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Cortisol at the emergency room rape visit as a predictor of PTSD and depression symptoms over time

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Summary
Background: Dysregulation of the hypothalamic-pituitary-adrenal axis, typically reflected by alterations in cortisol responsivity, has been associated with exposure to traumatic events and the development of stress-related disorders such as posttraumatic stress disorder (PTSD) and depression.
Methods: Serum cortisol was measured at the time of a post sexual assault medical exam among a sample of 323 female victims of recent sexual assault. Analyses were conducted among 235 participants who provided data regarding history of previous assault as well as PTSD and depression symptoms during at least one of the three follow-ups.
Results: Growth curve models suggested that prior history of assault and serum cortisol were positively associated with the intercept and negatively associated with the slope of PTSD and depression symptoms after controlling for covariates. Prior history of assault and serum cortisol also interacted to predict the intercept and slope of PTSD and depression symptoms such that women with a prior history of assault and lower ER cortisol had higher initial symptoms that decreased at a slower rate relative to women without a prior history and those with higher ER cortisol.

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Conclusions: Prior history of assault was associated with diminished acute cortisol responsivity at the emergency room visit. Prior assault history and cortisol both independently and interactively predicted PTSD and depression symptoms at first follow-up and over the course a 6-month follow-up.

1. Introduction

Approximately 18% of adult women in the United States report forcible or drug- or alcohol-related rape (Kilpatrick et al., 2007; Black et al., 2011). Among the many deleterious outcomes associated with rape, posttraumatic stress disorder (PTSD) and depression are highly comorbid conditions (Breslau et al., 2000; Au et al., 2013) that are particularly prevalent among rape victims (Resnick et al., 1993; Zinzow et al., 2012a). Rape victims with PTSD often exhibit dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Bremner et al., 2007; Meewisse et al., 2007; Yehuda, 2009; Kellner et al., 2010; Trickett et al., 2010; Bicanic et al., 2012), the stress response system that involves the release of stress hormones and neurotransmitters, and it has been hypothesized that PTSD and depression may share a common diathesis (Bres-lau et al., 2000). However, despite high comorbidity between PTSD and depression, studies have suggested different patterns of HPA axis responsivity such that PTSD is associated with hypocortisolism and depression is associated with hypercortisolism (for review see Ehlert et al., 2001; Handwerger, 2009). However, at least one study has found that rape victims with PTSD and depression evidence similar patterns of hypocortisolism (e.g., Bicanic et al., 2012), and temporal relationships between acute cortisol and the subsequent development of PTSD or depression are not well understood. HPA axis activity is modulated by cortisol, a glucocorticoid, through both positive and negative feedback. Historically, elevated levels of cortisol were thought to reflect exposure to stress (Chrousos and Gold, 1992), with higher cortisol levels reflecting exposure to a more severe stressor (Robins et al., 1987). However, more recent traumatic stress research does not support a linear relationship between cortisol and stressor severity (see Meewisse et al., 2007, for review). Discrepancies may relate to the measure of cortisol targeted (e.g., basal vs. reactivity), the population studied (men vs. women, children vs. adults), and limited measurement of critical moderators (e.g., recency of traumatic event exposure, prior traumatic event, prior PTSD, developmental timing of traumatic event exposure, traumatic event characteristics).

Among injured patients, acute cortisol levels have been associated with subsequent psychological functioning. For instance, low levels of salivary cortisol measured in motor vehicle accident (MVA) survivors presenting to the emergency room have been found to predict higher PTSD and depression at 6 months (Ehring et al., 2008). Furthermore, in women, low cortisol at the time of the MVA also was associated with prior trauma exposure (PTE) and prior diagnoses of PTSD or major depression (Ehring et al., 2008). Lower in-hospital 15-h urinary cortisol has been associated with increased likelihood of PTSD at 1-month post-traumatic event (Delahanty et al., 2000), but this study did not measure depression symptoms. Low salivary cortisol collected in the morning within 2 days after an acute trauma was associated with increased risk for PTSD at 1-month and 6-month follow-ups; however, high salivary cortisol in the afternoon was associated with increased risk for PTSD at follow-up (McFarlane et al., 2011). The authors suggested that high levels of comorbid depression, which has been associated with higher evening cortisol (e.g., Vinberg et al., 2008) could have accounted for these paradoxical findings; however, the authors found only weak associations between afternoon cortisol and 6-month depression symptoms (McFarlane et al., 2011). Findings that low acute salivary cortisol predicts PTSD and depression symptoms at follow-up also have been replicated in a sample of mothers with symptoms of PTSD related to their child's injury (Ostrowski et al., 2007). Finally, among recent rape victims, lower plasma cortisol, measured within hours of the rape, has been associated with prior history of trauma, and prior history of physical or sexual assault, but not cortisol, was associated with rape-related PTSD at follow-up (Resnick et al., 1995).

However, not all studies corroborate findings that acute low levels of cortisol are associated with increased risk for PTSD. For instance, in a sample of women whose children were facing an acute life-threatening illness, those with PTSD had significantly higher salivary cortisol levels at a medical check-up, which suggested a link between PTSD and hypercortisolism in a natural (as opposed to lab-based) stressful situation (Stoppelbein et al., 2012). Further, among pediatric injury patients, those with higher urinary cortisol levels at the emergency room had higher PTSD symptoms when assessed 6 weeks after the accident after controlling for depressive symptoms (Delahanty et al., 2005). Thus, findings regarding associations between acute cortisol and PTSD and depression symptoms over follow-up are somewhat mixed and require further study.

Epidemiological studies suggest that approximately 20% of rape victims receive post-assault medical care (Resnick et al., 2000; Zinzow et al., 2012b), and those who seek medical care are typically seen within 72—96 h (Logan et al., 2007). Recent victims of rape who report the incident to medical, police or other service providers are at high risk of PTSD (Rothbaum et al., 1992). Thus, rape victims seeking post-assault care may represent an important population in which to study biological indicators of the stress response. In addition, the rape exam may increase distress due to elements of the exam that may serve as rape related reminders, further supporting the potential importance of examining cortisol in this acute setting. Similarly, characterization of any potential impact of interventions designed to help victims cope with the post-assault exam and promote adaptive coping behaviors on cortisol could provide relevant context for understanding the complex relationship between cortisol and psychological functioning both in the immediate aftermath of rape and over time (Resnick et al., 1999).

The aims of this study were three-fold: (1) to examine whether prior assault history predicts acute lower levels of cortisol measured at the post-rape medical exam; (2) to examine associations between prior assault history and cortisol in predicting PTSD and depression symptoms at 6 weeks post-assault; and (3) to examine associations between prior assault history and cortisol in predicting PTSD and depression symptoms over the course of a 6-month follow-up.

2. Methods

2.1. Participants

Participants were adolescent girls and women age 15—71 who were victims of sexual assault within the previous 72 h and who participated in a medical rape examination. The rape exam is designed to treat medical concerns and to gather forensic evidence related to rape or suspected rape. All participants were recruited when they presented for forensic examinations at a major Southeastern academic medical center. Individuals who could not provide informed consent to participate in the study (e.g., those with mental retardation, adolescents without a parent present, those with serious injury or interfering health condition, extreme intoxication, or extreme distress that would interfere with the ability to attend to information about the study) were considered ineligible. Informed consent was obtained by specially trained project assistants at the time of the initial medical examination. Procedures were approved by the medical center Institutional Review Board.

Participants were recruited from 1997 to 2003 as part of an ongoing treatment outcome study examining the effectiveness of a brief video intervention (Resnick et al., 2007a,b). Of 467 eligible victims who presented to the Emergency Room during this period, 361 (77.3%) gave consent to participate in the study and 323 (89%) provided blood samples that were sufficient for cortisol analysis. Individuals who consented and provided blood samples did not differ from non-participants in terms of reported race or marital status; however, participants were slightly younger on average than non-participants (Mean = 26.63, SD = 9.96 vs. Mean = 28.96, SD = 13.00, $F(1,463) = 4.44$, $p < .05$).

As described elsewhere (Resnick et al., 2007a), a dismantling study was conducted with assignment to either full video or video components compared to standard care. Of the 323, 122 (37.8%) were assigned to the non-video intervention condition while 201 (62.2%) were assigned to the video treatment.[1] There were no statistically significant differences in terms of age, race, marital status, or prior history of assault between women who were in the video condition and the non-video condition. Although not a primary focus of the current analysis, the video intervention has been associated with decreased PTSD and depression symptoms, particularly in previous assault victims (Resnick et al., 2007b), therefore, we controlled for video intervention in analyses predicting PTSD and depression symptoms assessed over the course of follow-up.

Participants for the present study were 235 (72.8% of the 323) sexual assault victims who completed at least one follow-up assessment (described below). Average age was 26.3 (SD = 10.3) years, and 57.4% (n = 135) were white, 41.7% (n = 98) were black, and 0.9% (n = 2) were Asian. Most participants (80.4%, n = 189) were single, 8.9% (n = 21) were divorced/separated, 1.7% (n = 4) were widowed, and 6.4% (n = 15) were married/cohabitating. Approximately 61.3% (n = 144) were high school graduates. Regarding covariates, 53.6% (n = 126) reported being a current smoker at follow-up, 52.8% (n = 124) reported seeking mental health treatment prior to the rape; 14.0% (n = 33) reported taking antidepressant medication, 8.9% (n = 21) reported taking oral contraceptives, 61.7% (n = 135) were assigned to the video condition at the ER exam, and 36.2% (n = 85) reported seeking mental health treatment at some point during follow-up.

2.2. Measures

2.2.1. Medical exam time frame

Demographic characteristics and medical exam data: As part of the medical examination, self-report information was gathered about age, race, marital status, and prescription medication use. Time of incident and time of exam procedures was also recorded by the medical practitioner.

Blood sample collection and processing for serum cortisol: Following other medical examination procedures, blood samples were collected in an untreated vacutainer tube (10 ml) by routine venipuncture. After a clot was formed (25—45 min at room temperature) the tube was centrifuged at 3000 rpm for about 15 min. The serum was then decanted and roughly equal aliquots were transferred to three capped 2 ml microtubes, each labeled with ID code, date and time and stored at −70 °C until transfer on dry ice to the laboratory. Samples were analyzed in duplicate using an enzyme immunoassay (EIA) kit from IBL International (Hamburg, Germany) at the National Institute on Aging, Laboratory of Personality and Cognition, Emotions and Psychophysiology Section. The average intra-assay coefficient of variation (CV) was 5.43%; the average inter-assay CV was 3.32%.

2.2.2. Follow-up interview assessment

Follow-up assessments were designed to be completed at 6 weeks, 12 weeks, and 24 weeks from the time of the assault. The average number of days elapsed between assault and the follow-up interview assessments was 50.0 (SD = 11.4) days for the first, 106.7 (SD = 20.4) days for the second, and 194.9 (SD = 74.5) for the third. Participants who completed at least one follow-up did not differ significantly from those who did not on age, F = .37, p = .54, race, χ^2 = 6.4, p = .17, or cortisol, F = .64, p = .42.

Prior history of rape or physical assault: Prior history of rape or physical assault was assessed at a first follow-up interview, which used slightly modified questions based on the National Women's Study interview (see Resnick et al., 1993, p. 986) and included incidents of previous vaginal, anal, or digital rape or physical attacks by someone who

[1] Of those assigned to video, 69% were randomly assigned to watch the full video and 16% and 15% were assigned to either the medical exam preparation or psychoeducation and instruction in coping conditions, respectively, as part of a subsequent dismantling phase of the study. Those assigned to any component or the full video were classified as being in the video condition for the purpose of this study.

intended to seriously injure or kill the participant, or physical attacks with a weapon or that resulted in injury.

Posttraumatic stress disorder: At each follow-up assessment, participants completed the PTSD Symptom Scale — Self-Report (PSS-SR; Foa et al., 1993), a 17-item measure of PTSD as assessed in the DSM-IV. The PSS-SR has been validated with female victims of sexual assault (Foa et al., 1993) and contains continuous ratings, allowing for sensitive assessment of changes in PTSD over time. Each symptom criterion is rated in terms of frequency of symptoms within the past 2 weeks on a scale of 0 = *not at all or only one time* to 3 = *almost always or five or more times per week*. Total scores range from 0 to 51.The PSS-SR has been shown to correlate highly with interview-based measures of PTSD (Foa et al., 1993) and has been used in numerous longitudinal studies assessing PTSD symptoms over time (e.g., Dunmore et al., 2001; Mayou et al., 2002).

Depression: The Beck Depression Inventory (BDI; Beck et al., 1961), a 21-item self-report scale, is among the most widely used instruments to measure depression. Each item is scored 0—3 and total scores range from 0 to 63, with higher scores indicating greater depressive severity. Beck and Steer (1984) demonstrated that the BDI has high internal consistency. A modified time frame was used to assess symptoms of depression on that day, specified as "the way you feel today, that is, right now."

Potential covariates: At the first follow-up interview, participants reported on factors that could affect cortisol responsivity such as whether they were a current cigarette smoker, whether they sought mental health treatment prior to the rape (possible indicator of pre-existing mental health problems or distress), and whether they were taking medications such as antidepressants or oral contraceptives prior to the rape. At each follow-up, participants also reported whether they received mental health treatment, a factor that could affect PTSD or depression trajectories. An affirmative response at any follow-up was coded as positive for receiving mental health treatment.

2.3. Procedures

A project coordinator supervised a small team of on-call responders who were available to go to the hospital 24 h per day to administer informed consent and study procedures in cases deemed appropriate as described above. Women and girls were asked to participate in a study evaluating how different types of information collected at the medical examination might be associated with later functioning. They were asked to allow information gathered as part of the medical exam to be included as part of the study consent and were also asked if they would allow a portion of blood drawn as part of the standard medical exam to be analyzed to examine hormones that may relate to stress. Consenting participants were randomly assigned to the video intervention or standard services (NV) condition. Women in the video condition watched the videotape followed by the forensic examination which included the collection of blood samples, while those in the standard treatment condition proceeded directly to the forensic examination. Follow-up interviews and self-report assessments were conducted at 6 weeks, 12 weeks and 24 weeks post-assault.

2.4. Analyses

Preliminary descriptive analyses as well as tests of bivariate associations and missing data were imputed in PASW Statistics Version 19.0. Tests of hypotheses were conducted using MPlus Version 6.0 (Muthen and Muthen, 2008). Prior studies of acute trauma have found that many of the usual predictors of cortisol response (i.e., time of day, use of alcohol, use of drugs, use of nicotine) are not associated with peritraumatic cortisol levels (see Delahanty et al., 2003). Nonetheless, we conducted preliminary analyses to confirm an absence of potential confounding factors. First, given the natural circadian rhythm of cortisol, an analysis of military time of day would be inappropriate. Accordingly, we created 4-h time bins and then rank ordered the bins on the basis of normative cortisol rhythms (Nomura et al., 1997); in this way, the 4-h time of day bin coded as "1" would be expected to show the lowest cortisol levels and the time of day coded as "6" would be expected to reflect highest cortisol levels in a normative sample. This strategy allowed us to test whether our observed cortisol levels showed the normative rhythmicity. This time of day bin was not associated with cortisol, $F(5,206) = 2.09$, $p = .07$, suggesting that the data did not reflect a diurnal rhythm effect. To further test for a potential time-of-day effect, we also plotted cortisol against military time of blood draw using a nonparametric smoother (i.e., Loess at 40%). This strategy allowed us to examine the observed pattern of cortisol over time without assumptions regarding rhythmicity (i.e., frequency/amplitude/rank of cycling). Visual inspection of the Loess curve did not support the presence of a diurnal rhythm in the observed data. Second, we examined whether being a current smoker was associated with serum cortisol and found no association, $F(1,223) = .70$, $p = .41$. Third, we examined whether mental health treatment prior to the rape (a proxy for prior distress or mental health problems) was associated with serum cortisol; those who reported prior mental health treatment had higher cortisol at the ER, $F(1,233) = 3.95$, $p < .05$. Fourth, we examined whether use of antidepressants or oral contraceptives were associated with serum cortisol. Antidepressants, $F(1,233) = .76$, $p = .38$, were not associated with serum cortisol, but oral contraceptive users had higher serum cortisol relative to non-users, $F(1,233) = 11.89$, $p < .001$.

For growth modeling, changes in PTSD and depression total scores were examined using an unconditional growth curve model to obtain intercept and slope fixed-effect estimates and to test for the presence of significant variance in these latent growth trajectory factors. Next, conditional growth curve models (controlling for assignment to video condition, oral contraceptive use, prior mental health treatment, and mental health treatment during follow-up) estimating the main effects of serum cortisol and prior history of assault as well as the interaction between serum cortisol and prior history of assault, were examined separately for PTSD and depression. Data from only three follow-up time points were available for analysis, thus, non-linear effects were not tested here. Time was parameterized such that the first follow-up/Time 1 (T1) was @0; subsequent time points were parameterized as months since T1. Models were estimated using robust Weighted Least Squares (WLSMV) to account for non-normality in the distributions of PTSD and BDI scores.

3. Results

3.1. Bivariate associations

As shown in Table 1, a history of prior assault was associated with lower serum cortisol at the emergency room visit. In bivariate analyses, serum cortisol was uncorrelated with PTSD or depression symptoms, but prior history of assault was associated with PTSD at T2 and with depression at T1 and T2. PTSD and depression symptoms were positively correlated with one another at each time point (r = .67—.73) and over time (r = .55—.74).

3.2. Longitudinal Modeling

Fig. 1 shows changes over time in PTSD and depression symptoms. Unconditional growth curve models predicting PTSD and depression fit the data well as indicated by non-significant chi-square model fit statistics; comparative fit index (CFI) statistics of 0.95 or above; and root mean square error of approximation (RMSEA) and standardized root-mean square residual (SRMR) indices of 0.05 and 0.08 or less, respectively. Unstandardized coefficients from unconditional models are presented in Table 2. Results suggest that PTSD and depression scores were significantly different than zero

Table 1 Bivariate correlations between serum cortisol, prior assault, covariates (video condition, smoking history, mental health treatment history, oral contraceptive use, and timerank) and PSS and BDI scores.

	Prior MH treat	Prior assault	Cortisol	FU MH treat	Current smoking	OC use	Timerank	T1 PSS	T2 PSS	T3 PSS	T1 BDI	T2 BDI	T3 BDI
Video	−.03	−.02	−.13*	−.07	−.01	−.11	−.11	−.06	−.04	−.12	−.07	−.17	−.08
Prior MH treat	1	.16*	.13*	.38***	.08	.19**	.06	.008	.05	.07	.09	.17	−.04
Prior assault		1	−.15*	.04	.18**	−.15*	.23*	.13	.21*	.06	.16*	.20*	.05
Cortisol			1	.18**	−.06	.20**	−.02	.10	.06	.07	.11	.00	.04
FU MH treat				1	.07	.12	−.05	.08	.13	.14	.08	.21*	.07
Current smoking					1	−.12	.18*	.19*	.37**	.19**	.19**	.30**	.15*
OC use						1	.16*	−.05	−.07	−.006	−.07	−.03	−.06
Timerank							1	−.08	−.12	−.03	−.03	−.02	−.05
T1 PSS								1	.55**	.57**	.73**	.70**	.51**
T2 PSS									1	.72**	.39**	.67**	.54**
T3 PSS										1	.49**	.62**	.68**
T1 BDI											1	.74**	.59**
T2 BDI												1	.60**
T3 BDI													1

Notes: video = video condition (1) versus no video (0); prior MH treat = mental health treatment prior to the rape; prior assault = prior assault (1) versus no prior assault (0); cortisol = serum cortisol measured at ER visit; FU MH treat = mental health treatment at one or more follow-ups; current smoking = smoking reported at one or more follow-ups; OC use = oral contraceptive use prior to the rape; timerank = blood draw time ranked by natural circadian rhythm; T1 = time 1; T2 = time 2; T3 = time 3.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

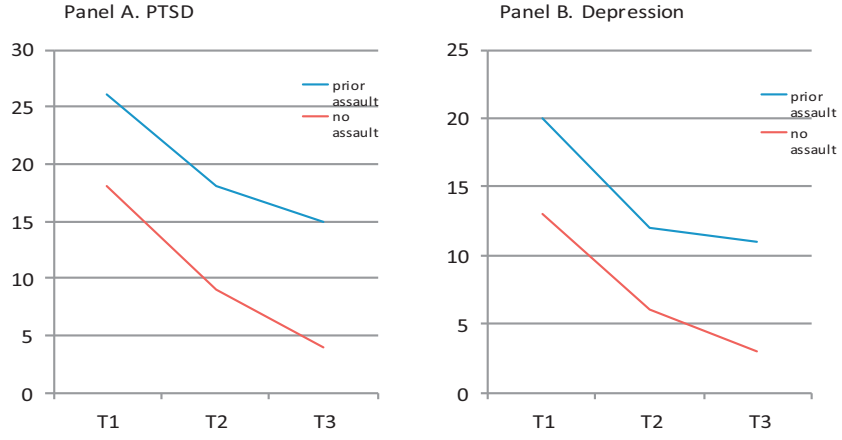

Figure 1 PTSD and depression symptoms by prior assault history.

Table 2 Unconditional and conditional growth models predicting PTSD and BDI over time from cortisol and prior assault.

	Intercept	Variance	Slope	Variance
Unconditional models				
PSS total score	21.97***	73.76***	−1.79***	2.53***
BDI total score	17.66***	104.54***	−1.39***	2.75***
	Intercept	**S.E.**	**Slope**	**S.E.**
Main effects conditional model for PSS				
Prior assault	.22***	.04	−.17**	.06
Cortisol	.18***	.04	−.12*	.05
Interaction conditional model for PSS				
Prior assault × cortisol	−.12*	.05	.41***	.10
Main effects conditional model for BDI				
Prior assault	.21***	.03	−.18***	.04
Cortisol	.15***	.03	−.14**	.04
Interaction conditional model for BDI				
Prior assault × cortisol	−.08	.05	.32***	.06

Note: all conditional models controlled for video condition, oral contraceptive use, prior mental health treatment-seeking, and mental health treatment-seeking over follow-up.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

at intercept and scores declined significantly over time. Furthermore, there was significant variance in both the intercept and slope of PTSD and depression.

Conditional models controlled for video condition assignment, oral contraceptive use, pre-rape mental health treatment, and mental health treatment during follow-up, and included the main effects of prior assault (yes-no) and cortisol (mean-centered) as well as the 2-way interaction between prior assault and cortisol. In main effects models, prior assault was associated with initial (T1) PTSD and depression symptoms, but negatively associated with PTSD and depression symptoms over time. Similarly, cortisol was positively associated with initial (T1) PTSD and depression symptoms and negatively associated with PTSD and depression symptoms over time.

Prior assault and cortisol also interacted to predict the intercept of PTSD symptoms and the slope of PTSD and depression symptoms. Specifically, those with a prior history of assault and lower ER cortisol had higher PTSD symptoms at T1 when compared to women without a prior history of assault and those with higher ER cortisol. Women with higher ER cortisol had a steeper decline in PTSD and depression symptoms over time, but this effect was attenuated for women who also had a prior history of assault such that their symptoms did not decline as swiftly over time.

4. Discussion

The present study yielded four key findings. First, an inverse association between prior assault and serum cortisol was found such that women with a prior history of assault evidenced lower serum cortisol compared to women without a prior assault history. Second, a prior history of assault was positively associated with PTSD and depression symptoms at T1; however, women with a prior history of assault evidenced a steeper decline in PTSD and depression symptoms over time relative to women without a prior history of assault. Third, higher serum cortisol at the ER was associated with higher PTSD and depression symptoms at T1, and with a swifter decline in PTSD and depression symptoms over time when compared to those with lower serum cortisol. Fourth, prior history of assault and serum cortisol at the ER interacted such that women with a prior history of assault who had lower ER cortisol had higher PTSD symptoms at T1 relative to women without a prior history who also had lower cortisol. Further, women with a prior history of assault who had *higher* ER cortisol evidenced a slight decrease in PTSD and depression symptoms over time, whereas women without a prior history of assault who had higher ER cortisol evidenced a steep decline in PTSD and depression symptoms over time. The finding that women with a prior assault history and higher ER cortisol had less of a decline in symptoms may relate to the fact that higher ER cortisol in this group was associated with lower T1 symptom scores, so this group was not as symptomatic at the initial assessment relative to prior assault victims with lower cortisol.

Consistent with prior research (Resnick et al., 1995), women with a prior history of assault had lower ER cortisol relative to women without a prior assault history. Also consistent with prior research (Au et al., 2013), PTSD and depression symptoms at each follow-up were highly correlated. The finding that serum cortisol at the ER was positively associated with PTSD and depression at T1 is consistent with findings from a sample of children and adolescents with acute injuries (Delahanty et al., 2005) and a sample of mothers coping with their child's life threatening illness (Stoppelbein et al., 2012), but conflicts with others showing that cortisol measured among predominantly male patients with acute injuries is negatively associated with PTSD symptoms at follow-ups ranging from 1 to 6 months (Delahanty et al.,

2000; Ehring et al., 2008). Previous investigations have used samples with exposure to different types of trauma (i.e., MVAs) and various sources of cortisol measurement (urinary, salivary). Further, they have examined prior trauma but have not considered the interaction between cortisol and prior trauma in models as in the current analysis. Here, women with a prior assault history who had lower ER cortisol had higher PTSD and depression symptoms at T1 relative to women without a prior assault, which is consistent with previous investigations (e.g., Ehring et al., 2008) and highlights the need to consider both variables concomitantly in models. Additionally, among women without a prior history of assault, higher ER cortisol was associated with a swifter decline in symptoms over the course of the study, suggesting that autonomic reactivity in response to an acute stressor may be adaptive and facilitate recovery in this subgroup, although other explanations (e.g., more social support) are also possible. Multivariate models revealed that, relative to women without a prior assault, women with prior assault histories reported greater initial PTSD and depression symptoms, which highlights the potential cumulative impact of repeated assault on PTSD symptoms (Filipas and Ullman, 2006; Walsh et al., 2012). However, prior assault victims had a steeper decline in PTSD and depression symptoms over time relative to non-assault victims, which may reflect regression to the mean as prior victims had greater initial distress. However, when the interaction between cortisol and prior assault was considered, associations between prior assault and PTSD and depression symptoms became more complex. Specifically, women with a prior assault history evidenced only slight decreases in PTSD and depression symptoms over time whereas women without a prior assault history evidenced a steep decline in PTSD and depression symptoms. Findings suggested that cortisol may differentially predict PTSD and depression symptoms in women with and without a prior assault history. Higher ER cortisol appeared to be a stronger predictor of recovery for women without a prior history of assault, whereas relationships between cortisol and PTSD and depression symptoms were attenuated among women with a prior history of assault.

A brief mention of bivariate analyses with covariates is warranted. Descriptive correlational data indicated an inverse association between exposure to the intervention and cortisol level, which may appear to be inconsistent with previous reports from this study (Resnick et al., 2007b). One potential hypothesis is that the video (which contains rape-related information) may be perceived as a stressor. The extant literature is mixed with regard to HPA axis functioning in response to stressor challenges and trauma cues, particularly among those with prior history of traumatic event exposure (e.g., Santa Ana et al., 2006; Carpenter et al., 2007; Gola et al., 2012). We also observed positive associations between OC use and pre-rape mental health treatment, which may be seen as consistent with some research suggesting that OC use may be prescribed to treat mood disorder symptoms (e.g., Joffe et al., 2003). However, in contrast to research showing an attenuated cortisol response among those using OCs (e.g., Kirschbaum et al., 1995; Rohleder et al., 2003), we found that OC use was positively associated with cortisol at the ER. In this sample, OC users were also less likely to have a prior assault history, so they may reflect a relatively healthier subgroup, although additional research is necessary to confirm this hypothesis.

4.1. Limitations and future directions

The present data, although unique, are not without limitations. This study includes a sample of recent sexual assault victims who reported their sexual assault to the police or medical service providers. Thus, participants in our study may not be representative of all rape victims as they may be a group with relatively high distress at the time of the post assault exam, and they may be at greater risk for PTSD or depression. PTSD and depression were measured with widely used and well-validated self-report instruments; however, formal psychiatric interviews may provide additional information about functional impairment that was not captured here. Further, although PTSD and depression are the most commonly reported mental health outcomes associated with traumatic event exposure, given the role of cortisol in stress regulation, it may be important to examine relationships between cortisol measured at the medical exam and functional outcomes including drug and alcohol use. Additionally, because blood samples were collected as part of the medical exam, serum cortisol was an efficient marker of HPA axis activity to collect; however, measuring HPA axis functioning in other ways (e.g., collecting saliva at several time points throughout the day for several days and using challenge paradigms) may provide critical information about the dynamic interplay of components of the HPA axis and the biological stress-response system (Chrousos, 2004; McFarlane et al., 2011). Finally, although we collected rich data on various covariates, we did not assess and control for menstrual cycle differences or pre-rape history of PTSD or depression. Cortisol itself may relate to prior history of PTSD rather than prior history of assault, which may be a vulnerability factor for subsequent PTSD following a new assault. Thus, future studies of this kind would benefit from the inclusion of these factors.

Despite these limitations, this study is important for several reasons. First, findings are partially consistent with previous research suggesting that a prior history of assault may be associated with a blunted or attenuated stress response subsequent to acute stressor. Second, this study highlights the role that cortisol responsivity and prior trauma may play in psychological adjustment following trauma even after controlling for mental health treatment seeking and other covariates. Specifically, higher levels of serum cortisol were associated with higher initial symptoms, but a swifter decline in symptoms over time; however, results differed for women with a prior history of assault such that low levels of cortisol predicted higher initial symptoms and less of a decline in symptoms over time when compared to women without such a history. These findings could have important clinical implications for women presenting to the ER for a rape-related medical exam. Specifically, there may be promise in delivering evidence-based psychotherapies for PTSD and depression to reduce symptoms and possibly ''normalize'' HPA axis responsivity to stress and/or stress related cues among rape victims. Longitudinal research that includes careful assessment of cortisol functioning and optimally includes challenge tasks or assessment in response to trauma

related cues and associates observed patterns with response to treatment and functioning is needed to evaluate the potential effects of treatment on HPA axis responsivity and meaningfulness of HPA axis responses as a correlate or predictor of psychological or behavioral responses.

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Conflict of interest

None declared.

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References

Au, T.M., Dickstein, B.D., Comer, J.S., Salters-Pednault, K., Litz, B.T., 2013. Co-occurring posttraumatic stress and depression symptoms after sexual assault: a latent profile analysis. J. Affect. Disord., http://dx.doi.org/10.1016/j.jad.2013.01.026.

Beck, A.T., Steer, R.A., 1984. Internal consistencies of the original and revised Beck Depression Inventories. J. Clin. Psychol. 40, 1365—1367.

Beck, A.T., Ward, C.H., Mendelsohn, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561—571.

Bicanic, I.A., Postma, R.M., Sinnema, G., De Roos, C., Olff, M., Van Wesel, F., Van de Putte, E.M., 2012. Salivary cortisol and dehydroepiandrosterone sulfate in adolescent rape victims with post traumatic stress disorder. Psychoneuroendocrinology 38, 408—415.

Black, M.C., Basile, K.C., Breiding, M.J., et al., 2011. The National Intimate Partner and Sexual Violence Survey (NISVIS): 2010 Summary Report. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA.

Bremner, D., Vermetten, E., Kelley, M.E., 2007. Cortisol, dehydroepiandrosterone, and estradiol measured over 24 hours in women with childhood sexual abuse-related posttraumatic stress disorder. J. Nerv. Ment. Dis. 195, 919—927.

Breslau, N., Davis, G.C., Peterson, E.L., Schultz, L.R., 2000. A second look at comorbidity in victims of trauma: the posttraumatic stress disorder-major depression connection. Biol. Psychiatry 48, 902—909.

Carpenter, L.L., Carvalho, J.P., Tyrka, A.R., et al., 2007. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. Biol. Psychiatry 62, 1080—1087.

Chrousos, G.P., 2004. Systemic inflammation and well-being. Autoimmun. Rev. 3 (Suppl. 1) S34—S35.

Chrousos, G.P., Gold, P.W., 1992. The concepts of stress and stress system disorders, Overview of physical and behavioral homeostasis. JAMA 267, 1244—1252.

Delahanty, D.L., Nugent, N.R., Christopher, N.C., Walsh, M., 2005. Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. Psychoneuroendocrinology 30, 121—128.

Delahanty, D.L., Raimonde, A.J., Spoonster, E., 2000. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biol. Psychiatry 48, 940—947.

Delahanty, D.L., Raimonde, A.J., Spoonster, E., Cullado, M., 2003. Injury severity, prior trauma history, urinary cortisol levels, and acute PTSD in motor vehicle accident victims. J. Anxiety Disord. 17, 149—164.

Dunmore, E., Clark, D.M., Ehlers, A., 2001. A prospective investigation of the role of cognitive factors in persistent posttraumatic stress disorder (PTSD) after physical or sexual assault. Behav. Res. Ther. 39, 1063—1084.

Ehlert, U., Gaab, J., Heinrichs, M., 2001. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus-pituitary-adrenal axis. Biol. Psychol. 57, 141—152.

Ehring, T., Ehlers, A., Cleare, A.J., Glucksman, E., 2008. Do acute psychological and psychobiological responses to trauma predict subsequent symptom severities of PTSD and depression? Psychiatry Res. 161, 67—75.

Filipas, H.H., Ullman, S.E., 2006. Child sexual abuse, coping responses, self-blame, posttraumatic stress disorder, and adult sexual revictimization. J. Interpers. Violence 21, 652—672.

Foa, E.B., Riggs, D.S., Dancu, C.V., Rothbaum, B.O., 1993. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. J. Trauma Stress 4, 459—473.

Gola, H., Engler, H., Schauer, M., Adenauer, H., Riether, C., Kolassa, S., Kolassa, I.T., 2012. Victims of rape show increased cortisol responses to trauma reminders: a study in individuals with war- and torture-related PTSD. Psychoneuroendocrinology 37, 213—220.

Handwerger, K., 2009. Differential patterns of HPA activity and reactivity in adult posttraumatic stress disorder and major depressive disorder. Harv. Rev. Psychiatry 17, 184—205.

Joffe, H., Cohen, L.S., Harlow, B.L., 2003. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. Am. J. Obstet. Gynecol. 189, 1523—1530.

Kellner, M., Muhtz, C., Peter, F., Dunker, S., Wiedemann, K., Yassouridis, A., 2010. Increased DHEA and DHEA-S plasma levels in patients with post-traumatic stress disorder and a history of childhood abuse. J. Psychol. Res. 44, 215—219.

Kilpatrick, D.G., Resnick, H.S., Ruggiero, K.J., Conoscenti, L., McCauley, J., 2007. Drug-facilitated, Incapacitated, and Forcible Rape: A National Study. , NIJ Grant No. 2005-WG-BX-0006.

Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1995. Preliminary evidence for reduced cortisol responsivity to psychological stress

in women using oral contraceptive medication. Psychoneuroendocrinology 20, 509—514.
Logan, T.K., Cole, J., Capillo, A., 2007. Sexual Assault Nurse Examiner program characteristics, barriers, and lessons learned. J. Forensic Nurs. 3, 24—34.
Mayou, R.A., Ehlers, A., Bryant, B., 2002. Posttraumatic stress disorder after motor vehicle accidents: 3-year follow-up of a prospective longitudinal study. Behav. Res. Ther. 40, 665—675.
McFarlane, A.C., Barton, C.A., Yehuda, R., Wittert, G., 2011. Cortisol response to acute trauma and risk of posttraumatic stress disorder. Psychoneuroendocrinology 36, 720—727.
Meewisse, M.L., Reitsma, J.B., de Vries, G.J., Gersons, B.P., Olff, M., 2007. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. Br. J. Psychiatry 191, 387—392.
Muthen, L.K., Muthen, B.O., 2008. Mplus, 6.0 ed. Muthen & Muthen, Los Angeles, CA.
Nomura, S., Fujitaka, M., Sakura, N., Ueda, K., 1997. Circadian rhythms in plasma cortisone and cortisol and the cortisone/cortisol ratio. Clin. Chim. Acta 266, 83—91.
Ostrowski, S.A., Christopher, N.C., van Dulmen, M.H., Delahanty, D.L., 2007. Acute child and mother psychophysiological responses and subsequent PTSD symptoms following a child's traumatic event. J. Trauma Stress 20, 677—687.
Resnick, H., Acierno, R., Holmes, M., Kilpatrick, D.G., Jager, N., 1999. Prevention of post-rape psychopathology: preliminary findings of a controlled acute rape treatment study. J. Anxiety Disord. 13, 359—370.
Resnick, H.S., Acierno, R., Amstadter, A.B., Self-Brown, S., Kilpatrick, D.G., 2007a. An acute post-sexual assault intervention to prevent drug abuse: updated findings. Addict. Behav. 32, 2032—2045.
Resnick, H.S., Acierno, R., Waldrop, A.E., King, L., King, D., Danielson, C., Kilpatrick, D.G., 2007b. Randomized controlled evaluation of an early intervention to prevent post-rape psychopathology. Behav. Res. Ther. 45, 2432—2447.
Resnick, H.S., Holmes, M.M., Kilpatrick, D.G., Clum, G., Acierno, R., Best, C.L., 2000. Predictors of post-rape medical care in a national sample of women. Am. J. Prev. Med. 19, 214—219.
Resnick, H.S., Kilpatrick, D.G., Dansky, B.S., Saunders, B.E., Best, C.L., 1993. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. J. Consult. Clin. Psychol. 61, 984—991.
Resnick, H.S., Yehuda, R., Pitman, R.K., Foy, D.W., 1995. Effect of previous trauma on acute plasma cortisol level following rape. Am. J. Psychiatry 152, 1675—1677.
Robins, H.I., Kalin, N.H., Shelton, S.E., Martin, P.A., Shecterle, L.M., Barksdale, C.M., 1987. Rise in plasma beta-endorphin, ACTH, and cortisol in cancer patients undergoing whole body hyperthermia. Horm. Metab. Res. 19, 441—443.
Rohleder, N., Wolf, J.M., Piel, M., Kirschbaum, C., 2003. Impact of oral contraceptive use on glucocorticoid sensitivity of pro-inflammatory cytokine production after psychosocial stress. Psychoneuroendocrinology 28, 261—273.
Rothbaum, B.O., Foa, E.B., Riggs, D.S., Murdock, T., Walsh, W., 1992. A prospective examination of posttraumatic stress disorder in rape victims. J. Trauma. Stress 5, 455—475.
Santa Ana, E.J., Saladin, M.E., Back, S.E., Waldrop, A.E., Spratt, E.G., McRae, A.L., Brady, K.T., 2006. PTSD and the HPA axis: differences in response to the cold pressor task among individuals with child vs. adult trauma. Psychoneuroendocrinology 31, 501—509.
Stoppelbein, L., Greening, L., Fite, P., 2012. The role of cortisol in PTSD among women exposed to a trauma-related stressor. J. Anxiety Disord. 26, 352—358.
Trickett, P.K., Noll, J.G., Susman, E.J., Shenk, C.E., Putnam, F.W., 2010. Attenuation of cortisol across development for victims of sexual abuse. Dev. Psychopathol. 22, 165.
Vinberg, M., Bennike, B., Kyvik, K.O., Andersen, P.K., Kessing, L.V., 2008. Salivary cortisol in unaffected twins discordant for affective disorder. Psychol. Res. 161, 292—301.
Walsh, K., Danielson, C.K., McCauley, J., Saunders, B.E., Kilpatrick, D.G., Resnick, H.S., 2012. National prevalence of PTSD among sexually revictimized adolescent, college, and adult women. Arch. Gen. Psychiatry 69, 935—942.
Yehuda, R., 2009. Status of glucocorticoid alterations in post-traumatic stress disorder. Ann. N. Y. Acad. Sci. 1179, 56—69.
Zinzow, H.M., Resnick, H.S., McCauley, J.L., Amstadter, A.B., Ruggiero, K.J., Kilpatrick, D.G., 2012a. Prevalence and risk of psychiatric disorders as a function of variant rape histories: results from a national survey of women. Soc. Psychiatry Psychiatr. Epidemiol. 47, 893—902.
Zinzow, H.M., Resnick, H.S., Barr, S.C., Danielson, C.K., Kilpatrick, D.G., 2012b. Receipt of post-rape medical care in a national sample of female victims. Am. J. Prev. Med. 43, 183—187.