As would be expected, 25/41 (61%) of the depressed adolescents in our sample were experiencing sleep disturbance (i.e., insomnia or hypersomnia). These adolescents were not differentially distributed across the mild/moderate (56%) and moderate/severe (64%) depressed groups, $\chi^2(1) = .25$, $p = .62$, or across those with (61%) versus without (61%) childhood maltreatment, $\chi^2(1) < .001$, $p = .99$. Therefore, sleep disturbance cannot better account for our pattern of results.
differentially distributed between the mild/moderate and moderate/severe depression groups (25% vs. 12%; \( \chi^2[1] = 1.16, p = .28 \)) or between the groups with versus without a history of maltreatment (12% vs. 11%; \( \chi^2[1] = .003, p = .96 \)).

Twenty-six adolescents reported a history of childhood maltreatment (37%). Therefore, the present sample consisted of the following groups: (a) no/minimal depression with no maltreatment \( (n = 27) \); (b) no/minimal depression with a history of maltreatment \( (n = 3) \); (c) mild/moderate depression with no maltreatment \( (n = 8) \); (d) mild/moderate depression with a history of maltreatment \( (n = 8) \); (e) moderate/severe depression with no maltreatment \( (n = 10) \); and (f) moderate/severe depression with a history of maltreatment \( (n = 15) \).

Participants with versus without a history of childhood maltreatment did not differ significantly in terms of sex, age, Tanner score, or parental Hollingshead index \( (\text{all } p > .15) \). Among the clinically depressed adolescents, there were no significant relations of childhood maltreatment to depression history status, age at first onset, or treatment status \( (\text{all } p > .35) \). However, those with a history of maltreatment were significantly more likely to have a comorbid diagnosis \( (61\% \text{ vs. } 28\%; \chi^2[1] = 4.45, p < .05) \).

The specific types of maltreatment assessed in our sample included physical abuse \( (n = 7) \), sexual abuse \( (n = 6) \), and emotional maltreatment \( (n = 24) \). As is typical in maltreated samples, most adolescents reported more than one form of maltreatment. We found no evidence for a differential distribution across mild/moderate and moderate/severe depression of physical abuse \( (19\% \text{ vs. } 8\%; \chi^2[1] = 1.05, p = .30) \), sexual abuse \( (19\% \text{ vs. } 12\%; \chi^2[1] = .36, p = .55) \), or emotional abuse \( (50\% \text{ vs. } 56\%; \chi^2[1] = .14, p = .71) \). The average age at start of maltreatment was 7.96 \( (SD = 4.89) \) and at end was 14.81 \( (SD = 2.40) \), with an average duration of 11.58 years \( (SD = 5.46) \). The presence versus absence of current maltreatment was not differentially distributed across the mild/moderate and moderate/severe depression groups \( (\chi^2[1] = .17, p = .68) \).

3.2. Within-group cortisol reactivity over time

Square-root transformed group cortisol concentrations (in \( \mu g/dL \)) at each time point were analyzed using a 5 (time) \( \times 3 \)

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(discussion of results: minimal depression, mild/moderate depression, moderate/severe depression) \( \times 2 \) (childhood maltreatment: presence versus absence) repeated-measures Analysis of Covariance (RMANCOVA) controlling for age and parental occupation status. There was a 2-way interaction of time by depressed group, Wilks’ \( \lambda < .05, F(8, 120) = 3.43, p < .05, \eta^2 = .16 \). This was qualified by a significant 3-way interaction of time by depressed group by childhood maltreatment in the quadratic trend, \( F(2, 63) = 3.39, p < .05, \eta^2 = .10 \).

Among those with no history of maltreatment, the three depression groups did not differ in terms of the shape of their cortisol curves over time, \( F(2, 40) = 1.18, p = .32, \eta^2 = .06 \). In contrast, among those with a history of maltreatment, there remained a significant time by depression group interaction, \( F(2, 21) = 3.72, p < .05, \eta^2 = .26 \). As hypothesized, the mild/moderate depressed group with maltreatment showed the strongest reactivity to the stressor, demonstrating a significant quadratic trend in the curve over time, \( F(1, 7) = 5.50, p < .05, \eta^2 = .45 \). In contrast, and also as hypothesized, the moderate/severe depressed group with maltreatment showed no reactivity to the stressor, demonstrating a significant downward linear trend in the curve over time, \( F(1, 14) = 24.67, p < .001, \eta^2 = .64 \).

3.3. Between-group cortisol parameters

As displayed in Table 2, baseline cortisol concentration was significantly positively correlated with age, and cortisol reactivity was significantly positively correlated with parental Hollingshead scores (i.e., related to lower parental occup-
pation status). In addition, among the clinically depressed adolescents, those with a comorbid diagnosis had higher cortisol reactivity than those without. Below we report on a series of ANCOVA models examining the effects of depression severity group, childhood maltreatment, and their interaction to cortisol baseline, reactivity, and AUC, controlling for age and parental Hollingshead index.

### 3.3.1. Cortisol baseline

The interaction of depression severity group and childhood maltreatment was significant, $F(2, 63) = 3.82$, $p < .05$, $\eta^2 = .11$. Adolescents with a history of childhood maltreatment had a significantly higher cortisol baseline than those without, but only among those with moderate/severe depression, $F(1, 63) = 5.18$, $p < .05$, $\eta^2 = .08$ (see Fig. 2). Indeed, among those with a history of maltreatment, the moderately/severely depressed, $F(1, 63) = 7.84$, $p < .01$, $\eta^2 = .11$, and the mildly/moderately depressed, $F(1, 63) = 5.76$, $p < .05$, $\eta^2 = .08$, adolescents had a significantly higher baseline than those with no/minimal depression. Among those with no childhood maltreatment, however, the three depression groups did not differ significantly (all $p$s > .25).

### 3.3.2. Cortisol reactivity

The interaction of depression severity group and childhood maltreatment approached significance, $F(2, 63) = 2.59$, $p = .08$, $\eta^2 = .08$. As hypothesized, the moderate/severe depressed adolescents with maltreatment had a significantly lower level of reactivity than those with no/minimal depression, $F(1, 63) = 5.57$, $p < .05$, $\eta^2 = .08$, and than those with mild/moderate depression, $F(1, 63) = 13.06$, $p < .005$, $\eta^2 = .17$ (see Fig. 3). Among those with no childhood maltreatment, however, the three depression groups did not differ significantly (all $p$s > .07).

It is important to note that the moderate/severe and mild/moderate groups with maltreatment did not differ in terms of their cortisol baseline, $t(21) = .66$, $p = .52$. Further, in the moderate/severe depressed and maltreated group, baseline cortisol did not correlate significantly with cortisol reactivity, $r = .02$, $p = .94$. Therefore, the blunted reactivity seen in the moderate/severe depressed group with maltreatment likely does not represent a ceiling effect.

### 3.3.3. Area under the curve

The interaction of depression severity group and childhood maltreatment was significant, $F(2, 63) = 3.41$, $p < .05$, $\eta^2 = .10$. Adolescents with a history of childhood maltreatment had a significantly greater AUC than those without, but only among those with mild/moderate depression, $F(1, 63) = 10.42$, $p < .005$, $\eta^2 = .14$ (see Fig. 4). Among those with no childhood maltreatment, however, the three depression groups did not differ significantly (all $p$s > .08).

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**Table 2** Relation of cortisol parameters to demographic and clinical characteristics of the sample.

<table>
<thead>
<tr>
<th></th>
<th>Cortisol baseline</th>
<th>Cortisol reactivity</th>
<th>AUC</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td>.02</td>
<td>-.11</td>
<td>-.15</td>
</tr>
<tr>
<td>Age</td>
<td>.38**</td>
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<tr>
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<td>.16</td>
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</table>

* $p < .05$.  
** $p < .01$. 

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**Figure 2** Mean cortisol baseline (in $\mu$g/dL) by childhood maltreatment history and depression severity.

**Figure 3** Mean cortisol reactivity (in $\mu$g/dL) by childhood maltreatment history and depression severity.

**Figure 4** Total cortisol exposure (in $\mu$g/dL) by childhood maltreatment history and depression severity.
4. Discussion

The present study is the first to our knowledge to examine the effect of a history of childhood maltreatment on HPA axis reactivity as moderated by depression severity. Consistent with hypotheses, a history of childhood maltreatment was associated with significantly higher cortisol reactivity and total cortisol exposure (i.e., AUC) to a psychosocial stress challenge. However, an intriguing differential association between childhood maltreatment and HPA axis function emerged when the sample was stratified by depression severity. Only those with a mild/moderate level of depression severity (i.e., BDI-II between 14 and 25) showed increased cortisol secretion in response to the TSST. In marked contrast, adolescents with a moderate/severe level of depression (i.e., BDI-II > 25) showed significant blunting of the cortisol response, particularly among those with a history of maltreatment. Indeed, cortisol levels decreased in a linear fashion across the sampling period in moderate/severe depression with a history of maltreatment. This pattern of results cannot be better accounted for by socio-economic status, age, pubertal status, or gender. Further, the mild/moderate and moderate/severe depression groups did not differ in baseline cortisol concentration, anti-depressant medication status, or the presence of a comorbid disorder, including post-traumatic stress disorder.

Our results are consistent with, and expand upon, the literature in adult MDD. Specifically, Burke et al. (2005) also reported blunted stress reactivity and impaired stress recovery in response to psychological challenge in MDD compared to controls, and described a similarly flat and unresponsive pattern of cortisol secretion, particularly in severe depression. Our results suggest that this pattern generalizes to an adolescent sample, and may be specific to severe depression. Future research is now needed to determine whether a blunted HPA axis is specific to particular symptoms, or qualitatively distinct subtypes (e.g., melancholic depression) of MDD.

In addition, our results are consistent with previous literature examining the effect of childhood maltreatment on HPA axis function. On the one hand, greater cortisol reactivity in challenge studies has been observed in adult samples with a history of abuse (Heim et al., 2000, 2001, 2002), as well as in adolescent samples with a history of adversity more generally (e.g., early parental loss, life-threatening illness, and abuse) (Rao et al., 2008). On the other hand, however, studies in adolescents employing the TSST, and examining maltreatment experiences similar to those assessed in the present study, have reported blunted cortisol reactivity (Carpenter et al., 2007; De Bellis et al., 1994). We suggest based on our results that differences in the severity of the depressed groups examined in these previous studies may help to reconcile these conflicting findings.

The complete dissociation of cortisol response between the mild/moderate and moderate/severe depressed adolescents with maltreatment suggests that the neurobiological stress response systems may be functioning very differently in these two groups. Previous research has suggested that individuals at genetic risk for depression, who would be prone to developing a more severe manifestation of the syndrome, express resistance (i.e., desensitization) of glucocorticoid receptors as a trait (Holsober et al., 1995; Modell et al., 1998). In these individuals, high levels of CRH release as a result of the stress of childhood maltreatment, in the context of this reduced glucocorticoid negative feedback, would ultimately lead to a downregulation in CRH receptors on ACTH-producing cells in the anterior pituitary. As such, this may suggest a mechanism to explain why individuals with a severe, potentially genetically-mediated depression, and a history of chronic adversity would be more likely to show a blunted cortisol response to acute stress.

In contrast, maltreated individuals with mild/moderate depressive symptoms may be experiencing the typical HPA abnormalities that have been well documented in the context of stress. That is, these individuals are able to maintain an increased secretion of glucocorticoids to an acute stressor despite negative feedback from glucocorticoid and mineralocorticoid receptors. This is achieved by increased expression of CRH and vasopressin in the paraventricular nucleus, decrease in glucocorticoid and mineralocorticoid receptors and hypertrophy of the adrenal glands (see Checkley, 1996 for a review). The fact that some studies have found higher levels of CRH in the cerebrospinal fluid of depressed individuals versus healthy controls (e.g., Catalán et al., 1998), whereas others have found lower CSF CRH levels in depression (e.g., Geraciotii et al., 1997), also supports the proposal that there may be two different groups of depressed individuals who may prone, respectively, to a normal versus a blunted cortisol response to stress. Future studies examining a broad array of neurohormonal indicators of HPA axis function are now required to more firmly determine the exact mechanism that accounts for the dissociation in cortisol response to stress in mild/moderate versus moderate/severe depressed individuals with a history of maltreatment.

The present results should be interpreted in light of the following limitations. First, the results should be replicated with a larger sample. Nevertheless, it is important to note that we obtained medium to large effect sizes for all comparisons, indicating the robustness of our effects. In particular, we had a small number of adolescents in the no/minimal depression group who had a history of childhood maltreatment. These adolescents had the lowest mean baseline cortisol level. However, this result is difficult to interpret given the size of this group. While this group did not represent the crucial comparison in the present study, future studies confirming and expanding upon the results presented here should nevertheless strive to include a higher number of healthy adolescents with maltreatment histories.

Future research is also needed to stratify the sample by socio-economic status, age, and gender. Lower socio-economic status significantly predicted higher cortisol reactivity in the present sample, and significant sex and age differences in cortisol reactivity have been reported in previous samples (Chopra et al., 2009; Gunnar et al., 2009; Kelly et al., 2008). While our results were robust when controlling for these demographic characteristics, this does not preclude the possibility that the pattern reported here may be further moderated by age, sex, or socio-economic status.

Our small sample also precluded examination of our effects separately for different types of abuse (physical versus sexual versus emotional). As noted earlier, we found no evidence for a differential distribution across mild/moderate and moderate/severe depression of physical abuse, sexual abuse, or emotional abuse. Therefore, the dissociation of HPA axis function found between these two groups...
cannot be better accounted for by a differential distribution of maltreatment type across mild/moderate and moderate/severe depression. Nevertheless, this is an important area for future research as different types of abuse may have different neurobiological consequences.

Second, our definition of the depression groups was based on self-report. Nevertheless, all adolescents in our mild/moderate and moderate/severe depressed groups did not differ significantly in the proportion who reported this history (50% vs. 60%; \( \chi^2[1] = .40, p = .53 \)). Further, recent reports have confirmed the validity of retrospective reports of maltreatment using the CECA in the study of depression (Brown et al., 2007). Fourth, in the present study we did not collect data regarding non-psychotherapeutic medications that may have affected cortisol function, nor did we provide urine screenings for substance use. However, we do note that our results were robust when controlling for self-reported alcohol/substance abuse. Finally, it is unclear how differential biases to recall childhood maltreatment would lead to the specific pattern of results seen here given that the mild/moderate and moderate/severe depressed groups did not differ significantly in the proportion who reported this history (50% vs. 60%; \( \chi^2[1] = .40, p = .53 \)).

The present study also had a number of strengths, including the use of an ecologically valid challenge paradigm and the use of rigorous, structured interviews to determine clinical diagnoses and childhood maltreatment history. In summary, the present findings suggest that HPA axis dysregulation in adolescent MDD is specific to those with a history of maltreatment, and shows an opposing pattern of response based on the severity of depression. These results have significant implications for our understanding of the neuroendocrinological pathology of MDD, and suggest that individual differences in both depression severity and maltreatment history should be considered in all future studies examining HPA axis reactivity in MDD.

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Conflicts of interest

Dr. Harkness, Mr. Stewart, and Dr. Wynne-Edwards report no biomedical financial interests or potential conflicts of interest.

Contributions

Dr. Harkness designed the study, supervised data collection, and wrote the manuscript. Mr. Stewart aided in conducting the diagnostic and childhood maltreatment interviews and undertook the statistical analyses. Dr. Wynne-Edwards wrote the study protocol and supervised the cortisol assays.

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