The Interaction of Childhood Maltreatment, Sex, and Borderline Personality Features in the Prediction of the Cortisol Awakening Response in Adolescents

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Abstract

Aims: The study aimed to investigate childhood maltreatment, sex, and borderline personality disorder (BPD) symptoms as prospective predictors of adolescent hypothalamic-pituitary-adrenal (HPA) axis reactivity. Method: A sample of 69 adolescents (30 female and 39 male) were selected from a larger longitudinal study of adolescent development and assessed at 3 time points. BPD symptoms were assessed at T1 (approx. 12.5 years), childhood maltreatment was assessed at T2 (approx. 14.9 years), and multiple assessments of salivary cortisol (cortisol awakening response; CAR) were undertaken at T3 (approx. 15.5 years). Results: Multivariate linear regression analysis revealed a significant main effect for childhood maltreatment but not for early BPD symptoms as a predictor of lower CAR in adolescence ($p = 0.047$). The association between childhood maltreatment and attenuated CAR was moderated by both early BPD symptoms ($p = 0.024$; no childhood maltreatment-dependent attenuation of CAR in the presence of BPD symptoms) and sex ($p = 0.012$; childhood maltreatment-dependent attenuation of CAR in females only). Furthermore, a 3-way BPD × childhood maltreatment × sex interaction ($p = 0.041$) indicated that the moderating effect of BPD symptoms was present in females only. Conclusion: These findings indicate that attenuation of the HPA axis occurs as a response to early maltreatment rather than being related to the early occurrence of BPD pathology. Traumatized female individuals with BPD symptoms might bypass adaptive HPA axis attenuation.

Keywords  
Cortisol · Hypothalamic-pituitary-adrenal axis · Borderline personality disorder · Sex · Adolescence

Introduction

The hypothalamic-pituitary-adrenal axis (HPA axis) is one of the major stress systems of the human body. Activation of the HPA axis in reaction to, or in anticipation of, a real or imagined stressor, leads the pituitary gland to
The secretion of ACTH activates the adrenal cortex to release several glucocorticoids and mineralocorticoids, including cortisol [1]. The development of the HPA axis is characterized by an initial reactive period after birth, followed by a stress-hyporesponsive period during childhood (commonly associated with secure attachment and supportive adult care) before the HPA axis reaches adult-level stress-hyporesponsive functioning during puberty [1].

Salivary cortisol is considered to be a reliable and valid measure of HPA axis functioning [2], and derived measures, such as the cortisol awakening response (CAR), have commonly been used to index HPA axis functioning in epidemiological research [3]. Although the exact function and regulation of the profound cortisol increase after awakening is still not fully understood, the CAR is considered a reliable measure of the reactivity of the HPA axis [4].

Preclinical and clinical studies suggest that experiences of childhood maltreatment lead to enduring changes in both the activity and, particularly, the reactivity of the HPA axis [5, 6]. In response to early life trauma, the HPA axis is initially overactive, producing excessive cortisol as an adaptive response to stress [7, 8]. However, chronic suppression, which is subsequently required following excessive overproduction of cortisol, seems to alter the glucocorticoid and CRF receptors, modifying the negative feedback mechanism and leading to an attenuation of the HPA axis response by late adolescence [9]. It has been suggested that this attenuation of the HPA axis diminishes the individual’s ability to cope with further stressors, rendering them more vulnerable to developing psychopathology when encountering continued stressors [10, 11]. However, it remains unclear whether attenuation of HPA axis functioning represents a potential pathophysiological mechanism for the development of mental illness or a protective adaption to environmental demands, or maybe both.

Borderline personality disorder (BPD) is a severe mental disorder that is characterized by a pervasive pattern of impulsivity as well as instability in affect regulation, interpersonal relationships, and self-image [12]. BPD is now recognized as both a dimensional construct [13] and as a developmental disorder [14], which is just as reliable and valid in adolescence as it is in adulthood [15]. Studying BPD symptoms across the lifespan is vital to understanding the factors that contribute to the developmental course of BPD. Recently, there has been growing interest in childhood BPD symptoms as potential precursors of later BPD [10, 16]. While BPD features tend to decline from adolescence to adulthood, rank order stability (preservation of the relative ordering of individuals) usually remains high [17].

In addition to trait-like features, BPD symptomatology includes acute dysfunctional behaviours (e.g., deliberate self-harm) [18], which often occur in reaction to stressful situations [19]. Such behaviours might arise from a particular vulnerability to stress and might even function as regulatory strategies to cope with exaggerated emotional stress reactions. Therefore, it is likely that the development of stress vulnerability in BPD involves alteration to HPA axis functioning. Indeed, studies investigating HPA axis functioning (i.e., CAR) in adults with BPD or adolescents with repetitive non-suicidal self-injury have both revealed increased CAR [20, 21], pointing to increased HPA axis activity. However, research on HPA axis functioning in BPD remains inconclusive, possibly due to the potential influence of childhood trauma, which is common among this population [22].

The development of BPD has been consistently associated with adverse childhood experiences, such as childhood maltreatment [23], and recent research on developmental pathways to BPD has identified the likely interaction of temperamental underpinnings of BPD with an adverse early environment that might explain how BPD features might already be present at an early stage of life [10, 24]. A complex dysregulation of the HPA axis (e.g., attenuated reactivity) has previously been suggested as a potential consequence of exposure to childhood maltreatment [25] rather than a neurobiological underpinning of the development of BPD pathology [22]. However, empirical data supporting this speculation are lacking. Because BPD symptomatology and adverse childhood experiences have both been linked to HPA axis dysfunction, it is possible that these “stressors” might interact. While childhood maltreatment might be associated with attenuated HPA axis functioning per se, the development of BPD (as indexed by childhood BPD symptoms) might lead to less attenuated/increased HPA axis functioning (in terms of the CAR).

Significant sex differences have been reported with regard to the development of the HPA axis [26] and BPD [27]. This is not surprising, given that adolescence is a period of increased divergence between males and females in physical characteristics, behaviour, and risk for psychopathology [28]. Therefore, sex is likely to be an important factor in the association between childhood maltreatment, BPD symptoms, and HPA axis functioning.

This study aimed to prospectively investigate the role of childhood maltreatment, early BPD symptoms, and their interaction in the development of HPA axis reactivi-
ity in adolescence. It was hypothesized that both early maltreatment and BPD symptomatology would independently predict CAR (e.g., early maltreatment would predict lower CAR and BPD symptoms higher CAR) and that BPD pathology would moderate the association between childhood maltreatment and blunted HPA axis reactivity. Additionally, sex was included as a potential exploratory moderator of any associations.

Materials and Methods

Sample
Participants were drawn from a sample of 2,479 sixth-grade students (from Melbourne/Australia) who were involved in a longitudinal study of adolescent development. The sampling strategy, which involved screening according to temperament profiles, has been described previously (reference left out for masked review). At Time 1 (T1), 238 participants (female/male = 122/116) aged 11–13 years (mean = 12.5; SD = 0.4) reported on current BPD symptoms. At Time 2 (T2), the same participants aged 14–16 years (mean = 14.9; SD = 0.4) retrospectively reported on adverse experiences during their childhood. At Time 3 (T3), 88 adolescents took part in the collection of salivary cortisol. Of these 88, participants were excluded for taking medication with an established effect on hormone levels, oral sores, failure to comply with collection protocols, and cortisol outliers (±3 SD). This procedure was in accordance with previous publications on hormones from the same study [29]. Finally, at T3, we had data from 69 participants (female/male = 30/39) aged 14–16 years (mean = 15.5; SD = 0.4) who took part in HPA axis assessment. Participants were only included in the analyses if they participated in all 3 assessments at T1–T3. The final sample, comprised of these 69 adolescents, did not significantly differ from the original screening sample (n = 2,479) in terms of temperament profiles (all p values >0.22), socioeconomic status (p = 0.97), or sex (p = 0.14).

Procedure and Measures
Saliva samples were collected from participants on 2 consecutive days at T3, following a previously published standard protocol [29]. HPA axis functioning was measured by the CAR, which is considered a reliable and established measure of HPA axis reactivity [4]. The CAR was calculated as the area under the curve of the salivary cortisol measure taken at awakening (baseline) and at 30 and 60 min after awakening. The mean of both days was calculated. Salivary cortisol was analysed in duplicate using an Elecsys E immunoanalyser system (Roche Diagnostics, Mannheim, Germany) by the Roche Cobas cortisol assay without modification of the manufacturer’s protocol. The Cobas cortisol assay is a competitive electrochemiluminescence immunoassay (ECLIA) based on polyclonal sheep anti-cortisol antibodies that was developed for serum cortisol measurement (5th–95th percentile of the reference range: 171–536 nmol/L), but has also been validated for measuring cortisol in saliva [30]. The intra-assay coefficients of variation were ≤2.7%, and the inter-assay coefficients of variation were ≤4.2%, respectively.

The Childhood Trauma Questionnaire (CTQ) [31], a 28-item self-report inventory, was used at T2 for the retrospective and dimensional assessment of childhood maltreatment. For each item, there is a 5-point Likert scale to express the frequency of occurrence. Three items load on to a minimization/denial scale and were not used in the current analysis. Although the CTQ provides scores on 5 subtypes of maltreatment (emotional abuse and neglect, physical abuse and neglect, and sexual abuse), given the co-occurrence of these types of childhood maltreatment, a total continuous score (range 25–125) was used in the analyses.

Early BPD symptoms were assessed at T1 using the BPD subscale of the Adolescent Personality Disorder (APD) scale. This is a 26-item age-appropriate dimensional measure developed from the scales used in the Children in the Community (CIC) study and updated for the DSM–IV [32]. BPD scores were derived by creating a mean item score; the BPD scores in the whole sample ranged from 1 to 3.92 (mean = 1.72; SD = 0.56; maximum range: 1–4); they were comparable with the CIC study (mean = 1.7; SD = 1.5) but had a wider distribution in our sample. Excellent internal consistency (α = 0.94) was found in the present study. The CIC self-report scales showed good convergent and prospective validity, matching or exceeding benchmarks established in previous comparisons between self-report instruments and structured clinical interviews [32, 33]. In the CIC study, DSM-III-R borderline, histrionic, and narcissistic features were highly stable (0.63 for males and 0.69 for females) across 8 years from adolescence to young adulthood [34].

Pubertal development was assessed, as it might potentially influence HPA axis functioning [35, 36], using the Pubertal Development Scale (PDS) [37], which shows good reliability and validity [38]. For girls, this measure included 12 items assessing the stage of breast development, hair growth, acne presence, and hip width. The date of onset for menarche was also obtained. For boys, the PDS included 11 items assessing genital development, hair growth, acne presence, and voice change.

Statistical Analyses
Multiple imputation (with 100 imputations) was employed to take account of the small amount of missing data in the sample of 69 participants (pubertal status: n = 2, BMI: n = 4, CTQ: n = 1, BPD: n = 2). A multivariate linear regression model was calculated to assess the influence of early BPD symptoms (BPD score at T1), childhood adversity (CTQ score at T2), and sex, as well as their interactions, on the CAR. Covariates (pubertal status at T2) were entered for adjustment of potential confounders. All continuous independent variables were centred prior to calculating interaction terms.

Results
At T1, the mean BPD score was 1.63 (SD = 0.34) for females and 1.67 (SD = 0.52) for males, and did not show significant sex differences (t(61) = −0.32, p = 0.75). At T2, the mean CTQ score was 31.98 (SD = 6.26) for females and 30.95 (SD = 5.19) for males, and did not show significant sex differences (t(61) = −0.72, p = 0.48). The mean CAR at T3 for females was 5.02 nmol/L (SD = 9.21) and 3.02 nmol/L (SD = 7.79) for males, and showed no
sex differences ($t[61] = 0.93, p = 0.36$). BPD and CTQ scores were significantly positively correlated for both females ($r = 0.54, p < 0.01$) and males ($r = 0.43, p < 0.01$).

Table 1 shows the results of the hierarchical linear regression model including sex, CTQ score, and BPD score as well as interaction terms between the 3 variables (including pubertal development as covariate). There was no significant main effect of the BPD score, but there was a significant main effect of CTQ score on the CAR, with higher CTQ scores predicting a lower CAR.

The regression model revealed significant 2-way interactions between sex and childhood maltreatment as well as between BPD and childhood maltreatment. Sex moderated the association between childhood maltreatment and CAR such that there was a negative association present in females and a positive association in males. In addition, a significant 3-way interaction between sex, childhood maltreatment, and BPD was found. Follow-up analyses revealed that the interaction between childhood maltreatment and BPD symptoms predicted CAR for females ($B = 1.629, \beta = 0.464, t = 2.000, p = 0.045$; overall model: $F(4, 23) = 1.651, p = 0.196, R^2 = 0.223$) but not males ($B = 0.057, \beta = -0.030, t = 0.106, p = 0.916$; overall model: $F(4, 31) = 0.231, p = 0.919, R^2 = 0.029$). Figure 1 illustrates the interaction between childhood maltreatment and early BPD symptoms predicting the CAR in females.

**Table 1.** Summary of findings of multivariate regression analysis predicting the cortisol awakening response at T3 (age 15 years) including sex, CTQ score, and BPD score

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Cortisol awakening response (total sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B/βa</td>
</tr>
<tr>
<td>Sex</td>
<td>0.435/–0.119</td>
</tr>
<tr>
<td>PDS</td>
<td>–1.076/–0.005</td>
</tr>
<tr>
<td>CTQ score</td>
<td>–0.652/–0.026</td>
</tr>
<tr>
<td>BPD score</td>
<td>–3.024/–0.032</td>
</tr>
<tr>
<td>Sex × CTQ score</td>
<td>0.987/0.300</td>
</tr>
<tr>
<td>Sex × BPD score</td>
<td>4.478/0.182</td>
</tr>
<tr>
<td>CTQ score × BPD score</td>
<td>1.917/0.121</td>
</tr>
<tr>
<td>Sex × CTQ score × BPD score</td>
<td>–1.979/–0.479</td>
</tr>
</tbody>
</table>

PDS, Pubertal Development Scale; CTQ, Childhood Trauma Questionnaire; BPD, borderline personality disorder. a Standardized beta weights (and model fit indices) are provided for the list-wise deletion sample (given that these statistics are not available from analyses utilizing multiple imputation in SPSS). Note that the pattern of significant and non-significant results was the same for analysis based on a list-wise deletion sample, except that the CTQ × BPD × sex interaction only trended toward significance ($p = 0.073$).

**Discussion**

Our study aimed to investigate the prospective associations between early maltreatment, early BPD symptoms, and their interaction with adolescent HPA axis functioning. While the study hypothesis that childhood
studies to system function, immune functioning, and cardiovascular function because deleterious effects of cortisol on this system have been shown to occur in the hippocampus, amygdala, and frontal cortex. Moreover, the described relationship between childhood trauma, BPD pathology, and HPA axis reactivity was only present for female adolescents.

These findings confirm that childhood maltreatment is an important factor that influences HPA axis dysfunction. The results might fit a previously formulated “attenuation hypothesis” [5, 9], in which lower cortisol concentrations seen in individuals with exposure to childhood trauma might be explained by allostatics, the body’s ongoing adaptive efforts to maintain homeostasis [39]. Hyposecretion of cortisol in response to prolonged exposure to trauma has been suggested to serve as a protective adaptive function because deleterious effects of cortisol have been shown to occur in the hippocampus, amygdala, frontal cortex, immune functioning, and cardiovascular system [8, 40]. Thus, blunted CAR might reflect the adaptive response of the HPA axis to limit a potentially damaging overactivation. Of course, it needs to be noted that assessment of childhood maltreatment in the current study was made retrospectively and temporally close to HPA axis assessment in adolescence. Thus, the effects of continuing stressors and/or recall bias cannot be ruled out.

The association between childhood maltreatment and HPA axis reactivity appeared to be moderated by sex, such that the negative association was present for females but not males. This is not surprising, given that sex differences in the development of HPA axis functioning have been well described previously [41, 42]. Earlier analyses of the data used in the present study have revealed differential development of HPA axis functioning, with a tendency for attenuation among females during adolescence [29]. The present findings suggest that females might be more prone to HPA axis attenuation in the presence of childhood maltreatment, which is consistent with findings of increased sensitivity to environmental stressors observed in adolescent girls [43]. In addition, sex differences might also arise from different types of traumatization among the sexes. While the CTQ has subscales for different types of maltreatment, the current sample size did not provide adequate statistical power to allow for additional subgroup analyses to further investigate this hypothesis.

Contrary to the hypothesis, BPD symptoms did not predict CAR when adjusting for experiences of childhood maltreatment. This seems to support the view that altered HPA axis functioning, previously reported in BPD, might largely arise from the high load of adverse childhood experiences among these individuals [44, 45]. Studies to date have consistently reported that HPA axis alterations have been related to experiences of abuse and neglect rather than to specific psychopathology, such as BPD, major depression, or posttraumatic stress disorder [46–48]. However, since the current study did not measure BPD symptoms at the time of HPA axis assessment, changes in BPD symptoms from childhood to mid-adolescence (despite overall moderate stability of such symptoms [44]) might have been responsible for the lack of association.

Most interestingly, the current study found that BPD symptoms moderated the association between childhood maltreatment and HPA axis functioning in such a way that HPA axis reactivity was less attenuated in the presence of BPD symptoms. Thus, in individuals who had experienced maltreatment, those who also had high levels of BPD symptoms exhibited higher HPA axis reactivity. This finding might be regarded as a sign of severe, chronic stress in individuals presenting with early BPD symptoms compared with traumatized individuals without symptoms of BPD. This is likely to be due to continuing adverse childhood experiences, such as a hostile parent-child relationship or dysfunctional family environment [44]. Alternatively, these findings might also point to a different developmental pathway for BPD, such that individuals with temperamental vulnerability to BPD might be unable to limit their acute stress response, which in turn leads to hippocampus, amygdala, and frontal cortex dysfunction [49]. Again, the moderating effect of BPD symptoms on the association between childhood maltreatment and HPA axis functioning was found in females but not males.

The findings of the interaction between childhood trauma, BPD pathology, sex, and the neurobiological stress response system are in line with previous research on the rather complex developmental pathways to BPD rather than a simplistic linear relationship between childhood maltreatment and BPD. Previous studies from our group have revealed that different experiences of childhood maltreatment acted as moderators of the relationship between temperament dimensions and an increase in BPD symptoms [24]. In addition, temperamental traits were found to interact with structural alterations in the hippocampus (a structure that is highly important in the

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activation of the HPA axis) when predicting adolescent BPD symptoms [50]. Altogether, the developmental pathways to BPD might include early neurobiological predisposition (i.e., genes, temperament), complex adverse early environment (i.e., child abuse and neglect), and neurobiological alterations (i.e., structural alterations of the hippocampus) that might all exert an influence on the functioning of the HPA axis.

Major strengths of this study include the longitudinal design, the dimensional assessment of BPD using an age-appropriate measure, and robust methods for measuring HPA activity. Although this study provides preliminary findings regarding a potential developmental interaction of early BPD symptoms, childhood maltreatment, and HPA axis functioning, there are several noteworthy limitations, and the current findings require replication in a study designed specifically for this purpose. The relatively small sample size might increase the risk of both type I and type II errors, and may likely have contributed to the non-significance of the overall model predicting CAR. Additionally, the lack of HPA axis measures at T1 and T2 and the lack of BPD measures at T2 and T3 do not allow full accounting for the longitudinal development of both HPA axis functioning and BPD symptoms. This fact did not allow for investigation of the directional relationship between HPA axis functioning and BPD pathology (e.g., HPA axis functioning predicting BPD development or concurrent HPA axis functioning and BPD development). A comprehensive inclusion of potentially confounding variables of HPA axis functioning should be the subject of future research. The use of self-report measures for the assessment of childhood maltreatment and BPD pathology might also be considered a limitation, especially as this self-report measure, used in a general population sample, assessed BPD symptoms rather than “clinical range” BPD. Therefore, the findings might not be readily generalized to clinical settings. Future research should aim to collect interview-based, multi-source data on both childhood maltreatment and psychopathology.

In conclusion, the current findings support the view that attenuation of the HPA axis does occur as an adaptive response to experiences of early maltreatment, predominantly in girls, and this does not seem to be related to the occurrence of early BPD pathology. Thus, previous findings of attenuated HPA axis functioning among individuals with BPD pathology are likely to be caused by the high load of childhood adversity among this group. Furthermore, traumatized individuals with BPD might bypass adaptive attenuation of HPA functioning due to current stress and psychopathology.

References


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