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Increased cortisol in women with intimate partner violence-related posttraumatic stress disorder☆

Sabra S. Inslicht[a,c,d,*], Charles R. Marmar[c,d], Thomas C. Neylan[c,d], Thomas J. Metzler[c], Stacey L. Hart[c,d], Christian Otte[e], Shannon E. McCaslin[c,d], G. Luke Larkin[f], Kelly B. Hyman[g], Andrew Baum[a,b]

[a]*Department of Psychology, University of Pittsburgh Sennott Square, 3rd Floor, 210 S. Bouquet Street, Pittsburgh, PA 15260, USA*
[b]*Department of Psychiatry, University of Pittsburgh Medical Center, University of Pittsburgh Cancer Institute, Behavioral Medicine and Oncology, 405 Iroquois Building, 3600 Forbes Avenue, Pittsburgh, PA 15213, USA*
[c]*Department of Veterans Affairs Medical Center, 4150 Clement Street (116P), San Francisco, CA 94121, USA*
[d]*Department of Psychiatry, University of California, San Francisco, CA 94121, USA*
[e]*Department of Psychiatry and Psychotherapy, University Hospital Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany*
[f]*Division of Emergency Medicine, Department of Surgery, Southwestern Medical Center, Parkland Memorial Hospital, University of Texas, Dallas, TX 75390-8579, USA*
[g]*Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System, University Drive C; Building 28 (151-C), Room 1A109, Pittsburgh, PA 15240, USA*

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Summary *Background*: Alterations of hypothalamic–pituitary–adrenal (HPA) axis function and sympathetic-adrenal activity have been proposed as key factors in biological models of posttraumatic stress disorder (PTSD).
Methods: We examined neuroendocrine function in female survivors of intimate partner violence (IPV) with lifetime (current or remitted) PTSD ($n=29$) and in women who were exposed to IPV but never developed PTSD ($n=20$). Salivary cortisol was collected as a marker of HPA axis function at 1, 4, 9, and 11 h after awakening. Platelet epinephrine and norepinephrine were assayed as markers of sympathetic-adrenal activation.
Results: Women with lifetime PTSD had significantly higher cortisol levels across the day compared to abuse-exposed participants without PTSD, after controlling for age,

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* Corresponding author. Address: Department of Psychiatry, PTSD Research Program, Veterans Affairs Medical Center, University of California, 4150 Clement Street (116P), San Francisco, CA 94121, USA. Tel.: +1 415 221 4810x3341; fax: +1 415 751 2297.
E-mail addresses: sabra.inslicht@ucsf.edu, sabra.inslicht@va.gov (S.S. Inslicht).

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depression, severity, and latency of abuse. There were no significant group differences in levels of platelet catecholamines.
Conclusions: Elevated cortisol levels may be a biomarker of IPV-related lifetime PTSD, reflecting long-lasting changes associated with trauma-exposure or possibly a reflection of risk for PTSD in women.

1. Introduction

Intimate partner violence (IPV) affects 22 million US women at some point in their lives and up to 1.9 million women each year (Tjaden and Theonnes, 1998), impacting women of all ages, ethnicities, and socioeconomic levels (Field and Caetano, 2004; McFarlane et al., 2005). IPV is a traumatic stressor, often involving prolonged and repeated episodes of violence that cumulatively undermine victims' expectations for safety and security. It is estimated that more than 60% of IPV victims develop posttraumatic stress disorder (PTSD; Golding, 1999). However, what makes some women more vulnerable to IPV-related PTSD and others resilient is not well understood. Discovering biomarkers or biological characteristics that may distinguish those with PTSD is important for advancing biological models, diagnostic screening, and treatment of PTSD. This study examined neuroendocrine activity as a correlate of PTSD among survivors of IPV.

Altered HPA axis activity is a central component of biological models of PTSD (Pitman, 1988, 1989; Yehuda and Harvey, 1997), although the precise nature and direction of these alterations have been inconsistent (reviewed in Yehuda, 2002). Differences may be related to age and gender, severity of co-morbid depression, type of trauma (e.g. interpersonal vs. natural disaster), and frequency, severity and recency of traumatic exposure (Yehuda, 2002). As a chronic interpersonal stressor that affects mostly women, prior research suggests that IPV-related PTSD should be associated with elevations in daily cortisol levels. For example, although exceptions exist (e.g. Young et al., 2004), higher cortisol was associated with PTSD in studies of repetitive interpersonal trauma such as adult women and children exposed to child abuse (e.g., De Bellis et al., 1999; Carrion et al., 2002; Lemieux and Coe, 1995). Another issue to consider is timing since trauma exprsure. Studies that found lower cortisol levels in PTSD more often included trauma survivors assessed several decades after the trauma exposure (e.g. Holocaust survivors and Vietnam veterans; Yehuda et al., 1990, 1995), whereas studies that found higher cortisol levels more often included participants who experienced traumas with shorter latency to endocrine assessment (e.g. Maes et al., 1998; Hawk et al., 2000). Consistent with this view several studies reported that recency of trauma exposure correlated with cortisol levels or reactivity (e.g. Rasmusson et al., 2001; Young et al., 2004). Of particular importance to biological models of PTSD, it is unclear from previous research whether HPA axis alterations associated with PTSD are state and/or symptom dependent or are more trait-like and do not remit with symptom abatement. If HPA axis alterations are long-lasting they may reflect indelible patterns acquired with trauma-exposure, or possibly an underlying vulnerability to the disorder.

Studies of survivors long after traumatic exposure (e.g. war veterans, Holocaust survivors, adult childhood abuse survivors) may not be representative of more recently trauma-exposed populations or those who face continuing risk of revictimization. IPV is a chronic and often ongoing stressor and recent research supports the presence of HPA axis dysregulation among IPV survivors (e.g. Seedat et al., 2003; Pico-Alfonso et al., 2004; Griffin et al., 2005). While two of these studies found associations of lower morning plasma cortisol with IPV (Seedat et al., 2003; Griffin et al., 2005) and IPV-related PTSD (Griffin et al., 2005), these studies used a single-point blood draw to assess cortisol, which is less reliable and representative than repeated measures across the day. The one study to date that examined diurnal cortisol in IPV found higher evening salivary cortisol levels, collected over 4 days, in physically abused women compared to nonabused controls, but no effect of PTSD status (Pico-Alfonso et al., 2004). In this study, participants were recruited from crisis shelters and most were living with the abuser during study participation. Perhaps, the high level of current threat in all abused women accounted for the similar levels of increased evening cortisol. In addition, possible effects of depression on cortisol were not controlled even though most participants with PTSD endorsed depressive symptoms.

Another promising correlate or potential biomarker of PTSD is alteration in catecholamine

levels. Trauma survivors with PTSD have been found to have higher catecholamine levels compared to healthy non-exposed controls in several studies (Southwick et al., 1999; O'Donnell et al., 2004). Greater levels of 15 or 24 h urinary catecholamines were found in PTSD compared with trauma exposed controls in motor-vehicle accident survivors (Hawk et al., 2000), Holocaust survivors (Yehuda et al., 1994), young adults exposed to mixed traumatic events (Young and Breslau, 2004b), and mothers of pediatric cancer patients (marginal trend; Glover and Poland, 2002). In contrast, no catecholamine increases were found in Vietnam veterans with PTSD (Pitman and Orr, 1990) or female childhood sexual abuse survivors compared to trauma-exposed controls (Lemieux and Coe, 1995). Finally, Vietnam veterans with PTSD had greater increases in plasma NE after exposure to combat sounds compared to combat-exposed controls (Blanchard et al., 1991). Thus, elevations in resting catecholamines may be due to the integration of resting and stress-related peaks during the day. While the above findings provide evidence of heightened catecholamine activity in PTSD, it is important to consider the possibility that the type and recency of trauma exposure and comorbidity may be influential factors. For example, major depression has been associated with higher resting and challenge evoked plasma NE and urinary NE (Roy et al., 1985-1987; Rudorfer et al., 1985; Grossman and Potter, 1999; Hughes et al., 2004). It is also unclear as to the extent to which these alterations are dependent upon symptom levels, associated with another underlying factor, or how long they last.

In the present study, we asked whether there would be group differences in salivary cortisol and platelet E and NE in abused women with lifetime PTSD and abuse-exposed controls. We used repeated sampling of salivary cortisol during waking hours to test for dysregulation in HPA activity. To assess sympathetic-adrenal activity, we used platelet catecholamines, since they reflect catecholamine concentrations found in plasma over the 7–12 days life of the cell (Omenn and Smith, 1978; Smith et al., 1985; Weir et al., 1986), providing a time-integrated measure likely to be more reliable and stable than plasma and urinary measures (Smith et al., 1985; Chamberlain et al., 1990; Carstensen and Yudkin, 1994). We predicted that salivary cortisol levels and platelet catecholamines would be higher in lifetime-PTSD participants, after controlling for age, depression, severity and latency of abuse. In secondary analyses, we explored the possibility that these alterations may be trait-like by examining relationships among neuroendocrine variables and the severity and timing of PTSD.

2. Methods

2.1. Design

Using a cross-sectional design, participants were assigned to one of two groups for the primary analyses; abuse survivors with lifetime IPV-related PTSD, including a current or past PTSD diagnosis (lifetime PTSD positive; LPP; $n=29$), and IPV exposed controls who did not meet criteria for current or past PTSD (lifetime PTSD negative; LPN; $n=20$). For secondary analyses, the LPP category was then broken down to PTSD current ($n=15$) and PTSD remitted ($n=14$).

2.2. Recruitment

Participants were a subsample ($n=49$) drawn from a group of 113 abused women who had previously participated in a study on the physical and mental health effects of IPV. Abuse survivors were initially identified during mandatory IPV screening of all female patients over 18 years of age who presented to an urban academic emergency department, designated as a Level I Trauma and Burn Center. However, at the time of the emergency visit all women recruited to this study were Level II or III patients, medically stable, ambulatory, and being treated as outpatients. Presenting complaints included routine medical concerns such as pain, cold and influenza symptoms, gynecological care, asthma, or minor injuries, suggesting that many of the women were using the ER as a proxy for primary care. Women were included in the original study if they had at least a sixth grade education, no evidence of cognitive impairment, and screened positive for ongoing or prior exposure to IPV. Patients were excluded if they were nonambulatory, had severe illness or acute physical trauma, injury, or burns, were not hemodynamically stable, required urgent medical care, or were admitted to surgical service or other inpatient unit. Women were also excluded if they experienced another traumatic event unrelated to IPV in the year prior to participation. Finally, a small group of non-abused women ($n=7$) originally recruited in the previous study meeting all of the above inclusion and exclusion criteria and who were negative on all measures of IPV provided data for a posthoc comparison of neuroendocrine values with our

primary control group of PTSD-free abused controls.

2.3. Procedures

The present study was approved by the University of Pittsburgh Institutional Review Board. Participants from the women's health study who experienced IPV were sent letters introducing the follow-up study. To control for possible menstrual cycle effects on endocrine measures, participants were seen within the first week following the start of menstruation.

Following written informed consent, a trained phlebotomist drew 50 ml of blood for assessment of catecholamines using a syringe. Participants completed self-report questionnaires about IPV, and physical and mental health. The first author interviewed participants on abuse characteristics, trauma history, and current and lifetime psychiatric diagnoses. For cortisol measures, participants were provided salivettes for saliva collection (for collection 1 day following interview at 1, 4, 9, and 11 h after awakening) and were asked to keep brief diaries to record adherence to the saliva collection protocol (e.g. collection times) and activities relevant for endocrine testing (e.g. eating, drinking, smoking). Participants were reimbursed $25 for their participation and provided referrals for counseling.

2.4. Measures

2.4.1. PTSD

Current and past PTSD was assessed using the *Structured Clinical Interview for the DSM-IV-Nonpatient version* (First et al., 1996). The interviewer was trained to 90% interrater reliability for diagnoses on audiotaped interviews. During the study, random interviews were audiotaped and reviewed by a senior clinician to ensure quality of administration and interrater agreement on diagnoses. The Impact of Event Scale (IES; Horowitz et al., 1979) was used to obtain a continuous measure of PTSD symptomatology.

2.4.2. Depression

Depressive symptomatology was measured with the *SCL-90-R* (Derogatis, 1997). The depression subscale has been found to be reliable, $\alpha = 0.90$, and stable over time, test–retest reliability $= 0.82$ (Derogatis, 1983). Lifetime and current diagnoses of major depressive disorder were also obtained with the *Structured Clinical Interview for the DSM-IV-Non-Patient version* (First et al., 1996).

2.4.3. Intimate partner violence

IPV was assessed with the *Domestic Safety Assessment* (DSA; Larkin et al., 2000), derived from the Abuse Assessment Screen (McFarlane et al., 1992). The DSA inquires about feelings of safety at home, and controlling behaviors, threats, physical violence, or forced unwanted sexual contact by an intimate partner or family member. IPV was operationalized as two or more incidents of intimate partner physical, sexual, or emotional abuse with at least one of those involving physical or sexual abuse.

The *severity of IPV* by an intimate partner was measured by the *Impact of Spousal Abuse Questionnaire* (ISA: Hudson and McIntosh, 1981). This 30-item questionnaire weights abuse items by seriousness of behaviors. The ISA has high internal consistency for each subscale (physical abuse $\alpha = 0.97$, non-physical abuse $\alpha = 0.91$) and acceptable discriminant validity (physical abuse $r = 0.73$, non-physical abuse $r = 0.80$; Hudson and McIntosh, 1981). In the present study, $\alpha = 0.91$ for physical abuse and $\alpha = 0.86$ for non-physical abuse.

2.4.4. HPA activity

Participants were provided salivettes for saliva collection and brief diaries for recording adherence to the collection protocol and activities (e.g. eating, drinking, or smoking) that may have occurred within 30 min prior to salivary cortisol collection. Patients were offered telephone reminders at their appropriate collection times. Samples were collected 1, 4, 9, and 11 h after awakening, avoiding lunch and dinner mealtimes. Salivary cortisol is stable at room temperature for 2–3 weeks (Groschl et al., 2001). Participants returned their samples by mail or in person. Three participants (1 LPN, 2 LPP) reported difficulties adhering to the collection times and were given new saliva collection kits to complete on the following day and telephone reminders. Samples were centrifuged and frozen at $-70\,^{\circ}C$. An enzyme immunoassay technique was used for determining salivary cortisol levels (Salimetrics, 2004). Intra-assay coefficient of reliability was 0.95.

2.4.5. Sympathetic activity

Platelet catecholamines were assayed as an index of SNS arousal. Blood samples were drawn into four 10 ml ethylene diamine tetra acetic acid (EDTA)-treated tubes, immediately placed on ice, and isolated for platelets. Platelet E and NE were determined by high-pressure liquid chromatography (HPLC) with electrochemical detection (Powell et al., 2002). Intra-assay coefficient of reliability was 0.98.

2.4.6. Potential confounding factors

Age, ethnicity, marital status, total household income, education, depression and interpersonal violence severity, latency, and age at onset (as measured with the DSA and ISA above), whether women were seen for physical injury compared to routine medical complaints, and time from initial emergency room visit to neuroendocrine sampling were assessed. A health questionnaire assessing medications, activity level, and intake of substances that may influence biological measures (e.g. weekly consumption of caffeinated beverages, cigarettes, alcoholic drinks, tobacco use, and use of medications and illicit drugs) was also administered.

2.5. Statistical analyses

All data were checked for expected ranges, presence of outliers and abnormal values, and to determine that distribution of variables met assumptions of statistical tests. E, NE, and cortisol levels were found to have substantial skew and kurtosis and were transformed using the logarithm (to the base 10) prior to analysis.

Subsequent analyses were conducted to identify group differences for potential confounds. Differences in characteristics of LPP and LPN groups were examined with independent sample *t*-tests for continuous variables and X^2-tests for categorical variables. Correlational analyses or independent sample *t*-tests were used to determine associations of these variables with neuroendocrine variables.

To test the main hypotheses regarding group differences in salivary cortisol, log-transformed values of cortisol centered at the mean of the four time points were examined using a linear mixed model fitting lifetime PTSD as a between-groups effect and time as a within-subjects repeated effect, with an autoregressive within-subjects covariance structure. The covariance structure was determined empirically by selecting the best fitting structure according to the Bayesian Information Criterion (BIC; Schwarz, 1978). We included analyses for linear and quadratic effects for time and for group×time interactions in each model. We included covariates that differed between groups and were associated with cortisol in this data or in previous research. Mixed-effects models are advantageous for repeated measures data because they use all available data, handle missing data appropriately, account for within subject correlations between repeated measurements, and do not assume homogeneity of variance across groups and time points (Gueorguieva and Krystal, 2004).

ANCOVA was used to test group differences in PTSD status and platelet catecholamines. The main independent variable was group (LPP, LPN) and the main dependent variables were levels of E and NE. Covariates were potential confounds or baseline differences in groups if related to E or NE in these analyses or in previous research. The primary neuroendocrine analyses were repeated controlling for medication use that could affect catecholamine or cortisol levels.

Secondary analyses examined potential neuroendocrine differences based on the timing of PTSD diagnosis among women with current PTSD, remitted PTSD, or no PTSD history using mixed models for cortisol data and ANCOVA for catecholamine data. Finally, in order to examine the possible effects of abuse exposure on outcome variables, neuroendocrine values in abused controls were compared with a small group ($n=7$) of non-abused controls using two-tailed *t*-tests.

3. Results

3.1. Sample characteristics

From the original sample of 113 IPV-exposed participants, we recruited 49 women for this study. Women in the current study were older ($M=35.11$ years, SD=11.13 years) than women from the full sample ($M=29.10$ years, SD=11.34 years, $t(174)=-2.82$, $p<0.01$),[1] but did not differ on ethnicity, education, income, or marital status. Sample characteristics are presented in Table 1. Ages ranged from 19 to 65 years ($M=38.18$ years, SD=11.97 years), 43% of participants were African-American, and 57% were White. The median annual household income was $21,000-$30,000. Approximately 67% of participants ($n=33$) reported ongoing involvement with the abuser during study participation.

Of the 49 women in this study, 15 had current PTSD, 14 had a past history of PTSD that remitted, and 20 never met criteria for PTSD. While exposed to a variety of traumatic events other than IPV over their lifetime, none of the 49 participants met criteria for current PTSD or PTSD in remission related to any traumatic stressor other than IPV during study participation. Participants with current vs. lifetime PTSD did not differ in demographics (age: $t(27)=-0.43$, $p=0.66$; ethnicity: X^2

[1] All *t*-tests were two-tailed unless otherwise indicated.

Table 1 Sample characteristics.

Background variable	Group[a]		Test
	LPP %(*n*) or *M*(SD) (*n*=29)	LPN %(*n*) or *M*(SD) (*n*=20)	
Age	41.32 (10.42)	34.35 (13.07)	$t(47)=-1.91$, $p=0.06$
Ethnicity			
African-American	51.7% (15)	30.0% (6)	X^2 (1, $N=49$)=2.28, $p=0.13$
Caucasian	48.3% (14)	70.0% (14)	
Marital status			
Single	24.1% (7)	50.0% (10)	X^2=(4, $N=49$) 5.34, $p=0.25$
Single but involved	17.2% (5)	10.0% (2)	
Married or living with partner	13.8% (4)	20.0% (4)	
Separated or divorced	41.4% (12)	20.0% (4)	
Widowed	3.4% (1)	0% (0)	
Annual household income			
$0-$10,000	13.8% (4)	30.0% (6)	X^2 (1, $N=49$)=1.67, $p=0.20$ (Kruskall-Wallis)
$11,000-$20,000	27.6% (8)	30.0% (6)	
$21,000-$30,000	27.6% (8)	15.0% (3)	
$31,000-$40,000	10.3% (3)	10.0% (2)	
$31,000-$40,000	6.9% (2)	0% (0)	
$41,000-$50,000	0% (0)	10.0% (2)	
>$51,000	13.8% (4)	5.0% (1)	
Grade 7-12 w/o graduating	3.4% (1)	30.0% (6)	X^2 (1, $N=49$)=3.19, $p=0.07$ (Kruskall-Wallis)
Graduated high school or equivalent	41.4% (12)	35.0% (7)	
Part college	34.5% (10)	15.0% (3)	
Graduated 2 year college/technical school	13.8% (4)	20.0% (4)	
Graduated 4 year college	3.4% (1)	0% (0)	
Graduate/professional school	3.4% (1)	0% (0)	
Depression severity on SCL-90R[b]	1.54 (1.29)	0.93 (0.80)	$t(43)=-1.96$, $p=0.03$
Latency since Last abuse (in days)	1128.30 (2517.17)	1163.30 (2817.38)	$t(47)=0.05$, $p=0.96$
Age at onset of intimate partner abuse	25.27 (10.54)	24.69 (13.93)	$t(47)=-0.17$, $p=0.87$
Severity of physical abuse	29.70 (24.23)	16.44 (18.98)	$t(45)=-2.03$, $p<0.05$
Severity of nonphysical abuse	39.39 (26.61)	20.98 (21.98)	$t(45)=-2.52$, $p<0.05$
Medications			
SSRI medication	13.8% (4)	5.0% (1)	X^2 (1, $N=49$)=1.00, $p=0.32$
Other antidepressants	6.9% (2)	0%(0)	X^2 (1, $N=49$)=1.44, $p=0.23$
Sedatives/benzodiazepines	13.8% (4)	15.0% (3)	X^2 (1, $N=49$)=0.01, $p=0.91$
Pain medicines	6.9% (2)	15.0% (3)	X^2 (1, $N=49$)=0.85, $p=0.36$
Estrogens and progestagens	17.2% (5)	10.0% (2)	X^2 (1, $N=49$)=0.51, $p=0.48$
Insulin	6.9% (2)	5.0% (1)	X^2 (1, $N=49$)=0.07, $p=0.79$

[a] LPP, lifetime PTSD positive; LPN, lifetime PTSD negative.
[b] We used a one-tailed *t*-test for SCL-90 depression subscale scores; all other *t*-tests were two-tailed.

(1, $N=29$)=0.03, $p=0.86$; marital status: X^2 (3, $N=29$)=6.72, $p=0.08$; income: X^2 (1, $N=29$)=1.25, $p=0.26$; or education: X^2 (1, $N=29$)=0.02, $p=0.89$). Those with current PTSD (15 of 29 participants with lifetime PTSD) were more likely to report an ongoing relationship with the abuser, X^2 (1, $N=29$)=8.62, $p<0.01$, more recent abuse ($M=80$ days SD=134.35 for current PTSD; $M=2211.29$ days, SD=3342.14 for PTSD in remission), $t(13.03)=2.38$, $p<0.05$, and a non-significant trend for younger age at abuse onset (current PTSD: $M=28.23$, SD=10.28; remitted PTSD: $M=21.36$, SD=9.71), $t(27)=-6.87$, $p=0.08$. Women with current and remitted PTSD did not differ on the primary neuroendocrine variables (cortisol AUC: $t(21)=0.38$, $p=0.71$; NE: $t(26)=-1.03$, $p=0.32$;

or E: $t(25)=0.37$, $p=0.37$). Since current and remitted PTSD participants did not differ on background and primary dependent variables and our main question focused on correlates of having developed PTSD over a lifetime, these groups were combined into a Lifetime PTSD Positive (LPP) group for our primary analyses, an approach taken in several previous studies (Breslau et al., 2004; Young and Breslau, 2004a,b).

The LPP and LPN groups did not differ in ethnicity, marital status, income, or education (Table 1). There was a marginal trend for age differences, $t(47)=-1.91$, $p=0.06$; the LPP group was slightly older ($M=41.32$ years, SD = 10.42 years) than the LPN group ($M=34.35$ years, SD = 13.07 years). Although age was not associated with neuroendocrine variables (Table 2), it has been previously been associated with cortisol (Kudielka et al., 2004; Otte et al., 2005) and with catecholamines (Aslan et al., 1981; Kjeldsen et al., 1982; Fleg et al., 1985). Thus, we covaried for age in subsequent neuroendocrine analyses. There were no group differences for health behaviors, including physical activity, smoking, or illicit drug, alcohol, caffeine, or medication use (Table 1).

In the present study, we attempted to recontact all previous IPV abuse-exposed participants. Endocrine testing occurred on average 21.9 months (SD = 18.9 months) following initial emergency department visit. There were no group differences in time since initial hospital visit, $t(47)=-0.07$, $p=0.95$. Review of presenting complaints indicated that only 5 of 49 women presented to the hospital with a physical injury or IPV-related concern (LPP, $n=3$; LPN, $n=2$) and none returned to the hospital for IPV or other injuries prior to neuroendocrine testing.

3.2. Abuse characteristics

LPP and LPN groups differed in severity of physical and emotional abuse, as measured by the ISA, $t(45)=2.03$, $p<0.05$ and $t(45)=2.52$, $p<0.05$, respectively. Women in the LPP group reported more severe physical abuse ($M=29.70$, SD = 24.23) and emotional abuse ($M=39.39$, SD = 26.61) than LPN controls ($M=16.44$, SD = 18.98; $M=20.98$, SD = 21.98). The LPP and LPN groups did not differ on relationship status (i.e. ongoing relationship with the abuser) during study participation ($X^2(1, N=49)=0.09$, $p=0.77$), latency since abuse ($t(47)=0.05$, $p=0.96$), or age at onset of abuse ($t(47)=-0.17$, $p=0.87$). The mean time since abuse among participants was 3.13 years (SD = 7.16 years), ranging from as recently as the previous day (in six women) to 29 years prior to neuroendocrine testing. Of relevance to our catecholamine measure (i.e. since platelet catecholamines reflect plasma concentrations for the 7–12 day life of the cell), 15 women reported that they experienced abuse within the previous 12 days. None of these abuse variables were associated with neuroendocrine outcomes (Table 2). However, we wanted to be certain that more severe abuse and recent abuse were not impacting our findings by acutely activating neuroendocrine levels. Thus, we included abuse latency and abuse severity as covariates in the main models. Abuse severity was summed from the physical and nonphysical abuse subscales on the ISA since they were highly correlated, $r=0.80$, $p=0.0001$).

3.3. Depression

Higher SCL-90 depression subscale scores were found in the LPP group (LPP: $M=1.54$, SD = 1.29,

Table 2 Correlations between demographics, abuse characteristics, depression, and neuroendocrine levels for the sample as a whole.

Variables	Cortisol AUC (log)	NE (log)	*E* (log)
Age	−0.17	−0.11	−0.05
Ethnicity	0.09	−0.22	−0.01
Annual household income	−0.13	0.08	0.11
Educational status	0.14	−0.16	0.06
Depression severity	0.06	−0.10	−0.17
Recency of last abuse in days	−0.20	0.18	0.13
Age at onset of intimate partner abuse	−0.11	−0.28, $p=0.07$	−0.18
Severity of physical abuse	0.18	−0.01	0.02
Severity of non-physical abuse	0.05	−0.05	0.07
PTSD symptoms*	−0.09	0.05	−0.06

Analyses were conducted with log transformed neuroendocrine data. Sample sizes for most variables (except for PTSD symptoms) were: cortisol: n=39; NE: n=45; E: n=44.

* PTSD symptoms were examined within the Lpp group only; Sample sizes within the Lpp group were: cortisol: n=21; NE: n=25; E: n=25.

Table 3 Raw neuroendocrine values by group.

Neuroendocrine measures	Group			
	LPN[a] *M*(SD)	LPP[a] *M*(SD)	PTSD current subdivision[b] *M*(SD)	PTSD remitted subdivision[b] *M*(SD)
Cortisol (μg/Dl)[c]				
1 h after awakening	398.61 (314.79)	489.77 (405.80)	372.70 (318.02)	560.46 (448.07)
4 h after awakening	136.44 (79.71)	186.27 (116.80)	169.10 (110.83)	189.31 (125.95)
9 h after awakening	180.89 (387.96)	413.43 (978.14)	217.89 (351.08)	520.23 (1217.74)
11 h after awakening	154.18 (195.09)	290.36 (371.20)	290.60 (443.71)	270.00 (312.66)
Platelet catecholamines (pM/mg)				
NE[d]	1.17 (0.46)	1.37 (0.85)	1.53 (1.07)	1.15 (0.47)
E[e]	0.08 (0.03)	0.09 (0.04)	0.08 (0.03)	0.10 (0.05)

*Analyses were conducted with log-transformed data. Untransformed and unadjusted data are presented here.
[a] LPP, lifetime PTSD positive, LPN, lifetime PTSD negative.
[b] Women from the LPP group are also shown as divided into PTSD current and PTSD remitted subdivisions.
[c] For cortisol: LPP, $n=21$–22; LPN $n=17$–18; PTSD current, $n=9$–10; PTSD remitted, $n=13$.
[d] For NE: LPP, $n=28$; LPN, $n=17$; PTSD current, $n=15$; PTSD remitted, $n=13$.
[e] For E: LPP, $n=27$; LPN, $n=17$; PTSD current, $n=14$; PTSD remitted, $n=13$.

LPN: $M=0.93$, SD$=0.80$, $t(43)=-1.96$, $p=0.03$ (one-tailed t-test for unequal variances), but no significant correlations were found between depression and neuroendocrine variables (Table 2). However, we considered that numerous studies have found associations between MDD and HPA function, E, and NE (Sacher et al., 1970; Carroll et al., 1976; Roy et al., 1985–1987; Rudorfer et al., 1985; Grossman and Potter, 1999; Hughes et al., 2004). To isolate the effects of PTSD, we covaried for depression severity in our primary neuroendocrine analyses.

3.4. Salivary cortisol

Salivary cortisol levels for all four time points were collected for 40 participants; nine participants did not provide samples due to compliance issues or concerns for participant safety, which did not allow for study materials to be taken home. The distribution of missing samples did not differ by group, $X^2(1, N=49)=1.58$, $p=0.21$, or by age, income, education, ethnicity, or marital status, or severity of physical or nonphysical abuse. As expected the nine missing samples were more likely to occur in women with current abuse, $X^2(1, N=49)=5.35$, $p<0.05$. Because the distributions of cortisol measurements at the four time points were substantially positively skewed, a logarithmic transformation was applied. After transformation (at each time point), there was one outlier with a cortisol value greater than three standard deviations from the mean (from the LPP group) and this data point was excluded. In addition, one participant from the LPP group reported taking a nasal glucocorticoid spray and her data was removed from the cortisol analyses. Area-under-the-curve (AUC) values were computed for preliminary analyses examining potential covariates. The raw cortisol values are listed in Table 3 and log transformed data are presented in Fig. 1.

A linear mixed model[2] was conducted fitting lifetime PTSD as a between-group effect, and time as a within groups effect on the log-transformed cortisol levels centered at the mean of the four saliva collections. Age, depression, abuse severity and latency were entered as covariates.

For the sample as a whole, latency of abuse was a significant predictor in the model, $F(1, 39.21)=4.37$, $p<0.05$, as more recent abuse was associated with higher cortisol, but age, depression, and abuse severity were not, $F(1, 38.84)=3.23$, $p=0.08$, $F(1, 39.93)=2.07$, $p=0.16$, and $F(1, 39.09)=0.02$, $p=0.89$. We found a significant linear effect of time, $F(1, 114.37)=20.95$, $p<0.0001$, indicating that for the sample as a whole cortisol decreased over the day. We also found a significant quadratic effect of time, $F(1, 125.71)=13.07$, $p<0.0001$, indicating an upward curve superimposed on the downward line. Related to the study hypotheses, there was a significant effect of group, $F(1, 39.23)=11.07$, $p<0.01$, even after adjusting for covariates. The LPP group had a higher adjusted mean level of

[2] Since previous researchers have used AUC to describe stress-related alterations in cortisol rather than mixed effects models of individual time points, we included results for AUC examined with one way analyses of covariance (ANCOVA) using covariates as described above. The ANCOVA analyses examining AUC for daily cortisol revealed significant group differences controlling for the above covariates, $F(1, 32)=8.46$, $p<0.01$. LLP women had higher AUC (log) levels ($M=22.32$, SD$=2.50$) than controls ($M=20.57$, SD$=2.56$).

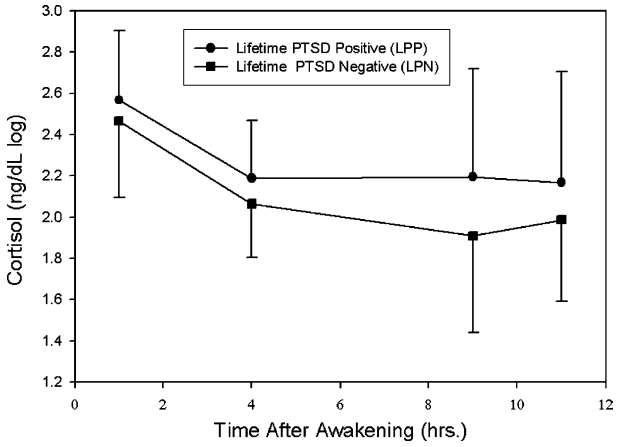

Figure 1 Diurnal salivary cortisol in LPP and LPN women.

cortisol ($M=2.14$ log ng/dL, SE$=0.008$ log ng/dL) than LPN controls ($M=1.86$ log ng/dL, SE$=0.07$ log ng/dL). There was no group$\times$time interaction, $F(1, 113.82)=0.03$, $p=0.86$.

We found similar results repeating these analyses controlling for medication use that could affect neuroendocrine function, including SSRI's, antidepressants, sedatives/benzodiazepines, pain medications, estrogens and progesterones, (Group effect: $F(1, 39.98)=11.78$, $p<0.001$), linear time effect $F(1, 105.73)=20.81$, $p<0.0001$, quadratic time effect $F(1, 123.20)=11.75$, $p<0.0001$, no group by time interaction $F(1, 106.30)=0.13$, $p=0.72$. In order to determine whether the group difference was due to high cortisol in the LPP group as opposed to relatively low cortisol in the trauma-exposed control group, we compared the LPN women with a small group ($n=7$) of non-abused controls, but found no significant differences, $t(22)=-0.15$, $p=0.88$ (t-test for unequal variances).

As a secondary analysis, we wanted to ensure that cortisol effects were not due to the timing of PTSD. When we compared the women divided into three groups (women with current PTSD, remitted PTSD, and abused controls) using mixed model analyses, we found a significant group effect, $F(1, 39.49)=5.53$, $p<0.01$, controlling for the covariates above. There were significant linear and quadratic effects for time, $F(1, 111.89)=18.45$, $p<0.0001$ and $F(1, 121.72)=13.02$, $p<0.0001$, but no group by time interaction, $F(1, 111.46)=0.24$, $p=0.79$. Only recency of abuse was a significant covariate in the model $F(1, 37.86)=4.56$, $p<0.05$), whereas age, depression, and abuse severity were not, $F(1, 38.39)=2.97$, $p=0.09$, $F(1, 41.18)=0.66$, $p=0.42$, and $F(1, 38.01)=0.01$, $p=0.93$. Pairwise comparisons indicated significant group differences between the controls ($M=1.87$, SE$=0.08$) vs. PTSD-remitted group ($M=2.17$, SE$=0.09$, $t(39.06)=3.22$, $p<0.01$) and a trend for controls vs. the PTSD-current group ($M=2.10$, SE$=0.11$; $t(38.91)=1.80$, $p=0.08$). Confirming our preliminary analyses, the PTSD current and remitted groups did not differ from one another, $t(40.99)=0.55$, $p=0.59$.

In order to determine whether increased cortisol levels in women with remitted PTSD might be related to the severity of potentially remaining PTSD symptoms, we examined whether the three groups differed on level of PTSD symptoms as measured on the IES and found a significant overall group effect, $F(2, 44)=19.01$, $p<0.0001$. Although women in the current PTSD group had greater PTSD symptoms ($M=47.77$, SD$=13.27$) than those with remitted PTSD ($M=21.57$, SD$=16.83$; $p<0.0001$) and LPN controls ($M=14.70$, SD$=15.57$; $p<0.0001$), women with remitted PTSD did not have greater levels of PTSD symptoms than those in the LPN group, $p=0.62$. Furthermore, continuous PTSD symptoms as measured by the IES was not associated with cortisol, $r=-0.09$, $p=0.70$ within the LPP group.

Finally, in order to confirm that the patterns of cortisol were not influenced by a depression diagnosis (major depressive disorder; MDD), we compared women within the LPP group meeting criteria for MDD on the SCID-IV with women who never experienced depression. Cortisol levels did not differ significantly for those who also had current MDD ($M=23.66$, SD$=2.60$; $n=7$) vs. women without current MDD ($M=21.65$, SD$=2.24$, $n=14$), $t(19)=-1.83$, $p=0.08$. Nor were there differences between women with lifetime MDD (defined as current or past MDD; $M=22.50$, SD$=2.71$; $n=16$) compared to women with no prior history of depression ($M=21.75$, SD$=1.71$, $n=5$), $t(19)=-0.57$, $p=0.57$.

3.5. Platelet catecholamines

Platelet NE and E were successfully collected for 45 of 49 participants. Two blood samples from controls were not obtained due to difficulties with the blood draw. In addition, one sample from each group had no detectable catecholamines and was excluded. Screening of log-transformed data indicated no outliers for NE. One E outlier remained and was excluded. Raw catecholamine values are listed in Table 3.

Our prediction that catecholamine levels would be higher in the PTSD group than in controls was not supported. An ANCOVA examining NE levels by PTSD status, controlling for age, depression, severity and

latency of abuse was not significant, $F(1, 35)=0.69$, $p=0.41$. The prediction that E would differ by PTSD status, using the same covariates, also was not evident, $F(1, 34)=0.75$, $p=0.39$.

In posthoc analyses examining the effects of abuse exposure on catecholamines, mean E and NE levels of the abused control group were compared with levels found in the group of nonabused comparison women. These analyses indicated no significant differences (E: $t(23)=-0.06$, $p=0.96$; NE: $t(23)=0.89$, $p=0.38$). Furthermore, catecholamine levels were not associated with abuse exposure variables (Table 2).

4. Discussion

Consistent with our primary hypothesis, the present study provided evidence that HPA axis activity is increased in women with lifetime PTSD, even after accounting for the effects of age, level of current depression, severity and latency of abuse. While cortisol decreased over the course of the day in both groups, average cortisol levels were higher in women with lifetime PTSD compared to controls. These data imply that increased salivary cortisol may be a correlate of lifetime PTSD associated with IPV since cortisol levels were significantly higher than in abuse-exposed women who never developed PTSD. While previous research indicated higher evening salivary cortisol in physically abused women compared to nonabused women but did not find an association with PTSD symptoms (Pico-Alfonso et al., 2004), the present study has further differentiated among psychiatric subgroups, demonstrating greater daily HPA activity in women with current or remitted PTSD compared to abused women who never developed PTSD.

These data have several important implications. This study extends the literature from research that has traditionally focused on mental health treatment-seeking individuals or male war veterans to an understudied and underserved group of nontreatment-seeking, impoverished women. Second, these data extend reports of increased cortisol in PTSD in those repeatedly traumatized and exposed to ongoing or threatened revictimization. Sixty-seven percent of participants in this study reported that they were still involved with the abuser at the time of endocrine assessment. Some women indicated that they were in ongoing danger and living in fear, and several reported that they were in hiding from their abusers. Extensive literature has described IPV as a repetitive and cyclical phenomenon (e.g. Walker, 1984). Even in cases in which abuse has ended, women may be fearful that the abuse could happen again.

Third, previous research on neuroendocrine function has been mixed, possibly due to differences in characteristics of the traumatic stressors studied. While several studies found that bodily injury was associated with the development of PTSD (Blanchard et al., 1995a; Koren et al., 2005), our data were not confounded by differences in severity of physical injury at the time of the hospital visit or in recency between hospital visit and neuroendocrine testing. While, we did find that women in the LPP group reported more severe emotional and physical abuse than abused controls and that latency of abuse was a significant predictor of cortisol in the mixed model, we found significant effects of PTSD even after controlling for these factors. These findings suggest an independent effect of lifetime PTSD on cortisol above and beyond characteristics and timing of the traumatic stressor, physical injury, or recency of hospital visit.

Previous research has also shown high rates of comorbid depression in PTSD (Blanchard et al., 1995b; Kessler et al., 1995; Boudreaux et al., 1998) and that HPA axis alterations were associated with depression (Holsboer, 1992; Heuser, 1998). In addition, several studies on trauma victims have shown elevated cortisol in persons with comorbid PTSD and MDD compared to persons with PTSD only, MDD only (Young and Breslau, 2004b) or no disorder (Young and Breslau, 2004a,b). Consistent with this literature, we too found greater depressive symptoms in our LPP group, however, having a comorbid diagnosis of current or lifetime depression was not associated with cortisol levels and our data suggested an independent effect of PTSD above potential effects of depression when depression was included as a covariate in our main model. Our findings are similar to those reported by Hawk et al. (2000), who also found a relationship of PTSD and urinary cortisol after controlling for depressive symptoms.

Women with current and remitted PTSD were similar in most respects except that women with current PTSD were more likely to be in a relationship with the abuser and to report more recent abuse than women with past PTSD. This finding suggests that greater distance in time and space from the trauma led to a reduction in PTSD symptoms. Interestingly, levels of cortisol were similarly elevated in both the current and remitted PTSD groups. In addition, this effect was not determined by acute symptomatology or residual PTSD symptoms in the PTSD remitted group since level of PTSD symptoms were similar in PTSD remitted women and LPN controls but significantly lower than PTSD

current women. Moreover, the severity of PTSD symptoms was not related to cortisol levels. The finding that cortisol levels remained elevated even when PTSD symptoms subsided may indicate that HPA axis dysregulation could be trait-like as opposed to having a state-like correspondence with PTSD symptoms. It is possible that long-lasting alterations may coincide with the onset of PTSD and be irreversible. Alternatively, alterations in HPA axis function may be associated with risk for PTSD. Considering the vast differences in cortisol findings across the literature, it will be important to establish the stability of these alterations over time within PTSD patients and across trauma populations.

One possible mechanism that could account for elevated cortisol in PTSD has been proposed by Heim and Nemeroff (1999). They hypothesize that genetics and adverse experiences occurring during critical developmental periods early in life sensitize central nervous system CRF pathways (Heim and Nemeroff, 1999). In turn, increased CRF activity could increase HPA axis function and cortisol output and produce long-lasting alterations in CRF neurocircuits that connect with amygdala and locus ceruleus, areas implicated in mood and anxiety disorders. This possibility was supported by a recent study (Sanchez et al., 2005) that found that repeated maternal separation in rhesus monkeys at age 3–6 months led to increased cortisol reactivity to subsequent separations and to flattened diurnal cortisol secretion at later ages. Since our study was conducted posttrauma, we do not know whether HPA axis alterations pre-existed trauma exposure or followed it. Future research in which pre- and posttrauma measures are obtained and putative genetic factors are ascertained would help determine if these alterations were present earlier in life and potentially could confer risk for PTSD.

Our hypothesis of elevated platelet catecholamines in the LPP group was not supported. This was surprising, since previous studies have found altered plasma and urinary catecholamines in PTSD (Blanchard et al., 1991; Hawk et al., 2000), and platelet catecholamine levels correlate with plasma catecholamine levels (Smith et al., 1985). We also did not find evidence to support the possibility that catecholamine dysregulation may be a result of trauma exposure, but not necessarily a distinct correlate of lifetime PTSD, since we did not find a significant association between abuse severity and catecholamine levels and no difference in our posthoc analysis comparing between LPN controls and nonabused women. One possible explanation for our lack of catecholamine findings is that catecholamine dysregulation in PTSD occurs centrally (Southwick et al., 1997, 1999; O'Donnell et al., 2004) and peripheral catecholamine activity does not necessarily reflect central catecholamine function (Peskind et al., 1986; Goldstein et al., 1987; Geracioti, 1993, 1994, 2001). Central catecholamine alterations associated with PTSD may have been missed by our measure. Another possibility is that increased catecholamine activation in PTSD is dependent on the reactivity to a stressor and, therefore, would be evident in challenge conditions. While platelet catecholamines provide an integrative index of basal and acute stress responses, they may not be sensitive enough to capture differences resulting from acute stress.

Several limitations of our study are noted. Ongoing danger for participants restricted our ability to recruit some participants and in our data collection, and participant safety is always paramount. The most severely abused women were likely in hiding, relocated, or had unlisted contact information. Several participants indicated that they could be endangered by taking home materials or by spending much time away from home, and thus complete cortisol and questionnaire data were not available for some. However, even though the most severely abused women were the least likely to participate, we found evidence to support our cortisol hypothesis. A number of participants in this study were also taking medications, but we did not see any differences by group and controlling for medication use did not affect our findings. Ideally, future research would replicate these findings in a medication-free sample.

Because trauma exposure in the absence of depression has been found in some studies to be associated with normal or low levels of cortisol (e.g. Yehuda et al., 1990, 1995; Young and Breslau, 2004a), and abuse in and of itself could lead to neuroendocrine alterations, our study would have benefited from including a larger non-abused control group in our primary model. A non-abused control group would be important to demonstrate that our group differences were in fact due to high cortisol in PTSD patients rather than low cortisol in abused controls. While we included a small group of nonabused controls in posthoc analyses, we recognize the limitations and propose that future studies include a larger and a priori determined trauma-free control group.

Regarding measurement issues, collection methods for diurnal cortisol vary considerably across studies. We chose time points that we believed would capture the morning rise and avoid the highly variable response to awakening. Perhaps, by waiting to collect our first sample until 1 h after awakening,

we may have missed an important change peak in cortisol. Furthermore, the present study was limited by our reliance on self-reported assessment of compliance with the saliva collection protocol. Although, we took several steps to ensure compliance such as telephone check and use of a collection diary, it would have been helpful to use an electronic monitoring device to ensure compliance. Finally, our platelet catecholamine measure has not been validated in prior PTSD studies.

This study underscores the public health imperative to study PTSD in the setting of recurrent traumatic exposure, poverty, minority status, and chronic nontraumatic stressors. Although this population presents unique challenges for research, our findings suggest that it is possible to use state of the art methods including biological assays with potential to inform prevention and intervention strategies.

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