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The Cortisol Awakening Response and Anterior Cingulate Cortex Function in Maltreated Depressed versus Non-Maltreated Depressed Youth

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Abstract

Symptomatology of depression among children who have (vs. have not) experienced maltreatment is greater in severity, more resistant to conventional treatment, and associated with elevated risk for suicide. Recent evidence implicates perturbations in stress regulatory systems and heightened negative self-appraisals as factors that increase the severity of psychopathology experienced by depressed maltreated (vs. non-maltreated) youth. Likely explanatory mechanisms for these differences are disturbances in the function of the hypothalamic-pituitary axis (HPA) and persistent negative self-referential biases supported by prefrontal cortex function including the dorsal anterior cingulate cortex (dACC). The cortisol awakening response (CAR) and the function of the dACC during a self-appraisal task were collected in maltreated and non-maltreated depressed youth. Hierarchical linear models were employed to model the CAR. Maltreatment group, dACC function during positive and negative self-appraisals as well as other key predictors, were included in the models. Post hoc analyses explored explanations for significant differences. Maltreated depressed youth exhibited a higher CAR compared to non-maltreated youth. At low levels of dACC activity during processing of negative self-descriptors maltreated and non-maltreated depressed youth's CAR did not differ. However, at elevated levels of dACC activity during processing of negative self-descriptors maltreated depressed youth exhibited significantly higher CAR compared to non-maltreated depressed youth.

Keywords

maltreatment; depression; cortisol awakening response; anterior cingulate cortex; adolescents

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1 Introduction

1.1 Maltreatment's effect on the Cortisol Awakening Response and Central Nervous Function

Cortisol is a key hormonal product of the hypothalamic pituitary adrenal (HPA) axis, and it is involved in the regulation of acute and sustained stress responses, circadian rhythms, and preparedness for the demands of a new day (Fries et al., 2009). The latter (anticipatory) function of cortisol can be assessed with the cortisol awakening response (CAR). CAR is characterized by a swift rise in cortisol levels shortly after awakening (above already high morning values) followed by a drop in values (Bublitz and Stroud, 2012, 2013; Fisher et al., 2016; Peng et al., 2014) and is regulated by central nervous system (CNS) structures (i.e. hippocampus, anterior cingulate cortex (ACC), pons and mid-brain). In particular, the prefrontal cortex (PFC) and hippocampus play an inhibitory role in the magnitude of CAR (Clow et al., 2010; Fries et al., 2009). Notably, the magnitude of the initial increase in cortisol is linked to cognitive abilities, e.g. executive functions (Aas et al., 2011; Law et al., 2015), as well as to personal expectations of meeting daily demands (Del Giudice and Belsky, 2010) that are known to be enabled by the PFC and hippocampus, respectively. Although prior research has not established links between the function of these areas and CAR magnitude, evidence suggests that CAR is regulated by pre-awakening CNS function and that CAR in turn, influences post-awakening CNS function and behavioral adaptation (Wu et al., 2015).

Childhood maltreatment is associated with dysfunction of both the HPA axis and CNS (Schalinski et al., 2015) that lasts well into adulthood; with the latter dysfunction predominantly localized in the PFC (van Harmelen et al., 2014b). For example, Lu and colleagues (2016) found that adults with (vs. without) a history of childhood maltreatment had higher CAR values, which correlated with overall exposure to maltreatment (Lu et al., 2016). Similar results of increased CAR linked to the presence (versus absence) of childhood maltreatment have also been found among healthy young adults (Lu et al., 2013) or low (vs. high) parental care (Engert et al., 2011). A wide range of psychopathological stress-related conditions (e.g., depression and trauma-related conditions) are also characterized by dysfunction of the CAR and challenges in meeting daily environmental demands (Holleman et al., 2012; Keeshin et al., 2014; Lu et al., 2016).

Alterations in PFC activity have also been reported among maltreated children (van Harmelen et al., 2014b; van Harmelen et al., 2010). Recent work suggests that the dorsal ACC (dACC) exhibits hyperactivity during processing of negative self-descriptors and social exclusion in maltreated versus non-maltreated samples (Quevedo et al., 2016; van Harmelen et al., 2014a). It is currently unknown whether neuroendocrine perturbations noted in adults with a history of maltreatment (Engert et al., 2011; Lu et al., 2016; Lu et al., 2013; Shea et al., 2005; Yehuda et al., 2001) are also present in adolescent maltreated populations. It is also unknown whether maltreatment status and PFC function interact to predict CAR. Investigating these questions may help describe the phenotypes of biological function that are linked to the more severe and chronic depression experienced by maltreated adolescents.

1.2 The Role of the ACC in Preparation for Daily Challenges

Examining specific neuroendocrine processes linked to maltreatment status amongst depressed individuals is important given the heterogeneous nature of depressive disorders (Savitz and Drevets, 2009) as well as the enduring CNS and endocrine abnormalities linked to maltreatment (Fisher et al., 2016; Holz et al., 2015). The function of the dACC, a key structure of the PFC, might influence CAR function based on maltreatment history among depressed individuals. For example, adults with self-reported childhood trauma showed both enhanced CAR and decreased cingulate cortex volume (Dannowski et al., 2012; Gonzalez et al., 2009). Moreover, salivary cortisol secretions after awaking have been linked to right middle cingulate gyrus volume reduction in subjects with childhood trauma (Lu et al., 2013). These past results suggest that both dACC functional and structural abnormalities, as well as CAR dysfunction, are associated with childhood maltreatment. It is still unknown if ACC function might influence the magnitude of the CAR differentially for depressed maltreated versus not maltreated patients.

The dACC, located in the PFC and near the dorsal aspect of the corpus callosum, is involved in the integration of visceral and affective processes as well as indexing affective saliency and allocation of cognitive effort (Shackman et al., 2011). The dACC has been a focus of neuroimaging inquiries due to its role in the regulation of processes that are disrupted amongst maltreated adolescents including social pain, identity formation, and self-appraisal processes (Eisenberger and Lieberman, 2004; Pfeifer et al., 2007; Pfeifer et al., 2009; Rudebeck, 2006). Specifically, in an earlier study, we found that higher left dorsal dACC activity during negative versus positive self-processing differentiated healthy youth, maltreated and non-maltreated depressed adolescents and was linked to maladaptive self-representation (Quevedo et al., 2016). Given that the dACC, plays a role in the regulation of CAR (Clow et al., 2010); these results raise the question of whether dACC activation during positive or negative self-descriptors might be linked to the emotional expectations of day-to-day challenges and could influence CAR. It was theorized that negative self-appraisals could lead to self-defeating expectations and attributions regarding upcoming challenges, which could modify the anticipatory function of the CAR. Here we tested whether dACC activity during positive or negative self-descriptors (previously established to differentiate maltreated from non-maltreated depressed youth) could be a moderator for the linear component of the CAR in these two sub-groups.

No research has examined the association between dACC activity and CAR, but PFC activity during emotion regulation has been linked to steeper morning-to-evening cortisol slopes (Pruessner et al., 2010; Tarullo et al., 2008; Urry, 2006). One possibility is that CAR might be mediated by top-down PFC regulation of the HPA axis (Pruessner et al., 2010; Tarullo et al., 2008; Urry, 2006). Specifically, because CAR plays a role to prepare visceral, affective, and cognitive systems for expected daily challenges, we hypothesized that the salience of negative versus positive self-relevant descriptors would affect the pattern of CAR.

In summary, there has been limited work examining the relationship between CNS functional activity during self-evaluation and HPA axis function to understand differences between maltreated vs. non-maltreated depressed youth. Here we studied the effects of

maltreatment status (exposed versus not exposed) on neuroendocrine function, as indexed by CAR and included dACC function during evaluations of positive and negative self-descriptors as a likely moderator of CAR. Our hypotheses were as follows: 1. Maltreated depressed youth would exhibit exaggerated CAR, compared to the non-maltreated, depressed youth. 2. dACC activity during negative or positive descriptors would influence the CAR response; directionality was exploratory given the lack of research on how dACC influences neuroendocrine function. Finally, due to the lack of prior work in this area, post hoc analyses were also conducted to investigate symptoms and behavioral correlates of CAR to facilitate interpretation of results.

2 Methods

2.1 Sample

Adolescents were recruited from a short-term inpatient psychiatric unit at the University of Minnesota Department of Psychiatry, via therapist referrals, radio, and flyers (N = 55). There was no significant difference in the recruitment source (inpatient psychiatry unit versus community) of maltreated depressed and depressed participants $\chi^2(1)=0.74$, $p=0.78$. Participants with a history of neurological injuries, substance dependency, autism, or mental retardation were excluded from the study. See Table 1 and 2 for characteristics of the sample.

The first author or a research associate conducted a videotaped psychological assessment with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present Version (K-SADS-P, Kaufman et al., 1997a) and the Children's Depression Rating Scale, Revised (CDRS-R, Poznanski et al., 1984). Total CDRS scores measured depression severity, and K-SADS scores indicated the number of depressive episodes and years depressed. Three items in the K-SADS surveyed initial, middle and terminal insomnia. Initial and terminal insomnia were the two more common forms of sleep disturbances in our sample, and a variable was computed adding the presence or absence of these two forms of sleep disturbances (range = 0-2) as well as a total insomnia variable adding presence of all three forms (range= 0-3) were used in post hoc analyses.

Adolescents also reported on pubertal development (Petersen et al., 1985), which yielded a continuous measure of puberty by averaging scores of puberty items for each participant using the relevant separate items for girls and boys (range 1-4, 1 indicating lowest and 4 indicating highest pubertal status respectively for the test item). Conflict and hostile interactions with parents were also measured via a self-report questionnaire completed by parents and children (Schubiner and Robin, 1990). Parents completed a measure of parenting strategies used to regulate their child's negative emotions (Malatesta-Magai, 1991) and also reported their income and any psychotropic medication their children were taking. The medication variable was entered as a present or not present factor (coded 1 or 0). Life events were measured via an adaptation of the Adolescent Life Experience Survey (Swearingen and Cohen, 1985), which does not include abuse or traumatic events but surveys other stressful events and their importance.

The post-traumatic stress disorder (PTSD) section of the K-SADS was used to establish a history of maltreatment. During this section the experimenters used the specific questions that probed for physical, sexual abuse, or exposure to domestic violence, and asked an additional question regarding the exposure to neglect (specifically: “Did your caregivers/parents ever deprived you of food, clothing, access to needed medical care” or “were you left alone to your own devices for a prolonged period of time?”). A count of the PTSD symptoms derived from maltreatment experiences, if present (coded 1) was used to generate a continuous measure of PTSD symptoms. Videos were double coded by two coders: diagnostic agreement for a depressive disorder was 98%; agreement on the presence of maltreatment was 100% (36%, $N = 20$, were depressed but not maltreated; 64%, $N = 35$ were depressed and maltreated). Among the 35 maltreated depressed participants, 27 (77%) met criteria for PTSD.

2.2 Procedures and Measures

2.2.1 Cortisol Sampling and Assaying—During the first session, participants were provided with materials and instructions to collect salivary samples over four non-consecutive days at three time points: awakening ($M = 7:56$ a.m., $SD = 3.5$ min), 30 min after awakening ($M = 8:27$ a.m., $SD = 3.75$ min), and 60 min after awakening ($M = 9:00$ a.m., $SD = 3.75$ min). No differences between groups were found in the reported sampling or wake up times by group membership, sex, or pubertal status. Maltreated sub-groups (sexual abuse, physical abuse, neglect, domestic violence exposure) were created with the most invasive form of maltreatment used for classification (sexual>physical>neglect>witness). Modalities of maltreatment were not mutually exclusive, and they did not differ in CAR (Table 2), supporting the decision of pooling all forms of maltreatment as one group.

Youth expelled saliva through a straw into pre-labeled vials. They were asked to take each sample before eating, drinking, or brushing their teeth and to not take samples if they were ill or within two days after having a fever. Participants completed a daily log at wakeup time and sampling time, kept samples in their refrigerator, and brought them to the scanning session. Samples were stored at -20°C until being assayed using a time-resolved fluorescence immunoassay (DELFI; intra-assay $CV < 6$, inter-assay $CV < 10$). All of the samples from each participant were included in the same assay batch, and the assay batches were balanced by group membership, puberty, and sex. Samples were assayed in duplicate and averaged. To normalize the distributions, log transformations of the cortisol values were computed. However, figures employ raw data for ease of interpretation.

2.2.2 Dorsal Anterior Cingulate Cortex (dACC) Activity during Positive and Negative Self-Descriptors—In the scanner, adolescents heard and saw the statement, “*What do I think about myself? I think...*” Then, they heard an equal number of positive and negative self-descriptors and used a button box to indicate whether the descriptors were self-descriptive or not. This task has been described in detail elsewhere (Quevedo et al., 2016).

Extracted dACC activity during appraisal of positive or negative self-descriptors that previously differentiated maltreated depressed vs. non-maltreated depressed and controls

(Quevedo et al., 2016) was used as a predictor. The dACC activity (cluster centered in $xyz = -14, 42, 22$, cluster size = 280) was used as a dependent variable and extracted with the eigenvariate function in SPM8 for the whole cluster. This resulted in dACC activity (see Figure 3) for positive or negative self-descriptors. To check group differences preliminary analyses compared the dACC activity for positive and negative self with a repeated measures analysis of variance (RM-ANOVA) with group as a between-subjects factors and brain activity as a within-subject factors: 2 groups (maltreated, non-maltreated) by 2 dACC functions (negative self-descriptors, positive self-descriptors). This analysis yielded a significant group difference with non-maltreated youth showing higher dACC activity for both negative and positive self-descriptors compared to maltreated youth $F(1, 52) = 7.78$; $p < .008$.

2.2.3 Missing Data—Twelve cortisol samples within nine participants had values that were more than 4 SDs above the mean; these samples were removed from the analyses. Data was missing at random as indicated by the Little's MCAR test: $\chi^2(52) = 1.39$, *ns*, and participants with missing cortisol data did not differ by sex, maltreatment group, puberty or severity of depression from those with complete data. No other data were missing.

2.3 Data Analysis

2.3.1 HLM Analyses—To address the nested structure of cortisol data, we conducted a series of hierarchical linear models (HLM) using the PROC MIXED procedure in SAS 9.2 (SAS Institute, Inc., 2009). First, unconditional models were used to estimate CAR observed data via fixed and random effects, (i.e., without predictors; see Equation 1 and 2) to predict individual intercepts, slope parameters ($\beta_{0i \text{ day}}$ and $\beta_{1i \text{ day}}$), and mean intercept and slopes (γ_{01} , γ_{02}). Variance/covariance structures (compound symmetry, autocorrelated, random effects and unspecified) were tested for the observed data. The unspecified variance structure was the best fit for the data. This initial model included time of awakening, time of the first sample, intercept, linear and quadratic terms.

$$\text{Log cort}_{i \text{ day time}} = \beta_{0i \text{ day}} + \beta_{1i \text{ wake up time}} = \beta_{0i \text{ time of first sample}} + \beta_{1i \text{ day}} * (\text{linear}) + \beta_{2i \text{ day}} * (\text{quadratic}) + \delta$$

Equation 1

$$\begin{aligned} \beta_{0i \text{ day}} &= \gamma_{00} + \delta_{0i} \\ \beta_{1i \text{ day}} &= \gamma_{01} + \delta_{1i} \\ \beta_{2i \text{ day}} &= \gamma_{02} + \delta_{2i} \end{aligned} \quad \text{Equation 2}$$

Note: δ = error, linear = 0, 1, 2, quadratic = 0, 1, 4, i = subject.

Second, conditional models including the predictors of interest were conducted starting with a model that tested the effect of 24 variables on cortisol at waking (intercept) and CAR (indicated by linear slope). The first model included time of first saliva sample, wake up time, gender, average puberty, medication, severity of depression, income, life events, (all known predictors of CAR), as well as our variables of interest: maltreatment group and dACC function during negative and positive self-descriptors. Variables entered on its own represent their effect on starting cortisol value (intercept), while variables entered as an interaction term with “linear” represents that variable’s effect on the increase in cortisol values from wake up to 30 minutes after wake up (slope), i.e. the CAR. To improve parsimony, after starting with 24 predictors, in subsequent models we removed non-significant predictors (one at a time) starting with the least significant. At each step, the fit indexes of the more complex model were compared with the simpler nested model (e.g. a model with 23 variables versus a model with 24 variables) as recommended for HLM model comparisons (Garson, 2013). The model conserved at each step was selected by examining each model’s fit, as indicated by the lowest BIC and AIC. This process resulted in a final model with 15 variables. The model with 15 predictors had a BIC of 1250.8 and an AIC of 1231.5 (compared to the model with 14 variables, BIC = 1365.7, AIC = 1345.7 it was a better fit). The model with 16 variables was like the model with 15 variables regarding model fit (BIC = 1250.8, AIC = 1231.5), but the model with 15 variables was chosen for the sake of parsimony. The solution for estimated parameters and Type 3 *F* tests of fixed effects for the final model are shown in Tables 3 and 4.

2.3.2 Post hoc analyses—We conducted ANOVAS and MANOVAS to examine self-reported, parent report, and experimenter rated variables that characterized the environment and the symptoms exhibited by depressed non-maltreated and maltreated groups to better understand the results of the a priori HLM models. We also sought to verify whether variables that differed between the groups or are known to influence CAR (e.g. insomnia) affected the CAR in post hoc HLM analyses.

3 Results

3.1 Unconditional Model

In the unconditional model, the mean linear slope of CAR was significant, $\gamma_{01} = 0.81$; $F(1, 205) = 21.03$; $p < .0001$, indicating a rise in cortisol from time of awakening to 30 mins post awakening.; as was the mean quadratic component, $\gamma_{02} = -0.24$; $F(1, 205) = 27.42$; $p < .0001$, indicating decrease in CAR after 30 mins after awakening. Neither time of wake-up nor time of the first cortisol sample predicted the cortisol intercept or linear slope $F(1, 205) = 0.03-0.25$; $p = 0.86-0.63$. Both the intercept and the slope were unrelated to the day of sampling (weekend versus weekday), $F(1, 207) = 0.03-0.62$; $ps = 0.85-0.43$.

3.2 Conditional Models

3.2.1 Effect of Maltreatment—We addressed the hypothesis that maltreated status would predict CAR. Figure 1 and Tables 3 and 4 show that, as predicted, a linear slope by group interaction was significant in the final model, with the maltreated depressed group having a

steeper increase in cortisol from time of awakening to 30 minutes later ($T_{\text{linear slope*group}} = -0.26$; $F(1, 178) = 13.54$; $p < 0.001$; compared to the non-maltreated depressed group).

3.2.2 Maltreatment by dACC activity for self-appraisals—We tested the hypothesis that CAR would differ between groups as a function of dACC activity during positive self-descriptors and negative self-descriptors. The linear slope by dACC for positive self-descriptors interaction term was not significant and, therefore, was removed in earlier models. However, the linear slope by dACC activity during negative self-descriptors was significant and conserved: $T_{\text{linear slope*ACC activity for negative*group}} = -0.34$; $F(1, 178) = 4.07$; $p < 0.05$ (see Table 3 and 4).

Figure 2 depicts the significant linear slope by dACC activity during negative self-descriptors by group interaction using a median split of values smaller than 0.0187 or values larger than 0.0188. At low levels of dACC activity (<0.187) during negative self-descriptors there was no difference between depressed and maltreated depressed youth in the linear slope of the CAR. Planned contrasts confirmed this finding ($T_{\text{Maltreated vs. Non-maltreated slope difference at ACC activity for negative at } -0.29} = 0.16$; $SE = 0.09$; $t(178) = 1.73$; $p = 0.08$).

However, at higher levels of dACC activity (>0.188) during negative self-descriptors, a significant difference in linear CAR was found for maltreated (versus non-maltreated) depressed youth. Specifically, at higher dACC values, maltreated youth had a steeper slope than depressed youth. Planned contrasts confirmed this

($T_{\text{Maltreated vs. Non-maltreated slope difference at ACC activity for negative at } 0.024} = 0.27$; $SE = 0.06$; $t(178) = 3.83$; $p < 0.001$; $T_{\text{Maltreated vs. Non-maltreated slope difference at ACC activity for negative at } 0.4} = 0.27$; $SE = 0.07$; $t(178) = 3.93$; $p < 0.001$).

3.3 Post hoc Analyses

Post hoc analyses were conducted to understand the interaction between CAR and group status by examining variables likely to affect CAR such as insomnia, parenting practices and PTSD symptoms. First, results from an ANOVA indicated that maltreated youth tended to report higher levels of total insomnia, $F(1, 42) = 3.01$, $p = 0.09$; $M = 5.54$, $SD = 2.87$) compared to the non-maltreated youth ($M = 4.13$, $SD = 2.00$). When adding initial and terminal insomnia, similar trends were noted, $F(1, 43) = 1.91$, $p = .14$; $M_{\text{depressed}} = 2.94$, $SD_{\text{depressed}} = 3.79$; $M_{\text{depressed+maltreated}} = 3.79$, $SD_{\text{depressed+maltreated}} = 2.06$.

Second, we conducted an MANOVA to examine caregiver's report of their strategies to regulate their children's negative emotions, as well the adolescent's report of conflicts with parents. Results indicated that the environment of maltreated youth showed a trend to be different from those who were not maltreated: $F(7, 44) = 2.13$, $p = .06$. Specifically, parents of maltreated (vs. non-maltreated) depressed youth were significantly more likely to use punishment to regulate their children's negative emotions ($F(1, 50) = 3.83$, $p = .05$), or other less supportive strategies to regulate their children's negative emotions ($F(1, 50) = 6.84$, $p = 0.01$). This suggests that depressed maltreated youth experience more parental punishment and less support than non-maltreated youth.

Third, simpler post hoc HLM analyses sought to elucidate if insomnia, other depression symptoms (e.g., anhedonia, depressed mood, irritability, suicide ideation), or home

environment variables (e.g., parenting style) explained higher CAR in the whole sample. Of the symptoms examined, only the added initial and terminal insomnia variable were significantly related to a higher increase in CAR, $F(1, 186) = 5.52, p = .020$. (Table A, supplements).

Fourth, post hoc HLM analyses were conducted on data from depressed maltreated youth. Results indicated that the severity of PTSD symptoms (i.e. higher number of symptoms) tended to be associated with steeper CAR, $F(1, 139) = 3.82, p = .053$ (see Table B in the supplemental material). In contrast, depression symptoms were not associated with CAR linear slope within the maltreated group.

4. Discussion

Maltreated depressed adolescents had a steeper CAR compared to depressed adolescents. Furthermore, dACC activity during processing of negative self-descriptors moderated CAR between the groups: at elevated levels of dACC activity, maltreated depressed adolescents had significantly higher CAR compared to non-maltreated depressed adolescents. In contrast, at low levels of dACC activity for negative self-descriptors there were no differences between maltreated and non-maltreated depressed adolescents. Additional results indicated that: 1) a greater number of negative life events was associated with lower cortisol levels at wake-up (intercept) for all participants, 2) higher family income was associated with steeper CAR, 3) advanced pubertal status was linked to lower cortisol levels at wake-up as well as a trend of a steeper CAR. In post hoc analyses, we found that higher levels of initial and terminal insomnia (in the whole sample) and higher levels of PTSD symptoms (within the maltreated group) were related to higher levels of CAR, two variables that differed between the groups.

This study sought to examine whether maltreatment status predicted distinct neuroendocrine rhythms amongst a sample of depressed adolescents. Confirming our hypothesis, we found that CAR was significantly higher among maltreated depressed youth compared to non-maltreated depressed youth. This supports the notion that maltreatment during childhood may result in a distinct form of depression with different neuroendocrine function relative to depression without this history. Similar results have been reported in children (Kaufman et al., 1997b) and adult populations (Lu et al., 2016). For example, Lu et al., (2016) found that adults with a history of child maltreatment had higher CAR compared to those who were not maltreated, irrespective of depression (Lu et al., 2016). In that study, those who reported maltreatment and had major depressive disorder (MDD) had the highest levels of cortisol after a dexamethasone suppression test, an indicator of HPA axis hyperactivity. Notably, MDD among non-maltreated participants was not associated with elevated cortisol levels (Lu et al., 2016). Our findings extend these results and suggest that HPA axis-related perturbations associated with childhood maltreatment begin shortly after maltreatment occurs.

As discussed in the introduction, unique clinical features distinguish maltreated depressed patients from non-maltreated depressed patients, such as prolonged and more severe depression and a lower responsiveness to treatment. This has led clinicians and researchers

to propose that depression following a history of childhood maltreatment constitutes a distinct syndrome with specific treatment needs (Shamseddeen et al., 2011). Supporting evidence includes findings that childhood maltreatment is a moderator of depression treatment response (Harkness et al., 2012; Nanni et al., 2012; Shamseddeen et al., 2011). The current study lends credence to the relevance of childhood maltreatment as unique contributor to profiles of depression in adolescence that could be relevant for clinical treatment and prognosis.

Post hoc analyses revealed that maltreated depressed youth experienced less supportive home environments and that their PTSD symptoms tended to be positively associated with CAR. Additionally, higher insomnia was linked to higher CAR in the whole sample, a symptom that tended to be more present among maltreated youth. These results support previous findings showing that maltreated youth have more prolonged sleep latency, decreased sleep efficiency, and more difficulty falling and staying asleep, compared to healthy and non-abused depressed adolescents (Glod et al., 1997). Similar results demonstrating sleep disturbances among maltreated versus non-abused samples have been reported in meta-analytic studies (Steine et al., 2012). Our findings suggest that a heightened state of arousal and vigilance that include abnormal sleep-arousal cycles may be linked to the exaggerated CAR observed in maltreated adolescents. However, given that the differences in sleep quality between maltreated and non-maltreated depressed participants were just a trend, this interpretation ought to be taken with caution and future research would be necessary to more strongly support this explanation. Negative self-appraisals, ongoing noxious family circumstances, as well as PTSD symptomatology could also underlie differences between depressed maltreated and depressed non-maltreated youth in CAR.

Our results also suggest that the elevated CAR among maltreated youth may be linked to current living situations. For example, previous work showed that adolescents living in an unsupportive home exhibited elevated CAR (Miller et al., 2007). Results from the present study are consistent with this finding and indicate that the parenting styles of maltreated (vs. non-maltreated) depressed youth were less supportive and oriented toward punishment as a regulatory strategy of their offspring's negative emotions. Overall, the results suggest that a combination of both detrimental family conditions and more severe mental health symptoms (i.e. presence of PTSD and more severe depression) as well as dACC supported negative self-biases could be associated with higher CAR among maltreated depressed adolescents. These causal variables are not necessarily mutually exclusive. The dACC abnormal function as well as the presence of PTSD symptoms could be related and overlapping factors linked to the experience of maltreatment. A more poly-symptomatic presentation among depressed maltreated youth is consistent with the altered dACC activity to negatively valenced self-relevance information previously reported, which could prompt higher arousal and vigilance for daily demands among maltreated depressed youth. Given that negative self-representations can be enduring and persist even after depression symptoms elapse (Phillips et al., 2010) it is possible that, over time, negative self-representations influence preparedness for daily demands, as measured by the CAR. However, other systems including those supporting rest and arousal may also contribute to the exaggerated CAR, due to the role of insomnia to elevated CAR. Given that family-based prevention programs have been found

to prevent depression (Sandler et al., 2011), these interventions may be particularly relevant for youth who live in homes where they have been neglected or abused in the past.

Our finding that depressed maltreated youth with elevated levels of dACC activity during negative self-descriptors had a higher CAR compared to non-maltreated youth, but that their CAR didn't differ at low levels of dACC activity, suggests that negatively biased cognitive processes (and the neural substrates enabling them) are associated with aberrant neuroendocrine rhythms. One of the functions of the dACC is to gauge emotional saliency (Crottaz-Herbette and Menon, 2006; Gasquoin, 2013). Past research has identified resolving emotionally charged conflicts as a function of the dACC (Botvinick et al., 2004), and the mid-ACC is part of a network associated with the experience of negative affect as the cognitive control processes to regulate such stimuli (Tolomeo et al., 2016). Interestingly, the ACC and other prefrontal areas increase their activity during the anticipation of unpredictable pain stimuli and conflict (Hsieh et al., 1999; Sohn et al., 2007) and in coordination with limbic structures, higher ACC activity is associated with the anticipation of such stimuli (Onoda et al., 2008). Among maltreated youth, the experience of higher saliency of negative self-relevant information (Quevedo et al. 2016) enabled by higher dACC activity may contribute to a heightened arousal system and increased preparedness for negative events (and their self-relevance), as indicated by elevated levels of CAR (Chen & Miller, 2012). The reviewed evidence points to how the ACC both enables behavioral regulation for- and anticipation of negative/conflictive events. Considering past and present results, we suggest the exaggerated CAR by ACC processing of negative self-relevant descriptors interaction in depressed maltreated youth points to intense mobilization of resources at daybreak which might be associated to expectations of failure and incompetence and/or of upcoming negative events among depressed maltreated youth. Considering higher conflict with parents and more frequent use of punishment in their families, such negative expectations, if present, may be appropriate and intense biological preparedness would be justified. The latter however are hypothesis, additional research is needed to investigate possible interactions between the HPA axis and ACC-supported self-representation as well as the role of other structures such as the pons and the hippocampus, which support sleep-arousal cycles and CAR negative feedback functions, respectively.

4.1 Limitations

First, participants reported their own time of saliva samples via a written daily diary. So, it is possible that some human error in the report of saliva timing is present. Second, due to significant overlap between types of maltreatment, we had to collapse participants across modalities of maltreatment experiences. Third, the genders were unevenly represented between the maltreated and non-maltreated group with more females in the former. Similar limitations, however, are common to maltreatment research and reflect the characteristics of maltreated samples. Types of abuse often co-occur, and physical or sexual abuse seldom occurs in the absence of neglect or outside of families at higher risk for spousal violence (Bidarra et al., 2016; Debowska et al., 2017; Dube et al., 2002; Schilling et al., 2016). Similarly, in the US, females are more likely to be victimized than males (Government, 2015). However, the inclusion of males was also restricted due to higher prevalence of females in depressed samples. Finally, it was not possible to include the use of oral

contraceptives (OC) as a predictor, a variable that may influence the CAR according to some (Kirschbaum et al., 1999) although others have found it to irrelevant to the CAR (Wust et al., 2000). Future studies should consider including other diagnoses such as depression co-morbid with externalizing symptoms to recruit a sample with a higher number of maltreated males. Larger sample sizes would also allow for a more in-depth assessment of how types of maltreatment modalities differentially impact neurocognitive and neuroendocrine function. Finally, although post hoc analyses yielded interesting possible explanations for CAR differences, the significance of these results was marginal and should be examined in future research with larger sample sizes.

An additional limitation is that the experimental design did not allow for strong inferences regarding the functional relationship between dACC activity and CAR. To determine if such a relationship exists (e.g., if ACC function is linked to CAR), CAR and ACC activity would need to be measured more closely in time. However, negative self-appraisals and cognitive biases tend to be stable and resistant to change and a robust causal mechanism for the onset and persistence of depression (Platt et al., 2017). This would suggest that ACC function during negative self-appraisals might have a stable causal impact in neuroendocrine preparedness for daily challenges.

4.2 Future directions and conclusion

This study highlights the need for future research on the psychopathology, phenotypic presentations, and prognosis of depressed adolescents with a history of maltreatment. Specifically, biomarkers such as neuroendocrine function linked to depressive symptoms may operate differently amongst maltreated versus non-maltreated youth. A future longitudinal study will be necessary to determine whether altered CAR and corticolimbic substrates of stress and emotion are in fact linked to a distinct presentation of psychopathology and how changes in these biomarkers predict the course of depression among maltreated individuals. Also, equivocal in the current literature is the extent CAR function operates differently in maltreated adolescents based on life circumstances such as timing of maltreatment, severity of maltreatment, and current living environment. Differences in neuroendocrine profiles based on maltreatment status also bring to light the need to understand which treatments may work better among depressed youth with a history of childhood maltreatment (Cohen, 2005; Cohen et al., 2010). Specifically, it is unknown whether trauma-focused or family-based interventions alleviate neurophysiologic abnormalities among depressed maltreated patients compared to non-trauma informed treatments.

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Highlights

1. Maltreatment may increase the cortisol awakening response, a measure of daily stress function, above and beyond the effects of current depression in adolescents.
2. Negative self-representations enabled by anterior cingulate function increase levels of stress preparedness among maltreated depressed adolescents.

Figure 1.
Cortisol Awakening Response for Maltreated versus Non-Maltreated Depressed Youth.

Figure 2.

Cortisol awakening response for maltreated and non-maltreated depressed youth by ACC activity during negative self-descriptors. Panel A shows CAR by group at low values of ACC activity during negative self-descriptors (≤ 0.0187). Panel B shows CAR by group at higher values of ACC activity during negative self-descriptors (> 0.0188).

Figure 3.
Dorsal Anterior Cingulate Cortex cluster used to extract brain activity during positive and negative self descriptors (Quevedo et al 2016).

Table 1

Demographics and Clinical Variables Relevant to Depressive Disorders.

	MDD	MDD + Maltreatment	Comparison Statistic
	n = 20	n = 35	
Age: <i>M (SD)</i>	15.04 (1.83)	14.84 (1.55)	$t(53) = 0.430$
IQ: <i>M (SD)</i>	110.70 (13.58)	111.94 (19.90)	$t(53) = -0.247$
Sex			
Male	12 (60.0%)	8 (22.9%)	$\chi^2(1) = 7.59^{**}$
Female	8 (40.0%)	27 (77.1%)	
Puberty: <i>M (SD)</i>	3.01 (0.62)	3.12 (0.39)	$t(53) = -0.802$
Ethnicity			
White	12 (60.0%)	15 (42.9%)	$\chi^2(6) = 12.17^{+}$
African American	3 (15.0%)	1 (2.9%)	
Hispanic	1 (5.0%)	6 (17.1%)	
Asian/Asian American	2 (10.0%)	0	
Native American	0	2 (5.7%)	
Mixed	2 (10.0%)	9 (25.7%)	
Other	0	2 (5.7%)	
Family Structure			
Married	14 (70.0%)	15 (44.1%)	$\chi^2(3) = .302$
Cohabiting	1 (5.0%)	4 (11.8%)	
Separated/Divorced	2 (10.0%)	8 (23.5%)	
Single	3 (15.0%)	7 (20.6%)	
Widowed	0	0	
Income			
35K or less	3 (15.0%)	16 (48.5%)	$\chi^2(2) = 8.08^{*}$
35–75K	7 (35.0%)	11 (33.3%)	
75K or more	10 (50.0%)	6 (18.2%)	
Antidepressants	7 (35.0%)	15 (42.9%)	$\chi^2(1) = .327$
Antipsychotics	0	3 (8.6%)	$\chi^2(1) = 1.81$
Mood stabilizers	0	1 (2.9%)	$\chi^2(1) = 0.58$
Anxiolytic	1 (5.0%)	5 (14.3%)	$\chi^2(2) = 1.13$
Depression Severity: <i>M (SD)</i>	55.00 (15.09)	68.83 (12.53)	$t(53) = -3.65^{**}$
Self Esteem: <i>M (SD)</i>	114.15 (23.52)	105.54 (16.25)	$t(53) = .115$
Attributional Style: <i>M (SD)</i>	11.9 (4.46)	10.14 (3.42)	$t(53) = .257$

Table 2

Cortisol Levels by Sample and Group and Number of Participants by Modality of Maltreatment.

	Non-Maltreated	Maltreated	Physical	Sexual	Witness of Domestic Violence	Number of modalities of abuse experienced		
						Neglect	One	Two +
Sample N (%)	20	35	13 (37.1)	14 (40.0)	22 (62.9)	32 (91.4)	12 (34.29)	23 (65.70)
Cortisol Wake-up (SD)	8.34 (5.75)	8.45 (5.75)	8.97 (8.74)	7.80 (2.51)	8.42 (6.87)	8.60 (5.99)	8.64 (3.44)	8.36 (6.72)
Cortisol levels 30 min (SD)	8.90 (3.88)	10.80 (5.91)	11.61 (6.61)	9.74 (4.61)	9.94 (5.77)	11.05 (5.89)	12.71 (6.12)	9.81 (5.67)
Cortisol levels 60 min (SD)	6.48 (2.97)	8.93 (4.66)	9.63 (3.29)	8.09 (3.26)	8.21 (3.49)	9.09 (4.76)	10.55 (6.11)	8.04 (3.50)
Change from Awakening to 30 min (SD)	.56 (5.18)	2.35 (5.03)	1.42 (5.13)	1.94 (4.39)	1.52 (4.35)	2.44 (4.99)	4.07 (6.08)	1.45 (4.26)

Note 1. 'One' signifies experience of one modalities of abuse, 'Two +' signifies two or more modalities of abuse.

Note 2. Abuse modalities weren't mutually exclusive. There was overlap between abuse modalities. Level of physical invasiveness determined the categories.

For example, if both sexual and physical were present participants was assigned to sexual, but if both physical and witnessing violence, were present participants were assigned to physical. The ranking was: sexual, physical, neglect and witness of domestic violence.

Table 3

HLM Analysis of CAR by group and by ACC Activity.

Effect	Group	Estimate γ	SE γ	df	t	p
Intercept		2.49	0.34	178	7.43	<.001
Time of First Saliva Sample		-.5E-6	0.00	178	-0.77	.443
Linear Slope		0.35	0.22	178	1.55	.123
Quadratic Slope		-0.23	0.05	178	-4.83	<.001
Puberty		-0.22	0.13	178	-1.72	.088
Linear*Puberty		0.14	0.07	178	1.96	.052
Linear*Medication		0.14	0.08	178	1.83	.069
Life Events						
Linear*Depression Severity		-0.02	0.01	178	-2.28	.024
		-0.02	0.00	178	-1.64	.102
Linear*Income						
dACC for Positive Self-Descriptors		0.03	0.01	178	2.04	.043
		-0.22	0.14	178	-1.59	.114
dACC for Negative Self-Descriptors		-0.26	0.16	178	-1.60	.112
Linear*ACC for Negative		0.08	0.11	178	0.75	.453
Linear Slope*Group	Depressed	-0.26	0.07	178	-3.68	<.001
	Depressed + Abused (Ref)	0.00		178		
Linear Slope*dACC for Positive *Group	Depressed	-0.14	0.11	178	-1.25	.211
	Depressed + Abused	0.10	0.11	178	0.89	.374
Linear Slope*dACC for Negative*Group	Depressed	-0.34	0.17	178	-2.02	.045
	Depressed + Abused (Ref)	0.00		178		

*p < 0.05. **p < 0.01

Table 4

Type 3 Tests of Fixed Effects.

Effect	Num DF	Den DF	F Value	Pr > F
Intercept	1	178	55.28	< .001
Time of First Saliva Sample	1	178	0.59	.443
Linear Slope	1	178	0.99	.320
Quadratic Slope	1	178	23.29	< .001
Puberty	1	178	2.94	.088
Linear*Puberty	1	178	3.82	.052
Linear*Medication	1	178	3.35	.069
Life Events	1	178	5.21	.024
Linear*Depression Severity	1	178	2.70	.102
Linear*Income	1	178	4.15	.043
dACC for Positive Self-Descriptors	1	178	2.53	.114
dACC for Negative Self-Descriptors	1	178	2.55	.112
Linear*ACC for Negative Self	1	178	0.77	.383
Linear*Group	1	178	13.54	< .001
Linear*dACC for Positive Self-Descriptors*Group	1	178	1.35	.260
Linear*dACC for Negative Self-Descriptors*Group	1	178	4.07	.045

*p < 0.05. **p<0.01