THE ROLE OF EARLY ADVERSE EXPERIENCE AND ADULTHOOD STRESS IN THE PREDICTION OF NEUROENDOCRINE STRESS REACTIVITY IN WOMEN: A MULTIPLE REGRESSION ANALYSIS

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Sensitization of stress-responsive neurobiological systems as a possible consequence of early adverse experience has been implicated in the pathophysiology of mood and anxiety disorders. In addition to early adversities, adulthood stressors are also known to precipitate the manifestation of these disorders. The present study sought to evaluate the relative role of early adverse experience vs. stress experiences in adulthood in the prediction of neuroendocrine stress reactivity in women. A total of 49 women (normal volunteers, depressed patients, and women with a history of early abuse) underwent a battery of interviews and completed dimensional rating scales on stress experiences and psychopathology, and were subsequently exposed to a standardized psychosocial laboratory stressor. Outcome measures were plasma adrenocorticotropin (ACTH) and cortisol responses to the stress test. Multiple linear regression analyses were performed to identify the impact of demographic variables, childhood abuse, adulthood trauma, major life events in the past year, and daily hassles in the past month, as well as psychopathology on hormonal stress responsiveness. Peak ACTH responses to psychosocial stress were predicted by a history of childhood abuse, the number of separate abuse events, the number of adulthood traumas, and the severity of depression. Similar predictors were identified for peak cortisol responses. Although abused women reported more severe negative life events in adulthood than controls, life events did not affect neuroendocrine reactivity. The regression model explained 35% of the variance of ACTH responses. The interaction of childhood abuse and adulthood trauma was the most powerful predictor of ACTH responsiveness. Our findings suggest that a history of childhood abuse per se is related to increased neuroendocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood. Depression and Anxiety 15:117–125, 2002. © 2002 Wiley-Liss, Inc.

Key words: trauma; chronic stress; development; depression; corticotropin-releasing factor

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Received for publication 14 May 2001; Accepted 17 September 2001

DOI: 10.1002/da.10015

Published online in Wiley InterScience (www.interscience.wiley.com).
INTRODUCTION

Adverse experiences early in life constitute a major risk factor for the development of mood and anxiety disorders in adulthood. One study comprised of almost 2,000 women revealed that those with a history of childhood sexual or physical abuse more often exhibited symptoms of depression and anxiety, and had more frequently attempted suicide than women without a history of childhood abuse [McCueley et al., 1997]. Moreover, parental loss and other childhood adversities also have been related to the development of depression and anxiety disorders in adulthood [Kendler et al., 1992; Kessler and Magee, 1993; Agid et al., 1999]. Untoward events in childhood have been reported to predispose to the development of post-traumatic stress disorder (PTSD) in response to adulthood trauma [Bremner et al., 1993; Zaidi and Foy, 1994]. However, in addition to early-life trauma, stress in adulthood also contributes to the likelihood of major depression and anxiety disorders, including PTSD. For example, the onset of depressive episodes is often associated with major life events or chronic stress [Kessler, 1997]. A monozygotic female twin study revealed that lifetime trauma, including both incidents in childhood and adulthood, as well as acute major life events and recent difficulties were significant predictors of an episode of major depression [Kendler et al., 1993]. Moreover, major life events and minor stressors before, during, or after traumatic events increase the risk for the development of PTSD [Green and Berlin, 1987; McFarlane, 1988].

Our group and others have suggested that the relationship between childhood adversities and the development of depression or anxiety disorders is mediated by alterations in central nervous system (CNS) corticotropin-releasing factor (CRF) systems [Heim and Nemeroff, 1999]. There is considerable evidence that CRF neurons in cortical, limbic, and brain stem regions represent the major regulator of the endocrine, autonomic, immune, and behavioral responses to stress [Owens and Nemeroff, 1991]. When directly injected into the CNS of laboratory animals, CRF produces many physiological and behavioral changes that are reminiscent of stress, depression, and anxiety [Britton et al., 1982; Sutton et al., 1982; Sirinathsinghi et al., 1983; Dunn and Berridge, 1990; Owens and Nemeroff, 1991]. Increased CRF concentrations have repeatedly been measured in the cerebrospinal fluid (CSF) of patients with major depression and anxiety disorders, including PTSD [Nemeroff et al., 1984; Bremner et al., 1997; Baker et al., 1999]. In fact, preclinical laboratory animal studies have provided evidence that CNS CRF hypersecretion and increased reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to acute stress in adulthood may be the persistent consequence of severe stress early in life [Plotsky and Meaney, 1993; Ladd et al., 1996; Coplan et al., 1996]. We have recently observed increased pituitary-adrenal responses to a standardized psychosocial laboratory stressor in adult women with a history of childhood sexual and/or physical abuse, which was particularly robust in abused women with depression or anxiety disorders [Heim et al., 2000]. Thus, stress early in life appears to result in persistent sensitization of CRF neuronal systems to even mild stressors in adulthood, contributing to the development of mood and anxiety disorders.

Stress experiences in adulthood, which have been related to depression and anxiety disorders, may also induce perturbations of neuroendocrine stress systems. For example, findings from laboratory animal studies suggest that chronic stress in adult rats is associated with increased CNS CRF activity [Chappell et al., 1986]. Even more intriguing are findings that one-time stress exposure in adult rats may induce sensitization of HPA axis responses to subsequent stress [van Dijken et al., 1993]. Thus, one might question what role adulthood stressors, such as trauma, life events, or chronic strain, may play in the development of HPA axis sensitization to stress in adult survivors of childhood abuse. Is the increased neuroendocrine stress vulnerability the consequence of early adverse experience or the product of adulthood stress, which these women may experience more frequently than non-abused women, or both? The present study sought to answer this question using multiple regression analyses on neuroendocrine responses of women to psychosocial stress induction.

METHODS

SUBJECTS

The study group is identical to a sample recruited for a project on the neurobiological consequences of early adverse experiences that recently have been published [Heim et al., 2000]. A total of 49 women were recruited into four study groups including 12 with no history of early-life stress or psychiatric disorder [controls (CON)], 14 abused as children without current major depression [early life stress/no major depressive disorder (ELS/non-MDD)], 13 abused as children with current major depression [early life stress/major depressive disorder (ELS/MDD)], and 10 with current major depression but no history of childhood abuse [no early life stress/major depressive disorder (non-ELS/MDD)]. All women were 18 to 45 years old with regular menses, no history of mania or psychosis, and no substance abuse or eating disorder within the previous 6 months. All women were free of hormonal and psychotropic medications. For assignment to the early-life stress groups, women must have had experienced repeated moderate to severe sexual or physical abuse before the first menstrual period [for detailed description, see Heim et al., 2000]. For assignment to the depression groups, a diagnosis of current major depression according to criteria of the Diagnostic and Statistical Manual for Mental Disorder, 4th Edition
PROCEDURE

The Structured Clinical Interview for DSM-IV (SCID) [First et al., 1997] was administered to each subject to generate a psychiatric diagnosis in all patients and controls. Severity of symptoms of depression and PTSD were rated by using standard dimensional rating scales [Hamilton, 1960; Blake et al., 1985]. Stressful childhood experiences were assessed using the Early Trauma Inventory (ETI) [Bremner et al., 2001]. Subjects were additionally evaluated for adulthood stressful experiences. The number of trauma experiences in adulthood was assessed by using the Trauma Assessment for Adults interview [Resnick et al., 1993]. The number and severity of major life events in the past year was rated using the Life Experiences Survey (LES) [Sarason et al., 1978]. Minor stress events in the past month were monitored using the Daily Hassles Scale (DHS) [Kanner et al., 1981].

All patients and volunteers were admitted as inpatients to the NIH-funded General Clinical Research Center at Emory University Hospital and underwent a psychosocial laboratory stress test as previously described [Kirschbaum et al., 1993]. Subjects remained at bed rest and were NPO except for water 2 hr before and throughout the test procedure. The psychosocial stress test was performed between 1:30 and 4:00 p.m. Briefly, subjects were brought to the test area in a wheelchair to avoid activation of the HPA axis due to walking. In the test area, they rested for 30 min in the chair and then walked into the test room with a committee of three persons sitting behind a desk. A microphone, a video camera, and a tape recorder were installed. Subjects were instructed to deliver a free speech in front of the committee on their qualifications for an open job position. Subjects prepared their speech as previously published [Heim et al., 2000]. After each mistake, subjects were told to restart at 2,083. The mental arithmetic task was performed for another 5 min. Blood samples were obtained from an indwelling catheter at 15 min intervals before (~15 and 0 min), during (15 min), and after the stress exposure (30, 45, 60, 75, and 90 min). Blood was collected in EDTA-containing tubes, placed immediately on ice, and centrifuged at 4°C for 10 min at 3,000 rpm. Plasma was separated, coded, stored at ~80°C, and assayed for ACTH and cortisol concentrations using radioimmunoassay techniques (ACTH: Nichols, San Juan Capistrano, CA; cortisol: DiaSorin, Stillwater, MN).

STATISTICAL ANALYSES

All statistical analyses were performed using SPSS. The four study groups were compared with respect to demographic, biographical and clinical features using frequency tests for categorical data, Kruskal-Wallis analysis of variance for ranked data, and one-way analysis of variance for continuous data. Maximum stress-induced hormone concentrations were compared between groups by using one-way analysis of covariance (factor: Group, covariate: Ethnicity) [Heimet et al., 2000].

To determine which variables might predict maximum plasma ACTH and cortisol concentrations after psychosocial stress induction, we performed multiple linear regression analyses entering demographic variables (age, education, and ethnicity), early adverse experience (history of childhood abuse, number of separate sexual and physical abuse events, and sexual and physical abuse score [Bremner et al., 2001]), adulthood stress (number of adulthood traumas [Resnick et al., 1993], negative life event score [Sarason et al., 1978], and daily hassles severity [Kanner et al., 1981]), and psychopathology (severity of depression [Hamilton, 1960] and severity of PTSD [Blake et al., 1985]). We additionally computed a product term of history of childhood abuse and the number of adulthood traumas as a representation of the interaction of these variables. We then performed stepwise multiple linear regression analyses to elucidate whether a history of childhood abuse or adulthood trauma or an interaction of these variables are predictors of maximum hormone concentrations after stress induction. Six subjects were excluded because of missing values that resulted in a total sample of 43 subjects for the multiple regression analyses. Five of the excluded subjects were abused and suffered from major depression and one excluded subject was in the group of depressed subjects without a history of child abuse. The results of the multiple regression analyses, however, should not be affected by disproportionate exclusion of cases from the four groups, since this procedure disregards group assignment of cases. The level of significance for all analyses was set at .05.

RESULTS

DESCRIPTION OF THE STUDY POPULATION

Table 1 summarizes the comparison of the four study groups with respect to demographics, abuse history, psychopathology, and maximum hormonal stress responses as previously published [Heim et al., 2000]. Briefly, groups did not differ with respect to age or educational status; however, there was a trend for more African-American women in the group of abused women without depression as compared to the group of abused women with depression. Abused women with and without major depression did not differ with respect to the
reported number and magnitude of childhood sexual and physical abuse experiences. There was no difference in the severity of depression between depressed women with and without a history of early-life stress. There was a significantly higher prevalence of syndromal PTSD in the group of abused women with current major depression as compared to abused women without major depression. Both groups of abused women exhibited increased peak ACTH concentrations during the psychosocial stress test compared to the other groups. Abused women with current major depression also demonstrated increased cortisol responses when compared to all other subject groups [for details see Heim et al., 2000].

Table 1 also depicts results of the comparison of the four study groups with respect to adulthood stress experiences. The four comparison groups did not significantly differ with respect to the number of adulthood traumatic experiences (such as war experience, accidents, assault, rape, disease, natural disaster, or other events threatening life or personal integrity). There was also no difference with respect to the mean number of negative life events in the past year; however, abused women with major depression reported more severe negative life events than controls. All three patients groups reported more frequent and more severe daily hassles in the past month as compared to controls.

**MULTIPLE REGRESSION ANALYSES**

Table 2 and Figure 1 present the results of the multiple linear regression analyses on maximum plasma ACTH concentrations in response to the psychosocial laboratory stress. Demographic variables in total did not significantly predict maximum ACTH responses to stress; however, age by itself was identified as a significant predictor of maximum ACTH concentrations. Childhood abuse variables significantly predicted maximum ACTH responses to stress, with a history of childhood sexual or physical abuse per se,
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as well as the number of separate kinds of abuse events, but not the total sexual and physical abuse score, identified as significant predictors. In addition, the number of trauma experiences during puberty and in adulthood was a predictor of maximum ACTH concentrations. Negative life events in the past year and daily hassles in the past month were not predictive of maximum ACTH concentrations. Psychopathology significantly added to the prediction of maximum ACTH responses. Severity of depressive symptoms, but not of PTSD symptoms, were identified as a significant predictor of ACTH responses. With respect to the direction of the regression effects, history of childhood abuse, adulthood traumas, and depression received positive β weights. Thus, these variables were positively related to maximum ACTH concentrations after stress. In contrast, age and the number of separate kinds of abuse events had a negative impact on ACTH responses to stress. The total model explained 35% of the variance of ACTH concentrations (F = 3.088; df = 11,42; P = .007). Because both a history of childhood abuse and the number of adulthood traumas were significant predictors of ACTH responsiveness, we multiplied these two variables to test whether there may be an additional effect of the interaction of these two predictor variables. History of childhood abuse, the number of adulthood traumas, and the interaction term were entered into a stepwise regression analysis. Indeed, the interaction of a history of childhood abuse and the number of adulthood traumas was the best predictor of ACTH reactivity to psychosocial stress (standardized β = .466, t = 3.574, P = .001).

Results of the multiple linear regression analysis on maximum plasma cortisol concentrations after psychosocial stress induction are depicted in Table 3. Significant predictors for maximum cortisol responses were a history of childhood abuse and the number of separate abuse events, but not the total severity score of the abuse. The number of adulthood trauma experiences and the negative life event score were not predictive of cortisol concentrations. However, the cumulated severity of daily hassles in the past month was a significant predictor of maximum cortisol levels. Again psychopathology added to the prediction of cortisol responses with severity of depression, but not of PTSD, predicting cortisol responses. As for the direction of the regression effects, history of childhood abuse and depression obtained positive β weights and, thus, were positively related to maximum cortisol responses. The number of separate abuse events and

TABLE 2. Linear multiple regression on peak plasma ACTH concentrations (pg/ml) in response to psychosocial laboratory stress induction as a function of demographic variables, childhood abuse, adulthood stress, and psychopathology (N = 43)*

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>R²</th>
<th>Corrected R²</th>
<th>ΔR²</th>
<th>ΔF</th>
<th>ΔP</th>
<th>Standardized β</th>
<th>t</th>
<th>P</th>
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<td>Demographics</td>
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<td>.024</td>
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<td>2.088</td>
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<td></td>
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<td>-.369</td>
<td></td>
<td></td>
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<td></td>
<td>.605</td>
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<td>.640</td>
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<td>Childhood abuse (&lt;puberty)</td>
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<td>.666</td>
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<td>.502</td>
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<td></td>
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<td>Adulthood stress</td>
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<td></td>
<td></td>
<td>-.282</td>
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<td></td>
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<tr>
<td>Daily hassles severity (past month)</td>
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<td>-.1697</td>
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<td></td>
<td>-.282</td>
<td>1.697</td>
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<td>Psychopathology</td>
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<td>5.659</td>
<td>.008</td>
<td>.542</td>
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<td>.007</td>
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<td>Hamilton depression score</td>
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<td></td>
<td></td>
<td>.542</td>
<td>2.903</td>
<td></td>
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<tr>
<td>Clinician-administered PTSD score</td>
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<td></td>
<td></td>
<td>.333</td>
<td>1.329</td>
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*Model: F = 3.088; df = 11,42; P = .007.

Figure 1. Scatterplot of the multiple linear regression analysis on peak plasma ACTH concentrations. Closed circle, controls; closed triangle, ELS/non-MDD; closed inverted triangle, ELS/MDD; closed square, non-ELS/MDD.
daily hassles obtained negative $\beta$ weights. The total model explained 18% of the variance of cortisol concentrations and did not reach the level of statistical significance ($F = 1.840; \text{df} = 11,42; \ P = .089$). There were no significant interaction effects of childhood abuse and adulthood stress experiences on cortisol responses to psychosocial stress.

**DISCUSSION**

Sensitization of central CRF systems as a consequence of early adverse experience has been implicated in the pathogenesis of mood and anxiety disorders [Heim and Nemeroff, 1999]. We have recently reported increased pituitary-adrenal reactivity to psychosocial stress induction in adult women with a history of childhood sexual or physical abuse [Heim et al., 2000]. Sensitization of central CRF systems due to early life stress may result in increased CRF release every time these women are stressed, ultimately inducing symptoms of depression and anxiety through extra-hypothalamic actions of this peptide. In support of this hypothesis are findings of a close relationship between major or minor stress events and the onset of major depression in adulthood [Kessler, 1997]. However, severe or chronic stress in adulthood may itself affect the dynamics of the stress response system. Thus, the question arises as to whether increased neuroendocrine reactivity to stress in adult survivors of childhood abuse is a consequence of the early adverse experience or of adulthood stress, including trauma, life events, and daily stress—which these women may frequently experience.

To approach this question, we measured adulthood stress experiences in women with a history of childhood sexual or physical abuse with and without current major depression as compared to depressed women and healthy controls without a history of childhood adversities. We found that there were no significant differences between groups with respect to the reported total number of adulthood traumas, such as accidents, natural disaster, war zone experiences, rape, assault, or other miscellaneous traumatic events. However, there was a trend for a greater number of traumas in adult survivors of childhood abuse with and without depression as compared to controls. Several other studies have focused on re-victimization of adult survivors of childhood abuse and generally found that adult survivors of childhood abuse are more likely to be assaulted or assaulted in adulthood than individuals without a history of childhood abuse [Cloitre et al., 1996; Schaaf and McCanne, 1998; Liem and Boudewyn, 1999]. Thus, the slightly elevated number of miscellaneous adulthood traumas in both groups of abused women may be due to higher rates of abusive experiences in adulthood. In addition to trauma experience in adulthood, we also monitored recent major life events and daily hassles. Adult survivors of childhood abuse reported more severe negative major life events in the past year as compared to all other groups. As compared to controls all three patient groups had experienced more frequent and more severe daily hassles in the past month. Although it is well known that major depression is often preceded by major life events and daily hassles [Kessler, 1997], we are not aware of any other study evaluating the prevalence of these stress events in survivors of childhood abuse as compared to non-abused individuals. Because these stress scores were also elevated in survivors of childhood abuse without current major depression, it is unlikely that elevated self-reported stress levels are due to a perception bias of depressed subjects.

Demographic variables, childhood abuse variables, and adulthood stress variables as well as psychopatho-

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**TABLE 3. Linear multiple regression on peak plasma cortisol concentrations (µg/dl) in response to psychosocial laboratory stress induction as a function of demographic variables, childhood abuse, adulthood stress, and psychopathology (N = 43)**

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>$R^2$</th>
<th>Corrected $R^2$</th>
<th>$\Delta R^2$</th>
<th>$\Delta F$</th>
<th>$\Delta P$</th>
<th>Standardized $\beta$</th>
<th>$t$</th>
<th>$P$</th>
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<tr>
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<td>.238</td>
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*Model: $F = 1.840; \text{df} = 11,42; \ P = .089$. 
ogy variables were then entered into multiple linear regression analyses on maximum hormonal responses to psychosocial stress induction. As for peak ACTH responses to psychosocial stress, age, history of childhood abuse, the number of separate kinds of abuse events, the number of adulthood traumas, and the extent of depression were identified as significant predictors with the total model explaining 35% of the variance. In this model, age was inversely related to peak ACTH responses. Clinical studies comparing young and elderly individuals have consistently reported that both basal activity of the HPA axis and reactivity to challenge increases during aging [Gotthardt et al., 1995; Lupien et al., 1999]. Thus, our findings are not in accordance with these studies; however, our sample did not include elderly women and may, thus, not be comparable.

A history of childhood abuse per se reached the highest β weight within the regression model (β = .666, t = 2.977, P = .006) and was positively related to maximum ACTH concentrations. This is a very important finding because it confirms that early adverse experience in fact is related to sensitization of the HPA axis to stress in women and that this effect is stable and large, even when adulthood stress experiences of diverse severity are controlled. This finding is consistent with results from preclinical studies in animal models of early-life stress [Plotsky and Meaney, 1993; Ladd et al., 1996; Coplan et al., 1996]. Findings from these animal models suggest that increases in gene expression, peptide concentration, and peptide-receptor density in CRF neuronal circuits connecting the amygdala and brainstem nuclei may represent the underlying mechanisms of this stress sensitization [Plotsky et al., in press].

Surprisingly, the number of separate abuse events was a significant predictor, which was negatively related to peak ACTH responses. This finding, however, needs qualification in terms of the meaning of this variable as assessed with the ETI [Bremner et al., 2001]. The ETI contains a list of items, which represent different kinds of abuse experiences. For example, in the sexual abuse category, the items range from having been exposed to sexual comments to having experienced forced invasive sexual intercourse. The variable “Number of separate abuse events” reflects the number of items answered with “Yes,” but does not consider the frequency within one kind of event (i.e., ten times forced invasive intercourse per month over 5 years is considered one event). In addition, if one kind of abuse includes other kinds of abuse, it is coded only under the most severe item (i.e., forced invasive intercourse includes sexual touching). Thus, it may well be that women with more “diverse” abuse experience did not experience the most severe abuse events possible. The ETI does not provide an objective severity rating of different kinds of abuse (i.e., kissing is considered as severe as intercourse). Altogether, it appears that this variable does not reflect the total frequency of the abuse, but is rather a reflection of the “diversity” of the abuse. The ETI “total score” integrates number, frequency, and duration of abuse events and thus is a better reflection of the total extent of abuse. This variable was positively related to ACTH responsiveness but did not reach the level of significance perhaps due to the non-normative distribution of these scores across the total study population. It is interesting, however, that greater diversity of the abuse was inversely related to peak ACTH levels. Despite the methodological problems outlined above, it may well be plausible that a greater diversity of (milder) abuse may reflect unpredictable chronic stress, which indeed may have opposite neuroendocrine effects than stereotype abuse of high intensity. Accordingly, in the animal literature chronic stress has been related to habituation, whereas single intense stress events may induce sensitization [Yehuda and Antelman, 1993; Liberzon et al., 1997].

Interestingly, the number of adulthood traumatic events was a significant predictor of maximum ACTH concentrations in response to stress with a positive β weight. Thus, the more traumatic events were experienced in adulthood, the higher the ACTH responses to stress. This finding suggests that increased neuroendocrine stress reactivity observed in women with a history of childhood abuse is, in fact, affected by adulthood trauma and is not an exclusive correlate of the early life stress. This finding is in accordance with findings from laboratory animal studies, which showed that exposure of adult rats to a single severe stress event results in sensitization of HPA axis responses to subsequent stress exposure [van Dijken et al., 1993].

Owing to this finding, we additionally computed an interaction term of childhood abuse and adulthood trauma to test the hypothesis that there may be an additional effect, if both types of stress have been experienced. In fact, the interaction term of childhood abuse and adulthood trauma turned out to represent the best predictor of ACTH responses to stress explaining 21% of the variance by itself (β = .466, t = 3.574, P = .001). This means that those women with a history of childhood abuse who experienced additional trauma in adulthood exhibited the highest ACTH responses to stress. To our knowledge, in animal models of early life stress, the additional effects of repeated severe adulthood adversities on brain systems involved in depression and anxiety have not been evaluated and future studies of this nature are warranted.

Psychopathology, specifically the severity of depressive symptoms, was positively related to maximum ACTH concentrations. It remains unclear however whether the depression is the cause or the consequence of enhanced neuroendocrine reactivity in these women. In contrast, symptoms of PTSD were not related to maximum ACTH responses to stress. This finding is obscure because PTSD in particular has been considered a sensitization disorder. This finding may possibly be explained by the fact that the vast majority of the patients suffered from both major depres-
sion and PTSD, which may mask a specific effect of PTSD. On the other hand, Liberson et al. [1999] observed normal ACTH responses to experimental stress in veterans with PTSD.

Similar results have been obtained for the prediction of maximum cortisol concentrations in response to psychosocial stress. Thus, a history of early life stress, the number of separate kinds of abuse events, and depression were significant predictors of maximum cortisol responses. The β weights were positive for history of early-life stress as well as depression and negative for the number of separate kinds of abuse events (see above for discussion). However, in contrast to the above findings for ACTH, maximum cortisol concentrations were not related to adulthood trauma or an interaction of childhood abuse and adulthood trauma. Instead, cortisol responses were predicted by the severity of daily hassles in the past month with severity of daily hassles negatively related to cortisol concentrations. This finding may reflect repeated activation and subsequent habituation of the adrenal cortex in response to these daily stressors over time. These findings also suggest that adulthood trauma and recent mild stress may differentially affect the pituitary and the adrenal gland and may induce a form of functional dissociation between these two components of the HPA axis.

This is the first study to evaluate the combined effects of early adverse experience and adulthood stressors of different severity on neuroendocrine stress reactivity. In summary, our findings confirm that a history of childhood abuse is related to increased pituitary reactivity in adult women, which even further increases if additional trauma is experienced in adulthood. Pituitary reactivity is further related to age, number of separate kinds of abuse events, and depression. Based on these findings, we propose that women who have been abused early in life will activate CRF-containing circuits and hypersecrete CRF every time they are stressed. Over time, repeated exposure to daily stress may result in adrenal habituation and through extra-hypothalamic actions of CRF may induce symptoms of depression and anxiety. Limitations of this investigation are that several potential predictors of pituitary-adrenal reactivity to stress have not been included. Thus, the model explained 35% of the variance of ACTH concentrations. Factors, which may account for further variance in HPA axis reactivity to stress, include genetics, coping styles, social support, and personality traits, such as self-esteem [Kirschbaum et al., 1992; Seeman et al., 1995; Biondi and Picardi, 1999]. Future studies identifying the role of these factors will help develop our understanding of the etiology of stress-related disorders and may provide novel strategies for the prevention and treatment of these disorders.

Acknowledgments. We thank M. J. Owens, Ph.D., B. Pearce, Ph.D., D. Knight, B.S., A. Borthayre, B.S., and S. Plott, B.S., for comprising the stress test committee and S. Böhm, B.S., and S. Welter, B.S., for their contributions.

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