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Associations of childhood trauma with hypothalamic-pituitary-adrenal function in borderline personality disorder and major depression

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Summary
Background: Alterations of the hypothalamus-pituitary-adrenal (HPA) axis are hallmarks in major depressive disorder (MDD) and there is some evidence about similar patterns in borderline personality disorder (BPD). This study examines HPA axis abnormalities with respect to clinical characteristics in both BPD ($n = 24$) and MDD patients ($n = 33$) as well as in healthy control participants ($n = 41$).
Method: A 0.5 mg dexamethasone suppression test was administered to evaluate basal cortisol release and HPA feedback sensitivity via salivary cortisol. Traumatic experiences in childhood as well as severity of borderline and depressive symptom severity and dissociation were obtained by self-report questionnaires.
Results: Compared to the healthy control group, BPD and MDD patients exhibited both enhanced cortisol concentrations before and after the administration of 0.5 mg dexamethasone. Higher cortisol levels were positively correlated to a history of childhood trauma, current dissociative symptoms and severity of borderline and depressive symptoms. Regression analyses revealed that some aspects of early trauma were associated with cortisol release before and after dexamethasone, whereas psychopathology did not contribute to the regression model.

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Conclusions: HPA dysfunctions appear to be related rather to childhood trauma than to psychopathology in adulthood. Exposure to childhood trauma may contribute to long-lasting alterations in HPA activity and might enhance the risk for the development of later mental disorder.

1. Introduction

Dysfunctions of the hypothalamic-pituitary-adrenal (HPA) axis have been proposed to play an important role in the psychopathology of major depressive disorder (MDD). Hypersecretion of cortisol is a prominent neuroendocrine finding in MDD (Pariante and Lightman, 2008; Schlosser et al., 2011) and there is increasing evidence that alterations in HPA activity may also contribute to borderline personality disorder (BPD) (Zimmerman and Choi-Kain, 2009; Wingenfeld et al., 2010b). Likewise, enhanced basal cortisol concentrations were also reported for BPD patients (Lieb et al., 2004; Wingenfeld et al., 2007a), but alterations of the HPA axis function in BPD seem to be influenced by comorbid symptomatology. Comorbid depressive symptoms were found to be positively related to cortisol levels in BPD, whereas severity of posttraumatic stress symptoms was negatively associated to basal cortisol release (Wingenfeld et al., 2007a).

In addition to the assessment of basal cortisol levels, the dexamethasone suppression test (DST) has extensively been used to detect abnormal HPA axis feedback regulation. Several studies demonstrated that depressed patients failed to suppress endogenous cortisol release after dexamethasone administration (Handwerger, 2009), indicating a reduced feedback sensitivity (Holsboer, 2000; Pariante and Miller, 2001; Pariante and Lightman, 2008). In BPD, findings were heterogeneous and DST results again varied by patterns of comorbid psychopathology (Wingenfeld et al., 2007b, 2010b; Zimmerman and Choi-Kain, 2009). A reduced cortisol suppression has been associated with comorbid depression (Rinne et al., 2002). Of note, reduced cortisol suppression to dexamethasone was also obtained in non-depressed BPD patients (Lieb et al., 2004), indicating that reduced feedback inhibition in BPD may depend not only on additional MDD diagnosis. However, there are also inconsistent results showing increased feedback inhibition in BPD patients (Carrasco et al., 2007).

Alterations of the HPA stress response system are supposed to be an important vulnerability factor for developing MDD (Dedovica et al., 2010) and might also influence some of the symptomatology associated with BPD (Wingenfeld et al., 2010b). Although the origin of these HPA axis abnormalities still remains not fully understood, traumatic experiences in childhood are supposed to play a major role in HPA axis irregularities (Heim et al., 2008a). Preclinical and clinical studies have frequently presumed that early life stress has long-lasting effects on the activity of the HPA axis by altering glucocorticoid receptor functioning (Kaufman et al., 2000; Teicher et al., 2003; Heim et al., 2008b). Likewise, exposure to childhood trauma is recognized as major antecedent for BPD and MDD (Zanarini et al., 1997; Johnson et al., 1999; MacMillan et al., 2001; Molnar et al., 2001). Consequently, HPA axis dysregulations have been suggested to act as one potential mechanism that mediates the effects of early life adversities on developing mood-related psychiatric symptoms.

In MDD, neuroendocrine research offered considerable evidence for a link between childhood maltreatment experiences and altered HPA function (Heim et al., 2008b). In BPD patients with a history of sustained childhood abuse, Rinne et al. (2002) also observed HPA axis dysregulations, but the relation between early traumatization and HPA alterations in BPD remain to be sufficiently clarified. It has been speculated that distinct symptom profiles may have different neuroendocrine correlates (Zimmerman and Choi-Kain, 2009) as, for example, dissociative symptoms were shown to be correlated with HPA reactivity (Simeon et al., 2007). Moreover, abnormal HPA axis functions have also been reported in other psychiatric disorders related to trauma experience like posttraumatic stress disorder (PTSD) and stress-related bodily disorders (e.g. fibromyalgia) (Heim et al., 2000; Wingenfeld et al., 2007c). Interestingly, and in contrast to MDD, the some of these findings suggested PTSD and bodily disorders to be associated with hypocortisolism (Heim et al., 2000; Yehuda, 2002; Wingenfeld et al., 2007c). However, HPA abnormalities related to childhood trauma experiences have also been found in the absence of current and lifetime psychopathology (Carpenter et al., 2009; Klaassens et al., 2009). In sum, research on the link between childhood adversities and HPA axis dysfunctions has revealed contradictory findings with both increased and decreased cortisol levels, suggesting that factors like different types of maltreatment and the psychiatric sequelae of early life stress contribute differentially to the observed HPA irregularities (Miller et al., 2007; Flory et al., 2009).

The objective of our study was twofold. Firstly, we compared basal cortisol levels and feedback sensitivity of the HPA axis between patients with MDD and BPD and healthy control subjects, as previous results were inconsistent, especially for BPD patients. We hypothesized that MDD as well as BPD patients would show an enhanced basal cortisol secretion and a reduced feedback sensitivity of the HPA axis in comparison to the healthy control group. Secondly, we further aim to investigate the association of childhood traumatic experiences and psychopathology with cortisol release, hypothesizing childhood trauma to be potent predictor of HPA axis dysregulations.

2. Methods

2.1. Participants

The clinical group consisted of 24 patients with BPD and 33 patients with MDD as primary diagnosis. All patients were consecutively recruited from the Clinic of Psychiatry and Psychotherapy Bethel, Ev. Hospital Bielefeld, and at the Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf & Schoen-Klinik Hamburg-Eilbek, Germany. The control group included

Table 1 Descriptive, clinical and neurocognitive characteristics of patients and controls.

	BPD (n = 24) N or M (SD)	MDD (n = 33) N or M (SD)	HC (n = 41) N or M (SD)	Statistics
Demographic variables				
Age	26.92 (5.98)	33.42 (8.96)	33.00 (10.44)	$F_{(2,97)} = 4.39$, $p = .02$
Gender (m/f)	(1/23)	(14/19)	(13/28)	$\chi^2 = 8.69$, $p = .01$
Education (years)	11.54 (1.56)	11.15 (1.58)	11.71 (1.57)	$F_{(2,97)} = 1.17$, $p = .32$
BMI [a]	24.00 (6.07)	23.59 (5.17)	23.73 (4.01)	$F_{(2,96)} = .05$, $p = .95$
Smoker	12	21	8	$\chi^2 = 15.50$, $p < .01$
Clinical measures				
BSL [b]	163.22 (70.02)	110.94 (52.18)	28.40 (21.11)	$F_{(2,91)} = 64.89$, $p \leqq 001$
BDI [b]	25.49 (9.51)	22.23 (9.26)	2.76 (3.65)	$F_{(2,91)} = 92.49$, $p \leqq .001$
DSS [a]	24.97 (16.97)	17.53 (11.76)	3.96 (4.73)	$F_{(2,96)} = 29.48$, $p \leqq .001$
CTQ EA [c]	15.09 (6.84)	12.03(5.89)	7.20 (2.82)	$F_{(2,89)} = 19.24$, $p \leqq .001$
CTQ PA [c]	8.50 (4.10)	7.88 (4.94)	5.95 (1.99)	$F_{(2,89)} = 4.31$, $p = .016$
CTQ SA [c]	8.27 (4.97)	6.93 (4.51)	6.07 (2.88)	$F_{(2,89)} = 2.19$, $p = .118$
CTQ EN [c]	16.42 (5.04)	15.07 (5.48)	10.17 (5.96)	$F_{(2,89)} = 11.12$, $p \leqq .001$
CTQ PN [c]	9.50 (3.32)	9.34 (4.11)	7.47 (3.32)	$F_{(2,89)} = 3.31$, $p = .041$
CTQ total [c]	57.78 (18.82)	51.25 (18.07)	36.86 (15.29)	$F_{(2,89)} = 12.42$, $p \leqq .001$

Note. BPD, borderline personality disorder; MDD, major depression disorder; HC, healthy controls; BMI, body mass index; BSL, Borderline Symptom List; BDI, Beck Depression Inventory; DSS, Dissociation Tension Scale; CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect.

[a] Data missing for one participant.

[b] Data missing for six participants.

[c] Data missing for eight participants.

41 healthy individuals responding to local advertisements. All participants underwent the Structured Clinical Interviews for DSM-IV Axis I and II (Wittchen et al., 1997) before being admitted to the study. Subjects suffering from serious somatic illness, neurological disorders, endocrine diseases, alcohol or drug dependence, lifetime psychosis, and mental retardation were excluded after exhaustive anamnesis and an additional examination by a psychiatrist in the case of the patient groups. Additional exclusion criteria were pregnancy, use of beta-blockers and acute infections.

For the clinical group, current use of antidepressant medication did not lead to exclusion. 59.6% of the clinical group were treated with psychotropic medication: SSRI (BPD: n = 5; MDD: n = 7), SSNRI (BPD: n = 2; MDD: n = 2), TAD (BPD: n = 2; MDD: n = 5), SNRI (MDD: n = 2), MAOI (MDD: n = 1). Further, female subjects using oral contraceptives were not withdrawn from study participation. However, the diagnostic groups did not differ concerning the use of oral contraceptives (BPD: n = 10; MDD: n = 3; controls: n =9; χ^2 = .4.48, p = .175) and menstruation status (χ^2 = .11, p = .946).

Basic demographic characteristics are presented in Table 1. The three diagnostic groups showed differences for age and gender distribution, indicating that patients with BPD were significantly younger than MDD patients (p = .031) as well as healthy controls (p = .036) and consisted of more females (χ^2 = 8.69, p = .01). The groups differed in smoking status with more BPD (50.0%) and MDD (63.6%) patients being smokers than controls (19.5%). Moreover, comorbid psychiatric conditions were highly prevalent in the clinical groups. In the BPD group, we found a high comorbidity with current depression (n = 13). Furthermore, nine BPD patients and six MDD patients also met criteria for an additional anxiety disorder, with posttraumatic stress disorder being the most prominent (BPD: n = 6, MDD: n = 2), and five BPD patients had a comorbid eating disorder. No patient of the BPD and MDD group met criteria for any additional diagnosis on axis II.

Written informed consent was obtained from all participants. The healthy participants received monetary compensation (100 €). The study was accepted by the University of Muenster Ethics Committee as well as by the Ethics Committee of the Medical Council of Hamburg.

2.2. Instruments and procedure

2.2.1. Endocrine assessment

We assessed free cortisol levels from saliva. Saliva samples were collected on two consecutive (preferably working) days at 0730 h, 1130 h, 1730 h, and 2000 h, using the Salivette collecting device (Sarstedt, Rommelsdorf, Germany). For evaluating cortisol negative feedback inhibition, participants took an oral dose of 0.5 mg of dexamethasone (DEX) at 2300 h on the first day (low-dose DST). All subjects were instructed to refrain from physical exercises, smoking, eating, drinking (except water) and brushing their teeth for 30 min before sampling. Saliva samples were stored in refrigerators until the morning after the second day and were then stored at −80 °C until later analysis. All biochemical analyses were performed using a commercial radioimmunoassay kit in the Department of Biological Psychiatry, University Medical Center Hamburg-Eppendorf (Germany). Interassay and intraassay coefficients of variation were below 8%.

2.2.2. Questionnaire data

Severity of borderline symptomatology was assessed by the Borderline Symptom List (BSL; Bohus et al., 2007). The BSL is a reliable self-report measure of borderline symptomatology based on the DSM-IV criteria for BPD. Internal consistency of the BSL in the current sample was excellent (α = .98).

Depressive pathology was measured by the Beck Depression Inventory (Beck and Steer, 1994). The BDI is a 21-item self-rating instrument with established reliability and validity. The internal consistency in this study was high (α = .94).

The Dissociation Tension Scale (Stiglmayr et al., 2001) is a measure for acute dissociative symptoms and aversive inner tension. Internal consistency of the DSS was very good (α = .93).

The Childhood Trauma Questionnaire (CTQ; Bernstein and Fink, 1998; Wingenfeld et al., 2010a) was used to assess history of self-reported childhood trauma across five dimensions: emotional, sexual, and physical abuse as well as emotional and physical neglect. The internal consistency in the current sample was high for the total score (α = .94) and the subscales emotional abuse (α = .89), physical abuse (α = .83), sexual abuse (α = .90) and emotional neglect (α = .94), but internal consistency for physical neglect (α = .62) was marginal.

2.3. Data analyses

Demographic, clinical and neurobiological data were analyzed using χ^2-test and one-way ANOVA followed by Bonferroni corrected post hoc comparisons. In order to control for any confounding effects of differences in age, gender and smoking status between the diagnostic groups, these variables were considered as covariates in subsequent analyses including cortisol measures. Repeated measure analysis of covariance (ANCOVA) was conducted to analyze endocrine data, with treatment and time as within-subject factors and group as between-subject factor.

As a marker for total cortisol secretion before and after dexamethasone administration, we computed the area under the curve (AUC). The DST response was further analyzed by percent cortisol suppression. To analyze associations between endocrine and clinical data we calculated Pearson correlations with Bonferroni adjustment (corrected alpha = .02).

Separate hierarchical multiple linear regression analyses were conducted to analyze simultaneously the associations of the study variables with endocrine data, i.e. AUC before and after DEX, respectively. In the first two steps, the regression analyses were controlled for age, gender and smoking status (step 1) and psychiatric diagnosis (step 2: major depression, borderline personality disorder) as potential confounding factors. In the third step, the set of psychopathology variables (depression, borderline symptoms, dissociation) was included in the model and, in the final step, early traumatic experiences (step 4: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) were entered into the regression analyses.

For all analyses significance level was set at .05. All analyses were conducted using PASW Statistics 18.0 (SPSS, Chicago, IL, USA).

3. Results

3.1. Endocrine data

Fig. 1 shows the distribution of salivary cortisol concentration before and after dexamethasone administration. A repeated-measures ANCOVA of the low-dose DST data revealed a significant effect of dexamethasone treatment

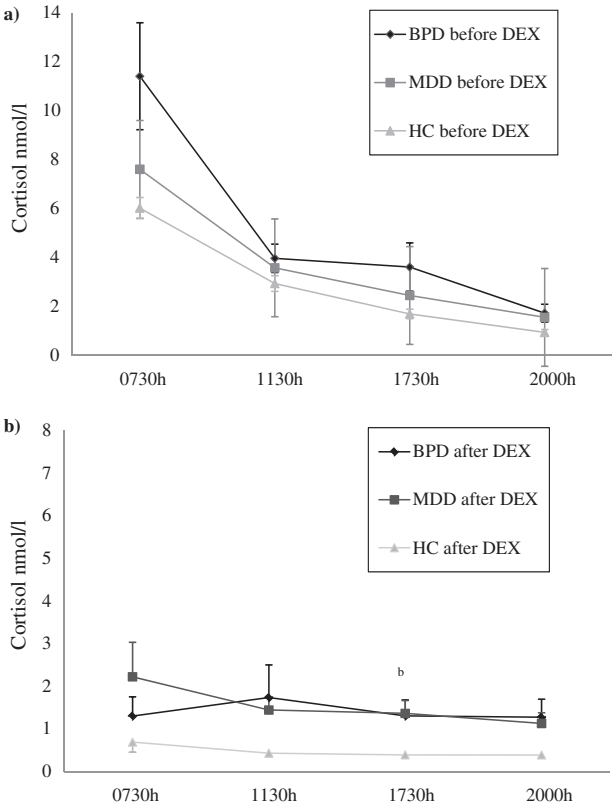

Figure 1 Cortisol concentrations (mean/standard error of the mean) before (a) and after (b) dexamethasone (DEX) intake in patients with borderline personality disorder (BPD) (n = 24), patients with major depressive disorder (MDD) (n = 33) and healthy control participants (HC) (n = 41). [a] For subjects with BPD versus control subjects, $p < .05$. [b] For subjects with MDD versus control subjects, $p < .05$.

($F_{(1,92)}$ = 5.09, p = .026) indicating a significant suppression of cortisol levels after DEX in all study groups. Cortisol concentrations showed a significant diurnal variation (main effect of time: $F_{(3,92)}$ = 7.98, p = .002) and were significantly higher in the patient groups compared with controls (main effect of group: $F_{(2,92)}$ = 5.236, p = .007). The interaction terms were not significant except for the time × treatment × group interaction ($F_{(6,92)}$ = 2.80, p = .043) indicating that the study groups had a distinct pattern of response to DEX over time and cortisol levels differentially decreased after DEX in the groups. None of the covariates age ($F_{(1,92)}$ = .58, p = .450), gender ($F_{(1,92)}$ = 1.40, p = .239) and smoking status ($F_{(1,92)}$ = .01, p = .913) had a significant effect on the DST response.

Post hoc comparisons indicated that BPD as well as MDD patients exhibited higher overall cortisol levels than the control subjects (BPD: p = .012; MDD: p = .048). BPD and MDD patients differed not significantly according to the DST data (p = .999).

Further post hoc analyses at each time of measurement revealed significant higher cortisol levels for BPD patients than controls at measurement 0730 h (p = .031) and, by trend, at 1730 h (p = .085) before DEX as well as at 1130 h (p = .086) after DEX. The comparison between MDD patients and control subjects showed significant differences only at

measurement 1730 h ($p = .040$) and, by trend, at 0830 h ($p = .054$) after DEX.

Given that antidepressants may affect HPA activity, we repeated the above analyses after exclusion of participants receiving psychotropic medication. Results of the medication-free subgroup (BPD: $n = 11$; MDD: $n = 12$; HC: $n = 41$) obtained by ANCOVA indicated again a significant effect of treatment ($F_{(1,58)} = 4.67$, $p = .035$) and time ($F_{(3,58)} = 10.17$, $p < .001$) as well as a main group effect ($F_{(2,58)} = 5.98$, $p = .004$). Cortisol levels after DEX were significantly higher in the medications-free patient groups compared to the healthy control subjects (treatment x group interaction: $F_{(2,58)} = 6.84$, $p = .002$). The significant three-way interaction time $\times$ treatment $\times$ group ($F_{(6,58)} = 6.32$, $p < .001$) and some pairwise comparisons indicated again distinct patterns of DST over time among the groups. There was a significant lower cortisol suppression in the medication-free MDD group after DEX at measurement 0730 h ($p = .023$) in comparison to the healthy control subjects. By contrast, the medication-free BPD group showed significant higher cortisol levels at 1130 h ($p = .042$), 1730 h ($p = .037$) and at 2000 h ($p = .036$) compared to the healthy control group. Again, age ($F_{(1,58)} = 1.89$, $p = .175$), gender ($F_{(1,58)} = .11$, $p = .738$) and smoking status ($F_{(1,58)} = .09$, $p = .766$) as covariates had no impact on the outcomes.

Due to the high comorbidity rates found in BPD patients, we additionally conducted separate subgroup analysis in the BPD group based on the presence or absence of comorbid MDD and PTSD, addressing the issue of differential responses to DST. Notably, no significant group difference between the different comorbid conditions were found ($F_{(3,20)} = .33$, $p = .806$).

DST data were further examined by analysis of AUC before and after DEX as well as percentage suppression of cortisol (see Table 2). Comparing the AUC values for cortisol pre- and post-dexamethasone using ANCOVA, we found a significant group effect for the AUC post-dexamethasone ($F_{(2,92)} = 3.93$, $p = .023$), whereas the group effect for AUC pre-dexamethasone just failed to reach statistical significance ($F_{(2,92)} = 3.05$, $p = .052$). Post hoc comparisons exhibited significantly higher AUC post-dexamethasone cortisol levels in MDD patients than in control subjects ($p = .028$), but there were no significant differences of AUC post-dexamethasone levels between participants with BPD and control subjects ($p = .166$). Post hoc comparison did not confirm any significant difference in AUC values between BPD and MDD patients (all $p > .562$).

The ANCOVA analyzing the percent cortisol suppression also revealed a significant group effect ($F_{(2,92)} = 3.16$, $p = .047$). However, subsequent post hoc comparisons failed to show any significant difference between the study groups (all $p > .09$), although the power to detect a difference in percent cortisol suppression between the diagnostic groups may have been low due to small sample size. When collapsing the groups into a depressed group (MDD patients) and a non-depressed group (BDP patients and healthy controls), percent cortisol suppression was significantly higher in the MDD group than in the combined group of BDP patients and healthy controls ($F_{(1,93)} = 6.22$, $p = .014$).

Again, the covariates age, gender and smoking status had no significant effects on the AUC values and percent cortisol suppression (all $p > .092$).

Analogous to the previous analyses, ANCOVAs were rerun with the medication-free subgroup. AUC analysis revealed again a main effect of group for pre-dexamethasone ($F_{(2,58)} = 3.73$, $p = .028$), post-dexamethasone values ($F_{(2,58)} = 3.24$, $p = .046$) and cortisol suppression percentage ($F_{(2,58)} = 3.19$, $p = .049$). However, most post hoc comparisons failed to detect significant differences among the groups. The only significant difference was between BPD patients and healthy control subjects indicating higher pre-dexamethasone levels in the BPD group ($p = .025$). In all analysis of medication-free participants, there were no effects of the covariates age, gender and smoking status on the results except for age which had an effect on cortisol suppression percentage by trend level ($p = .074$).

Likewise, the analyses were repeated in the BPD subgroups (with and without MDD and/or PTSD), investigating the effects of comorbidity on the outcomes. Again, the ANOVA revealed no group effects for pre-dexamethasone AUC ($F_{(3,20)} = .07$, $p = .976$), post-dexamethasone AUC ($F_{(3,20)} = 1.38$, $p = .277$) and percent cortisol suppression ($F_{(3,20)} = 1.60$, $p = .221$).

3.2. Clinical data

As expected, both clinical groups reported higher levels of depressive and borderline symptoms than control subjects (all $p < .001$, see Table 1). In comparison to MDD patients, BPD subjects showed more borderline symptomatology ($p = .001$), but there was no significant difference in depressive symptoms between both patient groups ($p = .363$). Furthermore, traumatic childhood experiences were more common in both clinical groups. BPD and MDD were more likely to report emotional abuse and neglect (all $p < .002$) than the healthy controls. BPD patients also reported more physical abuse ($p = .028$) compared to healthy controls but showed no difference according to sexual abuse ($p = .118$) and physical neglect ($p = .103$). No group differences were observed between MDD patients and control subjects in respect to physical abuse, sexual abuse and physical neglect (all $p > .104$). Moreover, no significant differences between both clinical groups were obtained according to self-reported traumatic experiences (all $p > .111$).

Table 2 Neuroendocrine response to the dexamethasone suppression test (mean/standard error of the mean) measured as area under the curve (AUC) before and after dexamethasone and percentage of suppression by dexamethasone in patients and controls.

	BPD ($n = 24$)	MDD ($n = 33$)	HC ($n = 41$)	Statistics
AUC before DEX	60.70 (7.90)	47.14 (5.32)	36.93 (2.75)	$F_{(2,92)} = 3.05$, $p = .052$
AUC after DEX	19.09 (7.02)	19.02 (3.83)	5.75 (.86)	$F_{(2,92)} = 3.93$, $p = .023$
Percent suppression	71.01 (8.31)	48.86 (14.91)	77.77 (5.74)	$F_{(2,92)} = 3.16$, $p = .047$

Note. AUC, area under the curve; BPD, borderline personality disorder; MDD, major depression disorder; HC, healthy controls.

3.3. Associations between cortisol and clinical data

Results of correlation analyses indicated that basal cortisol secretion quantified by the pre-dexamethasone AUC was positively associated with self-reported emotional childhood abuse, severity of depression, dissociation and borderline symptomatology. Post-dexamethasone AUC values were positively related to emotional, physical and sexual abuse, physical neglect, overall childhood trauma (CTQ total score) and all measurements of psychopathology (see Table 3). The only variable associated to cortisol suppression was physical abuse experience with high physical abuse being related to a lower suppression of cortisol.

We computed two separate hierarchical multiple linear regression analyses: one for each of the dependent variables of interest (AUC before and after DEX). In each analysis, sociodemographic variables (step 1: age, gender, smoking status) and diagnostic status (step 2: diagnosis of MDD, diagnosis of BPD) were entered to control for potential confounding factors. The set of psychopathology variables (step 3: depression, borderline symptoms, dissociation) was entered as the third block and CTQ subscales (step 4: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) were entered jointly as a set of predictors in the final block.

In the hierarchical regression analyses of the AUC before DEX, neither the first step (sociodemographic variables: $F_{(3,86)} = 2.19$, $p = .095$), the second step (diagnostic status: $F_{(5,86)} = 2.22$, $p = .060$) nor the third step (psychopathology: $F_{(8,86)} = 1.58$, $p = .143$) did contribute significantly to any of these regression models. Including the CTQ variables on the fourth step, the regression model also did not reach statistical significance ($F_{(8,86)} = 1.58$, $p = .143$), but some CTQ variable contributed to the model (see Table 4). Thus, only experiences of childhood trauma predicted significantly higher AUC values ($F_{(13,86)} = 1.96$, $p = .037$). As shown in Table 4, emotional and physical abuse were significant predictors of basal cortisol release over the day, while emotional and physical neglect did not contribute to the model. However, when only analyzing the impact of CTQ scores a significant model could be revealed: $F_{(5,86)} = 3.92$, $p = .003$, $\Delta R^2 = .15$. Again, emotional and physical abuse were the significant predictors.

Analyzing the cortisol release after DEX, again, the first two steps of the regression analyses (sociodemographic variables: $F_{(3,86)} = .73$, $p = .54$; diagnostic status: $F_{(5,86)} = 1.07$, $p = .38$) did not provide any significant prediction. After the addition of the psychopathology variables on the third step, the regression model reached statistical significance ($F_{(8,86)} = 2.24$, $p = .033$). The final model of the hierarchical regression analyses ($F_{(13,86)} = 2.35$, $p = .011$) added incremental predictive variance, but only on trend level: childhood trauma $\Delta R^2 = .11$, $p = .058$. Results for the regression analysis are also presented in Table 4. Although the model on the third step reached statistical significance, depressive symptoms contributed only by trend level ($p = .088$) to the prediction of cortisol after DEX (positive beta weight). In the final model, emotional neglect ($p = .013$) and, by trend, emotional abuse ($p = .088$) served as significant predictors (positive beta weight), while emotional neglect contributed with a negative beta weight to the model. Depressive symptoms were not confirmed as predictor of cortisol after DEX in the final model.

Table 3 Correlations between salivary cortisol and clinical measures.

	AUC before DEX	AUC after DEX	Percent suppression
Clinical measures			
CTQ EA[c]	.29*	.34*	−.17
CTQ PA[c]	−.05	.30*	−.37*
CTQ SA[c]	.15	.26*	−.05
CTQ EN[c]	.12	.18	−.09
CTQ PN[c]	.04	.24	−.11
CTQ total	.15	.33*	−.18
BSL[a]	.28*	.37*	−.12
BDI[a]	.23	.37*	−.12
DSS[b]	.30*	.25*	−.17

Note. AUC, area under the curve; DEX, dexamethasone; CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect; BSL, Borderline Symptom List; BDI, Beck Depression Inventory; DSS, Dissociation Tension Scale.

[a] Data missing for six participants.

[b] Data missing for one participants.

[c] Data missing for eight participants.

* Significant correlation after Bonferroni adjustment ($p < .02$).

4. Discussion

In this study, we investigated the associations of childhood trauma and psychopathology with HPA activity, i.e. cortisol levels before and after dexamethasone, in a sample of BPD and MDD patients as well as healthy control participants. Our results suggested some HPA axis abnormalities in the patient groups investigated in comparison to healthy control subjects. Consistent with our hypothesis, HPA axis hyperactivity indicated by enhanced salivary cortisol concentrations before and after dexamethasone administration was found in both borderline and depressed patients compared to the control subjects, which might indicate some neuroendocrine similarities between these two disorders. Although basal and post-dexamethasone cortisol levels were elevated in both MDD and BPD patients, analyzes of percentage cortisol suppression did not confirm a reduced feedback sensitivity in these two groups compared to controls. Thus, our results were, in part, compatible with previous studies emphasizing enhanced cortisol release in borderline and depressive psychopathology (Pariante and Miller, 2001; Wingenfeld et al., 2010b; Wingenfeld and Wolf, 2011). Against our prediction, however, we found MDD and BDP not associated with a decreased glucocorticoid feedback inhibition which was hypothesized to be a possible mechanism underlying hypercortisolism in MDD and BPD. However, despite the absence of a clear evidence for a reduced feedback sensitivity, responses to low-dose DST in the patients groups tended to differ from healthy controls, especially in the case of the MDD group.

Furthermore, comorbid MDD and/or PTSD did not contribute to the DST results in the BPD group, indicating that hypercortisolism in BPD seem not to depend on comorbid

conditions such as MDD or PTSD in our sample. Thus, the current data do not replicate the finding by Rinne et al. (2002) which suggest differences between BPD patients with and without PTSD and MDD, respectively. However, in our study, base rates of comorbid combinations within the BPD group were rather small and results of subgroup analyses should be regarded as preliminary. In the current sample only six BPD patients suffered from comorbid PTSD whereas in one of our previous studies 16 out 21 BPD patients had also PTSD (Wingenfeld et al., 2007a). In this previous sample, we found influences of the severity of PTSD and depressive symptoms but only on a correlative level (Wingenfeld and Driessen, 2007). In sum, although the issue of comorbidity in BPD still remains to be clarified, the here presented data together with the study by Lieb et al. (2004) suggested BPD patients to have an enhanced basal cortisol activity.

The main objective of the present study was to investigate the association between childhood trauma and psychopathology with HPA axis function. Based on prior studies, we hypothesized that HPA axis dysregulations were particularly linked to early childhood adversities. We found moderate correlations between measurements of psychopathology, childhood trauma and enhanced cortisol release. Our findings support and augment previous results suggesting an association of HPA activity and early life stress (Heim et al., 2008b; Zimmerman and Choi-Kain, 2009). In our study, we found these associations primarily for post-dexamethasone cortisol levels, possibly indicating a relation to a decreased sensitivity to DEX. However, percentage of cortisol suppression was only associated with physical abuse. Thus, our results accord with earlier suggestions that early childhood adversities might contribute to long-lasting alterations in central glucocorticoid receptor functioning (McGowan et al., 2009). The fact that all measurements of psychopathology were associated with cortisol release before and after DEX providing further evidence for a link between HPA axis

Table 4 Results of the multiple regression analyses.

Dependent variable	Predictor variable[a]	Model 1		Model 2		Model 3		Model 4	
		R^2	β	R^2	β	R^2	β	R^2	β
AUC before DEX (N = 89)		.04		.07		.05		.13	
	Age		−.22		−.12		−.11		−.01
	Gender		−.08		−.02		−.02		.08
	Smoking status		.19		.11		.10		−.02
	Diagnosis of MDD				.07		.03		.12
	Diagnosis of BPD				.24		.18		.17
	PSYCH								
	BDI						−.07		−.26
	BSL						−.01		.14
	DSS						.20		.21
	CTQ								
	EA								.47*
	PA								−.36*
	SA								.24
	EN								−.25
	PN								−.08
AUC after DEX (N = 89)		−.01		.01		.10		.17	
	Age		−.11		−.05		−.05		−.10
	Gender		−.07		−.05		−.06		.04
	Smoking status		.11		−.01		.04		−.07
	Diagnosis of MDD				.19		−.17		−.04
	Diagnosis of BPD				.11		−.21		−.15
	PSYCH								
	BDI						.42		.40
	BSL						.22		.01
	DSS						−.03		−.03
	CTQ								
	EA								.32
	PA								.13
	SA								.19
	EN								−.51*
	PN								.27

Note. AUC, area under the curve; DEX, dexamethasone; CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect; PSYCH, psychopathology; BDI, Beck Depression Inventory; BSL, Borderline Symptom List; DSS, Dissociation Tension Scale.

[a] Questionnaire data were not complete for 11 participants.

* $p < .05$.

dysregulations, i.e. hyperactivity, and depression, borderline symptoms and dissociation, respectively (Simeon et al., 2007; Heim et al., 2008b; Wingenfeld et al., 2010b).

While simple correlation analyses showed only positive associations between measurements of childhood trauma, psychopathology and cortisol release, hierarchical multiple linear regression revealed a more detailed and less expected picture: when simultaneously analyzing variables of psychopathology and childhood trauma we found that psychopathology was not associated with cortisol release. Only depressive symptoms were related to cortisol release after dexamethasone treatment but only trend level, suggesting a slight association between depression and enhanced cortisol release in the DST. Of note, others also suggested that the degree of HPA axis dysfunction appeared to be rather independent from depression symptom severity (Michopoulos et al., 2008; Vreeburg et al., 2009). This accords also with earlier observations that hypersecretion of cortisol may represent an endophenotype of depression which could also be found in asymptomatic individuals at high risk for depression (Mannie et al., 2007).

Furthermore, some aspects of childhood trauma were found to be associated differentially with cortisol release. While emotional abuse was positively associated with basal cortisol release, an opposite effect was found for physical abuse. It seemed that the more physical abuse the participants reported the lower were the basal cortisol levels. Similarly, emotional neglect was negatively associated with cortisol levels after dexamethasone, when simultaneously analyses with the other CTQ subscales. Contrary, emotional abuse was positively associated with cortisol release after DEX by trend. Our findings could not fully confirm the results of one study showing emotional abuse (also measured with the CTQ) to be related to diminish cortisol release in the combined dexamethasone/corticotropin releasing hormone (DEX/CRH) test (Carpenter et al., 2009). In the study by Rinne et al. (2002), childhood physical and sexual abuse was associated with enhanced cortisol release in the DEX/CRH test, while BPD patients without abuse experiences seem to have even lower cortisol values compared to healthy controls. Whether these patients had experienced other forms of early life stress, e.g. emotional neglect might be only speculated. In sum, there is growing evidence that different types of trauma may be involved in the regulation of the HPA axis but up to now it remains unclear which type of trauma contributed most to HPA abnormalities and in which direction. Fortunately, research has begun to address this question (Rinne et al., 2002; Carpenter et al., 2009).

Our study results had some limitations which need to be mentioned. First, the current study is based on a cross-sectional, correlational design which precludes firm conclusions on the directionality and causality of the observed results. Experimental designs are needed to elucidate the underlying mechanisms. It would be also useful to investigate a healthy control group with childhood trauma. A further limitation was that only self-report data of early childhood trauma were available and no assessment of acute stressor (e.g. daily hassles) or even adult traumatization and associated posttraumatic stress symptoms was performed. It should be taken into account that stress in adulthood can influence the HPA system above and beyond the effects of childhood trauma (Heim and Nemeroff, 2002). In one of our own studies we have shown that various aspects of childhood trauma, as well as trauma in adulthood and current stressors differentially influences psychopathology. Furthermore, and despite our procedure to control for confounding factors, we cannot rule out that these factors (e.g. age, gender, smoking status) may have influenced our results, which is a major limitation of our study. Similarly, the use of psychotropic medication and hormonal contraceptives may represent other confounding factors. However, in the current study, our results could be confirmed after exclusion of participants receiving antidepressant medication. Using larger samples in future research would allow disentangling effects of childhood trauma, psychopathology and possible confounding factors on HPA axis via more sophisticated statistical models, which was not possible in our sample. However, the strength of the present study is the use of multiple cortisol measures, such as basal activity and challenge conditions. For future studies, it would be indeed useful to have additional HPA axis measurements (e.g. cortisol awakening response) and different neuroendocrine challenge tests like the adrenocorticotropic hormone (ACTH) challenge test or the combined dexamethasone and corticotropine-releasing hormone (DEX/CRH) test as more sensitive markers of feedback sensitivity. Furthermore, the cross-sectional design of the study limits the interpretations. A further strength is the direct comparison between patients with BPD and MDD. Up to now, both patient groups have mostly been investigated separately.

In summary, our study results support the relevance of HPA functioning in the pathogenesis of BPD and MDD. The presented findings suggest that BPD and MDD patients may have some neuroendocrine similarities, including enhanced cortisol secretion. Moreover, childhood trauma seems to play an important role within the regulation of HPA axis. Future study should aim to further disentangle the effects of different types of traumatic experiences.

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Conflict of interest

There were no conflicts of interest, financial or otherwise, to declare.

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