# Hypothalamic-Pituitary-Adrenal Axis Function in Dissociative Disorders, Post-Traumatic Stress Disorder, and Healthy Volunteers

Daphne Simeon, Margaret Knutelska, Rachel Yehuda, Frank Putnam, James Schmeidler, and Lisa M. Smith

**Background:** This study investigated basal and stress-induced hypothalamic-pituitary-adrenal (HPA)–axis alterations in dissociative disorders (DDs).

**Methods:** Forty-six subjects with DD without lifetime post-traumatic stress disorder (PTSD), 35 subjects with PTSD, and 58 healthy comparison (HC) subjects, free of current major depression, were studied as inpatients. After a 24-hour urine collection and hourly blood sampling for ambient cortisol determination, a low-dose dexamethasone suppression test was administered, followed by the Trier Social Stress Test.

**Results:** The DD group had significantly elevated urinary cortisol compared with the HC group, which was more pronounced in the absence of lifetime major depression, whereas the PTSD and HC groups did not differ. The DD group demonstrated significantly greater resistance to, and faster escape from, dexamethasone suppression compared with the HC group, whereas the PTSD and HC groups did not differ. The three groups did not differ in cortisol stress reactivity, but both psychiatric groups demonstrated a significant inverse correlation between dissociation severity and cortisol reactivity, after controlling for all other symptomatology. The PTSD subgroup with comorbid DD tended to have blunted stress reactivity compared with the HC group.

**Conclusions:** The study demonstrates a distinct pattern of HPA-axis dysregulation in DDs, emphasizing the importance of further study of stress-response systems in dissociative psychopathology.

**Key Words:** Cortisol, dissociative disorders, HPA axis, neuroendocrinology, PTSD, stress

Dissociative disorders (DDs), along with post-traumatic stress disorder (PTSD), comprise a major group of psychiatric disorders whose pathogenesis is linked intimately to traumatic stress. About one third of seriously victimized children followed prospectively into adulthood manifest lifetime PTSD (Widom 1999); dissociative conditions are at least as common a sequel to such victimization (Putnam 1985; Chu and Dill 1990), or a complex admixture of both types of symptoms can occur (Zlotnick *et al.* 1996). Although frequently overlapping or alternating, *dissociative* versus *post-traumatic stress* states at their purest present with apparently opposite phenomenological patterns (amnesia, depersonalization, and decreased arousal in DD vs. intrusions, hypermnesia, and hyperarousal in PTSD), implying distinct and possibly contrasting neurobiological underpinnings.

The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the regulation of the stress response. The studies of pituitary-adrenocortical hormones that have been conducted in stress-spectrum disorders involve mostly PTSD, major depression, and nonpsychiatric individuals with trauma histories (Bremner *et al.* 1997, 2003; Carroll 1982; Heim *et al.* 2001; Sachar *et al.* 1970; Smith *et al.* 1989; Yehuda 1997; Yehuda *et al.* 1990, 1993; Young and Breslau 2004a). There has been very limited investigation of individuals manifesting primarily with dissociative psychopathology, and the few HPA-axis studies in DD largely are confounded by comorbidity. A study of 19 adult women with childhood sexual abuse reported hypersuppression in response to low-dose dexamethasone (Stein *et al.* 1997); however, 13 of the women had PTSD and 15 had DD, not permitting a dissection of the two diagnoses. However, a study of adult dissociative identity–disorder patients with extensive PTSD comorbidity reported resistance to dexamethasone suppression (Vermetten et al, unpublished data, 2003). The latter finding is similar to a report of elevated ambient cortisol and resistance to low-dose dexamethasone in a dissociative sample of 9 depersonalization disorder subjects who were free of PTSD and current major depression (Simeon *et al.* 2001).

Animal studies demonstrate that HPA-axis responsivity to acute stressors is altered in animals that previously have been stressed. Adult rats subjected to neonatal maternal separation secrete increased adrenocorticotropic hormone (ACTH) in response to mild foot-shock stress and have increased hypothalamic corticotropin-releasing factor (CRF) concentrations (Ladd *et al.* 1996). However, hyperreactivity is not the ubiquitous stress response in previously stressed animals; chronically severely stressed subordinate male rats have elevated ambient cortisol levels compared with dominant rats, yet in response to novel stressors, some subordinate rats have a heightened cortisol response, whereas others have a blunted one (McKittrick *et al.* 1995).

Human studies of HPA-axis responsivity to psychosocial stress in trauma-spectrum disorders generally have revealed heightened reactivity. In a study of adult women, those with a history of childhood abuse, with or without current major depression, demonstrated heightened ACTH responsivity to psy-

From the Department of Psychiatry (DS, MK, RY, JS, LMS), Mount Sinai School of Medicine, New York; the Department of Psychiatry (RY), Bronx Veteran Affairs Hospital, New York, New York; and the Department of Psychiatry and Pediatrics (FP), University of Cincinnati College of Medicine and Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

Address reprint requests to Daphne Simeon, M.D., Department of Psychiatry, Mount Sinai School of Medicine, Box 1230, One Gustave L. Levy Place, New York, NY 10029; E-mail: daphne.simeon@mssm.edu.

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chosocial stress, whereas cortisol reactivity was heightened only in the abused group with major depression; many participants had PTSD comorbidity (Heim *et al.* 2000). Similarly, adult women with abuse-related PTSD showed greater cortisol reactivity to trauma scripts during anticipation, exposure, and recovery compared with control subjects (Elzinga *et al.* 2003).

To our knowledge, there are no studies examining acute HPA-axis reactivity to psychosocial stress as a function of dissociative symptoms. However, there is evidence of autonomic blunting to stressful stimuli in acute and chronic dissociative states, which suggests that dissociative individuals are less acutely reactive to traumatic stress. In the acute aftermath of rape, women high in dissociation were reported to have decreased heart rates and galvanic skin responses (Griffin *et al.* 1997). In the acute aftermath of motor vehicle accidents, 15-hour urine norepinephrine and epinephrine were inversely correlated with severity of peritraumatic dissociation (Delahanty *et al.* 2003). With respect to chronic dissociative symptoms, a sample of depersonalization disorder participants, compared with anxiety disorder and healthy control participants, was characterized by reduced magnitude and increased latency of skin conductance responses to unpleasant stimuli (Sierra *et al.* 2002). Similarly, in depersonalization disorder (DPD), 24-hour urine norepinephrine was strongly inversely correlated ($r = -.88$) with depersonalization severity (Simeon *et al.* 2003).

The goal of the current study was to conduct the first extensive systematic investigation of HPA-axis function in DDs. We predicted that the DD group would have elevated ambient cortisol compared with healthy volunteers, whereas the PTSD group would have decreased ambient cortisol; that the DD group would demonstrate resistance to low-dose dexamethasone challenge, whereas the PTSD group would show hypersuppression; and that the DD group would show blunted cortisol reactivity to psychosocial stress compared with controls, whereas the PTSD group would show heightened reactivity. We also predicted that dissociation severity would be associated with greater childhood trauma, elevated basal cortisol, resistance to dexamethasone suppression, and blunted cortisol stress reactivity.

## Methods and Materials

### Participants

Subjects were recruited into three groups, a DD group free of lifetime PTSD, a PTSD group, and an HC group free of lifetime axis I and II disorders. Participants were 18–60 years old. They were recruited via newspaper advertisements and postings or were self-referred via Internet websites and other resources. Exclusion psychiatric criteria for DD and PTSD subjects were current major depression, eating disorder, or substance use disorder as well as lifetime psychotic or bipolar I disorder. Subjects were medically and neurologically healthy, had no history of head trauma, had normal baseline physical examination and routine laboratory testing, had not been not taking any medications including psychotropic medications for at least 2 months, had negative urine toxicology testing, and had negative pregnancy testing. Smokers of more than five cigarettes daily were excluded. Women were tested irrespective of menopausal status and menstrual-cycle timing. No over-the-counter medications or supplements were allowed for at least 3 days before admission. The study was approved by the institution's review board, and all subjects signed written informed consent before evaluation.

### Measures

Subjects were diagnostically evaluated with the Structured Clinical Interview for DSM-IV Dissociative Disorders (Steinberg 1994), the Structured Clinical Interview for DSM-IV Axis I disorders (First *et al.* 2002), and the Structured Interview for DSM-IV Personality Disorders (Pfohl *et al.* 1995). Post-traumatic stress disorder subjects also were evaluated with the Clinician-Administered PTSD Scale (CAPS; Blake *et al.* 1995), both to establish PTSD diagnosis and to measure symptom severity.

Subjects completed the Dissociative Experiences Scale (DES; Bernstein-Carlson and Putnam 2003), a 28-item self-report measure assessing a wide range of dissociative symptoms. Items are responded to in 10% increments ranging from 0 to 100%, and total DES score is the mean of all items. The DES has good test–retest reliability (.79–.96), high internal consistency (Cronbach's $\alpha = .95$), and strong convergent, discriminant, and criterion validity. Participants also completed the Hamilton Rating Scale for Depression (Hamilton 1960), the Hamilton Rating Scale for Anxiety (Hamilton 1959), and the Liebowitz Social Anxiety Scale (Heimberg *et al.* 1999).

Two trauma measures were given, the clinician-administered Childhood Trauma Interview (CTI; Fink *et al.* 1995) and the self-report Childhood Trauma Questionnaire (short form; CTQ-SF; Bernstein *et al.* 2003). The CTI is a detailed interview of childhood interpersonal trauma that quantifies frequency, duration, age range, severity, and perpetrator types for separations or losses, physical neglect, emotional abuse, physical abuse, witnessing of violence, and sexual abuse; it has high interrater reliability and good construct validity. The CTQ-SF consists of 25 items rated on a five-point scale; it has high internal consistency (Cronbach's $\alpha = .95$), good test–retest reliability (ICC = .88), and good convergence with the CTI. Five questions pertain to each of five types of trauma (emotional abuse, emotional neglect, physical neglect, physical abuse, and sexual abuse), and confirmatory factor analysis has supported its latent structure (Bernstein *et al.* 2003).

### General Clinical Research Center Procedures

Subjects were admitted to the Mount Sinai General Clinical Research Center (GCRC) from 6:00 PM on day 1 until 4:00 PM on day 3. Subjects ate standardized meals at fixed hours (8:00 AM, 12:00 PM, and 6:00 PM) and were allowed low-level ambulatory activity or bed rest during daytime hours. Sleeping time was set at 11:00 PM to 7:30 AM. Cigarette smoking was not allowed. An intravenous catheter lock was placed in subjects' forearms by 8:00 PM of day 1, and a 24-hour urine collection commenced at 10:00 PM. Starting at 8:00 AM on day 2, 16 hourly serial blood samples were drawn for determination of ambient plasma cortisol levels. At 11:00 PM, subjects received a single oral .5-mg dexamethasone dose. The low rather than the standard 1-mg dose was selected to better distinguish between increased and decreased suppression, facilitating distinction from the hypersuppression pattern that has been reported in PTSD (Yehuda *et al.* 1993). On day 3, plasma cortisol was measured at 8:00 AM and 2:00 PM, with concomitant measurement of plasma dexamethasone levels.

At 2:00 PM of day 3, participants underwent a standardized psychosocial stress test, the Trier Social Stress Test (TSST), which has been shown to induce mild to moderate psychosocial stress in healthy individuals (Kirschbaum *et al.* 1993). The TSST is a public-performance test and consisted of a 5-min preparation phase and a 10-min presentation phase (speech and math task). Plasma cortisol levels were measured after the preparation phase

(2:10 PM), after the presentation phase (2:20 PM), and during recovery (2:50 PM and 3:20 PM). After TSST completion, participants rated the stressor on a seven-point Likert scale (1, hardly any; 4, moderate; 7, worse ever).

### Sample Analyses

Blood samples were thoroughly mixed with anticoagulant and processed by centrifuge at 3000 rpm for 15 min at 4°C. Plasma was transferred to plastic tubes and immediately frozen at −80°C. Urine samples collected during any 24-hour period were added to a 2-L polyethylene container that was refrigerated for the duration of the collection. Subsequently, the entire urine sample was mixed thoroughly, volume was recorded, and samples were transferred into aliquots and stored at −80°C. Samples were assayed for cortisol and dexamethasone by using standard radioimmunoassay technique. For plasma cortisol, the intra-assay coefficient of variation was 5%, and the inter-assay coefficient of variation was 7.5%, with a lower detection limit of .16 μg/dL. For urinary cortisol, the intra-assay coefficient of variation was 8.4%, and the interassay coefficient of variation was 11.6%. For plasma dexamethasone, the intra-assay coefficient of variation was 4.9%, and the inter-assay coefficient of variation was 5.9%.

### Statistical Analyses

Analyses of covariance were used to compare symptom and trauma scores between groups. Three sets of group comparisons were conducted for cortisol measures (DD–HC, PTSD–HC, DD–PTSD), because we were interested in differences between group pairs rather than in three-way patterns of comparison. Univariate or repeated-measures analyses of covariance were used, as appropriate, all covarying for age, gender, and body mass index. The DST repeated-measures analysis used the 8:00 AM and 2:00 PM time points, covarying for 8:00 AM and 2:00 PM dexamethasone levels and for pre-DST 8:00 AM and 2:00 PM cortisol levels. The TSST repeated-measures analysis used four time points (2:10 PM, 2:20 PM, 2:50 PM, and 3:20 PM), covarying for 2:00 PM cortisol levels. *Peak cortisol stress reactivity* was defined as the difference in plasma cortisol levels between 2:20 PM and 2:00 PM. Pearson's correlations were used to examine relationships between dissociation severity and cortisol measures within each group; partial correlations were used to control for the impact of post-traumatic stress depression, anxiety, and social anxiety symptoms.

The following secondary analyses were performed. To investigate the impact of lifetime major depression (LMD) on cortisol measures, we examined the PTSD and DD subgroups with and without LMD, by using the analyses described in the prior paragraph. To investigate the impact of DD comorbidity on PTSD findings, we examined the PTSD subgroups with and without DD, also by using the analyses described in the prior paragraph.

Two PTSD subjects had missing time points for serial plasma cortisol determinations and were not included in this analysis. One DD and two PTSD subjects were removed from the DST analyses because of undetectable 8:00 AM dexamethasone levels. One HC subject withdrew before the DST, and one HC subject withdrew before the TSST. One DD and two PTSD subjects did not complete the TSST. Body mass index was not available for two DD, two PTSD, and three HC subjects. These missing data account for the minor discrepancies in sample sizes in the next section.

## Results

### Demographic and Clinical Characteristics

A total of 139 subjects were recruited and participated in at least a portion of the biological study: 46 DD, 35 PTSD, and 58 HC subjects. Ethnic distribution was 57.6% White, 22.3% African-American, 5.8% Hispanic, 13.6% Asian, and .7% American Indian. Groups differed significantly in years of age [DD: 31.2 ± 10.3 y; PTSD: 41.5 ± 11.5 y; HC: 32.8 ± 10.8 y; $F(2) = 10.28$, $p < .001$] but not gender [$\chi^2(2) = 1.60$, $p = .45$; DD: 26 women, 20 men; PTSD: 19 women, 16 men; HC: 26 women, 32 men].

Axis II personality disorders in the DD and PTSD groups were as follows, respectively: paranoid, 11% versus 29%; schizoid, 15% versus 3%; schizotypal, 2% versus 0; antisocial, 2% versus 0: borderline, 11% versus 29%; histrionic, 7% versus 3%; narcissistic, 2% versus 6%; avoidant, 20% versus 26%; dependent, 4% versus 3%; and obsessive-compulsive, 35% versus 35%. The following index traumas characterized the PTSD group: accidents, 3; assaults, 3; witnessing violence, 4; fires, 2; military trauma, 3; adult rape, 3; September 11, 2; traumatic separation, 1; traumatic death of close others, 5; childhood sexual abuse, 7; and childhood physical abuse, 2.

Table 1 displays group comparisons for symptoms and childhood trauma. In the DD group, 36 participants had a diagnosis of depersonalization disorder (DPD), and 10 had DD not otherwise specified (DDNOS). Participants with dissociative disorder not otherwise specified (DDNOS) had significantly earlier age of disorder onset than did DPD participants (DDNOS, 10.1 ± 8.7 y; DPD, 17.3 ± 9.0 y) [$t(44) = 2.26$, $p = .029$], higher dissociation scores (DDNOS, 43.2 ± 17.4 y; DPD, 25.0 ± 14.1 y) [$t(44) = 3.43$, $p = .001$], and greater childhood trauma scores (DDNOS, 56.3 ± 18.1 y; DPD, 40.5 ± 13.3 y) [$t(44) = 2.96$, $p = .005$].

In the PTSD group, 9 participants had comorbid DD (PTSD-DD), whereas 26 participants did not (PTSD-noDD). The two PTSD subgroups did not significantly differ in age [$t(33) = 1.28$, $p = .21$] or gender [$\chi^2(1) = .47$, $p = .49$]. Comorbid DD diagnoses in the PTSD-DD subgroup were DPD ($n = 4$), DDNOS ($n = 3$), and dissociative identity disorder ($n = 2$). The PTSD-DD subgroup had a significantly earlier age of onset of PTSD (18.1 ± 14.3 y) compared with the PTSD-noDD subgroup (30.2 ± 13.0 y) [$t(33) = 2.35$, $p = .025$]. Five of the nine PTSD-DD participants had childhood-onset PTSD (before age 18 y), in contrast to only 4 of the 26 PTSD-noDD participants. The PTSD-DD subgroup also had significantly greater post-traumatic stress, dissociation, and childhood trauma compared with the PTSD-noDD subgroup.

### Basal Urinary Cortisol

The DD group had higher basal urine cortisol than did the HC group [$F(1,95) = 3.84$, $p = .05$], whereas the PTSD group did not differ from the HC [$F(1,83) = .20$, $p = .65$] or the DD [$F(1,71) = 1.80$, $p = .18$] groups. There were no significant covariate effects (Figure 1).

### Basal Plasma Cortisol

There were no significant average group effects or group × time interaction effects, for any of the group pairs [DD–HC: group $F(1,95) = 1.93$, $p = .17$, group × time $F(15, 1425) = 1.23$, $p = .24$; PTSD–HC: group $F(1,82) = .00$, $p = .99$; group × time $F(15, 1230) = 1.36$, $p = .16$; DD–PTSD: group $F(1,70) = 1.33$, $p = .25$, group × time $F(15, 1050) = 1.12$, $p = .34$] (Figure 2).

**Table 1.** Clinical Characteristics, Psychopathology, and Childhood Trauma in the Dissociative Disorder (DD), Post-traumatic Stress Disorder (PTSD), and Healthy Comparison (HC) Groups

| Variable | DD ($n$ = 46) | PTSD ($n$ = 35) | HC ($n$ = 58) | $p$ |
|---|---|---|---|---|
| Age of onset (year) | 15.7 ± 9.3 | 27.1 ± 14.2 | N/A | <.001 |
| Duration (year) | 15.5 ± 13.4 | 14.4 ± 13.1 | N/A | .73 |
| DES | 29.0 ± 16.5 | 23.4 ± 15.4 | 3.0 ± 2.8 | <.001 |
| CAPS | N/A | 66.7 ± 13.1 | N/A | N/A |
| HRSA | 12.0 ± 5.0 | 13.9 ± 5.5 | 2.0 ± 2.6 | <.001 |
| HRSD | 9.8 ± 5.0 | 11.5 ± 4.9 | 2.1 ± 1.6 | <.001 |
| LSAS | 43.2 ± 35.4 | 48.2 ± 44.8 | 6.9 ± 10.3 | <.001 |
| CTQ Total | 43.7 ± 15.6 | 61.5 ± 26.1 | 33.8 ± 9.2 | <.001 |
| CTQ–Physical Abuse | 7.1 ± 3.2 | 11.0 ± 5.7 | 6.2 ± 2.5 | <.001 |
| CTQ–Emotional Abuse | 10.8 ± 5.1 | 14.0 ± 7.0 | 6.9 ± 2.5 | <.001 |
| CTQ–Physical Neglect | 7.5 ± 3.1 | 9.5 ± 4.3 | 6.3 ± 2.1 | <.001 |
| CTQ–Sexual Abuse | 6.2 ± 3.2 | 11.8 ± 8.2 | 5.6 ± 2.3 | <.001 |
| CTQ–Emotional Neglect | 12.0 ± 5.2 | 15.1 ± 6.3 | 9.0 ± 3.8 | <.001 |
| CTI Total | 487.2 ± 553.7 | 804.0 ± 655.0 | 236.4 ± 403.5 | <.001 |
| CTI–Separations | 22.1 ± 21.6 | 20.5 ± 23.4 | 23.5 ± 24.6 | .84 |
| CTI–Physical Neglect | 64.5 ± 95.6 | 78.7 ± 137.8 | 16.2 ± 30.2 | .003 |
| CTI–Emotional Abuse | 190.5 ± 195.2 | 306.5 ± 280.9 | 85.9 ± 160.6 | <.001 |
| CTI–Physical Abuse | 87.5 ± 123.6 | 207.2 ± 229.8 | 52.5 ± 123.8 | <.001 |
| CTI–Sexual Abuse | 7.7 ± 25.9 | 28.2 ± 58.2 | 1.5 ± 5.8 | .001 |
| CTI–Witnessing Violence | 114.8 ± 274.0 | 163.0 ± 196.8 | 56.8 ± 133.8 | .057 |

CAPS, Clinician-Administered PTSD Scale; CTI, Childhood Trauma Interview; CTQ, Childhood Trauma Questionnaire; DES, Dissociative Experiences Scale; HRSA, Hamilton Rating Scale for Anxiety; HRSD, Hamilton Rating Scale for Depression; LSAS, Liebowitz Social Anxiety Scale.

### Dexamethasone Suppression Test

Compared with the HC group, the DD group showed significant resistance to dexamethasone suppression [group: $F(1,90)$ = 5.71, $p$ = .019] and showed a significant group × time interaction effect [$F(1,90)$ = 4.61, $p$ = .034] indicating faster escape from suppression in DD subjects between 8:00 AM and 2:00 PM. The PTSD group did not differ from the HC group [group: $F(1,75)$ = .02, $p$ = .903; group × time: $F(1,75)$ = 1.50, $p$ = .224] or from the DD group [group: $F(1,62)$ = 2.69, $p$ = .106, group × time: $F(1,62)$ = .70, $p$ = .405]. There were significant gender effects in all comparisons, with females demonstrating greater suppression than males across diagnostic groups (Figure 3).

### Trier Social Stress Test

The TSST induced significant increases in plasma cortisol in all groups [$p$ < .001]. There were no differences in cortisol stress reactivity between any group pairs (Figure 4) [DD–HC: group × time $F(3,276)$ = .33, $p$ = .80; PTSD–HC: group × time $F(3,234)$ = .47, $p$ = .70; DD–PTSD: group × time $F(3,198)$ = 1.09, $p$ = .36]. Similarly, peak cortisol stress reactivity did not differ significantly between any groups (DD, 4.5 ± 4.1 μg/dL; PTSD, 2.5 ± 3.9 μg/dL; and HC, 3.6 ± 3.7 μg/dL) [DD–HC: $F(1,94)$ = 1.05, $p$ = .31; PTSD-HC: $F(1,81)$ = .33, $p$ = .57; and DD–PTSD: $F(1,68)$ = 1.32, $p$ = .25]. There were no significant age or gender effects.

Subjective stress experienced during the TSST differed among groups (DPD, 4.7 ± 1.1; PTSD, 5.1 ± 1.1; and HC, 3.9 ± 1.0) [$F(2)$ = 10.58, $p$ = .001]. Gender had a significant effect on stress scores, with females experiencing greater stress than males

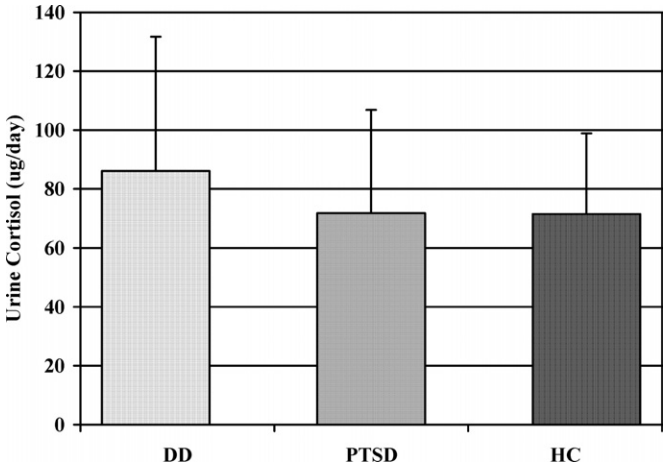


**Figure 1.** Twenty-four–hour basal urinary cortisol in the dissociative-disorder (DD; $n$ = 44), post-traumatic stress–disorder (PTSD; $n$ = 32), and healthy-comparison (HC; $n$ = 56) groups (bars represent standard deviations).

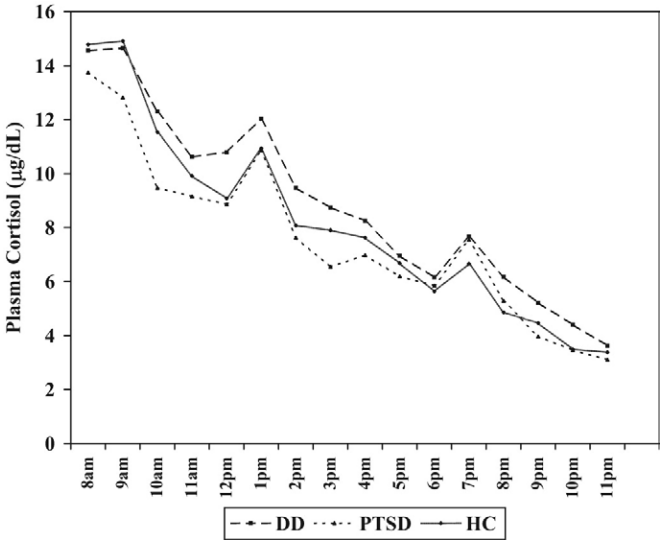


**Figure 2.** Day 2 basal hourly plasma cortisol levels in the dissociative-disorder (DD; $n$ = 44), post-traumatic stress–disorder (PTSD; $n$ = 31), and healthy-comparison (HC; $n$ = 56) groups.

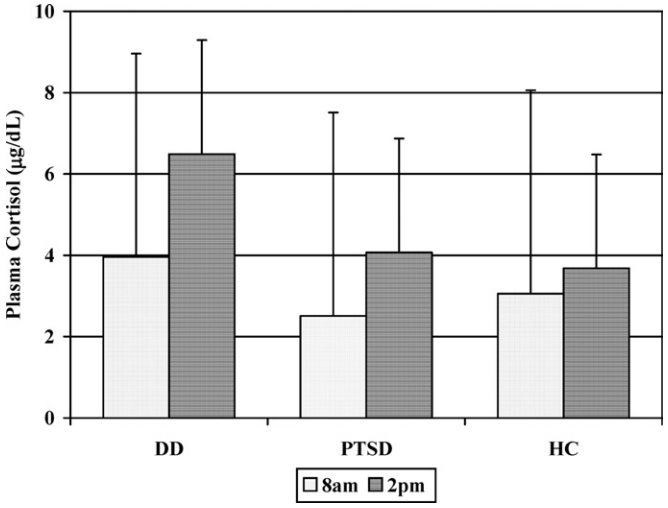


**Figure 3.** Plasma cortisol levels at 8:00 AM and 2:00 PM in response to an 11:00 PM .5-mg oral dexamethasone challenge in the dissociative-disorder (DD; $n = 43$), post-traumatic stress–disorder (PTSD; $n = 28$), and healthy-comparison (HC; $n = 56$) groups (bars represent standard deviations).

[$F(1,131) = 6.18$, $p = .01$], whereas age did not. Stress ratings were not significantly correlated with peak cortisol stress reactivity in any group.

### Relationships Between Cortisol Measures in the Three Groups

Table 2 presents the relationships between the various cortisol measures within each of the three study groups.

### Impact of LMD on Cortisol Measures

Twenty-five DD participants had comorbid LMD, whereas 21 did not. The DD-noLMD subgroup had significantly elevated urinary cortisol compared to the HC group [$F(1,72) = 9.54$, $p =$

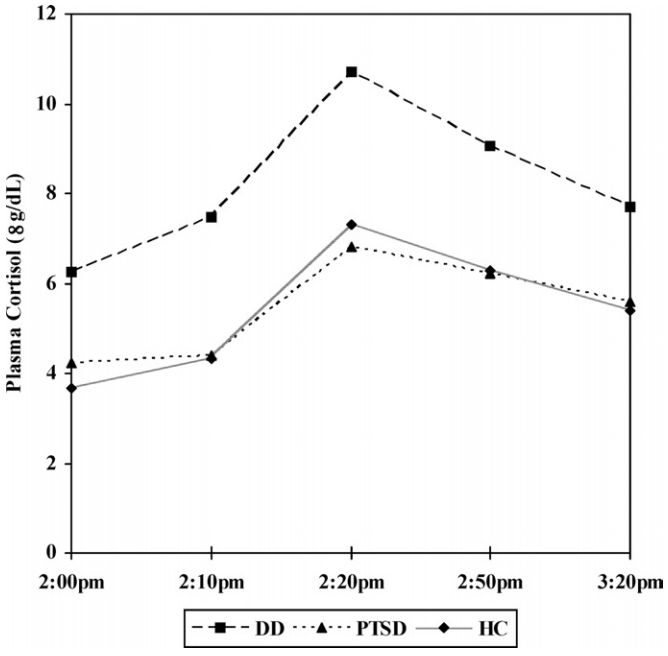


**Figure 4.** Plasma cortisol levels in response to the Trier Social Stress Test in the dissociative-disorder (DD; $n = 43$), post-traumatic stress–disorder (PTSD; $n = 29$), and healthy-comparison (HC; $n = 55$) groups.

**Table 2.** Relationships Between Cortisol Measures in the Dissociative Disorder (DD; $n = 46$), Post-traumatic Stress Disorder (PTSD; $n = 35$), and Healthy Comparison (HC; $n = 58$) Groups

| | UC | MPC | DST |
|---|---|---|---|
| MPC | DD: .04 (.79)<br>PTSD: .49 (.004)[b]<br>HC: .31 (.02)[a] | | |
| DST | DD: .14 (.37)<br>PTSD: −.10 (.58)<br>HC: −.24 (.07) t | DD: −.10 (.49)<br>PTSD: −.05 (.80)<br>HC: .17 (.22) | |
| TSST | DD: −.07 (.66)<br>PTSD: −.05 (.78)<br>HC: .27 (.04)[a] | DD: −.06 (.69)<br>PTSD: .17 (.34)<br>HC: .09 (.49) | DD: −.02 (.89)<br>PTSD: .01 (.96)<br>HC: −.35 (.008)[b] |

Pearson's correlation is followed by two-tailed $p$ value in parentheses (t indicates trend significance).

DST, percentage 8:00 AM dexamethasone suppression; MPC, mean plasma cortisol; TSST, Trier Social Stress Test; UC, urinary cortisol.

[a] Significance < .05.

[b] Significance < .01.

.003] and tended toward a significantly higher urinary cortisol than the DD-LMD subgroup (DD-noLMD, 101.7 ± 52.8 µg/d; DD-LMD, 71.9 ± 33.1 µg/d) [$F(1,39) = 3.68$, $p = .06$]. The two DD subgroups did not significantly differ in hourly plasma cortisol diurnal pattern [$F(15,585) = .73$, $p = .76$], and neither DD subgroup differed significantly from the HC group [DD-noLMD: $F(15,1080) = 1.39$, $p = .14$; DD-LMD: $F(15, 1110) = 1.03$, $p = .42$]. The two DD subgroups did not differ in DST 8:00 AM suppression (DD-noLMD, 72.6% ± 29.0%; DD-LMD, 70.2% ± 38.0%) [$F(1,37) = .20$, $p = .66$] or in TSST peak cortisol stress reactivity (DD-noLMD, 4.6 ± 4.9 µg/dL; DD-LMD, 4.3 ± 3.2 µg/dL) [$F(1,38) = .001$, $p = .97$].

Twenty-five PTSD participants had comorbid LMD, whereas 10 did not. The two PTSD subgroups did not differ in urinary cortisol from each other (PTSD-noLMD, 69.7 ± 21.6 µg/d; PTSD-LMD, 72.5 ± 39.6 µg/d) [$F(1,27) = .30$, $p = .59$], or from the HC group [PTSD-noLMD: $F(1,60) = .06$, $p = .80$; PTSD-LMD: $F(1,74) = .35$, $p = .56$]. The two PTSD subgroups also did not differ from each other in diurnal plasma cortisol pattern [$F(15,390) = 1.28$, $p = .21$], and the PTSD-noLMD subgroup did not differ from the HC group [$F(15,900) = .70$, $p = .79$]. The PTSD-LMD subgroup showed a diurnal pattern significantly different from the HC group [$F(15,1095) = 1.74$, $p = .039$], characterized by greater reactivity surrounding the physiologic stressor of the three mealtimes.

The PTSD-LMD subgroup tended to have significantly greater suppression compared with the PTSD-noLMD subgroup (PTSD-LMD, 86.2% ± 12.7%; PTSD-noLMD, 69.5% ± 31.3%) [$F(1,24) = 3.39$, $p = .07$]; comparison to the HC group (77.7% ± 27.7%) did not reveal differences for either subgroup [PTSD-LMD, $F(1,72) = 1.83$, $p = .18$; PTSD-noLMD, $F(1,58) = .02$, $p = .88$]. Similarly, the two PTSD groups did not differ in TSST peak cortisol stress reactivity (PTSD-noLMD, 1.5 ± 3.5 µg/dL; PTSD-LMD, 3.0 ± 4.1 µg/dL) [$F(1,25) = .46$, $p = .51$].

### PTSD Subgroups Without and with DD Comorbidity

The two PTSD subgroups did not differ from each other in any cortisol measures. Compared with the HC group, the PTSD-DD subgroup showed a tendency toward lower basal urinary cortisol (56.3 ± 20.7 µg/d) [$t(65) = 2.01$, $p = .07$] and a tendency toward blunted peak cortisol stress reactivity (1.2 ± 3.3 µg/dL) [$t(63) = 1.79$, $p = .08$].

### Relationships Between Childhood Trauma, Dissociation, and Cortisol

The CTQ-SF and CTI were highly intercorrelated [$r(131) = .70$, $p < .001$] and yielded similar associations to other variables; therefore, only CTQ-SF analyses are presented for brevity. Dissociation was significantly correlated with childhood trauma in the DD [$r(43) = .56$, $p < .001$] and the PTSD [$r(34) = .46$, $p = .005$] groups but not in the HC group [$r(53) = .06$, $p = .69$]. Dissociation severity and childhood trauma were not significantly associated with basal cortisol or with response to dexamethasone in any group.

With respect to the TSST, in the DD group, both dissociation severity and childhood trauma were significantly inversely correlated with peak cortisol stress reactivity [DES: $r(43) = -.32$, $p = .03$; CTQ-SF: $r(41) = -.43$, $p = .004$]. In the PTSD group, dissociation severity was significantly inversely correlated with peak cortisol stress reactivity [$r(31) = -.38$, $p = .03$], with a similar tendency after controlling for PTSD symptom severity [partial $r(30) = -.33$, $p = .06$], whereas childhood trauma was not [$r(31) = -.27$, $p = .14$]. Controlling for depression, anxiety, and social-anxiety scores preserved the inverse relationship between dissociation severity and cortisol stress reactivity in both psychiatric groups [DD: partial $r(39) = -.38$, $p = .015$; PTSD: partial $r(39) = -.38$, $p = .038$].

## Discussion

This study is the first demonstration of HPA-axis dysregulation in a large DD sample that was free of major comorbidity. The main findings were as follows: (1) the DD group had higher basal urinary cortisol than did the HC group, which especially was marked in the absence of LMD; (2) the DD group showed greater resistance to and faster escape from dexamethasone suppression than did the HC group; and (3) although the three groups did not differ in cortisol reactivity to psychosocial stress, both the DD and the PTSD groups demonstrated a significant inverse relationship between dissociation severity and cortisol stress reactivity, even when controlling for all other symptomatology.

Ambient and DST cortisol findings in the DD group replicate those from an earlier pilot study (Simeon *et al.* 2001), revealing basal HPA-axis hyperactivity with elevated cortisol and diminished pituitary negative-feedback inhibition. The ambient and DST cortisol findings are similar to those encountered in a sizable portion of individuals with major depression (Heim *et al.* 2001; Sachar *et al.* 1970), even when depression is in remission (Young *et al.* 2000; Young and Breslau 2004, 2004b) and are compelling given the exclusion of current depression and the examination of the impact of LMD in our dissociative sample.

The psychosocial stressor induced significant increases in plasma cortisol in all groups, along with considerable subjectively perceived stress. However, the failure to demonstrate blunted stress reactivity in the DD group compared with controls, as we originally hypothesized, is difficult to interpret given performance of the TSST while the HPA axis still was impacted by the DST, resulting in the assessment of an admixture of reactivity and escape from suppression. The HC and PTSD groups were significantly more suppressed at the start of the TSST, thus not precluding the possibility that they might otherwise have demonstrated a more robust cortisol response than the DD group. Another possible explanation of the failure to show group differences may be the measurement of only cortisol and not ACTH (Heim *et al.* 2000). Yet another explanation may relate to the exclusion of lifetime PTSD from the DD group, resulting in a more pure but markedly less severe dissociative group with only moderately elevated dissociation and childhood trauma scores. As a result, the PTSD subgroup with comorbid DD had markedly higher dissociation and trauma scores than the DD group and did show a tendency toward blunted cortisol stress reactivity. Given that PTSD is reported to be associated with heightened reactivity (Elzinga *et al.* 2003; Heim *et al.* 2000), the PTSD-DD subgroup finding of the current study could be accounted for by the more severe dissociative symptoms. In support of this hypothesis, we also found a significant relationship between dissociation severity and blunted cortisol stress reactivity in both the DD and the PTSD groups, even after controlling for PTSD, depression, anxiety, and social-anxiety severity. The finding that dissociation and childhood trauma were negatively associated with cortisol reactivity contrasts with a report in which childhood trauma and major depression were associated with heightened HPA-axis reactivity to psychosocial stress (Heim *et al.* 2002). One plausible explanation of this difference may relate to sampling, that is, a primarily dissociative sample versus a primarily depressive sample, suggesting that HPA-axis reactivity to stress may fundamentally differ in dissociation (hyporeactive) versus depression (hyperreactive).

The relationship between the various cortisol measures of this study is of interest and differed between groups. In the HC group, the ambient urinary, dexamethasone suppression, and TSST cortisol levels were significantly intercorrelated, reflecting a well-regulated HPA axis; individuals with higher basal cortisol had enhanced negative-feedback inhibition and heightened stress reactivity, reflecting a more active and reactive HPA axis. These intercorrelations were not as robust in the two psychiatric groups, presumably reflecting some degree of HPA-axis dysregulation. Of particular interest, ambient urinary and plasma cortisol levels were significantly intercorrelated in the PTSD and HC groups but not in the DD group. The most likely explanation for this finding is that urine sampling occurred over a 24-hour period, whereas blood sampling took place only between 8:00 AM and 11:00 PM. Therefore, the unsampled 8-hour period from 11:00 PM to 7:00 AM may have been characterized by elevated cortisol secretion in the DD group, such as has been described previously in major depression, with elevated cortisol nadir values during the late-night and early-morning hours (Yehuda *et al.* 1996). If so, higher cortisol production during this phase of the diurnal cycle in the DD group would have a twofold consequence: a weaker correlation between urinary and plasma cortisol levels as sampled in this study, as well as less-pronounced (and not statistically significant) plasma cortisol elevations in the DD group compared with the HC group, in contrast to the significant urinary cortisol elevation.

Although the primary focus of this study was to elucidate HPA function in DD, we briefly comment here on the PTSD cortisol findings. The absence of basal cortisol or DST abnormalities in the group as a whole mirrors the considerable inconsistencies in the PTSD HPA-axis literature; many variables are reported to potentially influence cortisol findings in PTSD (Yehuda 2002; Rasmusson *et al.* 2003). Notably, a large community survey did not reveal abnormal ambient cortisol levels in PTSD (Young and Breslau 2004a, 2004b). The current finding of a tendency toward hypersuppression in the PTSD participants with comorbid lifetime depression is consistent with several reports of hypersuppression in PTSD (Yehuda 2002), possibly reflecting more severe illness in this subgroup.

All study findings taken together suggest a preliminary model of HPA-axis dysregulation in DDs that is characterized by basal hyperactivity yet blunted acute reactivity to acute psychosocial stressors, at least as a function of increasing dissociation severity. The study demonstrates clear differences in HPA-axis dysregula-

tion between DDs and PTSD, highlighting the need for further extensive study of stress-response systems in dissociative psychopathology, whether it occurs independently of and in the context of PTSD.

Important strengths of the study include large sample sizes, strict selection and diagnostic criteria, control of several major confounds, and several cortisol measures that examine various components of HPA-axis regulation. The two most important limitations of the study were the timing of the TSST, as well as the measurement of cortisol but not ACTH as the sole pituitary-adrenocortical hormone. A minor limitation was not controlling for stage of menstrual cycle or for menopause. With respect to menopausal status, reanalysis of the data after excluding the two DD, five PTSD, and three HC menopausal women did not affect the findings. Although we administered a low dose of dexamethasone, in accord with the PTSD comparison group and related literature, administration of the standard DST challenge dose (1 mg) would be of interest given the DD group's resistance to suppression.

Another limitation, one that is inherent to the nature of the disorders under study rather than to the study design itself, is the propensity of individuals who are highly and chronically traumatized early in life to have both PTSD and DD, sometimes referred to as "complex PTSD," "complex trauma," or "Disorders of Extreme Stress" (van der Kolk *et al.* 2005) and to manifest the greatest severity of both sets of symptoms. In this study we chose to examine a relatively pure DDs sample that was restricted in its composition, consisting largely of DPD participants with a minority of DDNOS. These individuals manifested more modest degrees of so-called traditional childhood maltreatment, as has been described elsewhere (Simeon *et al.* 2001). Also, certain types of traumatic stressors commonly encountered in such DD groups are not tapped by standard childhood maltreatment scales, such as sudden death of family and close friends; growing up with severely mentally ill parents; or experiencing a severe, traumatic episode of mental illness that triggers chronic depersonalization (Simeon *et al.* 2003). In addition to maltreatment, prospective studies have found that serious disruptions of the early mother–infant dyad contribute to increased dissociation scores in late adolescence and adulthood (Carlson 1998; Hesse and Main 2006; Lyons-Ruth *et al.* 2006; Ogawa *et al.* 1997). Genetic contributions to dissociation also have been reported by some researchers (Becker-Blease *et al.* 2004; Jang *et al.* 1998).

Thus, the DD-group exclusion criterion of lifetime PTSD resulted in a dissociative sample that was not representative of more extreme dissociative manifestations such as dissociative identity disorder, which typically is characterized by very severe childhood trauma and very high PTSD comorbidity. Our preliminary finding of a tendency toward blunted cortisol stress reactivity in the PTSD subgroup with DD, as well as the finding of blunted cortisol stress reactivity as a function of increasing dissociation severity, suggest that this comorbid and prevalent DD + PTSD population merits further investigation. A future study could examine this complex-trauma group on its own standing, comparing it with pure DD and PTSD samples. The effort to procure purer DD versus PTSD samples in research has to be carefully weighed against the clinical reality of such individuals' frequently shared traumatic antecedents and phenomenological overlaps.

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