PERGAMON

Psychoneuroendocrinology 28 (2003) 733–750

PNEC

www.elsevier.com/locate/psyneuen

Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse

J.D. Bremner [a,b,c,*], M. Vythilingam [d], E. Vermetten [a,b,c], J. Adil [a,b,c], S. Khan [a,b,c], A. Nazeer [a,b,c], N. Afzal [a,b,c], T. McGlashan [e], B. Elzinga [a,b,c], G.M. Anderson [f], G. Heninger [e], S.M. Southwick [e], D.S. Charney [d]

[a] *Department of Psychiatry and Behavioral Sciences, Emory Center for Positron Emission Tomography, Emory University School of Medicine, 1364 Briarcliff Road, Atlanta, GA 30322, USA*

[b] *Department of Radiology, Emory Center for Positron Emission Tomography, Emory University School of Medicine, 1364 Briarcliff Road, Atlanta, GA 30322, USA*

[c] *Atlanta VAMC, 1670 Clairmont Road, Decatur, GA 30033, USA*

[d] *The Program for Mood and Anxiety Disorders, National Institute of Mental Health, 9000 Rockville Pike, Bldg 15k, Rm 102, Bethesda, MD 20892-2670, USA*

[e] *Department of Psychiatry, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06510, USA*

[f] *Yale Child Study Center, Yale University School of Medicine, 333 Cedar St, New Haven, CT 06510, USA*

Received 21 February 2001; received in revised form 16 July 2002; accepted 22 July 2002

Abstract

Preclinical studies show that animals with a history of chronic stress exposure have increased hypothalamic-pituitary-adrenal (HPA) axis reactivity following reexposure to stress. Patients with posttraumatic stress disorder (PTSD) have been found to have normal or decreased function of the HPA axis, however no studies have looked at the HPA response to stress in PTSD. The purpose of this study was to assess cortisol responsivity to a stressful cognitive challenge in patients with PTSD related to childhood abuse. Salivary cortisol levels, as well as heart rate and blood pressure, were measured before and after a stressful cognitive challenge in

* Corresponding author. Present address: PET Center/Nuclear Medicine, Emory University Hospital Room E154, Emory University School of Medicine, 1364 Clifton Road, Atlanta, GA 30322, USA. Tel.: +1-404-712-0108; fax: +1-404-712-7435.

E-mail address: jdbremn@emory.edu (J.D. Bremner).

0306-4530/03/$ - see front matter Published by Elsevier Science Ltd.
doi:10.1016/S0306-4530(02)00067-7

patients with abuse-related PTSD ($N = 23$) and healthy comparison subjects ($N = 18$). PTSD patients had 61% higher group mean cortisol levels in the time period leading up to the cognitive challenge, and 46% higher cortisol levels during the time period of the cognitive challenge, compared to controls. Both PTSD patients and controls had a similar 66–68% increase in cortisol levels from their own baseline with the cognitive challenge. Following the cognitive challenge, cortisol levels fell in both groups and were similar in PTSD and control groups. PTSD patients appeared to have an increased cortisol response in anticipation of a cognitive challenge relative to controls. Although cortisol has been found to be low at baseline, there does not appear to be an impairment in cortisol response to stressors in PTSD.
Published by Elsevier Science Ltd.

Keywords: PTSD; Childhood abuse; Stress; Cortisol; Hippocampus

1. Introduction

Posttraumatic stress disorder (PTSD) is a disabling condition (Fairbank et al., 1999; Schlenger et al., 1999) associated with exposure to traumatic events, which has been reported to affect 8% of individuals in US at some time in their lives (Kessler et al., 1995). Childhood abuse, which may affect as many as one in five individuals in this country (McCauley et al., 1997), is one of the most common traumatic events that lead to the development of PTSD (Kessler et al., 1995). Given the sheer magnitude of this problem, it is especially important to understand the effects that early psychological trauma can have on the individual, including both behavioral and biological consequences (Saigh and Bremner, 1999; Bremner, 2002).

The hypothalamic-pituitary-adrenal (HPA) axis (Yehuda et al., 1995a,b,c) plays an important role in the response to stress. Corticotropin-releasing factor (CRF) released during stress (Chappell et al., 1986) from nerve terminals originating in the paraventricular nucleus of the hypothalamus increases the secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary, which in turn stimulates release of glucocorticoids from the adrenal (Arborelius et al., 1999). CRF release from the hypothalamus is inhibited by the hippocampus (Herman et al., 1989; Jacobson and Sapolsky, 1991). Some studies have shown that stressors, including early stressors such as maternal deprivation, result in chronic increases in plasma glucocorticoid levels (Dallman and Jones, 1973; Sapolsky et al., 1997) with a potentiation of glucocorticoid and CRF responsiveness to subsequent stressors (Fride et al., 1986; Stanton et al., 1988; Levine et al., 1993; Plotsky and Meaney, 1993; Makino et al., 1995; Coplan et al., 1996; Ladd et al., 1996; Smith et al., 1997; Takahashi et al., 1998). Other studies have not been consistent with potentiation of cortisol response to stress, while some studies even suggest that chronic stress is associated with a diminution of stress responsiveness (Daniels-Severs et al., 1973; Katz et al., 1981; Young and Akil, 1985; Rivier and Vale, 1987). Chronically stressed animals have also been shown to develop an inability to terminate the glucocorticoid response to stress (Sapolsky et al., 1984a,b), and deficits in feedback inhibition of the HPA axis by glucocorticoids (Young et al., 1990). The deficits in the negative feedback effects of dexamethasone on the HPA axis, could be related to observed decreases in gluco-

corticoid receptor binding in the hippocampus (Sapolsky et al., 1984b; Makino et al., 1995; Smith et al., 1997). Stress has been associated with damage to the hippocampus with associated impairments in new learning and memory (Sapolsky et al., 1990; McEwen et al., 1992; Sapolsky, 1996), which may lead to a release of inhibition of CRF release from the hypothalamus. A variety of mechanisms have been proposed for stress-induced hippocampal deficits, including glucocorticoids potentiating the toxicity of excitatory amino acids (Sapolsky, 1996), decreased brain-derived neurotrophic factor (BDNF) (Nibuya et al., 1995; Smith et al., 1995; Duman et al., 1997), inhibition of neurogenesis (Gould et al., 1998), or a combination of these factors. These observations suggest that early stressors lead to long-term alterations in the HPA axis, characterized primarily by an increase in HPA axis reactivity.

Early stress is also associated with life-long increases in sensitivity of the noradrenergic system (Bremner et al., 1996a,b; Francis et al., 1999; Sanchez et al., 2001; Vermetten and Bremner, 2002). Noradrenergic input stimulates release of CRF from the paraventricular nucleus of the hypothalamus. Maternal separation resulted in an increased release of norepinephrine in the paraventricular nucleus of the hypothalamus. Maternal separation also resulted in a decrease in the alpha-2 autoreceptor of the locus coeruleus (Francis et al., 1999). Since the alpha-2 receptor is inhibitory, this would be expected to result in an increase in locus coeruleus activity, with increased noradrenergic reactivity. In summary, early stress is associated with lasting increases in noradrenergic responsivity.

Patients with PTSD have been found to have alterations in the HPA axis and noradrenergic systems. Studies of baseline HPA axis function in patients with PTSD have been inconsistent. Studies comparing males with chronic combat-related PTSD to controls found long-term alterations in HPA axis function including increased levels of CRF in cerebrospinal fluid (CSF) (Bremner et al., 1997a; Baker et al., 1999), and blunted ACTH response to CRF challenge (consistent with CRF overdrive) in some studies (Smith et al., 1989) but not others (Rasmusson et al., 2001). However, some studies of patients with chronic combat (Mason et al., 1986; Yehuda et al., 1991b) or holocaust-related (Yehuda et al., 1995c) PTSD found decreased cortisol measured in 24 h urine, as well as decreased cortisol based on plasma concentrations sampled over a 24 h period (Yehuda et al., 1994) in patients with chronic combat-related PTSD, while other studies in PTSD related to combat (Pitman and Orr, 1990; Mason et al., 2002) or abuse (Lemieux and Coe, 1995; De Bellis et al., 1999a) found no difference (Mason et al., 2002) or increased cortisol (Pitman and Orr, 1990; Lemieux and Coe, 1995; De Bellis et al., 1999a) in 24 h urine volumes. Studies in combat-related chronic PTSD found normal cortisol response to standard dexamethasone suppression test (DST) (Kudler et al., 1987), while an excessive suppression of cortisol with low dose (0.5 mg) dexamethasone was found in both patients with combat (Yehuda et al., 1993, 1995a) and abuse-related PTSD (Stein et al., 1997b). Other studies in combat-related PTSD found an increased number of glucocorticoid receptors on peripheral lymphocytes (Yehuda et al., 1991a, 1995a,b). Adult patients with chronic and severe PTSD were found to have reduced volume of the hippocampus (Bremner et al., 1995, 1997b; Gurvits et al., 1996; Stein et al., 1997a), which as noted above may contribute to increased CRF, although there was no change in

hippocampal volume in childhood (De Bellis et al., 1999b) and new-onset (Bonne et al., 2001) PTSD. Several studies have found increased noradrenergic function in PTSD. These studies measured norepinephrine directly in plasma or urine, or indirectly through assessment of psychophysiological markers of heart rate and blood pressure (reviewed in Bremner et al., 1996a,b). Most studies found increased responsivity of this system, not necessarily at baseline, but more consistently with exposure to a stressful traumatic reminder (Pitman et al., 1987). Studies in children with abuse in which diagnosis of PTSD was not established found increased catecholamines in 24 h urine (including norepinephrine, epinephrine, and dopamine) (De Bellis et al., 1994). Studies in children with the diagnosis of PTSD are also consistent with elevations in catecholamine (De Bellis et al., 1999a). These findings are consistent with animal studies showing increased noradrenergic activity following early stress.

Findings related to the HPA axis in PTSD patients are often not congruent with findings from animal studies and in some cases seem paradoxical. They raise the question of how glucocorticoids could cause hippocampal damage if cortisol levels in PTSD are normal or low. For example, cortisol levels in the aftermath of rape in adulthood were not found to be elevated in women who subsequently developed PTSD (Resnick et al., 1995; Yehuda et al., 1998). Studies in PTSD performed to date have largely focused on characterizing possible baseline differences between PTSD patients and controls. Study paradigms that involve experimental perturbation of the cortisol system, as seen during stressful challenges, may add additional information about function of the HPA axis in PTSD.

The cortisol system can be highly susceptible to the influence of psychological factors (Bourne et al., 1967; Miller, 1968; Rubin et al., 1969; Miller et al., 1970; Hofer et al., 1972a,b), making the interpretation of findings of baseline HPA axis function in PTSD difficult to interpret. Several studies have demonstrated the feasibility of using cognitively challenging tasks such as mental arithmetic, simulated driving, or public speaking, as laboratory tests in the study of the stress response, and have applied this paradigm to research on aging and depression, with findings of blunted cortisol response in depression (Wittersheim et al., 1985; Gotthardt et al., 1995; Trestman et al., 1991; Seeman et al., 1995a,b; Kirschbaum et al., 1996; Lupien et al., 1997). One study showed that women with depression and a history of childhood abuse had increased cortisol response to a public speaking stressor (Heim et al., 2000). Recently, in a study on neuroendocrine responses to white noise and combat sounds, veterans with PTSD showed enhanced cortisol levels compared to veteran controls without PTSD and non-veteran controls (Liberzon et al., 1999). The timeframe of the cortisol assessment (only once before and once immediately after exposure) was inappropriate to distinguish baseline levels and cortisol reactivity to stress, however. Thus, it remained unclear whether the elevations reflected enhanced chronic activation or anticipatory anxiety to the combat sounds and white noise. There are no other studies to date that have examined the effects of stressful perturbation on HPA axis functioning in PTSD. The purpose of the present study was to assess cortisol and sympathetic (heart rate and blood pressure) response to a stressful challenge in patients with PTSD and controls. Based on findings in animal studies,

we hypothesized an increased cortisol and sympathetic response to stressful cognitive challenge in PTSD patients relative to controls.

1.1. Methods

Subjects included 41 men and women, 18 years of age or older who underwent a stressful cognitive challenge in conjunction with measurement of cortisol, heart rate and blood pressure, and behavioral responses. Subjects included men and women with civilian PTSD ($N = 23$) and healthy men and women without trauma or PTSD ($N = 18$). There was no difference in mean age between PTSD patients (43 (10 SD)) and healthy subjects (49 (10 SD)), or in years of education between PTSD patients (16 (2 SD)) and healthy subjects (16 (3 SD)). Thirteen out of 23 (57%) of the PTSD patients were women and 10/23 (43%) men, 12/18 (67%) of healthy subjects were female and 6/18 (33%) were men. All subjects were recruited by advertisement and gave written informed consent for participation in the study. The written informed consent included information about how they would undergo a stressful challenge which involved problem solving and other tasks under time pressure. All women were premenopausal as determined by subject history. Subjects were admitted to a General Clinical Research Center (GCRC) scatter bed located at the Yale Psychiatric Institute (YPI) for measurement of salivary cortisol, heart rate and blood pressure, and behavioral response to stressful cognitive challenge. The scatter bed is a single room located in the YPI inpatient unit which was dedicated to GCRC research in psychiatric patients. PTSD patients were included with a history of childhood physical or sexual abuse, defined as rape, attempted rape, molestation, physical assault or attack with injury, before the age of 18, as measured by the Early Trauma Inventory (ETI) (Bremner et al., 2000), and the diagnosis of PTSD based on the Structured Clinical Interview for DSMIV (SCID) (Spitzer et al., 1987). Patients were excluded if they presented with a history of current alcohol or substance abuse or dependence in the past six months, schizophrenia, or an eating disorder, as determined by the SCID, serious medical disorder as determined by laboratory tests and physical examination, organic mental disorder, neurological disorder, or head trauma. All patients were medication free four weeks or more before the study. Healthy subjects met the same inclusion criteria for PTSD patients with the exception of having a history of psychological trauma or the diagnosis of PTSD or other psychiatric disorder based on the SCID.

All subjects were evaluated with the SCID for co-morbid psychiatric diagnoses. Nine out of 23 PTSD patients (39%) fulfilled criteria for a lifetime history of major depression and one (4%) for current major depression. Two patients (9%) fulfilled criteria for lifetime (not current) history of panic disorder without agoraphobia, and three patients (13%) had a current and lifetime history of generalized anxiety disorder. Eight patients (34%) met criteria for current and lifetime social phobia, three patients (13%) had lifetime simple phobia, and two (9%) had current simple phobia. One patient (4%) met current and lifetime criteria for agoraphobia, and one (4%) for obsessive compulsive disorder. None of the patients had current (past six months) alcohol or substance abuse/dependence. Three PTSD patients (13%) fulfilled criteria

for a lifetime history of alcohol dependence, one (4%) for a lifetime history of polysubstance abuse, and one (4%) for lifetime history of polysubstance dependence.

PTSD subjects were assessed with the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), a reliable and valid measure of PTSD symptom level with subcomponents for the individual symptom clusters. Subjects were also assessed with the Civilian Version of the Mississippi Scale for Combat-Related PTSD, a self-report measure of current PTSD symptom severity that is a continuous measure (Kulka et al., 1990). Severity of childhood abuse, and traumatic events in adulthood, were evaluated with the ETI, a reliable and valid instrument for assessment of childhood and adult abuse and trauma (Bremner et al., 2000). Baseline dissociative state symptom levels were assessed with the Clinician Administered Dissociative States Scale (CADSS), a reliable and valid instrument (Bremner et al., 1998). PTSD patients had a mean CAPS score of 79 (28 SD), mean CADSS score of 14 (15 SD), and Civilian Mississippi Scale score of 117 (16 SD). Mean score on the ETI-self report scale for severity of childhood trauma was 60 (28 SD).

Subjects were admitted to a scatter bed of the GCRC for cognitive challenge. All subjects were studied between 2:00 and 4:00 p.m. Subjects were placed in a hospital bed with application of dynamap cuff for measurement of heart rate and blood pressure, baseline ratings and salivary cortisol. Subjects then rested in a hospital bed for 60 min while listening to a tape with relaxing music and sounds with measurement of heart rate, blood pressure, and salivary cortisol at 60, 10, and 5 min before the initiation of the cognitive challenge. Immediately before the initiation of the challenge, a physician wearing a white laboratory coat entered the room and initiated a series of cognitively challenging tasks which lasted for 20 min. The cognitive tests were based on a protocol previously used in studies of aging (Seeman et al., 1995a,b) and included challenging arithmetic (multiplication, division, addition and subtraction), cognitive tasks (stroop task, e.g. looking at the word red spelled in the color green and naming the color green), problem solving, matching figures to numbers and memory for figure-number pairings, and unscrambling words. Each individual task was scored by the rater and performed under time pressure. Negative feedback regarding the score and the time spent in the task, was consistently given, and level of difficulty was increased until subjects were unable to successfully complete the tasks. After the end of the cognitive tasks the physician left the room. Heart rate and blood pressure were measured at 2, 4, 6, 7, 10, 12, 14, 15, 16, 18, 20, 30, 35, 45, 60, 75 and 90 min after the initiation of the cognitive challenge. Salivary cortisol was measured at 0, 10, 15, 20, 30, 35, 45, 60, 75, and 90 min after the initiation of the challenge.

Saliva samples were collected using Salivette collection devices and stored at 70 °C. Salivette tubes were centrifuged (0–4°C) to prepare saliva which was analyzed for cortisol using an ^{125}I immunoradiometric assay kit available from Diagnostic Products Corporation (Los Angeles, CA). Samples and standards (200 μl) were determined in duplicate; standard concentrations ranged from 67 pg/ml to 3.0 ng/ml. Day-to-day coefficients of variation for low (398 pg/ml) and high (4.12 ng/ml) concentration quality assessment (QC) samples were 10.1 and 8.4%, respectively.

In subjects with a single inadequate or missing sample data was interpolated. Sub-

jects with two or more adjacent samples or critical (e.g. time 0) samples missing were excluded from analysis.

Repeated measures ANOVA with Duncan's Multiple Range Test was used to compare cortisol, heart rate and blood pressure response to cognitive challenge between the groups. Pearson correlations were used to compare behavioral data and cortisol, heart rate and blood pressure data.

2. Results

2.1. Cortisol levels in response to cognitive challenge

The cognitive stress challenge resulted in an increase in cortisol levels in both PTSD patients and controls (main effect for time: $F = 6.10$; df = 12; $p < 0.0001$). Salivary cortisol levels were elevated in PTSD patients relative to controls during the hour preceding the cognitive stressor and during the course of the stress challenge (i.e. from −60 to +20 min) ($F = 6.79$; df = 1,38; $p < 0.0001$). Specifically cortisol levels were elevated in the time period before the cognitive challenge in anticipation in patients with PTSD relative to controls (Fig. 1). Cortisol levels were elevated by an average of 61% in PTSD patients at the −60, −30, −5 and 0 min time points ($F = 5.05$; df = 1,38; $p = 0.03$). As can be seen in Fig. 1, the greatest increase was at the −5 time point, where cortisol levels were double in PTSD relative to controls. During the time of the cognitive challenge (from time 15 to 20) and for an additional 15 min after the termination of the challenge, cortisol levels increased in both PTSD patients and controls, and remained elevated by an average of 46% in PTSD patients

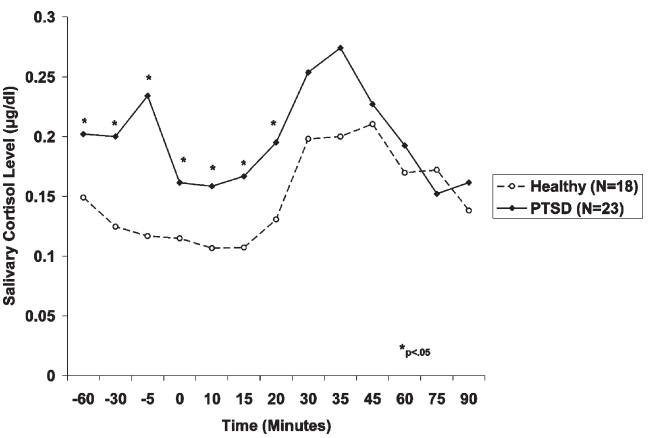

Fig. 1. Cortisol response to stressful cognitive challenge. There were elevated levels of cortisol in both the time period in anticipation of challenge (from time −60 to 0) and during the cognitive challenge (time 0–20). PTSD patients and controls showed similar increases in cortisol relative to their own baseline in response to the cognitive challenge (i.e. no time by diagnosis interaction). In the recovery period (time 45–90 min) there was no difference in cortisol levels between PTSD patients and controls.

relative to controls during these time points, eventhough the magnitude of increase from each group's own baseline was similar (68% in PTSD and 66% in controls) (no significant time by diagnosis interaction). In the recovery phase (45, 60, 75, and 90 min after initiation of the challenge) cortisol levels decreased in both groups, and there was no difference in cortisol levels between patients and controls in this time period. Cortisol values returned to the pre-challenge baseline in controls, and actually fell 20% below the pre-challenge baseline in PTSD patients. Baseline cortisol levels at the −60 min time point were correlated with log transformed area under the curve (AUC) values for the 0–35 min time period of the challenge in the healthy subjects ($r = 0.72$; df = 16; $p = 0.0011$) and the PTSD patients ($r = 0.48$; df = 22; $p = 0.0199$).

2.2. Heart rate and blood pressure responses to cognitive challenge

Cognitive challenge resulted in a significant increase in heart rate in patients and controls (main effect for time: $F = 12.78$; df = 19,646; $p < 0.0001$) (Fig. 2). During the anticipatory period preceding the challenge there was no significant difference in heart rate between PTSD patients and controls. During the onset and initial part of the challenge (from −10 to +10 min) PTSD patients had statistically non-significant 6% higher heart rates than controls, and both groups showed a similar increase in heart rate in response to the cognitive challenge, with PTSD patients increasing from 72 to 81 b.p.m. (13%) from 10 min before the challenge to 10 min into the challenge, and controls increasing from 71 to 79 b.p.m. (12%) in the same time period. Heart rate continued to be higher in the recovery phase in PTSD patients, on an average 3% higher than in controls (an effect that was not statistically significant),

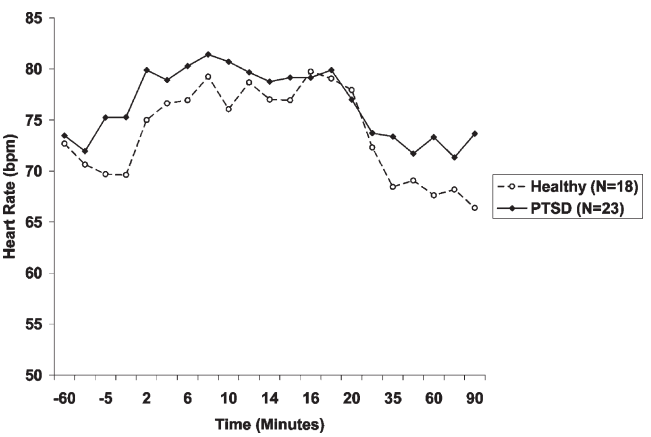

Fig. 2. Heart rate response to stressful cognitive challenge. Cognitive challenge resulted in a significant increase in heart rate in both patients and controls. PTSD patients showed a pattern of increased heart rate immediately before and during the cognitive challenge (from −10 to 10 min) that was not statistically significant.

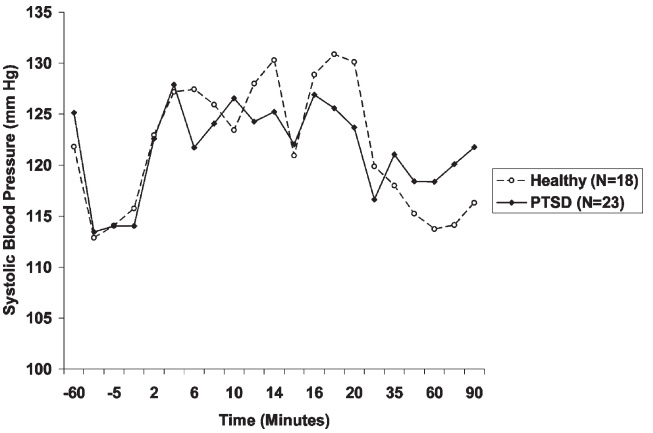

Fig. 3. Systolic blood pressure response to challenge. Cognitive challenge resulted in a significant increase in systolic blood pressure in both patients and controls, however, there was no difference in systolic blood pressure between groups.

returning to 72 b.p.m. versus 69 b.p.m. in controls 20 min after termination of the challenge.

Cognitive challenge resulted in an increase in blood pressure in both patients and controls, including an increase in diastolic blood pressure ($F = 9.44$; df = 16,665; $p < 0.0001$) (Fig. 3) and systolic blood pressure ($F = 9.37$; df = 16,665; $p < 0.0001$) (Fig. 4). There was no statistically significant difference in blood pressure between patients and controls. Average blood pressure in PTSD was 117/70 com-

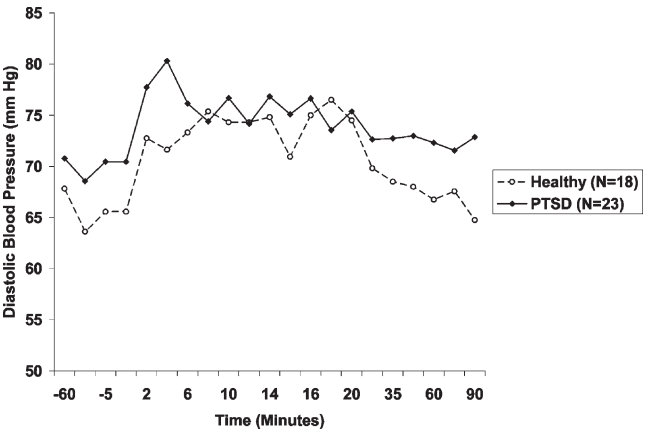

Fig. 4. Diastolic blood pressure response to cognitive challenge. Cognitive challenge resulted in a significant increase in diastolic blood pressure in both PTSD patients and controls. There was a non-significant pattern of higher diastolic blood pressure in the period immediately before and during the early part of the cognitive challenge (from time −10 to 10 min) in PTSD patients relative to controls, as well as during the recovery period.

pared to 116/66 in controls in the time period before the start of the cognitive challenge. Both groups had a similar 14% increase in diastolic blood pressure during the challenge, increasing to 127/80 in PTSD patients and 127/75 in controls. In the recovery period blood pressure continued to be higher in PTSD, e.g. 20 min after the end of the challenge blood pressure was 118/68 in PTSD compared to 115/63 in controls, although these differences were not statistically significant differences.

2.3. Gender differences in cortisol response to cognitive challenge

Male PTSD patients showed a pattern of higher cortisol levels during cognitive challenge relative to females with PTSD and to male and female controls (Fig. 5). Male PTSD patients showed higher cortisol levels from time 0 baseline to 35 min after the start of the challenge although these differences were not statistically significant. Heart rate was significantly higher in women versus men during the cognitive challenge and the recovery period ($F = 5.25$; df = 1,34; $p = 0.03$) (Fig. 6); there was no interaction between diagnosis and gender. There were no differences in blood pressure response by gender to cognitive challenge.

2.4. Relationship between behavioral variables and cortisol response to stress

Both PTSD patients and controls had a similar increase in subjective distress during the cognitive challenge. In PTSD patients Subjective Units of Distress (SUDS) ratings increased from a mean of 22 (22 SD) at −60 min and 16 (20 SD) at −5 min to 58 (32 SD) at 20 min after initiation of cognitive challenge (termination of 20 min cognitive challenge period). In controls SUDS ratings increased from mean of 16 (21 SD) to 13 (13 SD) and 51 (18 SD) at −60, −5 and +20 min, respectively. In controls there was a more significant correlation between percent increase in cor-

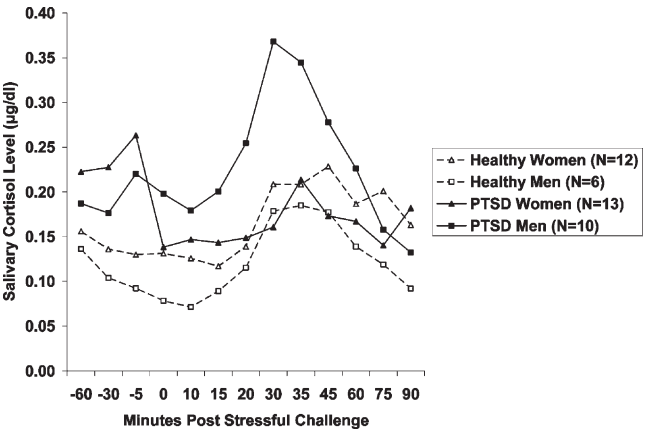

Fig. 5. Gender differences in cortisol response to cognitive challenge. There was a pattern of greater cortisol response to challenge in men with PTSD relative to the other groups that was not statistically significant.

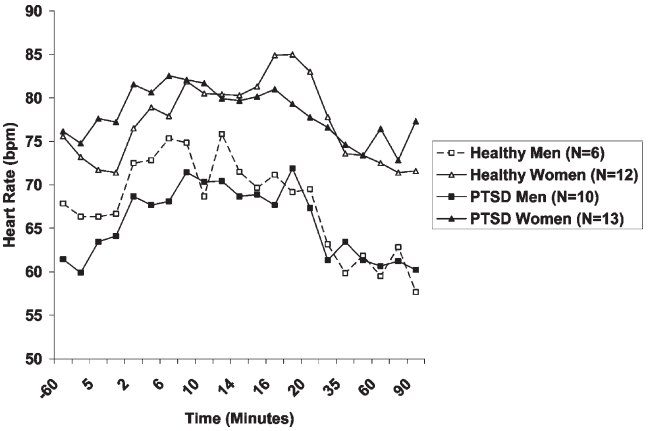

Fig. 6. Gender differences in heart rate response to cognitive challenge. Women had a higher heart rate during the cognitive challenge and in the recovery period; there was no interaction between gender and diagnosis.

tisol from baseline during cognitive challenge and absolute increase in SUDS ratings from baseline ($r = 0.67$; df = 6; $p = 0.09$) than in PTSD patients ($r = 0.23$; df = 17; $p = 0.35$). There was no correlation with baseline CAPS, CADSS, or Mississippi score and cortisol levels in the PTSD patients. There was no relationship between age and cortisol response to stress in patients or controls. There was no significant difference in cortisol response to stressors in PTSD patients with or without current depression.

3. Discussion

PTSD patients in this study had increased cortisol levels in anticipation of and during a stressful cognitive challenge compared to healthy subjects. Both PTSD patients and controls showed a similar 1.5-fold increase in cortisol levels during the stressor relative to their own baseline. We did not find evidence for an exaggerated cortisol response to cognitive stressors in PTSD. Following the termination of the stressful tasks, cortisol levels dropped in both the PTSD and healthy groups to a level that was nearly identical to the healthy group's pre-stress cortisol level.

Stress-induced increases in cortisol in response to the cognitive stress challenge were similar in the PTSD and healthy control groups. The absence of exaggerated cortisol response, relative to their own baseline, in PTSD, may be related to the nature of the cognitive stress challenge. Prior studies of combat-related PTSD found that trauma-specific stressors, such as hearing sounds of gunfire or a traumatic script, but not the cognitive stressor of performing mental arithmetic, resulted in increased heart rate and blood pressure responses (Blanchard et al., 1982; Pitman et al., 1987; McFall et al., 1990). Our own preliminary data show that trauma-specific stressors, such as reading of a personalized traumatic script, result in greater cortisol responses

than cognitive stressors in PTSD. We also have preliminary data on these PTSD patients at rest measuring cortisol every 15 min over a 24 h time period. The baseline measurements show that resting cortisol is not elevated, in fact during afternoon time periods it is lower than controls. This together with the fact that cortisol levels fell to levels essentially identical to controls in the recovery period suggest that patients respond to the novel testing environment and threat of cognitive challenge in an atypical manner with an exaggerated cortisol response, leading to higher levels of cortisol in the 1 h time period preceding the challenge. This finding may be the result of heightened anticipatory anxiety, or a different interpretation of the environment, among patients in the PTSD group. This would be consistent with prior studies of exaggerated startle response to the threat of the experimental context of a testing environment in PTSD (Morgan et al., 1995). It is also consistent with clinical observations that PTSD patients appear to have an inability to dampen responses to cues that do not represent true threat, an effect that may be related to dysfunctional neural circuitry involving medial prefrontal cortex, amygdala, or other brain regions (Bremner et al., 1999a,b).

If one follows the logic that the novel environment represents a stressor then the current findings would be consistent with the hypothesis of an increased cortisol responsivity to stressors in PTSD. A salient point is that the cortisol response to the cognitive challenge itself is certainly not blunted, as one might conjecture to be the case based on findings of low cortisol levels at baseline in PTSD, increased negative feedback of dexamethasone, and findings in depression (another stress-related disorder) of blunted cortisol response to stress. A lower correlation between baseline (time point −60 min) cortisol and cortisol response to stress (measured by the log transformed AUC from 0 to 35 min) in PTSD patients relative to controls, as well as a robust cortisol response to stress on top of an elevated baseline cortisol, are also consistent with a relative resistance to the negative feedback effect of endogenous cortisol, rather than enhanced feedback. Studies show increased feedback suppression to dexamethasone feedback at central brain areas such as the hippocampus, however the meaning of these findings is unclear since it is not clear if dexamethasone crosses the blood–brain barrier. Increased cortisol response to stress and a relative insensitivity to cortisol feedback would be consistent with studies in animals showing that stress is associated with increases in HPA axis function, increased glucocorticoid responsivity to stressors, and insensitivity to glucocorticoid feedback. The results are also of interest relative to previous findings of HPA axis function in PTSD. As reviewed above, in contrast to findings from the animal literature, several studies have shown decreases in cortisol levels measured in 24 h urine in patients with chronic PTSD. Other findings, such as increased glucocorticoid receptors on lymphocytes and increased suppression with low doses of dexamethasone in PTSD (suggesting increased central glucocorticoid receptors), are also not consistent with hypercortisolemia. Our own preliminary data of diurnal cortisol levels in civilian PTSD also did not find baseline increases in cortisol levels. Interpreted in conjunction with the current study, findings of baseline decreases in cortisol in PTSD may be related to a suppression of cortisol function, to compensate for periods of increased cortisol responsiveness to stressors. Cortisol levels have been related to psychological

function, and PTSD patients may have normal or low baseline cortisol levels in response to chronic suppression of responsiveness and psychological avoidance, while the introduction of stressors over which the patient has no control may result in exaggerated cortisol responses. In this light, low cortisol may be an adaptation to periods of hypercortisolemia during stress. There is some evidence to support the idea that cortisol function may be affected by prior episodes of stress-induced cortisol release. For example, studies in humans showed that exposure to a stress with increased cortisol release was associated with a blunting of the normal cortisol rise seen following a mid-day meal (Follenius and Brandenberger, 1980). However, exposure to a prior stressor did not result in a significant blunting of cortisol response to subsequent stressors in man. These studies suggest that prior stress-induced cortisol release can affect cortisol responsiveness, although the type of stimulus plays an important role in the degree of cortisol release.

The current study did not find significant increases in measures of sympathetic function in response to a cognitive stressor. This is consistent with prior studies that did not find an increase in heart rate and blood pressure responses to neutral cognitive stressors in PTSD, although those prior studies did find an increase in these parameters with traumatic stressors (Blanchard et al., 1982). Those findings in conjunction with the current study suggest that cortisol is a more sensitive indicator of the stress response than outcomes such as heart rate and blood pressure.

There are several limitations and points of clarification related to the current study that deserve comment. The data in this study are limited by the absence of measurement of phase of the menstrual cycle in women with and without PTSD. Also small sample size limits comparisons of men and women with and without PTSD. The cognitive stress challenge may have been interpreted in different ways by PTSD patients and controls. PTSD patients may have responded with anger, dissociative responses or an increase in PTSD symptoms, to the cognitive challenge, in a way not experienced by the controls.

Acknowledgements

The authors would like to thank Heather Palumberi, M.S., Jacque Piscitelli, M.A., Helen Sayward, M.S., Tami Rowe-Padhy, M.S., Sarah Dubuque, B.A., Sandi Capelli, R.N., Susan Insall, R.N., Kathy West, B.S., Monica Lee-Carter, and Willy Ford for assistance in conducting these studies. Thanks to Theresa Seeman, PhD, for advise on development of the cognitive challenge protocol. These studies were made possible by the General Clinical Research Center Grant, a GCRC Clinical Associate Physician (CAP) Award and a VA Career Development Award to Dr Bremner, NIMH #1R01MH56120-02, and the Conte Center for the Study of Early Life Stress at Emory University.

This work was supported by grants NIMH R01 #MH56120-01A1 and VA Career Development Award (Dr Bremner), the Yale General Clinical Research Center, the Emory Conte Center for Early Life Stress, and the National Center for PTSD.

References

Arborelius, L., Owens, M.J., Plotsky, P.M., Nemeroff, C.B., 1999. The role of corticotropin-releasing factor in depression and anxiety disorders. J. Endocrinol. 160, 1–12.

Baker, D.B., West, S.A., Nicholson, W.E., Ekhator, N.N., Kasckow, J.W., Hill, K.K., Bruce, A.B., Orth, D.N., Geracioti, T.D., 1999. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am. J. Psychiatry 156, 585–588.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., 1995. The development of a clinician-administered PTSD scale. J. Trauma. Stress 8, 75–90.

Blanchard, E.B., Kolb, L.C., Pallmeyer, T.P., Gerardi, R.J., 1982. A psychophysiological study of posttraumatic stress disorder in Vietnam veterans. Psychiatr. Q. (N. Y.) 54, 220–229.

Bonne, O., Brandes, D., Gilboa, A., Gomori, J.M., Shenton, M.E., Pitman, R.K., Shalev, A.Y., 2001. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. Am. J. Psychiatry 158, 1248–1251.

Bourne, P.G., Rose, R.M., Mason, J.W., 1967. Urinary 17-OCHS levels in combat: data on seven helicopter ambulance medics in combat. Arch. Gen. Psychiatry 17, 104–110.

Bremner, J.D., 2002. Does Stress Damage the Brain? Understanding Trauma-related Disorders from a Neurological Perspective. W.W. Norton, New York.

Bremner, J.D., Krystal, J.H., Putnam, F., Marmar, C., Southwick, S.M., Lubin, H., Charney, D.S., Mazure, C.M., 1998. Measurement of dissociative states with the clinician administered dissociative states scale (CADSS). J. Trauma. Stress 11, 125–136.

Bremner, J.D., Krystal, J.H., Southwick, S.M., Charney, D.S., 1996a. Noradrenergic mechanisms in stress and anxiety: I. Preclinical studies. Synapse 23, 28–38.

Bremner, J.D., Krystal, J.H., Southwick, S.M., Charney, D.S., 1996b. Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. Synapse 23, 39–51.

Bremner, J.D., Licinio, J., Darnell, A., Krystal, J.H., Owens, M., Southwick, S.M., Nemeroff, C.B., Charney, D.S., 1997a. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am. J. Psychiatry 154, 624–629.

Bremner, J.D., Narayan, M., Staib, L.H., Southwick, S.M., McGlashan, T., Charney, D.S., 1999a. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am. J. Psychiatry 156, 1787–1795.

Bremner, J.D., Randall, P.R., Scott, T.M., Bronen, R.A., Delaney, R.C., Seibyl, J.P., Southwick, S.M., McCarthy, G., Charney, D.S., Innis, R.B., 1995. MRI-based measurement of hippocampal volume in posttraumatic stress disorder. Am. J. Psychiatry 152, 973–981.

Bremner, J.D., Randall, P., Vermetten, E., Staib, L., Bronen, R.A., Mazure, C.M., Capelli, S., McCarthy, G., Innis, R.B., Charney, D.S., 1997b. MRI-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse: a preliminary report. Biol. Psychiatry 41, 23–32.

Bremner, J.D., Staib, L., Kaloupek, D., Southwick, S.M., Soufer, R., Charney, D.S., 1999b. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder (PTSD): a positron emission tomography study. Biol. Psychiatry 45, 806–816.

Bremner, J.D., Vermetten, E., Mazure, C.M., 2000. Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the early trauma inventory. Depress. Anxiety 12, 1–12.

Chappell, P.B., Smith, M.A., Kilts, C.D., Bissette, G., Ritchie, J., Nemeroff, C.B., 1986. Alterations in corticotropin-releasing factor-like immunoreactivity in discrete rat brain regions after acute and chronic stress. J. Neurosci. 6, 2908–2914.

Coplan, J.D., Andrews, M.W., Rosenblum, L.A., Owens, M.J., Friedman, S., Gorman, J.M., Nemeroff, C.B., 1996. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc. Natl. Acad. Sci. USA 93, 1619–1623.

Dallman, M.F., Jones, M.T., 1973. Corticosteroid feedback control of ACTH secretion: effect of stress-induced corticosterone secretion on subsequent stress responses in the rat. Endocrinology 92, 1367–1375.

Daniels-Severs, A., Goodwin, A., Keil, L.C., Vernikos-Danellis, J., 1973. Effect of chronic crowding and cold on the pituitary-adrenal system: responsiveness to an acute stimulus during chronic stress. Pharmacology 9, 348–356.

De Bellis, D., Lefter, L., Trickett, P.K., Putnam, F.W., 1994. Urinary catecholamine excretion in sexually abused girls. J. Am. Acad. Child Adol. Psychiatry 33, 320–327.

De Bellis, M.D., Baum, A.S., Birmaher, B., Keshavan, M.S., Eccard, C.H., Boring, A.M., Jenkins, F.J., Ryan, N.D., 1999a. A.E. Bennett Research Award: developmental traumatology. Part I: biological stress systems. Biol. Psychiatry 45, 1259–1270.

De Bellis, M.D., Keshavan, M.S., Clark, D.B., Casey, B.J., Giedd, J.N., Boring, A.M., Frustaci, K., Ryan, N.D., 1999b. A.E. Bennett Research Award: developmental traumatology. Part II: brain development. Biol. Psychiatry 45, 1271–1284.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606.

Fairbank, J.A., Ebert, L., Zarkin, G.A., 1999. Socioeconomic consequences of traumatic stress. In: Saigh, P.A., Bremner, J.D. (Eds.), Posttraumatic Stress Disorder: A Comprehensive Text. Allyn & Bacon, Needham Heights, MA, USA, pp. 180–198.

Follenius, M., Brandenberger, G., 1980. Evidence of a delayed feedback effect on the mid-day plasma cortisol peak in man. Horm. Metab. Res. 12, 638–639.

Francis, D.D., Caldji, C., Champagne, F., Plotsky, P.M., Meaney, M.J., 1999. The role of corticotropin-releasing factor—norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol. Psychiatry 46, 1153–1166.

Fride, E., Dan, Y., Feldon, J., Halevy, G., Weinstock, M., 1986. Effects of prenatal stress on vulnerability to stress in prepubertal and adult rats. Physiol. Behav. 37, 681–687.

Gotthardt, U., Schweiger, U., Fahrenberg, J., Lauer, C.J., Holsboer, F., Heuser, I., 1995. Cortisol, ACTH, and cardiovascular response to a cognitive challenge in aging and depression. Am. J. Physiol. 268, R865–R873.

Gould, E., Tanapat, P., McEwen, B.S., Flugge, G., Fuchs, E., 1998. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc. Natl. Acad. Sci. USA 95, 3168–3171.

Gurvits, T.G., Shenton, M.R., Hokama, H., Ohta, H., Lasko, N.B., Gilberson, M.W., Orr, S.P., Kikinis, R., Lolesz, F.A., McCarley, R.W., Pitman, R.K., 1996. Magnetic resonance imaging study of hippocampal volume in chronic combat-related posttraumatic stress disorder. Biol. Psychiatry 40, 192–199.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., Nemeroff, C.B., 2000. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 284, 592–597.

Herman, J., Schafer, M., Young, E., Thompson, R., Douglass, J., Akil, H., Watson, S.J., 1989. Evidence for hippocampal regulation of neuroendocrine neurons of hypothalamo-pituitary adrenocortical axis. J. Neurosci. 9, 3072–3082.

Hofer, M.A., Wolff, C.T., Friedman, S.B., Mason, J.W., 1972a. A psychoendocrine study of bereavement. I. 17-Hydroxycorticosteroid excretion rates of parents following death of their children from leukemia. Psychosom. Med. 34, 481–491.

Hofer, M.A., Wolff, C.T., Friedman, S.B., Mason, J.W., 1972b. A psychoendocrine study of bereavement. II. Observations on the process of mourning in relation to adrenocortical function. Psychosom. Med. 34, 492–504.

Jacobson, L., Sapolsky, R., 1991. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenal axis. Endocr. Rev. 12, 118–134.

Katz, R.J., Roth, K.A., Carroll, B.J., 1981. Acute and chronic stress effects on open field activity in the rat: implications for a model of depression. Neurosci. Biobehav. Rev. 5, 247–251.

Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the national comorbidity survey. Arch. Gen. Psychiatry 52, 1048–1060.

Kirschbaum, C., Wolf, O.T., May, M., Wippich, W., Hellhammer, D.H., 1996. Stress- and-treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. Life Sci. 58, 1475–1483.

Kudler, H., Davidson, J., Meador, K., Lipper, S., Ely, T., 1987. The DST and posttraumatic stress disorder. Am. J. Psychiatry 144, 1068–1071.

Kulka, R.A., Schlenger, W.E., Fairbank, J.A., Hough, R.L., Jordan, B.K., Marmar, C.R., Weiss, D.S., 1990. Trauma and the Vietnam War Generation: Report of Findings from the National Vietnam Veterans Readjustment Study. Brunner/Mazel, New York.

Ladd, C.O., Owens, M.J., Nemeroff, C.B., 1996. Persistent changes in CRF neuronal systems produced by maternal separation. Endocrinology 137, 1212–1218.

Lemieux, A.M., Coe, C.L., 1995. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosom. Med. 57, 105–115.

Levine, S., Weiner, S.G., Coe, C.L., 1993. Temporal and social factors influencing behavioral and hormonal responses to separation in mother and infant squirrel monkeys. Psychoneuroendocrinology 4, 297–306.

Liberzon, I., Abelson, J.L., Flagel, S.B., Raz, J., Young, E.A., 1999. Neuroendocrine and psychophysiologic responses in PTSD: a symptom provocation study. Neuropsychopharmacology 21, 40–50.

Lupien, S.J., Gaudreau, S., Tchiteya, B.M., Maheu, F., Sharma, S., Nair, N.P., Hauger, R.L., McEwen, B.S., Meaney, M.J., 1997. Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. JCEM 82, 2070–2075.

Makino, S., Smith, M.A., Gold, P.W., 1995. Increased expression of corticotropin-releasing hormone and vasopressin messenger-ribonucleic acid (messenger RNA) in the hypothalamic paraventricular nucleus during repeated stress-association with reduction in glucocorticoid messenger-RNA levels. Endocrinology 136, 3299–3309.

Mason, J., Wang, S., Yehuda, R., Lubin, H., Johnson, D., Bremner, J.D., Riney, S., Charney, D.S., Southwick, S.M., 2002. Marked lability of urinary free cortisol levels in sub-groups of combat veterans with posttraumatic stress disorder. Psychosom. Med. 64, 238–246.

Mason, J.W., Giller, E.L., Kosten, T.R., Ostroff, R.B., Podd, L., 1986. Urinary free cortisol levels in post-traumatic stress disorder patients. J. Nerv. Ment. Dis. 174, 145–149.

McCauley, J., Kern, D.E., Kolodner, K., Dill, L., Schroeder, A.F., DeChant, H.K., Ryden, J., Derogatis, L.R., Bass, E.G., 1997. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA 277, 1362–1368.

McFall, M.E., Murburg, M.M., Ko, G.N., Veith, R.C., 1990. Autonomic responses to stress in Vietnam combat veterans with posttraumatic stress disorder. Biol. Psychiatry 27, 1165–1175.

McEwen, B.S., Gould, E.A., Sakai, R.R., 1992. The vulnerability of the hippocampus to protective and destructive effects of glucocorticoids in relation to stress. Br. J. Psychiatry 160, 18–24.

Miller, R.G., Rubin, R.T., Clark, B.R., Crawford, W.R., Arthur, R.J., 1970. The stress of aircraft carrier landings: I. Corticosteroid responses in naval aviators. Psychosom. Med. 32, 581–588.

Miller, R.G., 1968. Secretion of 17-hydroxycorticosteroids (17-OHCS) in military aviators as an index of response to stress: a review. Aerospace Med. 39, 498–501.

Morgan, C.A., Grillon, C., Southwick, S.M., Davis, M., Charney, D.S., 1995. Fear-potentiated startle in posttraumatic stress disorder. Biol. Psychiatry 38, 378–385.

Nibuya, M., Morinobu, S., Duman, R.S., 1995. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J. Neurosci. 15, 7539–7547.

Pitman, R.K., Orr, S.P., Forgue, D.F., de Jong, J.B., Claiborn, J.M., 1987. Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch. Gen. Psychiatry 44, 970–975.

Pitman, R., Orr, S., 1990. Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. Biol. Psychiatry 27, 245–247.

Plotsky, P.M., Meaney, M.J., 1993. Early postnatal stress and the hypothalamic-pituitary-adrenal axis. Mol. Brain Res. 18, 195–200.

Rasmusson, A.M., Lipschitz, D.S., Bremner, J.D., Southwick, S.M., Charney, D.S., 2001. Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. Biol. Psychiatry 50, 965–977.

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.

Rivier, C., Vale, W., 1987. Diminished responsiveness of the hypothalamic-pituitary-adrenal axis of the rat during exposure to prolonged stress: a pituitary-mediated mechanism. Endocrinology 121, 1320–1328.
Rubin, R.T., Rahe, R.H., Arthur, R.J., Clark, B.R., 1969. Adrenal cortical activity changes during underwater demolition team training. Psychosom. Med. 31, 553–564.
Saigh, P.A., Bremner, J.D. (Eds.), 1999. Posttraumatic Stress Disorder: A Comprehensive Text. Allyn & Bacon, New York.
Sanchez, M.M., Ladd, C.O., Plotsky, P.M., 2001. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. Dev. Psychopathol. 13, 419–449.
Sapolsky, R.M., 1996. Why stress is bad for your brain. Science 273, 749–750.
Sapolsky, R., Krey, L., McEwen, B., 1984a. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. Proc. Natl. Acad. Sci. USA 81, 6174–6177.
Sapolsky, R.M., Alberts, S.C., Altmann, J., 1997. Hypercortisolism associated with social subordinance or social isolation among wild baboons. Arch. Gen. Psychiatry 54, 1137–1143.
Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1984b. Stress down-regulates corticosterone receptors in a site-specific manner in the brain. Endocrinology 114, 287–292.
Sapolsky, R.M., Uno, H., Rebert, C.S., Finch, C.E., 1990. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J. Neurosci. 10, 2897–2902.
Schlenger, W.E., Fairbank, J.A., Jordan, B.K., Caddell, J.M., 1999. Combat-related PTSD: prevalence, risk factors and comorbidity. In: Saigh, P.A., Bremner, J.D. (Eds.), Posttraumatic Stress Disorder: A Comprehensive Text. Allyn & Bacon, Boston, MA, USA, pp. 69–91.
Seeman, T.E., Berkman, L.F., Gulanski, B.I., Robbins, R.J., Greenspan, S.L., Charpentier, P., Rowe, J.W., 1995a. Self esteem and neuroendocrine response to challenge: Macarthur studies of successful aging. J. Psychosom. Res. 39, 69–84.
Seeman, T.E., Singer, B., Charpentier, P., 1995b. Gender differences in patterns of HPA axis response to challenge: Macarthur studies of successful aging. Psychoneuroendocrinology 20, 711–725.
Smith, M.A., Davidson, J., Ritchie, J.C., Kudler, H., Lipper, S., Chappell, P., Nemeroff, C.B., 1989. The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. Biol. Psychiatry 26, 349–355.
Smith, M.A., Kim, S.Y., VanOers, H.J.J., Levine, S., 1997. Maternal deprivation and stress induce immediate early genes in the infant rat brain. Endocrinology 138, 4622–4628.
Smith, M.A., Makino, S., Kvetnansky, R., Post, R.M., 1995. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNA in the hippocampus. J. Neurosci. 15, 1768–1777.
Spitzer, R.L., Williams, J.B.W., Gibbon, M., 1987. Structured Clinical Interview for DSMIV. New York State Psychiatric Institute, New York.
Stanton, M.E., Gutierrez, Y.R., Levine, S., 1988. Maternal deprivation potentiates pituitary-adrenal stress responses in infant rats. Behav. Neurosci. 2, 692–700.
Stein, M.B., Koverola, C., Hanna, C., Torchia, M.G., McClarty, B., 1997a. Hippocampal volume in women victimized by childhood sexual abuse. Psychol. Med. 27, 951–959.
Stein, M.B., Yehuda, R., Koverola, C., Hanna, C., 1997b. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol. Psychiatry 42, 680–686.
Takahashi, L.K., Turner, J.G., Kalin, N.H., 1998. Prolonged stress-induced elevation in plasma corticosterone during pregnancy in the rat: implications for prenatal stress studies. Psychoneuroendocrinology 23, 571–581.
Trestman, R.L., Coccaro, E.F., Bernstein, D., Lawrence, T., Gabriel, S.M., Horvath, T.B., Siever, L.J., 1991. Cortisol responses to mental arithmetic in acute and remitted depression. Biol. Psychiatry 29, 1051–1054.
Vermetten, E., Bremner, J.D., 2002. Circuits and systems in stress. I. Preclinical studies. Depress. Anxiety 15, 126–147.
Wittersheim, G., Brandenberger, G., Follenius, M., 1985. Mental task-induced strain and its after-effect assessed through variations in plasma cortisol levels. Biol. Psychiatry 21, 123–132.
Yehuda, R., Boisoneau, D., Lowy, M.T., Giller, E.L., 1995a. Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Arch. Gen. Psychiatry 52, 583–593.

Yehuda, R., Giller, E.L., Levengood, R.A., Southwick, S.M., Siever, L.J., 1995b. Hypothalamic-pituitary adrenal (HPA) functioning in posttraumatic stress disorder: the concept of the stress response spectrum. In: Friedman, M.J., Charney, D.S., Deutch, A.Y. (Eds.), Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD. Raven Press, New York, pp. 367–380.

Yehuda, R., Kahana, B., Binder-Brynes, K., Southwick, S., Mason, J.W., Giller, E.L., 1995c. Low urinary cortisol excretion in holocaust survivors with posttraumatic stress disorder. Am. J. Psychiatry 152, 982–986.

Yehuda, R., Lowry, M.T., Southwick, S.M., Mason, J.W., Giller, E.L., 1991a. Increased number of glucocorticoid receptors in posttraumatic stress disorder. Am. J. Psychiatry 148, 499–504.

Yehuda, R., Southwick, S.M., Nussbaum, E.L., Giller, E.L., Mason, J.W., 1991b. Low urinary cortisol in PTSD. J. Nerv. Ment. Dis. 178, 366–369.

Yehuda, R., Resnick, H.S., Schmeidler, J., Yang, R.-K., Pitman, R.K., 1998. Predictors of cortisol and 3-methoxy-4-hydroxyphenylglycol responses in the acute aftermath of rape. Biol. Psychiatry 43, 855–859.

Yehuda, R., Southwick, S.M., Krystal, J.H., Bremner, J.D., Charney, D.S., Mason, J., 1993. Enhanced suppression of cortisol with low dose dexamethasone in posttraumatic stress disorder. Am. J. Psychiatry 150, 83–86.

Yehuda, R., Teicher, M.H., Levengood, R.A., Trestman, R.L., Siever, L.J., 1994. Circadian regulation of basal cortisol levels in posttraumatic stress disorder. Ann. N. Y. Acad. Sci., 378–380.

Young, E.A., Akil, H., 1985. Corticotropin-releasing factor stimulation of adrenocorticotropin and beta-endorphin release: effects of acute and chronic stress. Endocrinology 117, 23–30.

Young, E.A., Akana, S., Dallman, M.F., 1990. Decreased sensitivity to glucocorticoid fast feedback in chronically stressed rats. Neuroendocrinology 51, 536–542.