The neuro-endocrine scars of sustained childhood abuse in adult female patients with borderline personality disorder
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Chapter 3.1

Hyperresponsiveness of Hypothalamus-Pituitary-Adrenal Axis to Combined Dexamethasone / Corticotropin-Releasing Hormone Challenge in Female Borderline Personality Disorder Patients with a History of Sustained Childhood Abuse

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Abstract

Background: In borderline patients a high coincidence of childhood abuse, MDD and PTSD has been reported. Animals exposed to early trauma show increased stress-induced HPA activity due to an enhanced corticotropin-releasing hormone (CRH) drive and glucocorticoid feedback resistance. In humans, Posttraumatic Stress Disorder (PTSD) and Major Depressive Disorder (MDD) are associated with decreased and increased resistance to glucocorticoid feedback respectively, which might reflect persistent changes in neuroendocrine sequelae following childhood abuse (in vulnerable subjects).

Method: The relationship between childhood abuse and functioning of the HPA-axis was investigated using a combined dexamethasone/corticotropin-releasing-hormone (DEX/CRH) test in 39 BPD patients (with (N=24) and without (N=15) sustained childhood abuse and comorbid PTSD (N=12) and/or MDD (N=11)) and 11 healthy controls.

Results: Chronically abused borderline patients had a significantly enhanced ACTH and cortisol response to the DEX/CRH challenge compared to non abused subjects. Comorbid PTSD significantly attenuated the ACTH response.

Conclusion: The hyperresponsiveness of the HPA-axis in the chronically abused BPD subjects might be due to the enhanced central drive to pituitary ACTH release. Sustained childhood abuse rather than BPD, MDD or PTSD pathology accounts for this effect. PTSD attenuates the ACTH response to DEX/CRH possibly due to an enhanced efficacy of HPA suppression by dexamethasone.
Introduction

Recent studies suggest that childhood abuse is an important factor in the pathogenesis of borderline personality disorder. (Herman et al 1989; Ogata et al 1990; Salzman et al 1993) However, there is also evidence that early trauma may increase vulnerability to the occurrence of a major depressive disorder (MDD) and post traumatic stress disorder (PTSD) in later life. (Gladstone et al 1999; Heim et al 1999; Stein et al 1997) Moreover MDD and PTSD are often diagnosed in borderline patients. (Zanarini et al 1998) In fact, 20 to 40% of borderline patients meet the DSM-IV criteria for PTSD in response to childhood abuse or superimposed on borderline pathology due to later traumatic experiences. (Gunderson et al 1993).

Patients suffering from MDD or PTSD often display major disturbances in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. For PTSD, several studies have demonstrated a much more potent suppression of the HPA axis by the synthetic glucocorticoid dexamethasone compared to healthy controls. This observation suggests that enhanced glucocorticoid feedback inhibition is a hallmark of PTSD. This enhanced glucocorticoid feedback is probably due to hypersensitivity on the part of the pituitary and/or brain glucocorticoid receptors (GRs). As a consequence of such heightened feedback, the circulating cortisol levels are low and the patients display symptoms of apparent hypocortisolism (Yehuda et al 1990; Yehuda et al 1993; Yehuda 1998). In contrast, glucocorticoid feedback inhibition has been found to be attenuated in a large population of depressed patients. These individuals display hypercortisolism and resistance to the suppression of the HPA axis by exogenous dexamethasone. (Carroll et al 1981a; Carroll 1982; Evans et al 1985). However, MDD and PTSD appear to share an enhanced central corticotropin releasing hormone (CRH) drive towards HPA axis activation. (Baker et al 1999; Bremner et al 1997; Gold et al 1986; Heim et al 2001; Holsboer et al 1987a; Kaufman et al 1998; Smith et al 1989; von Bardeleben et al 1988).

Recent animal research data suggest that adverse circumstances during early development may permanently affect the HPA axis and cognitive functioning (Oitzl et al 2000). The long-term effects of deprivation of rat infants from maternal care include an enhanced CRH and/or arginine vasopressin AVP drive from the hypothalamus, an enhanced glucocorticoid response to stress, and altered expression of mineralo- and glucocorticoid receptors in the brain. (Coplan et al 1996; Francis et al 1999; Hatalski et al 1998; Plotsky et al 1993; Sutanto et al 1995; Wolk et al 2001). The enhanced drive by adrenocorticotropic hormone (ACTH) secretagogues is important, as it is known that AVP synergizes and thus potentiates CRH action on to release ACTH from pituitary corticotrophs. (De Goeij et al 1992; Lim 2000) These preclinical HPA axis studies have prompted the examination of the specific influences mediated by the effects of early abuse on adult HPA axis function in a clinical population. Research with traumatized children and most recently with adult female victims of childhood sexual abuse has also demonstrated persistent changes in the HPA axis characterized by an enhanced central drive. (De Bellis et al 1994; Heim et al 2000a; Heim et al 2001; Kaufman et al 1997)

Several studies have been conducted in order to evaluate HPA axis function in borderline patients using the dexamethasone suppression test. The results of these studies have been
inconclusive, however, because the potential effects of a concurrent MDD and/or PTSD have not been taken into account. (Baxter et al 1984; Carroll et al 1981b; Kontaxakis et al 1987; Krishnan et al 1984; Steiner et al 1984; Sternbach et al 1983) In one study, MDD patients with a comorbid borderline personality disorder displayed less suppression of cortisol after dexamethasone than MDD patients without a comorbid borderline disorder. This finding indeed suggests that borderline pathology enhances the feedback inhibition of the HPA axis during depression. Unfortunately, the presence of potential comorbid PTSD was not taken into account in this study. (Soloff et al 1982) (For review, see Lahmeyer (Lahmeyer et al 1989))

Taken together, these findings raise the question of whether alterations in HPA activity in BPD patients are associated with the borderline personality disorder, a comorbid MDD and/or PTSD, or the occurrence of severe childhood abuses sustained childhood abuse. In the present study, we tested the hypothesis that severely abused borderline patients can be distinguished from both not (severely) abused borderline patients and healthy controls by a hyperresponsive HPA axis using a combined dexamethasone/corticotropin releasing hormone challenge test (DEX/CRH test). The test evaluates HPA activity in terms of central CRH/AVP drive and glucocorticoid feedback at the level of the pituitary gland, which is the target organ for both dexamethasone and CRH. (De Kloet 1997; Heuser et al 1994; Holsboer 1989; Hundt et al 2001; Modell et al 1997; von Bardeleben et al 1989; Zobel et al 2001). Differences in the DEX/CRH test between borderline patients are hypothesized to be associated with sustained severe childhood abuse and a comorbid PTSD or MDD can be expected to mitigate and enhance these effects, respectively.
Methods

Subjects:
Physically healthy females (18-50 years) with a possible diagnosis of BPD were recruited from psychiatric outpatient clinics, community mental health centers, and by advertising in newspapers and on the Internet. Given this heterogeneous sampling frame, a rigorous diagnostic procedure was applied to select a homogeneous study population with a (moderately) severe DSM-IV borderline personality disorder. In order to be included in the study, all of the patients had to obtain a score of 110 or more on the borderline trait and distress scale of a self-report screener for personality disorders (ADP-IV), meet 5 or more of the criteria for a borderline personality disorder on a semi-structured borderline diagnostic interview (SIDP-IV), and attain a score of 20 or more on the basis of a semi-structured borderline severity interview (BPDSI). The exclusion criteria were: schizophrenia, a life-time episode of mania, current major depression not lasting more than 4 weeks, current opiate or cocaine abuse/dependence, and current alcohol or cannabis dependence according to a fully structured psychiatric interview (CIDI). A total of 39 subjects qualified for participation in the study.

Eleven healthy female controls were recruited via newspaper advertisements and identified as free of a history of life-time and current mental disorders and current disorders based on the results of structured diagnostic interviews for DSM-IV Axis I (CIDI) and Axis II (SIDP-IV) disorders. None of the controls reported early traumatization during the structured trauma interview (STI). The healthy controls were paid to participate in the study.

All of the eligible subjects were screened for somatic conditions and physically examined to exclude medical illness. An electrocardiogram, a complete blood count, routine blood chemistry, and urine analyses were performed. In contrast to the protocol of Heuser which required a medication free period of one week (Heuser et al., 1994) in the present study all of the subjects had to be medication free for at least 14 days prior to the neuro-endocrine challenge test (fluoxetine six weeks). They were also not allowed to drink alcohol one week prior to the test.

All of the patients and controls provided their -fully informed- written consent. The “Toetsingscommissie Patientgebonden Wetenschappelijk Onderzoek te Arnhem” (officially authorized Dutch Ethical human rights committee) approved of the procedures used in this study.

Assessment:

Diagnosis of BPD (inclusion criteria):
Assessment of DSM-IV Personality Disorder (ADP-IV) (Schotte et al 1998). Prescreening for the presence of a DSM-IV borderline personality disorder was performed using a self-report questionnaire, the Assessment of DSM-IV Personality Disorder (ADP-IV). The ADP-IV consists of 94 items representing the 80 criteria for the 10 different DSM-IV personality disorders and 14 criteria for the depressive and passive-aggressive personality disorders. The item response format emphasizes the pathology conceptualization of the DSM-IV by scoring an item on both a 7-point trait and a 3-point trait-related distress scale. In order to proceed to the next phase in the diagnostic procedure, the BPD subjects had
to attain a score of 110 or more on both the borderline and borderline distress scales. (Schotte et al 1998).

**Structured Interview for DSM-IV Personality Disorders (SIDP-IV).** The presence or absence of a DSM-IV borderline personality disorder was determined using the validated Dutch version of the SIDP-IV. (Jong et al 1996; Pfohl et al 1995) Three psychologists trained by the Dutch translators of the SIDP-IV administered the SIDP-IV. In order to be included in the study, the patient had to meet at least five of the nine borderline criteria.

**Borderline Personality Disorder Severity Index (BPDSI).** (Arntz et al 2002; Weaver et al 1993) The BPDSI was used to select only those borderline patients with moderate to severe pathology. The BPDSI is a semi-structured interview that measures the frequency of borderline symptoms across the past 3 months along a 10-point scale including 0 (no occurrence), 1 (one occurrence in three months), 5 (6 or 7 occurrences in three months or once every two weeks), and 10 (daily). In order to be included in the study, the patients had to score 20 or more on the BPDSI.

**DSM IV axis I Diagnosis:**

*Composite International Diagnostic interview (CIDI)* (Smitten et al 1997; WHO 1997) Diagnosis of Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD). The diagnosis of a MDD and/or PTSD conform the DSM-IV Axis I criteria was obtained using the Dutch version of the computer supported Composite International Diagnostic Interview (CIDI), version 2.1, lifetime module, which explores the presence of both life-time and current DSM-IV mental current disorders as well as a history of a disorder.

**Assessment of childhood abuse:**

*Structured Trauma Interview (STI)* (Draijer 1989)

The Structured Trauma Interview was used to assess traumatic experiences. In this interview, patterns of both physical and sexual abuse are explored along with the occurrence of behaviors such as auto-mutilation, attempted suicide, outbursts of anger, and re-victimization, which are often seen in abused individuals. The frequencies of abuse and related behaviors are scored along a 7-point scale (0 = none, 1 = only once; 2 = once or twice a year; 3 = once or twice in six months; 4 = once or twice a month; 5 = once or twice a week; 6 = daily). The severity of the subjective perception of the abuse is measured along a 5-point scale ranging from 0 (= not distressing) to 4 (= very seriously distressing).

The criteria for the assignment of the borderline patients to the group of “not or mild” childhood abuse or the group of “moderate to severe” childhood abuse was based on an abuse frequency score of 3 and higher and onset of the abuse at an age younger than 16 years.

In a previous study, frequency of abuse was found to be a very reliable predictor of the neuroendocrine sequelae of childhood abuse. (Rinne et al 2000) In addition, frequency of abuse highly correlated with other abuse parameters such as duration in years (r=0.792, p<0.000) and age of onset (r=-0.810, p<0.000).
Neuro-endocrine challenge procedure:
For the combined dexamethasone suppression corticotropine releasing hormone challenge test (DEX/CRH), the refined procedure developed at the Max Planck Institute in Munich was adopted. (Heuser et al 1994).
Participants ingested an oral dosage of 1.5 mg of dexamethasone at 11:00 p.m. the evening before the challenge. To check for ingestion of the dexamethasone, 50 mg of riboflavin was added to the capsule. Riboflavin is rapidly cleared by the kidneys, and the subjects were therefore asked to collect their urine on the morning of the test. On the same morning, the participants were allowed a light breakfast and instructed not to eat or drink after 11:00 a.m. with the exception of water or herbal tea. The participants arrived at the research unit at 1:30 p.m. The riboflavin concentrations in their morning urine were analyzed before 3:00 p.m. They were asked to rest supine on a bed; a cannula was inserted 1:35 p.m.; in the forearm vein and kept open by heparinization. At 3:00 p.m. (after baseline sampling), 100 μg of CRH (Ferring BV, Hoofddorp, The Netherlands) reconstituted in 1 ml of 0.9% saline was administered in the cannula within 30 seconds. Blood samples for cortisol and ACTH plasma level measurement were collected at the following times: 3:00 p.m. (baseline level before CRH ), 3:30 p.m., 3:45 p.m., 4:00 p.m., and 4:15 p.m. Blood, heart rate, and temperature were also measured at the same time points.
Afternoon cortisol and ACTH baseline plasma levels without a challenge probe were measured on a different day. These baseline measurements were taken at the same points in time as the DEX/CRH challenge test measurements.
All of the blood samples were extracted by vacuum into three plain tubes (5 ml); the first tube was discarded. The tubes were immediately placed on ice; after centrifugation, the plasma was kept frozen at -70°C until analysis. Cortisol and ACTH plasma levels were measured using commercially available assays. The cortisol assay was obtained from Boehringer Mannheim and the ACTH assay from Nichols Institute Diagnostics.
The intra- interassay coefficients of variation for cortisol measurement were less than 6% and 10% respectively. The intra- interassay coefficients of variation for ACTH measurement were less than 3.2% and 6.3% respectively.

Statistical analysis:
To start with, all of the continuous measures with distributions departing from normality according to the Shapiro-Wilk W test were normalized using van der Waerden’s method. (Conover 1999; Royston 1982; Royston 1995; Royston 19982; Shapiro et al 1965)
Demographic differences between the BPD patients with sustained childhood abuse (abused BPD), the BPD patients with no or mild childhood abuse (non or mildly abused BPD), and the healthy control subjects (controls) were tested using chi-square tests and univariate analyses of variance when appropriate. Possible differences with regard to psychopathology (MDD and/or PTSD) for the chronically abused versus non or mildly abused BPD patients were also tested using chi-square tests.
Our main hypothesis was that a history of sustained childhood abuse (and not borderline personality disorder as such) would affect the results of the combined DEX/CRH test. The hypothesis was tested using multiple comparison ANOVAs with post-hoc analyses.
using Duncan’s test when the variances were equal and Tamhane’s T2 test when the variances were not equal. The contrasts in these analyses involved the abused BPD, non or mildly abused BPD, and healthy control subjects.

To test the hypothesis that the observed effect is not due to a comorbid MDD and/or PTSD, stepwise backward analyses of covariance were performed using only the data from the BPD patients. Each of the backward analyses of covariance started from the full model involving the factors: sustained childhood abuse, comorbid MDD, comorbid PTSD, and the interactions between these factors. In each step thereafter, the term that contributed the least (alpha 10%) was omitted until the final model was attained or no terms were left.

In both the individual univariate analyses of variance and the stepwise backward analyses of variance, correction for age, body mass index, and contraceptive pill usage was made where necessary.

ACTH and cortisol response to the DEX/CRH test was quantified by calculating the area under the concentration time curve (AUC) by using the trapezoid method. (Heuser et al 1994)

The dependent variables were baseline afternoon ACTH and cortisol plasma levels without the challenge probe, plasma levels after dexamethasone suppression and the AUCs for ACTH and cortisol response after the CRH challenge.

The ACTH and cortisol response to DEX/CRH was also additionally analyzed by using repeated measures ANOVA. The analysis of covariance for a childhood abuse history, PTSD and MDD was performed by using a repeated measures ANCOVA.
Results

Sample characteristics:
No significant differences were detected between the chronically abused BPD patients, non or mildly abused BPD patients, and healthy controls with respect to body mass index, contraceptive pill and nicotine usage, or living situation. However, the abused BPD patients were significantly older and had significantly fewer years of education than the healthy control subjects, whereas the non-abused BPD subjects did not differ significantly from both other groups. Significantly more of the healthy controls were employed than both the chronically abused or mildly abused BPD patients. The two BPD subgroups did not differ significantly with regard to comorbidity or the total BPDSI score (see Table 1).

<table>
<thead>
<tr>
<th>Cohort characteristics</th>
<th>Abused BPD (N=24)</th>
<th>Mild. abused BPD (N=15)</th>
<th>Controls (N=11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>31.21(±8.58)</td>
<td>26.20(±6.41)</td>
<td>24.64(±5.12)</td>
<td>0.028</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>22.75(±4.32)</td>
<td>22.13(±2.77)</td>
<td>21.73(±2.49)</td>
<td>0.709</td>
</tr>
<tr>
<td>Use of nicotine</td>
<td>15 (58.3%)</td>
<td>10 (66.7%)</td>
<td>7 (63.7%)</td>
<td>0.798</td>
</tr>
<tr>
<td>Contraceptive pill</td>
<td>10 (41.7%)</td>
<td>6 (40%)</td>
<td>6 (54%)</td>
<td>0.810</td>
</tr>
<tr>
<td>Married/living together</td>
<td>13 (54%)</td>
<td>8 (53%)</td>
<td>5 (45%)</td>
<td>0.934</td>
</tr>
<tr>
<td>Mean years of education</td>
<td>11.21(±2.25)</td>
<td>13.87(±4.39)</td>
<td>15.9(±2.34)</td>
<td>0.002</td>
</tr>
<tr>
<td>Employment status</td>
<td>8 (33%)</td>
<td>8 (53%)</td>
<td>10 (91%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Psychiatric Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPDSI total score</td>
<td>31.93(±8.86)</td>
<td>33.54(±7.17)</td>
<td>-</td>
<td>0.558</td>
</tr>
<tr>
<td>PTSD [+ MDD] *</td>
<td>7 [4] (29%)</td>
<td>5 [2] (33.3%)</td>
<td>-</td>
<td>0.784</td>
</tr>
<tr>
<td>MDD [+PTSD] *</td>
<td>6 [4] (25%)</td>
<td>5 [2] (33.3%)</td>
<td>-</td>
<td>0.574</td>
</tr>
</tbody>
</table>

BPDSI = Borderline Personality Disorder Severity Index; PTSD = Posttraumatic Stress Disorder; MDD = Major depressive Disorder

* [+ MDD] = with comorbid MDD and [+ PTSD] = with comorbid PTSD

19 of the BPD subjects reported exposure to different kinds of DSM-IV PTSD “A” criteria as adults. 13 of them belonged to the sustained childhood abused subgroup. 5 of the 6 subjects who reported one or few exposures to one or few PTSD “A” criteria in the absence of a history of sustained childhood abuse suffered from concurrent PTSD. 22 BPD subjects did not use any medication. 7 subjects used only SSRI’s. 5 subjects benzodiazepines and 4 subjects used both and 1 subject used a tricyclic antidepressant.

Mean afternoon baseline ACTH and cortisol plasma levels:
Comparison of the chronically abused BPD patients, non or mildly abused BPD patients, and healthy controls showed no significant differences in the baseline levels of ACTH or cortisol between the three groups (ACTH: F(2,47)=1.197 with p=0.311; cortisol: F(2,47)=0.364 with p=0.697).
Stepwise backward analyses of variance did not show an effect of a comorbid MDD or...
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PTSD on the baseline levels of ACTH. For the baseline levels of cortisol, a significant interaction between MDD and childhood abuse was found (F(1,35)=4.922 with p=0.033); neither the main effect of MDD nor the main effect of childhood abuse proved significant. Analysis of the baseline cortisol levels for the abused BPD patients showed particularly high levels for patients with depression; a similar effect of depression was not found for the non-abused patients.

**ACTH and cortisol plasma levels after 1.5 mg dexamethasone:**
The ACTH and cortisol plasma levels after DEX suppression were not found to differ significantly between the chronically abused BPD patients, non or mildly abused BPD patients, or healthy controls (ACTH: F(2,47)=0.815 with p=0.449; cortisol: F(2.47)=0.358 with p=0.701).

Stepwise backward analyses of covariance did not show a significant effect of childhood abuse, MDD, or PTSD on the suppression of ACTH plasma levels. For suppression of cortisol plasma levels, a trend towards a significant interaction (at the 10% level) was found between PTSD and depression (F(1,35)=3.36 with p=0.075) with the main effects of PTSD (F(1,35)=9.24 with p=0.004) and depression (F(1,35)=3.36 with p=0.075) also showing a trend towards significance (on 10% level).

All of the BPD patients with both PTSD and MDD showed minimal post DEX cortisol plasma levels (i.e. maximal suppression).

The BPD patients without any comorbidity showed a higher mean post DEX cortisol plasma level while the BPD patients with comorbid depression but without concurrent PTSD showed the highest mean post DEX cortisol plasma levels (e.g. least suppression) (see Figure 1).

![Figure 1](image-url)

Mean cortisol plasma levels after 1.5 mg DEX and before CRH administration (DEX suppression test)
Stepwise backward analysis of covariance (PTSD, MDD, childhood abuse):
Interaction:
PTSD*MDD p=0.043; main effect MDD p= 0.072; main effect PTSD p=0.005
ACTH and cortisol plasma concentration time curves after DEX/CRH:
The AUCs were found to be significantly different when the chronically abused BPD patients, non or mildly abused BPD patients, and healthy controls were compared. A significantly larger mean AUC for the ACTH response was found for the chronically abused BPD patients when compared to the non or mildly abused BPD patients and the healthy controls with no significant difference between the latter two groups (F(2,47)=7.353 with p=0.002). The additional repeated measurement ANOVA with Bonferroni correction for multiple testing confirmed the robust significant difference (F(2,47)=7.179 with p=0.002). (Figure 2) The mean AUC for the cortisol response of the abused chronically abused BPD patients showed a trend towards statistical significance was also found to be significantly larger (at the 10% level) than that of compared with the nonabused non or mildly abused BPD patients (F(2,47)=2.574 with p=0.087), while the healthy controls did not differ significantly from either of the BPD groups. The trend for cortisol disappeared vanished in an additional repeated measures ANOVA with Bonferroni correction for multiple testing for cortisol(F(2,47)=1.528 with p=0.119). (Figure 3)

Figure 2
Mean ΔACTH plasma response to the combined DEX/CRH challenge over time
* ANOVA of the AUC's (chronically abused, non-abused BPD and controls) p=0.002
‡ Stepwise backward analysis of covariance in BPD sample (PTSD, MDD, childhood abuse) childhood abuse: p=0.001 and PTSD: p=0.049

Figure 3
Mean Δ cortisol plasma response to the combined DEX/CRH challenge over time
* ANOVA AUC's (chronically abused, non-abused BPD and controls) p=0.08
‡ Stepwise backward analysis of covariance in BPD sample (PTSD, MDD, childhood abuse) childhood abuse p=0.031
The stepwise backward analyses of covariance revealed significant effects. Chronically abused BPD patients had higher mean AUC’s for both the ACTH response (F(1,36)=12.084 with p=0.001) and cortisol response (F(1,36)=5.026 with p=0.031) when compared to non or mildly abused BPD patients. The additional repeated measurement ANCOVA with Bonferroni correction for multiple testing confirmed the robust significant differences for the ACTH response (F(1,36)=10.757 with p=0.002) and cortisol (F(1,36)=4.294 with p=0.45).

In addition, the BPD patients with a comorbid PTSD were found to have a significantly lower mean AUC for the ACTH response than the BPD patients without a comorbid PTSD (F(1,36)=4.139 with p=0.049) (Figure 4). This statistically significant effect of PTSD changed into a trend towards statistical significance in the additional repeated measurement ANCOVA with Bonferroni correction for multiple testing (1,36)=3.454 with p=0.071).

**Figure 4**

ACTH response to DEX/CRH in all BPD patients with and without PTSD.

PTSD mitigates ACTH response significantly p=0.049 (Ancova RM p=0.071)
Discussion

The results of the present study show significantly higher plasma ACTH and cortisol concentrations after a DEX/CRH challenge for severely traumatized borderline patients with a history of sustained childhood abuse when compared to a group of mildly or not chronically abused borderline patients. This heightened ACTH and cortisol response is associated with childhood abuse and appears to be independent of BPD pathology and independent of a comorbid PTSD and/or MDD. Nevertheless, a comorbid PTSD was found to attenuate the ACTH response to DEX/CRH in sustained and severely abused as well as in non or mildly abused BPD patients while a comorbid MDD did not have a modifying influence, probably because of considerable overlap with comorbid PTSD (see below). BPD patients who experienced sustained childhood abuse did not differ from nonabused or mildly abused BPD patients and controls with respect to dexamethasone suppression. In the BPD patients with a MDD, cortisol escaped dexamethasone suppression; in BPD patients with a PTSD, the opposite was observed - namely increased suppression. There was a marked interaction between PTSD and MDD, as the expected resistance to dexamethasone suppression during major depression was not observed in the case of comorbid PTSD. In other words, the cortisol levels after dexamethasone suppression for comorbid PTSD and MDD are comparable to the levels for PTSD alone.

Comparison of the chronically abused borderline patients with the non or mildly abused borderline patients and healthy controls showed no significant effect of the factor sustained childhood abuse on the real baseline afternoon plasma levels of ACTH and cortisol, as measured in the afternoon concentrations. However, a significant interaction between childhood abuse and depression was observed with the presence of both factors associated with higher basal cortisol plasma levels.

The demographic data revealed significant differences between the traumatized, non-traumatized, and control subjects with respect to age, mean years of education, and employment status. All of the analyses were therefore corrected for age when necessary. The traumatized BPD patients had the least amount of education on average, which may reflect the adverse life circumstances experienced during childhood. The lower occupational status of the BPD patients in general may reflect the disabling pathology of BPD. The body mass index, use of nicotine, contraceptive pill and medication, which was stopped at least two weeks prior to the DEX/CRH test did not interfere with the outcome, nor did the length of the medication free period prior to the test.

The most striking finding in our study is that a history of sustained childhood abuse is associated with a hyperresponsiveness of ACTH release, which is likely to be independent of BPD, MDD, and PTSD pathology. There are only a few reports in which the lasting effects of early trauma on the HPA axis are examined using endocrine challenge tests. First, in young sexually abused girls with concurrent dysthymia, a blunted ACTH and normal cortisol response to a CRH challenge has been observed. Second, an increased ACTH and normal cortisol response to CRH challenge has been observed for abused children with a concurrent major depression still living under adverse circumstances. (De Bellis et al 1994; Kaufman et al 1997). Third, two recent studies have revealed a hypersensitive stress axis in early abused adult females after exposure to a laboratory stress
paradigm or a CRH challenge. An enhanced ACTH and cortisol response in the CRH challenge study was observed in early abused subjects without MDD while the ACTH response was eliminated in early abused subjects with comorbid MDD. (Heim et al 2000b; Heim et al 2001). Unfortunately, the presence of a comorbid PTSD was not controlled for in the analyses although the authors mentioned that the abused and depressed adult subjects suffered more from a concurrent PTSD than the subjects without MDD. (Heim et al 2001) In contrast to these results, we did not find a significant interaction between sustained childhood abuse and depression, probably because of a considerable overlap of MDD with PTSD. However, the patients with a MDD and a comorbid PTSD exhibited hypersuppression of circulating ACTH and cortisol to DEX during pre-treatment alone, which is in line with previous reports. (Halbreich et al 1989; Yehuda et al 1993). In addition to this, from DEX/CRH studies investigating familiar susceptibility for MDD we know that the cortisol response to DEX/CRH of the abused -mostly not depressed- BPD subjects is not as high as that found in MDD patients in a DEX/CRH study, but rather comparable to the cortisol response of non-MDD family members at high risk for depression. An increased responsivity of the HPA axis in not depressed subjects turns out to be a risk factor for depression after stress. (Holstboer et al 1995) This further underscores the potential susceptibility of the chronically abused BPD patient to stress and stress related disorders like MDD.

One or two methodological notes merit mention at this point. Even though the ACTH response after DEX/CRH appeared to discriminate between the chronically abused patients on the one hand, and the non or mildly abused patients and healthy controls on the other hand, only a trend towards statistical significance in the case of the cortisol response after DEX/CRH was found. Only within the patient group, moreover, did childhood abuse lead to statistically significant outcomes. The cortisol (but not ACTH) responses of the healthy controls to the DEX/CRH test varied widely, which certainly influenced the significance of the comparisons to the chronically abused and non or mildly abused patients. The considerable variance of the cortisol response within the healthy control group also occurred despite very careful selection procedures. However, we omitted to control for irregularities of the day night rhythm, which could be a probable confounder and we do not have a satisfactory explanation for this finding. Another potential confounder might be the menstrual cycle of the subjects. Although we controlled for the contraceptive pill usage, which had no effect on the outcome, we did not control for the phase of the menstrual cycle. Finally, the negative results regarding the expected enhancing effect of MDD on the ACTH/cortisol response to DEX/CRH should be interpreted with care because the statistical power for the MDD group was markedly diminished by the frequent occurrence of a comorbid PTSD and it’s overriding neuroendocrine effect. (see Table 1). The present results are in line with the results of studies of animals exposed to early and sustained life stress, which are the only studies we can refer to in the form of maternal deprivation, which is a laboratory model for neglect and perhaps abuse. The results show rodent and primate infants exposed to such early life stress to display generally increased CRH mRNA and AVP m-RNA expression in the parvocellular CRH
neurons of the hypothalamic paraventricular nucleus (PVN) which still persists in adulthood. (Albeck et al 1997; Coplan et al 1996; Feldman et al 1995; Hatalski et al 1998; Levine et al 2000; Pihoker et al 1993). In addition, the maternal deprivation studies revealed that the basal and stress-induced HPA responses are also enhanced, although pronounced differences are found depending on the strain and gender of the animal and the timing and duration of the maternal separation. (De Kloet et al 1998; Van Oers et al 1998; Van Oers et al 1997).

These findings indicating aberrant HPA response after sustained childhood early trauma suggest that the DEX/CRH challenge test provides important information on the function of the pituitary corticotrophs when the CRH/AVP drive and feedback inhibition mediated by glucocorticoid receptors have been taken into consideration. (Holsboer et al 1996; Holsboer et al 1987b; Holsboer et al 1994; von Bardeleben et al 1985). The magnitude of the response to exogenous CRH depends, on the one hand, on the pituitary CRH receptors and the V3 receptors as AVP potentiates CRH in the stimulation of ACTH release by a factor 3 to 6. (De Goeij et al 1992; Lim 2000). On the other hand, the magnitude of the response depends on the glucocorticoid receptors activated by dexamethasone, which determines the level of glucocorticoid inhibition. (Modell et al 1997) While these receptors are maximally stimulated by the DEX pretreatment, the glucocorticoid hyposensitivity associated with MDD is expected to decrease inhibition of ACTH release and the hypersensitivity associated with PTSD is expected to produce the opposite effect.

In addition to this, the AVP signaling pathway is resistant to dexamethasone and the main site of action of dexamethasone in the suppression of stress-induced HPA activity is at the pituitary level (De Kloet et al 1975; De Kloet 1991; De Kloet 1997).

Based on the above considerations, the following conceptual framework may be constructed. The hyperresponsiveness of ACTH and cortisol release in the severely traumatized patients with a history of sustained childhood abuse after the DEX/CRH challenge indicates an increased sensitivity of the pituitary CRH receptor and/or resistance to DEX suppression. However, no statistically significant effect of the factor childhood abuse was detected for DEX suppression. The most proximal cause of the enhanced ACTH response in the traumatized subjects might therefore be increased pituitary CRH receptor sensitivity either as an intrinsic property of this receptor or caused by enhanced activity of the AVP-V3 receptor system. (Lim 2000) The amplitude of the ACTH response to DEX/CRH is substantially modified by the sensitivity of the glucocorticoid receptors of the pituitary corticotrophs. (vide supra) (Modell et al 1997).

On the basis of the above, it can be hypothesized that sustained childhood abuse increases primarily the CRH/AVP drive (i.e., CRH receptor sensitivity). This assumption is supported by the finding that concurrent PTSD attenuated the ACTH response to DEX/CRH significantly among the chronically abused patient group and the non or mildly abused patient group as well. The severely abused PTSD patient subgroup nevertheless had a significantly enhanced ACTH response when compared to the nonabused PTSD patient subgroup (see Figure 4). Five of the twelve BPD patients with a comorbid PTSD did not experience sustained childhood abuse. PTSD was in these cases associated with one or very few exposures to PTSD “A” criteria. This interesting although preliminary, finding
suggests that the neuroendocrine sequelae of sustained severe childhood abuse and PTSD at least in BPD patients are clearly distinct. Sustained childhood abuse is likely to be associated with increased pituitary CRH receptor sensitivity but not with alterations of the pituitary glucocorticoid receptors. The chronically abused BPD group did not show a statistically significant differential effect on the DEX suppression at pretreatment compared with the non or mildly abused group and controls. In addition, the neuroendocrine sequelae of sustained childhood abuse in our BPD population are likely to be independent of PTSD, which has been found to be associated with hypersensitive glucocorticoid receptors in the pituitary corticotrophs. This hypersensitivity of the glucocorticoid receptors to cortisol and dexamethasone in connection with PTSD, as demonstrated by maximal suppression during DEX pretreatment (see Figure 1), attenuates the ACTH response to CRH after DEX pretreatment (see Figure 4). These preliminary results support the assumption that sustained childhood abuse is associated with an increased CRH/AVP drive and PTSD with increased negative feedback inhibition. Our study provides no conclusive information about the consequences of chronic traumatic stress during adulthood without a history of childhood abuse. Future research has to address this question. The results of this study with a preliminary character have to be replicated in larger samples with PTSD patients without BPD and chronically abused subjects with and without BPD and PTSD in order to provide a more profound insight in the suggested different pathophysiological mechanisms. In these studies, comorbid MDD has to be taken into account as a probable confounder. This is the second study in which we have successfully isolated a distinct, homogeneous, and large subgroup of the otherwise very heterogeneous population of borderline patients on the basis of a probably important etiological factor, namely sustained childhood abuse, and the profound neuroendocrine alteration related to this. In a previous study, we found a severely blunted prolactin response to a m-chlorophenylpiperazine (m-CPP) challenge among chronically abused female BPD patients. (Rinne et al 2000). The HPA axis alterations, which are expected to render chronically abused BPD patients susceptible to stress and stress-related disorders may be of particular significance for future psychopharmaceutical research. The fact that the neuroendocrine dysfunctions are related to childhood abuse and not to the diagnosis of BPD also compels us to reconsider the borderline concept for this large and rather homogeneous subgroup of BPD patients. Though our neuroendocrine data do not support the suggestion put forth by some authors, namely that BPD can be construed as a complex PTSD, a trauma-related concept for the childhood abused BPD subgroup is nevertheless preferable because it recognizes the serious neuroendocrine alterations induced by sustained childhood abuse. (Herman 1992) In conclusion, within the heterogeneous BPD population, a relatively homogeneous subgroup can be identified with sustained childhood abuse as a probable etiologic factor. This severely traumatized group of patients shows HPA axis alterations in the form of hyperresponsiveness of ACTH and cortisol release after the DEX/CRH challenge. The neuroendocrine sequelae associated with sustained childhood abuse and PTSD appear to be very distinct. The different characteristics of the two are the enhanced pituitary CRH receptor responsiveness associated with sustained childhood abuse and the enhanced pituitary glucocorticoid receptor function associated with PTSD.
Moreover, the latter PTSD condition appears to override the decreased efficacy of dexamethasone suppression associated with MDD in the investigated BPD population.

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