The neuroendocrinology of childhood trauma in personality disorder

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KEYWORDS
Corticotropin releasing hormone/factor; Cortisol; Childhood trauma; Personality disorder; Posttraumatic stress disorder

Summary
Background: Childhood trauma has been associated with elevated central corticotropin releasing hormone (CRH) drive in adults meeting general DSM-IV criteria for personality disorder. It is not clear how this may be related to pituitary or adrenal responsiveness in personality disorder. It was hypothesized that high levels of childhood trauma would be associated with blunted cortisol and adrenocorticotropin releasing hormone (ACTH) response to the combined dexamethasone (DEX)/CRH test in adults meeting general DSM-IV criteria for personality disorder.

Method: 24 healthy, medication free adults with personality disorder (N = 16) and a group of healthy controls (N = 8) underwent semi-structured diagnostic interviews and completed the Childhood Trauma Questionnaire (CTQ). Across two separate study sessions separated by at least a week, cerebrospinal fluid (CSF) was sampled by lumbar puncture for measurement of CRH concentration (N = 17), and peripheral blood cortisol and ACTH levels were measured after challenge with DEX/CRH (N = 24).

Results: As hypothesized, high CTQ score was associated with a blunted cortisol and ACTH response to DEX/CRH challenge. Indices of cortisol and ACTH response (peak level and area under the curve (AUC)) to DEX/CRH were in turn significantly negatively correlated with CSF CRH concentration.

Conclusion: Childhood trauma in adults with personality disorder is associated with blunted cortisol and ACTH secretion following DEX/CRH challenge. These effects are independent of depression or posttraumatic stress disorder. Previous work would suggest that blunted pituitary–adrenal response is related to elevated central CRH drive. Corroborating this, CSF CRH levels were significantly and negatively correlated with peak level and AUC of both cortisol and ACTH.

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1. Introduction

The established association of childhood trauma with the development of personality disorder (Johnson et al., 1999, 2006a, b) may represent an important clue regarding the biological mechanism of personality disorder. Animal models of the neurobiological effect of disrupted parental care have implicated corticotropin-releasing hormone (CRH) as a mediator of the effect of early life stress on the abnormal development of stress reactivity (Coplan et al., 2001; Plotsky et al., 2005). We have previously shown that in adults meeting DSM-IV general criteria for personality disorder, regardless of specific DSM-IV categorical diagnoses, history of childhood trauma and poor parental bonding predict elevated cerebrospinal fluid (CSF) levels of CRH (Lee et al., 2005, 2006). The relationship between childhood trauma and CRH may be specific to emotional neglect, as measured the Emotional Neglect subscale of the Childhood Trauma Questionnaire (Lee et al., 2005). These results parallel those found in samples that include depressed patients (Carpenter et al., 2004). However, unlike the case of severe depression, the presence of a personality disorder diagnosis itself is not consistently associated with HPA axis abnormalities, even when examining more "affective," Cluster-B subtypes such as borderline personality disorder (Rinne et al., 2002).

It is not clear if findings of elevated CSF CRH in adults with histories of childhood maltreatment reflect a chronically elevated "baseline" CRH level, or anticipatory reactivity to lumbar puncture. It is known that pituitary CRH receptors react to chronic CRH stimulation with decreased membrane receptor concentration and uncoupling of the receptor from intracellular adenylyl cyclase (Wynn et al., 1988). Such a reaction would be expected to result in decreased sensitivity to exogenous CRH. Confirmation of this prediction was found by Newport et al. (2003), who measured ACTH response to CRH infusion and on a separate study session, CSF concentration of CRH sampled by lumbar puncture. In this study, ACTH response to CRH infusion was found to be inversely correlated with CSF concentration of CRH. If CSF CRH were chronically elevated in personality disordered individuals with histories of significant childhood maltreatment, then it would be expected that their pituitary-adrenal response to exogenous CRH would be blunted.

Some of the existing literature would support this prediction. Recent data in psychiatrically normal groups has found that history of childhood trauma is associated in adulthood with decreased pituitary-adrenal response (ACTH and cortisol, respectively) to exogenous CRH (Carpenter et al., 2009; Klaassens et al., 2009), as was first noted in adolescent girls with a history of Sexual Abuse (De Bellis et al., 1994). These results were interpreted to be consistent with peripheral down regulation of CRH receptors in the face of high central CRH "drive". Similar findings have been reported with PTSD, which may be associated over the long term with blunted pituitary response to exogenous CRH (Ströhle et al., 2008; Smith et al., 1989). On the other hand, childhood trauma in currently depressed patients seems to be associated with enhanced pituitary-adrenal response, possibly due to a depression-related increase in vasopressin drive. This has been found in children with depression (Kaufman et al., 1997) and in adult males and females with depression (Heim et al., 1998, 2008). There may be important, unaccounted for sources of variability however, as not all data fit this pattern (Rasmussen et al., 2001).

In order to more strictly control for the effects of PTSD and MDD related effects, we sought to study the relationship between childhood trauma and pituitary/adrenal response to exogenous CRH in a personality-disordered but non-depressed, non-PTSD sample. We tested the hypothesis that history of exposure to significant childhood trauma would be associated with blunted ACTH and cortisol response to challenge with dexamethasone and CRH (DEX/CRH). Dexamethasone, a synthetic steroid, primarily binds to pituitary glucocorticoid autoreceptors and increases negative feedback on CRH release (Deuschle et al., 1998; Miller et al., 1992; Meijer et al., 1998), diminishing CRH secretion (Galarde et al., 2002). This may minimize, to some extent, the possible confounding effects of recent life stress on the state of the HPA axis at the time of CRH challenge, as has been demonstrated in a study of the effects of mild experimental stress on the DEX/CRH (Oshima et al., 2001). Additionally, lumbar puncture was performed on a separate study session in order to obtain cerebrospinal fluid for measurement of central corticotropin-releasing hormone. For the personality disordered group, patients were selected who met DSM-IV general criteria for personality disorder. This study group was chosen over a narrowly defined group in order to maximize the generalizability of the study while acknowledging that there are no validated biological boundaries between or biomarkers for currently defined personality disorders, Axis II-AXIS II comorbidity is common (Lenzenweger et al., 2007), personality disorder NOS is in fact one of the most highly prevalent Axis II disorders (Verheul and Widiger, 2004), and considerable heterogeneity is present in even single disorders such as borderline personality disorder (Critchfield et al., 2008).

2. Method

2.1. Participants

Participants were 24 adults who were either normal controls (n = 8) or personality disordered (PD; n = 16) (see Tables 1 and 2). Ten of the PD subjects had Childhood Trauma Questionnaire (CTQ) Total scores ≥9 and formed the high trauma subgroup. 6 of the PDs and all of the 8 normal controls had mean CTQ Total scores ≤6, and together formed the low trauma subgroup (see Section 2.2 below for the rationale regarding CTQ cutoff scores). See Table 3 for the distribution of specific DSM-IV personality disorder diagnoses across the trauma groups. All procedures were approved by the Institutional Review Board (IRB) and General Clinical Research Center (GCRC) of the University of Chicago. All subjects provided written informed consent, using IRB approved consent forms. Subjects were recruited by advertisements in local newspapers seeking volunteers for biological studies of personality. In order to minimize bias, no mention was made of childhood trauma in the recruiting media. Both personality disordered and normal control subjects were recruited from the same community, using the same recruitment methods. Normal control subjects had no lifetime history of Axis I or Axis II psychopathology, and no history of psychiatric treat-
ment in first degree relatives. Personality disordered subjects met DSM-IV general criteria for personality disorder, but did not meet DSM-IV criteria for PTSD, current MDD, current substance dependence, or lifetime history of psychotic or bipolar mood disorder. Past but not current major depression was allowed. All subjects were free of psychotropic medications for at least 30 days prior to study, had normal thyroid function, urine and blood chemistry, and hematological tests. Additionally all subjects had negative urine drug and alcohol breathalyzer test results at screen and on the days of testing. Due to the important effect that menstrual cycle has on HPA axis function, women of childbearing potential were studied within 10 days of their last menstrual cycle to minimize the chance of studying females in mid-luteal phase. Additional exclusionary criteria were being actively suicidal, current endocrine disorder, being pregnant, and taking oral contraceptives.

### 2.2. Measures

History of childhood trauma was measured by the Childhood Trauma Questionnaire (CTQ; Bernstein and Fink, 1988), a 70 item questionnaire assessing the pattern of childhood exposure to childhood abuse and neglect. The CTQ has exhibited good convergent validity with measures of posttraumatic stress disorder, dissociation, alexithymia and depression,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics.</th>
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<tr>
<td></td>
<td>Low CTQ PD (6)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (50%)</td>
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<tr>
<td>Male</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>African American</td>
<td>2 (33.3%)</td>
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<tr>
<td>Asian</td>
<td>1 (16.7%)</td>
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<tr>
<td>Weight</td>
<td>79.20 (SD 31.8)</td>
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<tr>
<td>Age</td>
<td>30.83 (SD 8.01)</td>
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<tr>
<td>GAF</td>
<td>60 (SD 10.06)</td>
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<tr>
<td>Hollingshead score</td>
<td>41 (SD 17.56)</td>
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<td>Hx of outpatient Tx.</td>
<td>3 (50%)</td>
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<tr>
<td>Hx of inpatient Tx.</td>
<td>1 (17%)</td>
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<th>Table 2</th>
<th>Axis I conditions.</th>
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<tr>
<td></td>
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<tr>
<td>Suicide attempt history</td>
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<tr>
<td>Self-injury</td>
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<tr>
<td>Major depression, current</td>
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<tr>
<td>Major depression, past</td>
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<tr>
<td>Dysthymia</td>
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<td>NIMH alcoholism, past</td>
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<tr>
<td>DSM-IV IED, any</td>
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<tr>
<td>PTSD</td>
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<td>Social phobia</td>
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<tr>
<th>Table 3</th>
<th>Axis II conditions.</th>
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<tr>
<td></td>
<td>Low CTQ PD (6)</td>
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<tr>
<td>Paranoid</td>
<td>0</td>
</tr>
<tr>
<td>Antisocial</td>
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<tr>
<td>Borderline</td>
<td>2 (33.3%)</td>
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<tr>
<td>Narcissistic</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Histrionic</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Avoidant</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Obsessive–compulsive</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Personality disorder NOS</td>
<td>3 (50%)</td>
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<tr>
<td>CTQ subscales</td>
<td>Number of subjects reporting scores in the severe range</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>0</td>
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<tr>
<td>Emotional Neglect</td>
<td>0</td>
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<tr>
<td>Physical Neglect</td>
<td>0</td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>0</td>
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and discriminant validity with measures of vocabulary and social desirability (Bernstein et al., 1994). Test–retest reliability over a 2- to 6-month interval of the CTQ is high, with values ranging from .79 to .81 (Bernstein and Fink, 1988; Bernstein et al., 1994). The CTQ Total score reflects contributions from the subscales of Physical and Emotional Abuse, Physical Neglect, Emotional Neglect, and Sexual Abuse. Although in theory, using CTQ Total score to define subgroups could be problematic if individuals varied in the relative distribution of trauma subtypes, in reality the subscale scores are highly correlated with each other. This fact is in accordance with the recognition that subtypes of childhood trauma are associated with common risk factors, such as parental psychopathology. Thus CTQ Total score was selected as the primary independent variable. In order to maximize power, we used an excluded middle design, recruiting subjects only with low and high CTQ scores. Low CTQ score was defined as CTQ Total score ≤ 6; high CTQ was defined as CTQ Total score ≥ 9. As normative data to inform cutoff scores on the 70-item CTQ was not available at the initiation of the study, cutoff scores were chosen to divide a previously studied population of personality disordered adults into thirds based on Total CTQ score (n = 186; Lee et al., 2006); the lowest third having a mean Total CTQ score comparable to that seen in our population of normal controls and the upper third having a mean Total CTQ score in the same range as that found in clinical populations seeking therapy for childhood abuse issues (Pavlo, 2001). Using these cutoff scores, subjects with CTQ scores from the upper third have significantly higher cerebrospinal corticotropin releasing hormone (CRH) levels those from the lower third (Lee et al., 2005). This is physiologically significant, in that cerebrospinal fluid CRH levels have previously been found to predict cortisol secretion after CRH challenge (Newport et al., 2003). Using these cutoff scores, our sample included 9 normal controls with low CTQ scores, 6 personality disorder subjects with low CTQ scores, and 10 personality disorder subjects with high CTQ scores (see Table 3). Of note, none of the normal control subjects had CTQ scores ≥ 9. To preserve statistical power, for exploratory analyses of relationships between CSF CRH and childhood trauma, we limited subtype specific analyses to the Emotional Neglect subscale, which we found previously to be correlated with CSF CRH.

All subjects were evaluated by trained clinical psychologist raters, with Axis I and Axis II diagnoses made according to DSM-IV criteria. Final psychiatric diagnosis was established by team best-estimate consensus, using information from semi-structured interviews by trained clinical raters using the Structured Clinical Interview for Diagnosis of Axis I disorders (SCID) and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP; Pfohl et al., 1989).

2.3. DEX/CRH challenge test

Diagnostic interview and self-report data were collected on the first day of study. Lumbar puncture and DEX/CRH testing occurred on separate study sessions at the General Clinical Research Center (GCRC) of The University of Chicago. The lumbar puncture session always preceded the DEX/CRH session by at least one week. All subjects provided negative urine drug screens, alcohol breathalyzer, and pregnancy tests at the beginning of every study session. Female subjects participated within 10 days of their last menstrual period. The evening before the CRH challenge, subjects were admitted to the GCRC. 16 h prior to administration of intravenous CRH (11 PM), subjects were administered 1.5 mg of dexamethasone orally by a research nurse. Subjects slept at the GCRC in quiet, non-stressful conditions. The next morning, subjects rested and were fed breakfast. At 12 PM, subjects received a heparinized intravenous cannula inserted into a forearm vein of the right arm for repeated blood draws. Blood samples were drawn beginning 60 min before CRH infusion, and at 30 min intervals following CRH infusion. Baseline hormonal measures were sampled at 1:30 PM (–150 min) and 4:00 PM (0 min). At 4:00 PM, 1 mcg/kg of body weight ovine CRH (oCRH) was administered through the catheter over a 60 s interval. Because peripheral CRH administration stimulates pituitary CRH receptors, the resulting pituitary output of ACTH and adrenal output of cortisol can be simultaneously measured as an index of CRH receptor sensitivity. Blood samples for ACTH and cortisol were drawn at +5, +15, +30, +60, +90, and +120 min after oCRH administration. At 6:00 PM, subjects were examined by a physician and discharged from the GCRC. Blood samples for hormone measurements were collected in tubes containing EDTA and centrifuged immediately in a refrigerated centrifuge. Plasma was separated and stored at −70 °C until assayed. Samples were assayed for ACTH and Cortisol by the Clinical Research Center (CRC) laboratory (CV% ACTH = 6.7, CV% cortisol = 7.1%). Blood pressure and heart rate were measured hourly beginning from 3:00 PM to 6:00 PM. Subjects additionally completed a visual analogue scale rating of subjective emotional state at −15, +5, +15, +30, +60, +90, and +120.

2.4. Lumbar puncture

The night before the lumbar sampling, subjects were admitted to the General Clinical Research Center (GCRC). The following morning at 8 am, subjects were placed in lateral decubitus position in their hospital bed. After application of intradermal lidocaine local anesthesia, a 22-gauge lumbar puncture needle was inserted through the L3–L4 interspace. Several fractions of CSF totaling 20 cc were obtained and chilled at the 7 bedside. The last 15 cc’s were immediately mixed and divided into 15 identical 1 cc aliquots for CSF analysis. The sample were transferred to a −70 °C freezer immediately after the procedure until assayed by radio-immunoassay (RIA). After the CSF samples were obtained, the subjects rested supine in bed for 4 h to minimize risk of post-lumbar puncture headache. CRH was analyzed using 125I-CRH (2000 Ci/mmol/Amesham) and CRH antibody (Linton and Lowry, 1986). The lower detection limit was 3.9 pmol/L and the intra-assay coefficient was 7% (Husum and Mathe, 2002).

2.5. Data analysis

Statistical analysis of the dependent variables (ACTH, cortisol) was conducted using Repeated Measures ANCOVA, with the between-groups factors of trauma (high vs. low), sex (male or female), personality disorder (personality disorder
or normal control), the within-groups factor of time, and the covariate of age. Huynh–Feldt significance levels are reported for instances in which assumptions of sphericity are violated. Statistical tests were two-tailed unless indicated otherwise. Exploratory analyses (Repeated Measures ANCOVA) were conducted on physiological measures (blood pressure and heart rate) as well as subjective emotional state as measured by visual analogue scale. In additional exploratory analyses, CSF CRH was correlated with peak ACTH, peak cortisol, and the CTQ subscale Emotional Neglect. A focused analysis of the Emotional Neglect subscale of the CTQ was chosen rather than testing all subscales to preserve statistical power, given our previous findings of a significant positive correlation between the specific CTQ subscale Emotional Neglect with CSF CRH concentration in adults with personality disorder. Given the hypothesized directionality, 1-tailed tests were utilized for this test; all other analyses utilized 2-tailed tests given the lack of strong directional hypotheses.

3. Results

3.1. Adverse events

There were no serious adverse events. A single subject (high CTQ PD) experienced reactivation of longstanding psoriasis in the form of erythema and itching, beginning immediately after CRH infusion and lasting approximately 40 min. This episode was not expected given the previous recent history of psoriasis.

3.2. Cortisol response to DEX/CRH challenge

RM-ANCOVA (covarying for age) revealed an overall effect of Trauma (F(1,20) = 5.896, p = .02), and an interaction for Trauma × Time (F(2.437, 48.735) = 3.575, p = .03; Huynh–Feldt corrected for non-sphericity; see Fig. 1). There were no significant main effects of or interactions with Personality Disorder or Gender. Follow up multivariate analysis of variance probing the interaction between Time and Trauma revealed the high CTQ vs. the low CTQ group had significantly lower cortisol levels at +60 min post CRH infusion (F(1, 24) = 7.260; p = .01), +90 (F(1, 24) = 4.924; p = .038) and +120 min (F(1, 24) = 4.460; p = .05), although a trend-difference was apparent as early as +30 min (F(1, 24) = 3.902; p = .06). ANCOVA of peak cortisol response, covarying for age, revealed that the high CTQ group was significantly associated with lower peak cortisol post CRH infusion (F(1, 23) = 4.593, p = .04; mean = 9.598 (SD = 5.805) vs. 15.099 (SD = 8.852)). There were no main effects or interactions with Gender or Personality Disorder. ANCOVA of cortisol area under the curve (AUC) post CRH infusion revealed that the high CTQ group was significantly associated with smaller cortisol AUC (F(1, 23) = 5.921, p = .02; mean = 71.292 (SD = 51.212) versus 112.175 (SD = 65.104)). There were no main effects or interactions with Gender or Personality Disorder.

ANCOVA of post-DEX but pre-CRH cortisol levels revealed that covarying for age, Trauma (high vs. low CTQ), but not Personality Disorder, was significantly related to cortisol level (F(1, 23) = 4.542; p = .05), with the high trauma group having lower cortisol levels (mean = .75 (SD = .533) vs. 1.81 (SD = 4.112)). There were no relationships between cortisol peak concentration or AUC with any of the specific personality disorder diagnosis represented in the sample (borderline, narcissistic, obsessive–compulsive, or avoidant).

3.3. ACTH response to DEX/CRH challenge

RM-ANCOVA (covarying for age) revealed a significant effect of Trauma (F(1, 20) = 8.102; p = .01) and a Trauma × Time interaction (F(3.223, 64.464) = 3.655; p = .02; Huynh–Feldt; see Fig. 2). No other main effects (Personality Disorder, Gender) or interactions were significant. Follow up multivariate analysis of variance, covarying for age, revealed that the high CTQ vs. the low CTQ group had significantly blunted ACTH response at +5 (F(1, 23) = 4.41; p = .05), +30 (F(1, 23) = 4.6; p = .04), +60 (F(1, 23) = 11.12; p = .003), +90 (F(1, 23) = 6.71; p = .02), and +120 (F(1, 23) = 8.96; p = .007). ANCOVA of peak ACTH response, covarying for age, revealed that the high CTQ group was significantly associated with lower peak ACTH post CRH infusion (F(1, 23) = 8.513, p = .01; mean = 17.9 (SD = 7.549) vs. 33.428 (SD = 16.991)). There were no main effects or interactions with Gender or Personality Disorder. ANCOVA of ACTH area under the curve (AUC) post CRH infusion revealed that the high CTQ group was significantly associated with smaller ACTH AUC (F(1, 23) = 11.456, p < .01; mean = 147.175 (SD = 43.802) versus 261.125 (SD = 110.868)). There were no main effects or interactions with Gender or Personality Disorder.

ANCOVA of post-DEX but pre-CRH ACTH level, covarying for age, found that neither Personality Disorder nor Trauma significantly predicted ACTH level. There was no association of peak ACTH concentration or AUC with a specific person-
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Exploratory analyses

17 out of 24 subjects consented to undergo lumbar puncture. CSF CRH concentration was significantly and inversely correlated with peak ACTH response (r = −.524, p = .02, n = 17; Spearman’s 1-tailed) and ACTH AUC (r = −.440, p = .04, n = 17; Spearman’s 1-tailed; Fig. 3). CSF CRH concentration was significantly negatively correlated with peak cortisol response (r = −.477, p = .036, n = 17; Spearman’s 1-tailed) and cortisol AUC (r = −.452, p = .03, n = 17; Spearman’s 1-tailed; Fig. 4). As hypothesized based on previously reported findings, in this group of subjects CSF CRH concentration was significantly correlated with CTQ Emotional Neglect (r = .434, p = .04, n = 17, Spearman’s one-tailed). CRH CRH concentration was not associated with specific diagnosis of borderline, narcissistic, avoidant, or dependent personality disorder.

Analysis of heart rate data from the DEX/CRH challenge session revealed a statistical trend for an effect of Time (F (7, 119) = 2.019, p = .06; heart rate decreased over time), but no effects of PD, Sex, or interactions with each other or with Trauma. A statistical trend was detected for the between-groups factor of Trauma (F (1, 17) = 3.747; p = .07), with the high CTQ group having a lower mean heart rate than the low CTQ group. Exploratory effects for the effect of CRH on blood pressure revealed no significant effects for systolic blood pressure. For diastolic blood pressure, a statistically significant interaction of time and personality disorder group was detected (F (7, 119) = 2.26; p = .03). Follow up testing revealed that the presence of personality disorder was associated with higher diastolic blood pressure 120 min post CRH infusion (F (1, 20) = 4.216; p = .05). Analyses of subjective emotional state, as measured by Visual Analogue Scale, revealed no significant between or within-groups effects.

4. Discussion

This is the first report triangulating the interrelationships between childhood trauma, DEX/CRH response, and CSF CRH levels in personality disorder. Personality disordered patients with histories of significant childhood trauma had blunted cortisol and ACTH response to DEX/CRH challenge. Thus the pattern was not an escape from negative feedback that has been found to characterize some forms of depressive disorder. The findings were not due to concurrent medications, current major depression, PTSD, sex, or age. Nor were the findings due to the presence or absence of personality dis-

![Figure 2](image)

**Figure 2** ACTH response to DEX/CRH challenge. Mean post ACTH cortisol levels: following CRH challenge (time = 0), ACTH levels in the low CTQ group (N = 14) are significantly higher than the high CTQ group (N = 10) at time point +5, +30, +60, +90, and +120 min. The error bars indicate the 95% confidence interval of the mean.

![Figure 3](image)

**Figure 3** Relationship between CSF CRH level and post DEX/CRH cortisol area under the curve (AUC).
order, as personality disorder itself failed to account for differences in pituitary or adrenal response to DEX/CRH challenge. Blunted cortisol and ACTH response to exogenous CRH is consistent with a theoretical model of pituitary CRH receptor desensitization in the face of chronically increased central CRH drive. Indeed, exploratory analysis from the subsample with CSF CRH provided important corroboration, as CSF CRH levels were negatively correlated with measures of pituitary and adrenal responsiveness to DEX/CRH challenge. This would be expected given previous reports of a negative relationship between central CRH level and ACTH following exogenous CRH (Newport et al., 2003; note that in this study dexamethasone was not given prior to CRH challenge). Thus, the results of this study are in line with our previous findings of increased central CRH levels in personality disordered patients who report severe childhood trauma. They are additionally suggestive of tetricly increased CRH drive. Indeed, exploratory analysis of the subsample with CSF data provided a replication of our two previous findings of a positive relationship between central CRH concentration and measures of emotional neglect from caregivers in childhood.

4.1. Previous findings

Our results are comparable with previously reported investigations of the relationship between HPA axis function and childhood trauma (De Bellis et al., 1994; Carpenter et al., 2007; Klaassens et al., 2009). They are most closely comparable with those of Klaassens et al. (2009), who also found that childhood trauma was related to blunted cortisol and ACTH response to DEX/CRH challenge in a sample of adults free of current or past Axis I psychiatric disorders. Our results are also generally consistent with findings of blunted ACTH and cortisol response from studies of adults with PTSD (Smith et al., 1989). Major depression may alter the relationship between trauma and pituitary response to exogenous CRH, as has been found in studies that include currently depressed patients (Heim et al., 2008). A candidate mechanism may be enhanced hypothalamic vasopressin drive in depressives that is able to potentiate the effect of CRH on pituitary receptors (Goekoop et al., 2010). However, definitive proof of this is not yet available and some evidence suggests that in fact PTSD is itself associated with increased vasopressin release (De Koet et al., 2008). Another possibility is that PTSD and major depressive disorder have divergent effects on negative feedback in the HPA axis, with PTSD associated with increased negative feedback control of the HPA axis (Yehuda et al., 1994; Grossman et al., 1996).

Overall, our findings indicate the childhood trauma in the context of personality disorder has a neuroendocrine profile that resembles that seen in chronic PTSD.

4.2. Limitations

Several important features of the study are worth mentioning. The cross-sectional design precludes causative interpretations, as it not known if history of childhood trauma precedes pituitary CRH receptor sub-sensitivity. This issue could be dealt with using a prospective study design. However, given that personality disorder is not diagnosed in childhood or adolescence, this would require choosing a population with personality disorder-like features, which raises methodological issues that require more attention. Another widely acknowledged limitation of retrospective measures of childhood trauma is the uncertainty regarding the extent to which retrospective accounts of childhood trauma reflect the actual behavior of parents and caregivers versus the subjective experience of them. This is a complex issue, and evidence to date suggest that overly simplistic interpretations of retrospective accounts as either invalid or valid do not reflect the true nature of the childhood environment. The current state of science shows that retrospective accounts are correlated with prospectively collected data (Widom et al., 2005) but are simultaneously affected by genetic factors (Kendler

![Figure 4](image-url) Relationship between CSF CRH level and post DEX/CRH ACTH area under the curve (AUC).
Thus it is possible that some of the relationship between CTQ scores and pituitary CRH receptor sensitivity reflects a common underlying genetic factor, rather than strictly an environmental or developmental effect. This is an important avenue for future exploration. Another limitation of the study is the small size of our sample. If personality disorders are biologically heterogeneous, this could increase the likelihood of Type I or Type II error. It must be emphasized that none of the current DSM-IV personality disorders have established biological boundaries, with the possible exception of schizotypal personality disorder. We did not study schizotypal subjects. Thus this remains a theoretical concern, which can only be addressed in the future with either a larger sample size, or with future knowledge of the real biological boundaries of personality disorder. Although a larger sample would be desirable, the study was designed to maximize statistical power while enabling resources to be dedicated to more complete characterization of the sample. This includes in depth assessment of Axis II disorders, use of an excluded middle design, exclusion of subjects on psychotropic or with confounding Axis I conditions, and measurement of central and peripheral indices of HPA axis function. Finally, it is possible that past history of depression may have a scar-like effect on response to DEX/CRH challenge, and represent a confound. Arguing against this is previous research showing that high risk groups have enhanced rather than blunted cortisol and ACTH response to DEX/CRH challenge (Modell et al., 1998). Preliminary analysis in the personality disordered sample revealed that high CTQ score predicted blunted ACTH response even after accounting for past history of depression (results available upon request from the PI). However, in order to validly test the effect of the interaction between past history of depression and trauma in personality disorder on DEX/CRH response, a study design in which high and low trauma groups are counterbalanced with respect to past history of depression would be necessary.

5. Conclusions

The findings from this study corroborate with previous reports on the relationship between childhood trauma and elevated central CRH drive. When combined with data from preclinical models of the effect of early life stress on central CRH function, this work provides evidence for both central and peripheral dysregulation of the stress system in personality disorder with childhood trauma.

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Conflicts of interest

There are no conflicts of interest to report.

Contributors

Royce J. Lee: PI of the project, performed primary data analyses
Aaron TenHarmsel: Performed secondary analyses and supervised data collection

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References


