Cortisol, Testosterone, and Prospective Risk for War-zone Stress-Evoked Depression

Adam R. Cobb, MA; Robert A. Josephs, PhD*; Cynthia L. Lancaster, PhD*; Han-Joo Lee, PhD†; Michael J. Telch, PhD**

ABSTRACT Introduction: The major challenges of efforts to reveal biological risk factors and biomarkers of depression include the complexity of underlying systems, interactions with other systems, and contextual factors governing their expression. Altered endocrine function is believed to be a central contributor to depressive illness, but across studies, evidence for a link between endocrine markers and depression has been mixed, inconclusive, or conditional in nature. In the present study, we evaluated basal testosterone (T), cortisol (C), and CO_2 inhalation-stress-reactivity measures of these hormones (T_R, C_R) as pre-deployment moderators of the later impact of war-zone stressors on depression symptoms in-theater. Materials and Methods: At pre-deployment, U.S. soldiers (N = 120) completed demographic, clinical and hormone measures, and during deployment, they completed monthly, web-based assessments of war-zone stressors and depression symptoms (N = 533 observations). Mixed effects models estimated the effects of the pre-deployment hormone profiles in moderating war-zone stressors' impact on in-theater depression. Models also tested whether hormonally linked risk for later stress-evoked depression depends on pre-existing depression. Results: Controlling for pre-deployment depression, high T was protective; whereas T_R had depressogenic effects that were amplified by pre-deployment depression. Further, high C was protective, but heightened C_R was depressogenic, but only among those with elevated pre-deployment depression. Conclusions: Findings highlight the importance of examining basal *and* reactivity measures of endocrine function, and use of prospective, longitudinal models to test hypothesized causal pathways associated with depression vulnerability in the war-zone. Results also suggest that pre-existing depression and cortisol may work in tandem to increase vulnerability for later stress-evoked depression in the war-zone.

INTRODUCTION

Depression is the second most prevalent mental health problem in war veterans, after post-traumatic stress disorder.[1,2] Further, depression most often follows PTSD onset, loads heavily on specific PTSD symptom factors (i.e., dysphoria and numbing), and contributes to negative mental and physical health outcomes beyond PTSD severity and prior combat exposure.[2] This supports military research efforts to identify risk and resilience factors specific to depression, and person-level and contextual factors governing its emergence and course.

The mechanisms of depression are not well understood, but it clearly involves biological vulnerability and stress.[3] Depression is heritable, but two-thirds of the risk is environmental.[4] Stressors are the most potent contributor,[5–7] with 50–80% of individuals having experienced a major stressor 3–6 mo prior to depression onset.[7] The impact of stress has also been observed to attenuate as a function of prior depressive episodes,[8–10] suggesting recurrence may lead to greater autonomy (i.e., less stress-dependence) of endogenous depressogenic processes. This supports studying depression within a diathesis-stress framework,[11] and determining whether risk for stress-linked depression depends on pre-existing depression.

Among research efforts targeting biomarkers and biological risk factors, abnormal endocrine activity is regarded a key contributor to depression etiology. Impaired hypothalamic-pituitary-adrenal (HPA) axis negative feedback is the most cited endocrine abnormality implicated in depression.[12] However, meta-analyses have revealed these effects are small, inconclusive[13] or conditional in nature.[14] Additionally, evidence supports the involvement of the hypothalamic-pituitary-gonadal (HPG) axis.[15] However, testosterone-depression studies have similarly been inconsistent,[16] with reliable effects observed only in certain sub-populations, especially older, hypogonadal men.[17–20]

Cortisol and testosterone are both stress-reactive,[21] suggesting prior mixed findings may be due, in part, to a lack of considering environmental stress. Understanding the role of endocrine systems in depression may be informed by examining how hormones are influenced by stress, and in turn, how hormonal activity moderates the stress response.[22,23] In support, evidence suggests a hormone-psychopathology association is informed by the presence of environmental stress,[24] consistent with the view that endocrine activity is shaped by adaptation to environmental demands.[25] Moreover, evidence for the dual involvement of cortisol and testosterone in risk for future stress-linked PTSD[26] is consistent with the functional inhibitory cross-talk that exists between the HPA and HPG axes.[27] Thus, a joint examination of cortisol and testosterone activity may be helpful in informing the association between environmental stress and depression.

*Department of Psychology, The University of Texas at Austin, 1 University Station, A8000, Austin, TX 78712.

†Department of Psychology, University of Wisconsin-Milwaukee, 2441 E. Hartford Ave., Milwaukee, WI 53211.

Views expressed this article may not necessarily be endorsed by the U. S. Army.

doi: 10.1093/milmed/usy065

The present study is among a series from the Texas Combat PTSD Risk Project, in which a primary aim was to identify biological risk factors for stress-related psychopathology in the war-zone.[26,28,29] Soldiers ($N = 120$) awaiting deployment provided saliva for hormone assays before and 30 min. after a 35% CO_2 / 65% O_2 inhalation challenge – a well-established stressor in clinical[30] and non-clinical samples.[31–34] Basal and CO_2 stress-reactivity hormone measures were examined as moderators of the later impact of war-zone stressors on depression symptoms in-theater.

Findings of an inverse testosterone-depression association[35] support the prediction that *higher* basal testosterone and *greater* testosterone stress reactivity (i.e., CO_2 challenge-evoked change in testosterone), would be associated with a reduced impact of stressors on depression in-theater (see Models 2.1, 2.2, 2.5, and 3.1). Findings of hypercortisolemia in depression,[12,14] support the prediction that *higher* basal cortisol and *greater* CO_2-evoked cortisol release would amplify the depressogenic effects of stressors (see Models 2.3, 2.4, 2.5, and 3.2). Additionally, evidence for inhibitory cross-talk between the HPA and HPG axes[27] supports the prediction that *higher* basal testosterone and *greater* CO_2-evoked testosterone release would mitigate the depressogenic effects of *higher* basal cortisol and *greater* CO_2-evoked cortisol release (see Models 3.3–3.6).

Finally, we examined whether the hormones modulate risk conferred by pre-existing depression, by promoting later stress-evoked recurrence. Because depression is relapsing, and based on evidence that stress-evoked hormonal reactivity interacts with prior depressive episodes to predict future episodes,[36] we hypothesized that hormonally linked risk might be further moderated by concurrent levels of depression (see Models 4.1–4.4). The prediction that risk would be conferred not only by *in situ* hormonal activity, but by concurrent linkage with depression is supported by evidence of hormonal involvement in emotional memory and affective processes,[37,38] and consistent with the possibility that hormones, once linked with depression, may facilitate return to the depressed state.

METHODS

All study procedures were reviewed and approved by the Institutional Review Boards (IRB) at the University of Texas at Austin in Austin, TX, USA; and Brooke Army Medical Center in San Antonio, TX, USA.

Participants

Soldiers ($N = 120$; male: $n = 104$; female: $n = 16$) were recruited from 9 Army units scheduled to deploy from Ft. Hood to Iraq between August 2007 and August 2009. Eligibility required: (1) age of 18 or older, (2) no prior deployments, and (3) planned deployment within 3 mo. Among the 223 soldiers attending recruitment, 184 consented, 6 did not deploy, 1 withdrew consent, and 16 completed no in-theater measures. Of the remaining, 24 were excluded due to endocrine abnormalities or exclusionary medications (i.e., antidepressants, steroids), 8 had invalid assays, and 9 did not provide included measures, leaving 120 soldiers represented in the analyses (see Table I).

Participants reporting severe depression, or other severe mental or behavioral health problems, whether in interview or self-report assessments, were referred to the PI (M. Telch), and the Army PI and medical director for the project (W. Schirner) for further evaluation. The medical director made all determinations of actions necessary to ensure participant welfare, including recommendations and referrals for treatment at Ft. Hood. Data on treatment utilization was unfortunately not available for the present analyses. However, all included soldiers were deemed fit for duty prior to deployment.

Pre-deployment Measures

Demographics and Lifetime Psychopathology

As part of a larger pre-deployment assessment, soldiers completed a demographics questionnaire, and the Structured Clinical Interview for Axis I DSM-IV Diagnoses (SCID-I-IV).[39] The SCID-I-IV was administered by doctoral students, supervised by the PI, with > 1 yr of experience using this instrument.

Cortisol and Testosterone

Between 2:00 and 5:00 pm, two 3 mL saliva samples were collected for cortisol (C) and testosterone (T) assays – first following a 20-min rest period immediately preceding a 35% CO_2 / 65% O_2 inhalation challenge, and again 30 min after the challenge. The difference (post-CO_2 minus pre-CO_2 levels) was used to calculate cortisol (C_R) and testosterone reactivity

TABLE I. Descriptive Statistics for Modeled Variables

Variable	*N*	%	*M*	*SD*
Male	104	86.67	—	—
Female	16	13.33	—	—
Lifetime DSM-IV Axis I Disorder[a]	64	53.33	—	—
Pre-Deployment Depression (CES-D-20)	120	—	10.99	8.36
Monthly average number of PTEs[b]	120	—	1.83	1.85
CEL Entries[c]	120	—	7	5.59
In-theater depression (CES-D-10)	120	—	7.65	5.11
C (pg/mL) Pre-CO_2	120	—	.12	.06
C (pg/mL) Post-CO_2	120	—	.15	.13
C_R (pg/mL) Post-Pre CO_2	120	—	.03	.12
T (pg/mL) Pre-CO_2	120	—	83.07	26.74
T (pg/mL) Post-CO_2	120		84.91	33.72
T_R (pg/mL) Post-Pre CO_2	120	—	1.84	23.05

CES-D-10, Center for Epidemiological Studies Depression Scale – 10 Items; CES-D-20, Center for Epidemiological Studies Depression Scale – 20 Items.

[a]Dichotomously coded (yes or no) presence of lifetime, including current, DSM-IV-TR Axis I Disorders.

[b]Average monthly number of traumatic war-zone stressors across soldiers and deployment months.

[c]Average total number of in-theater Combat Experience Log (CEL) entries, across soldiers. Basal salivary cortisol (C) and testosterone (T) were measured before and 30 min after a single inhalation of 35% CO_2 / 65% O_2 gas at pre-deployment, and reactivity measures (C_R, T_R) were derived by subtracting pre-CO_2 from post-CO_2 hormone levels.

(T_R), which can be conceived as indices of stress recovery by previous definitions.[14] Hormone concentrations were assayed in duplicate by Salimetrics (State College, PA, USA). Intra-assay and inter-assay variances were acceptable (4.6% and 9.9%, respectively, for testosterone, 3.5% and 5.1% for cortisol).

35% CO_2 Inhalation Stress Challenge

The CO_2 stressor followed standard procedures.[31–34] A 3-min video presented the rationale, instructions, and demonstration of procedures. Participants took one full capacity breath of the gas through a plastic mask, and held this breath for 5 s, followed by normal breathing until the effects of the gas subsided (~30 s).

Pre-deployment Depression Symptoms

Depression was assessed with the 20-item Center for Epidemiological Studies Depression Scale (CES-D-20).[40] This validated instrument assesses depressive symptomology, with items rated according to frequency (0 = "Rarely / None of the time"; 3 = "Most / All of the time"). Internal consistency for the CES-D-20 was good in the present sample ($\alpha = 0.90$).

In Theater Measures

During deployment, monthly emails were sent with reminders and web links to complete the Combat Experiences Log (CEL),[41] which assesses the occurrence of stressors and severity of symptoms.

Potentially Traumatic War-zone Stressors

CEL items adapted from the Deployment Risk and Resilience Inventory[42] assessed stressors experienced in the past 30 d (present vs. absent). Three of the authors (AC, CL, and MT) selected items that would meet PTSD DSM-5 criteria A1 for a trauma[26] and excluded items not meeting these criteria (e.g., "conflict(s) with other soldiers"). Two free-response items allowing reporting of stressors that were not included in the checklist were coded by hand. The coding of these items produced perfect agreement among raters (see supplementary Table S1 for items).

In-Theater Depression Symptoms

In-theater depression was assessed with the 10-item Center for Epidemiological Studies Depression Scale (CES-D-10).[43] Items assessing core depression symptoms were rated according to frequency (0 = "Rarely / None of the time"; 3 = "Most / All of the time"). The CES-D-10 is well validated highly correlated with the 20-item version.[44,45] Internal consistency in the present sample was good ($\alpha = 0.81$).

Statistical Analyses

Mixed effects models estimated the main and interactive moderation effects of basal cortisol (C), basal testosterone (T), and cortisol (C_R) and testosterone reactivity (T_R) to the 35% CO_2 challenge on the later impact of war-zone stressors (PTEs) on monthly in-theater depression (CES-D-10) (Full maximum likelihood estimation was used to determine functional forms of in-theater symptoms, and to compare deviance statistics of nested models, whereas restricted maximum likelihood produced the final estimates.[46] Unstructured variance-covariance matrices were specified across models. Degrees of freedom were derived using Satterthwaite approximations.[47] Local effect sizes were derived from *t*-statistics with the following formula: $r = \sqrt{(t^2 / (df + t^2))}$. The number of days deployed was centered at 8 mo, and entered in its raw metric. Gender (male = 0, female = 1) and past or current psychopathology (absent = 0, present = 1) were entered dichotomously. All other continuous predictors, including pre-deployment depression (DEP) (CES-D-20), hormone indices, and war-zone stressor indices, were z-transformed for ease of interpretation.

Basal and reactivity hormone variables (C, T, C_R, and T_R) were *z*-transformed separately for each sex in order to remove sex differences in absolute levels and variability. We further assessed the validity of including both sexes by examining effects and residuals for all tested models, which indicated comparable patterns of effects and prediction accuracy (or equivalently, error) for males and females. For all models including hormone reactivity, we controlled for basal levels corresponding to each reactivity index. Stressor variables were parsed into between- and within-subject components to avoid imposing the assumption that between- and within-subject effects are equal.[48] Between-subject stressor effects reflect average monthly exposure to potentially traumatic stressors (PTE_{BP}), whereas within-subject stressor effects reflect monthly deviation around the individual's own average (PTE_{WP}). Moderation effects were probed by centering each moderator 1 SD above and below the respective means to estimate the conditional effects of stressors given a particular pre-deployment profile of the moderators (i.e., high vs. low basal hormones, CO_2-evoked hormone reactivity, and depression symptom severity).[49]

Our analyses can be summarized in four steps. In step 1, we examined main effects by entering the hormone indices separately (C, T, C_R, *or* T_R), followed by all hormone indices to estimate incremental main effects (C, T, C_R, *and* T_R; Model 1; see supplementary Table S2). In step 2, we examined singular stress-moderation effects by entering two-way interactions between each hormone variable and PTEs (e.g., T × PTE_{BP}; C_R × PTE_{WP}, etc.) in separate models (referred to as "singular hormone diathesis-stress models") (Hypotheses 1.1–1.4; Models 2.1–2.4), followed by modeling them together to estimate incremental stress-moderation effects (Model 2.5) (referred to as "incremental hormone diathesis-stress models"). In step 3, we tested whether basal and reactivity hormone measures interact within (e.g., C × C_R × PTEs) and across the HPA and HPG axes (e.g., C × T_R × PTEs) as stress moderators (Models 3.1–3.6) (referred to as "interacting diathesis-stress models"). In step 4, we tested whether any of the hormone diathesis-stress effects, modeled separately, were further moderated

by DEP (Models 4.1–4.4). See supplementary Table S2 for a list of these models (Models 1–4.4) with detailed specifications.

RESULTS

Preliminary Models of DEP

Table I provides demographics and descriptive statistics for all modeled variables. Preliminary models of in-theater depression revealed sex ($b = 4.48$, SE = 2.20, $t = 2.04$, $p = 0.044$), and life-time psychopathology ($b = 3.24$, SE = 1.56, $t = 2.08$, $p = 0.039$) were significantly associated with DEP (see supplementary Table S3). In contrast, there were no associations between DEP and any of the hormone measures (all p's > 0.10).

Preliminary Models of In-Theater Depression

Unconditional growth models of in-theater depression revealed an intra-class correlation of 50.80%. The best fitting change trajectories were similar to those previously reported.[41,50] There were 533 observations of 120 soldiers, who each completed an average of 4.44 ($SD = 3.37$; range: 1–14) in-theater assessments. Among the 120 soldiers, 29 (24.17%) fell above, and 91 (75.83%) fell below the cutoff for clinically significant depression at pre-deployment (CES-D-20 ≥ 16).[40] Among those depressed at pre-deployment, 19 (65.51%) scored above the clinical cutoff for depression at some point during deployment (CES-D-10 ≥ 10).[43] Among those not depressed at pre-deployment, 35 (38.46%) scored above the cut-off in-theater.

Main Effect Predictors of In-Theater Depression

Supplementary Table S4 presents main effects including all covariates (see Statistical Analyses; Step 1, Model 1). Race and ethnicity were non-significant predictors in preliminary models, and so were excluded. Females reported higher levels of in-theater depression than males ($b = 2.10$, SE = 1.01, $t = 2.09$, $p = 0.039$, $r = 0.20$) (note the smaller number of women in the sample ($n = 16$)). Lifetime psychopathology was a non-significant predictor of in-theater depression ($p = 0.081$), whereas DEP significantly predicted higher in-theater depression ($b = 1.42$, $SE = 0.38$, $t = 3.70$, $p < 0.000$, $r = 0.31$). Monthly within-soldier increases in stressors (PTE_{WP}), significantly predicted higher in-theater depression ($b = 0.41$, $SE = 0.17$, $t = 2.43$, $p = 0.016$, $r = 0.11$), whereas the effect of average stressor exposure (PTE_{BP}), was non-significant ($p = 0.357$). Neither T ($p = 0.910$), T_R ($p = 0.084$), C ($p = 0.319$), nor C_R ($p = 0.073$) predicted in-theater depression directly. (Additionally, in models with each hormone index entered separately, but controlling for all other covariates, none of the hormone measures were found to directly predict in-theater depression (all p's > 0.10). Furthermore, these null findings held irrespective of whether models controlled for the main effects of PTE exposure.)

Singular and Incremental Hormone Diathesis-Stress Models of In-Theater Depression

The following results are limited to tests of our primary hypotheses, evaluating the interactive effects of DEP, hormone indices, and war-zone stress on in-theater depression.

Singular Hormone Diathesis-Stress Models

Supplementary Table S5 presents findings for the singular hormone stress-moderation models (see Statistical Analyses, Step 2, Models 2.1–2.4), which tested whether any of the hormone indices, modeled separately, moderate the effects of PTEs.

Testosterone and testosterone reactivity × war-zone stressors. As hypothesized, the T × PTE_{WP} interaction ($b = -0.45$, SE = 0.20, $t = -2.30$, $p = 0.022$, $r = 0.11$) revealed a significant potentiating effect on PTE_{WP} on depression for those with low T ($b = 0.72$, SE = 0.21, $t = 3.37$, $p = 0.001$, $r = 0.16$), but not high T ($b = -0.19$, SE = 0.31, $t = -0.60$, $p = 0.550$, $r = 0.03$; Model 2.1; see supplementary Figure S1). In contrast to predictions, the T_R × PTE_{WP} interaction was significant ($b = 0.44$, SE = 0.21, $t = 2.13$, $p = 0.034$, $r = 0.10$), indicating a significant impact of PTE_{WP} on depression for those who exhibited increases in T_R ($b = 0.94$, SE = 0.30, $t = 3.17$, $p = 0.002$, $r = 0.15$), but not decreases in T_R ($p = 0.821$; Model 2.2; see supplementary Figure S2). Neither T ($p = 0.654$) nor T_R ($p = 0.611$) moderated PTE_{BP} effects on depression.

Cortisol and cortisol reactivity × war-zone stressors. Neither C (Model 2.3) nor C_R (Model 2.4) moderated the effects of either stressor index (PTE_{WP} or PTE_{BP}) on in-theater depression (C × PTE_{BP}: $p = 0.914$; C × PTE_{WP}: $p = 0.137$; C_R × PTE_{BP}: $p = 0.471$; C_R × PTE_{WP}: $p = 0.998$).

Incremental Hormone Diathesis-Stress Models

Table II presents findings for the incremental hormone stress-moderation model, in which all hormone indices were entered to estimate independent stress-moderation effects (see Statistical Analyses, Step 2; Model 2.5). Only T_R emerged as a significant moderator of PTE_{WP} on depression (T_R × PTE_{WP}: $b = 0.49$, SE = 0.25, $t = 1.99$, $p = 0.048$, $r = 0.09$; see supplementary Figure S3), indicating a significant impact of PTE_{WP} on in-theater depression for soldiers who displayed elevations in T_R ($PTE_{WP} \mid T_R+$: $b = 0.81$, SE = 0.34, $t = 2.37$, $p = 0.018$, $r = 0.11$), but not declines in T_R ($PTE_{WP} \mid T_R-$: $p = 0.530$). All other hormone × PTE interactions were non-significant (p's > 0.10).

Interacting Hormone Diathesis-Stress Models of In-Theater Depression

Next, we examined whether basal and reactivity measures interact both within (e.g., C × C_R × PTEs) and across the HPA and HPG axes (e.g., C × T_R × PTEs) as moderators of stressors (see Statistical Analyses, Step 3; Models 3.1–3.6). Results are presented in supplementary Table S6. T and T_R did not significantly

TABLE II. Incremental Hormone-Stress Models

Parameter	*b*	SE	*df*	*t*	*p*		Effect Size
(Intercept)	7.72	0.59	119.70	13.13	0.000	****	0.77
Time	0.04	0.06	494.60	0.69	0.492		0.03
$Time^2$	−0.04	0.01	475.60	−4.73	0.000	****	0.21
Sex	1.16	1.05	106.30	1.10	0.272		0.11
Lifetime Axis I Diagnosis	1.28	0.77	113.90	1.66	0.100	*	0.15
Pre-Deployment CES-D-20	1.45	0.41	122.10	3.56	0.001	***	0.31
PTE_{BP}	−0.26	0.33	143.90	−0.80	0.426		0.07
PTE_{WP}	0.32	0.19	470.70	1.65	0.099	*	0.08
Cortisol (C)	−0.34	0.39	103.10	−0.86	0.390		0.08
Cortisol reactivity (C_R)	0.56	0.37	107.60	1.52	0.133		0.14
Testosterone (T)	0.14	0.39	107.80	0.36	0.717		0.03
Testosterone reactivity (T_R)	−0.49	0.40	109.70	−1.21	0.229		0.11
C × PTE_{BP}	−0.01	0.26	181.10	−0.03	0.977		0.00
C × PTE_{WP}	−0.25	0.25	476.40	−1.01	0.311		0.05
C_R × PTE_{BP}	−0.16	0.30	183.80	−0.54	0.592		0.04
C_R × PTE_{WP}	−0.41	0.32	482.20	−1.27	0.205		0.06
T × PTE_{BP}	0.07	0.32	127.20	0.21	0.837		0.02
T × PTE_{WP}	−0.26	0.22	479.40	−1.15	0.250		0.05
T_R × PTE_{BP}	−0.08	0.38	131.70	−0.21	0.834		0.02
T_R × PTE_{WP}	0.49	0.25	460.40	1.99	0.048	**	0.09
PTE_{WP} | T_R −	−0.18	0.28	449.30	−0.63	0.530		0.03
PTE_{WP} | T_R +	0.81	0.34	473.40	2.37	0.018	**	0.11

This table presents results from multi-level growth models including each of the hormone indices in interaction with both the between-soldier (PTE_{BP}) and within-soldier (PTE_{WP}) variance component of stressors in order to evaluate the incremental contribution of the hormone variables to the impact of in-theater stressors on depression symptoms. PTE_{BP}: reflects the total between-soldier effect of having a higher monthly average exposure to PTEs, across deployment months. PTE_{WP}: indicates the effect of having 1 additional PTE relative to the individual soldier's monthly average number of stressors, in any single deployment month. Effect sizes (*r*) were derived from the t-statistics, using the following formula: $r = \sqrt{(t^2 / (df + t^2))}$, where *t* equals the value of the *t*-statistic for each parameter, and *df* equals the degrees of freedom associated with the *t*-statistics. *$p < 0.10$, **$p < 0.05$, ***$p < 0.01$, ****$p < 0.000$.

interact in moderating the effects of PTE_{BP} on depression (T × T_R × PTE_{BP}: $p = 0.900$). However, the T × T_R × PTE_{WP} interaction was significant (PTE_{WP}: $b = -0.49$, SE = 0.23, $t = -2.14$, $p = 0.033$, $r = 0.10$), indicating a pronounced impact of PTE_{WP} on depression given low T *and* high T_R (PTE_{WP}: $b = 1.66$, $SE = 0.41$, $t = 4.10$, $p < 0.000$, $r = 0.20$). All other high-low combinations of T and T_R were non-significant (all *p*'s > 0.10; see Fig. 1; Model 3.1). In contrast, interactive effects including C and C_R were non-significant (all *p*'s > 0.10; Model 3.2).

Finally, all three-way interactions consisting of each possible cross-axis combination of hormone indices (i.e., T × C, T × C_R, T_R × C, T_R × C_R) and one of the two stressor variables (i.e., PTE_{BP}, PTE_{WP}) were non-significant (all *p*'s > 0.10; Models 3.3–3.6).

DEP × Hormone Diathesis-Stress Models of In-Theater Depression

Finally, we explored whether the hormone stress-moderation effects were further moderated by DEP (see Statistical Analyses, Step 4; Models 4.1–4.4). Results are presented in Table III.

DEP significantly moderated the T_R × PTE_{WP} interaction on in-theater depression (DEP × T_R × PTE_{WP}: $b = 0.86$, SE = 0.28, $t = 3.10$, $p = 0.002$, $r = 0.14$; see Fig. 2; Model 4.2). Given high DEP, increases in T_R ($b = 2.10$, SE = 0.43, $t = 4.86$, $p < 0.000$, $r = 0.23$), but not decreases in T_R ($b = -0.55$, SE = 0.35, $t = -1.18$, $p = 0.238$, $r = 0.06$) amplified the effects of PTE_{WP} on in-theater depression. In contrast, given low DEP, T_R was non-significantly related to the impact of PTE_{WP} ($p > 0.10$).

DEP significantly moderated the C × PTE_{WP} interaction on in-theater depression (DEP × C × PTE_{WP} $b = -1.02$, SE = 0.35, $t = -2.91$, $p = 0.004$, $r = 0.13$; see Fig. 3; Model 4.3). High depression and low C at pre-deployment significantly potentiated the impact of PTE_{WP} ($b = 2.04$, SE = 0.46, $t = 4.40$, $p < 0.000$, $r = 0.20$), whereas high depression and high C predicted a non-significant relation between PTE_{WP} and in-theater depression ($p = 0.077$). In contrast, given low DEP, the impact of PTE_{WP} was not significant, irrespective of C (*p*'s > 0.10).

Finally, DEP significantly moderated the C_R × PTE_{WP} interaction on in-theater depression ($b = 0.78$, SE = 0.27, $t = 2.87$, $p = 0.004$, $r = 0.13$; Model 4.4; see Fig. 4). Given high DEP, C_R significantly amplified the impact of PTE_{WP} (C_R+: $b = 2.00$, SE = 0.45, $t = 3.64$, $p < 0.000$, $r = 0.17$; C_R−: $b = 0.11$, SE = 0.46, $t = 0.24$, $p = 0.811$, $r = 0.01$). In contrast, given low DEP, there is no significant relation between C_R and the impact of PTE_{WP} on in-theater depression (PTE_{WP} | C_R+: $p = 0.058$; PTE_{WP} | CR−: $p = 0.262$).

DISCUSSION

These findings revealed profiles of DEP, basal hormones and hormone stress-reactivity that predict depressogenic reactions to

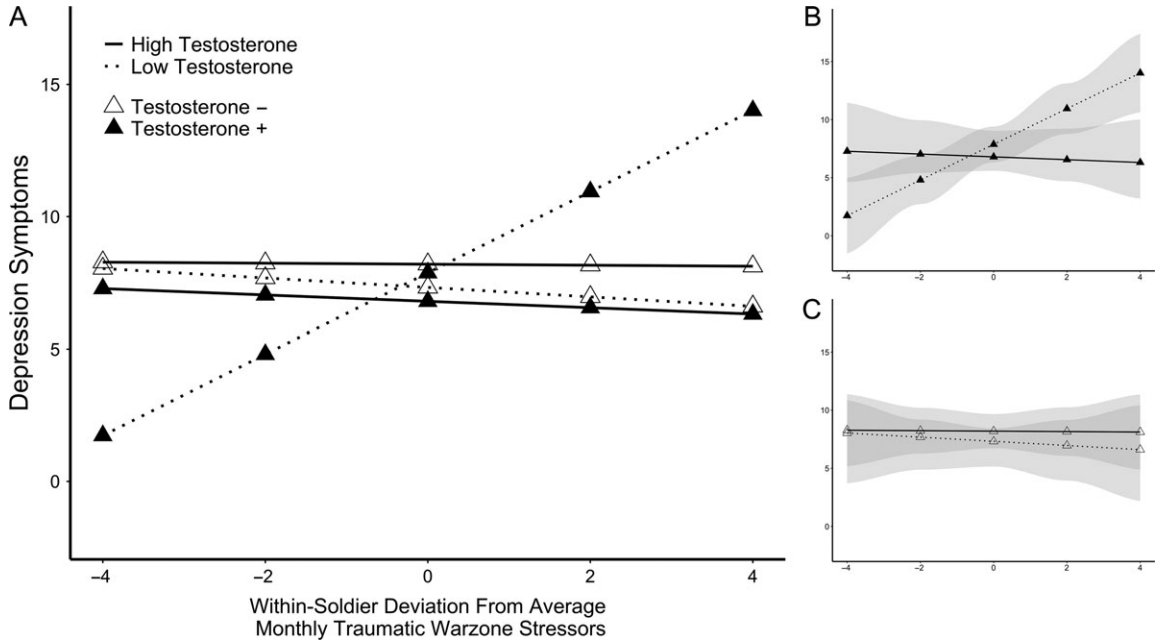

FIGURE 1. Basal testosterone and testosterone reactivity to a 35% CO_2 challenge jointly moderate the impact of within-soldier deviations from average monthly exposure to traumatic war-zone stressors on in-theater depression symptoms. The main plot (A) represents the effects of within-soldier deviations from their own average monthly exposure to potentially traumatic war-zone stressors (PTEWP) for soldiers exhibiting low basal testosterone (dotted lines) or high basal testosterone (solid lines) and decreases (empty triangles) or increases (filled triangles) in salivary testosterone levels from pre-to-post CO_2 inhalation at pre-deployment. Models controlled for gender, past and current Axis I DSM-IV-TR psychopathology, and DEP severity. Shaded regions (subplots B and C) indicate asymmetric bootstrap-derived 95% confidence limits. Undulations reflect variation in data density across the length of each regression line.

TABLE III. Single Basal and Reactivity Hormone-Stress Moderation Models Further Moderated by DEP Symptoms

Parameter	*b*	SE	*df*	*t*	*p*		Effect Size
Dep × T × PTE_{BP}	0.09	0.44	120.40	0.21	0.835		0.02
Dep × T × PTE_{WP}	−0.20	0.24	450.20	−0.81	0.417		0.04
Dep × T_R × PTE_{BP}	0.11	0.45	142.20	0.25	0.805		0.02
Dep × T_R × PTE_{WP}	0.86	0.28	449.80	3.10	0.002	***	0.14
PTE_{WP} | Low Dep, T_R−	0.36	0.35	433.60	1.04	0.300		0.05
PTE_{WP} | High Dep, T_R−	−0.55	0.46	445.50	−1.18	0.238		0.06
PTE_{WP} | Low Dep, T_R+	−0.41	0.47	460.40	−0.87	0.384		0.04
PTE_{WP} | High Dep, T_R+	2.10	0.43	437.70	4.86	0.000	****	0.23
Dep × C × PTE_{BP}	0.64	0.48	169.80	1.34	0.184		0.10
Dep × C × PTE_{WP}	−1.02	0.35	469.80	−2.91	0.004	***	0.13
PTE_{WP} | Low Dep, Low C	−0.37	0.41	455.50	−0.92	0.357		0.04
PTE_{WP} | High Dep, Low C	2.04	0.46	461.10	4.40	0.000	****	0.20
PTE_{WP} | Low Dep, High C	0.27	0.33	451.00	0.83	0.407		0.04
PTE_{WP} | High Dep, High C	−1.39	0.78	480.10	−1.77	0.077	*	0.08
Dep × C_R × PTE_{BP}	−0.17	0.38	182.60	−0.44	0.663		0.03
Dep × C_R × PTE_{WP}	0.78	0.27	484.20	2.87	0.004	***	0.13
PTE_{WP} | Low Dep, C_R−	0.38	0.34	449.20	1.12	0.262		0.05
PTE_{WP} | High Dep, C_R−	0.11	0.46	476.50	0.24	0.811		0.01
PTE_{WP} | Low Dep, C_R+	−0.85	0.45	442.90	−1.90	0.058	*	0.09
PTE_{WP} | High Dep, C_R+	2.00	0.55	458.20	3.64	0.000	****	0.17

This table presents results from multi-level growth models including three-way interactions of testosterone indices and stressors in interaction with DEP symptoms, based on scores on the CES-D-20 (Dep), to examine whether baseline depression moderates the hormone stress-moderation effects (e.g., Dep × T × PTE_{BP}). Omnibus effects (e.g., Dep × T_R × PTE_{BP}, etc.) are followed by conditional effects (PTE_{WP} | Low Dep, T_R−, etc.), which indicate the effects of PTEs given each combination of high (+1 SD from the mean) or low (–1 SD from the mean) basal hormone levels (i.e., C, T) measured prior to the pre-deployment CO_2 challenge, or increases (+ 1 SD from 0) or reductions (−1 SD from 0) in salivary hormone levels (i.e., CR −/+, TR −/+) from pre-to-post CO_2 challenge. PTE_{BP}: reflects the total between-soldier effect of having a higher monthly average exposure to PTEs, across deployment months. PTE_{WP}: indicates the effect of having 1 additional PTE relative to the individual soldier's monthly average number of stressors, in any single deployment month. Effect sizes (*r*) were derived from the t-statistics, using the following formula: $r = \sqrt{(t^2 / (df + t^2))}$, where t equals the value of the t-statistic for each parameter, and df equals the degrees of freedom associated with the t-statistics. *$p < 0.10$, **$p < 0.05$, ***$p < 0.01$, ****$p < 0.000$.

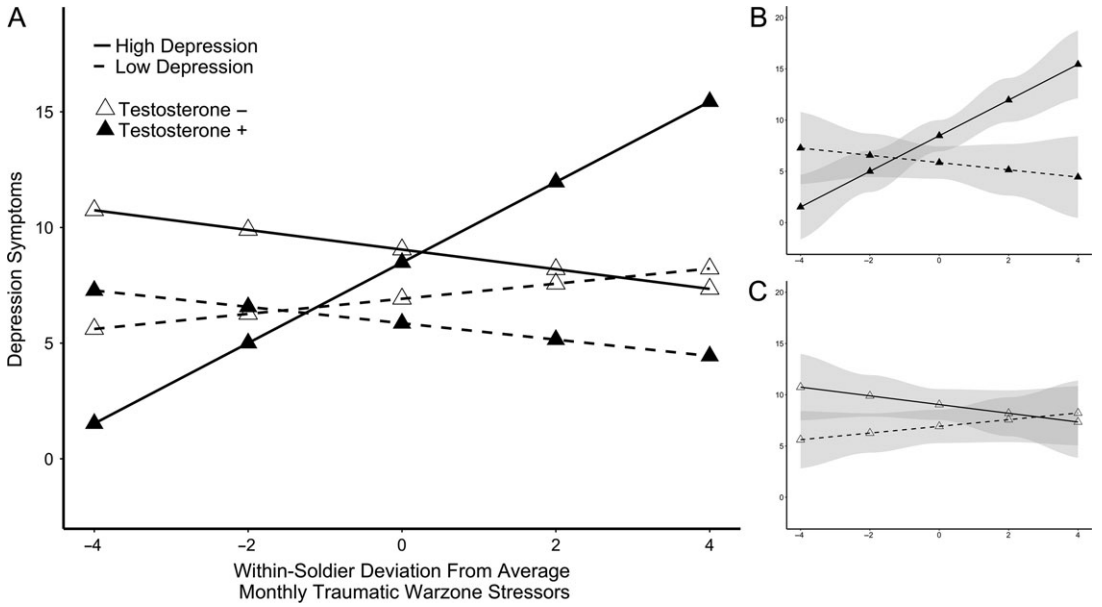

FIGURE 2. Baseline depression and testosterone reactivity to a 35% CO_2 challenge jointly moderate the impact of war-zone stressors on in-theater depression symptoms. The main plot (A) represents the effects of within-soldier deviations from their own average monthly exposure to potentially traumatic war-zone stressors (PTE_{WP}) for soldiers exhibiting testosterone decreases (empty triangles) or testosterone increases (filled triangles) in response to the 35% CO_2 inhalation challenge, and low (dashed lines) or high (solid lines) depression based on scores on the CES-D- 20 at pre-deployment. Models controlled for gender, and past and current Axis I DSM-IV-TR psychopathology. Shaded regions (subplots B and C) indicate asymmetric bootstrap-derived 95% confidence limits. Undulations reflect variation in data density across the length of each regression line.

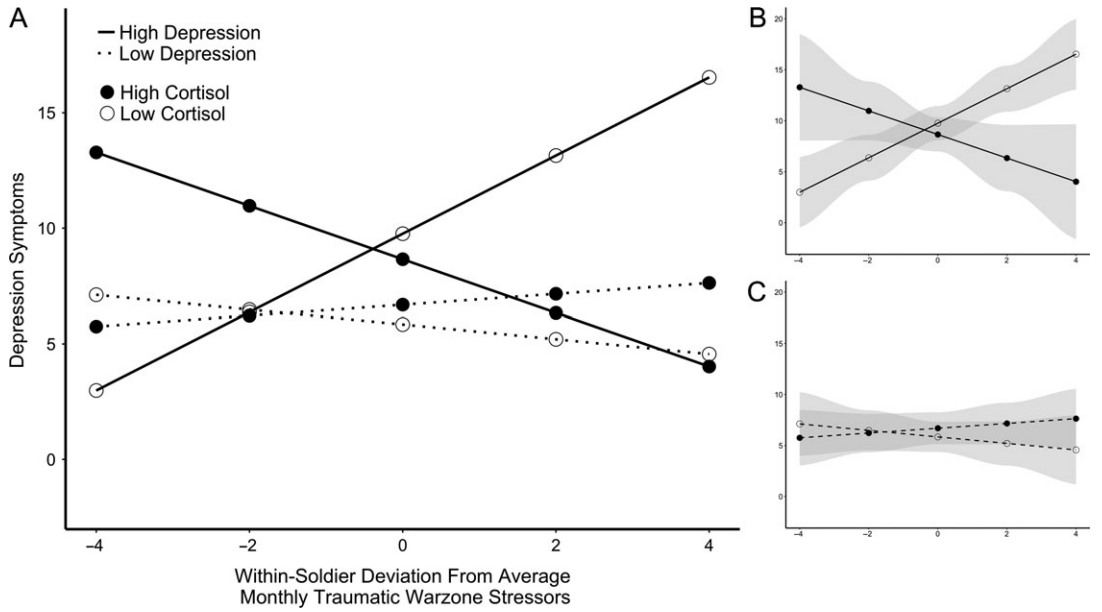

FIGURE 3. Baseline depression × basal cortisol jointly moderate the impact of war-zone stressors on in-theater depression symptoms. The main plot (A) represents the effects of within-soldier deviations from their own average monthly exposure to potentially traumatic war-zone stressors (PTE_{WP}) for soldiers exhibiting low basal cortisol (empty circles) or high basal cortisol (filled circles) and low (dotted lines) or high (solid lines) depression based on scores on the CES-D-20 at pre-deployment. Models controlled for gender, and past and current Axis I DSM-IV-TR psychopathology. Shaded regions (subplots B and C) indicate asymmetric bootstrap-derived 95% confidence limits. Undulations reflect variation in data density across the length of each regression line.

monthly increases in war-zone stressors. Specifically, low testosterone and elevated stress-evoked testosterone release strengthened the association between monthly increases in stressors and depression, and the effects of testosterone stress-reactivity were more pronounced in soldiers who were depressed at pre-deployment. In contrast, whereas testosterone's effects were also independent of DEP, the stress-moderation effects of cortisol critically depended on concurrent depression – among

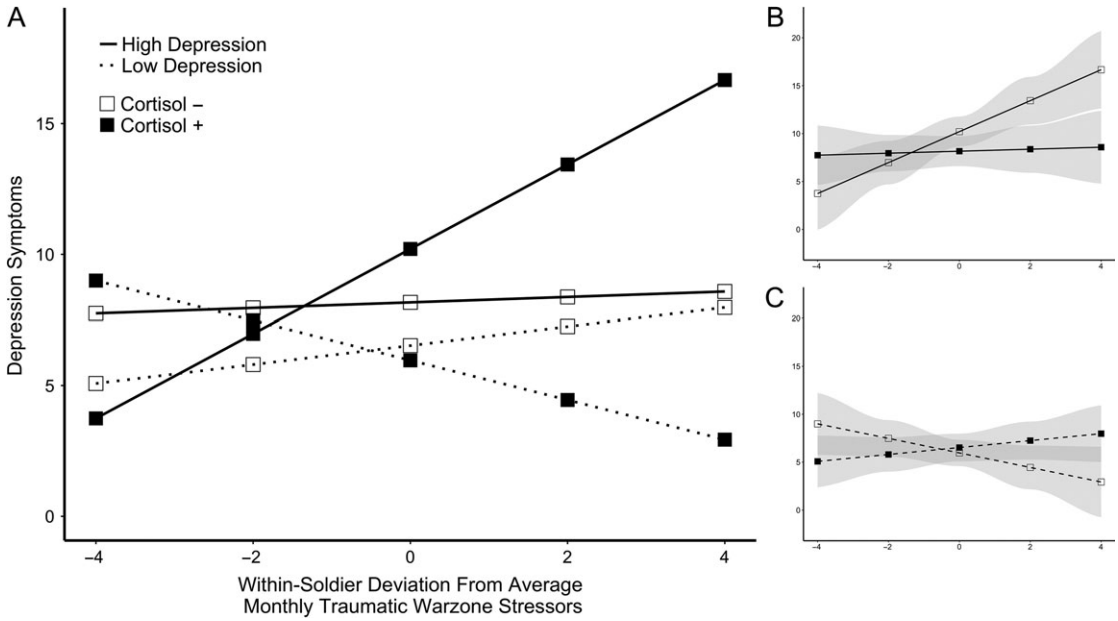

FIGURE 4. Baseline depression and cortisol reactivity to a 35% CO_2 challenge jointly moderate the impact of war-zone stressors on in-theater depression symptoms. The main plot (A) represents the effects of within-soldier deviations from their own average monthly exposure to potentially traumatic war-zone stressors (PTE_{WP}) for soldiers exhibiting cortisol decreases (empty squares) or cortisol increases (filled squares) in response to the 35% CO_2 inhalation challenge, and low (dotted lines) or high (solid lines) depression based on scores on the CES-D-20 at pre-deployment. Models controlled for gender, and past and current Axis I DSM-IV-TR psychopathology. Shaded regions (subplots C and B) indicate asymmetric bootstrap-derived 95% confidence limits. Undulations reflect variation in data density across the length of each regression line.

depressed soldiers, high basal cortisol protected against war-zone stress-evoked depression, whereas elevated stress-evoked cortisol release amplified stressors' impact. Finally, contrary to predictions based on HPA-HPG reciprocal suppression,[27] no cross-axis effects were found, suggesting the hormone effects operated independently. Overall, the findings support simultaneous examination of basal and endocrine stress-reactivity markers, and baseline depression severity within a diathesis-stress framework when estimating risk for depression.

The finding that low testosterone elevated risk for stress-evoked depression is consistent with sex differences in depression prevalence,[15] findings linking low testosterone to depression,[17–19] and evidence that testosterone ameliorates depression.[35] However, contrary to predictions, testosterone reactivity amplified the depressogenic impact of monthly stressors. One viable explanation for this pattern of effects is that there may be functional overlap in the effects of low basal and high stress-evoked testosterone. Supporting this possibility is evidence that short-term elevations in testosterone are followed by declines that can last up to several days[51,52] – effects possibly mediated by auto-regulation.[53]

Given evidence for hippocampal atrophy in depression,[54] and that hippocampal neurogenesis mediates treatment effects in depression,[55] the literature examining testosterone as a hippocampal neurotrophic factor offers a related account. For instance, testosterone may protect against glucocorticoid-mediated hippocampal neural degeneration by suppressing HPA function,[27] and directly enhancing neuron survival.[56] However, consistent with the depressogenic effects of testosterone reactivity, evidence suggests these effects depend on the duration of testosterone exposure. In animals, testosterone administration for at least 30 d has produced neurotrophic effects,[56–58] whereas shorter treatments (15 d[57]; 21 d[59]) have produced no effects, and still shorter durations have actually diminished new neuron survival in the hippocampus (5 d[60]).

In contrast to the testosterone findings, the stress-moderating effects of basal cortisol and cortisol reactivity were observed *only* among those with elevated depression at pre-deployment. Contrary to predictions based on evidence for hyper-corticolism in depression,[12,14] among soldiers with high DEP, elevated cortisol predicted an inverse relation, whereas low cortisol predicted of a strong positive relation between monthly stressors and in-theater depression. These findings are consistent with evidence that low cortisol predicts earlier relapse in recurrent major depression,[61] and with the interpretation that adaptive benefits may explain observations of hyper-corticolism in depression.[12] The present findings suggest these benefits may arise only in the context of elevated stress, consistent with observations of a reduced impact of stressors given a greater number of previous depressive episodes.[9,10] These observations have been interpreted as reflecting enhanced autonomy of depressogenic processes following depression onset. However, the present findings suggest that cortisol elevations in depression may be an adaptive response that buffers the impact of stressors, thereby reducing risk for recurrence, but *only* in the context of elevated stress.

The protection conferred by high basal cortisol did not extend to reactivity, although the findings for cortisol reactivity were consistent with predictions and existing literature. Burke et al's[14] meta-analysis found a pattern of blunted acute stress reactivity in depressed individuals, but higher cortisol levels at least 25-min post-stressor onset, and this pattern was more pronounced in studies of more severely depressed patients. Other evidence has shown that a history of major depression combined with greater cortisol release during anticipatory stress enhances risk for future depressive episodes.[36] Extending these findings, we found that soldiers depressed at pre-deployment who also exhibited pronounced stress-evoked increases in cortisol (pre-to 30 min. post-CO_2 challenge) were most susceptible to the later depressogenic impact of monthly elevations in war-zone stressors.

Limitations

A few study limitations should be noted. First, most soldiers provided in-theater data, but missing observations were not uncommon. However, there were no patterns in missing data across deployment months, and our statistical approach is robust to missing observations. Second, because depression is multifactorial and multiply determined, and given the inherent constraints of model complexity, the present approach is necessarily limited in terms of attending to the constellation of factors that contribute to depression. For instance, we were unable to validly assess the effects of several potentially important variables, including sex, age, and physical health. Third, hormone sampling under conditions of fasting would be less than ideal for indexing hormonal reactivity to a laboratory stress challenge, but it may be worthwhile for future studies to also obtain fasting levels, as this may help guide use of routine tests of endocrine function for informing risk assessments. Fourth, we relied on self-report measures of in-theater stressors and depression, and did not have repeated hormone measures in the war-zone, which would be useful for determining how hormone profiles may be functionally impacted by stress exposure, and influence stress reactions over time. Still, the prospective design enhances confidence in evaluating relations between hormone profiles and the depressogenic impact of stressors, and the use of a diathesis-stress framework is consistent with most etiological models,[3] in which stress is given a determinant role in the pathophysiology of depression.

Conclusions

The major challenges of discovering biomarkers and biological risk factors for depression and other stress-linked psychopathologies include the complexity of biological systems, their reciprocal interactions with other systems, and the variety of contextual factors governing their expression. The present study addressed these issues in evaluating a more complete and functional etiological model that views endocrine systems as nested within individuals, interacting with other endogenous factors, and subject to the fluctuating contextual influence of environmental stress. Future work should similarly implement dynamic measures of stress-reactivity, and aim for identifying susceptible individuals by examining clusters of individual difference and contextual factors. In addition to informing the etiology of stress-related psychopathology, such an approach may contribute to enhancing identification of those most vulnerable to depression and other stress-related mental disorders.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

ACKNOWLEDGEMENTS

This research was funded by the U.S. Army RDECOM Acquisition Center, Natick Contracting Division, and U.S. Defense Advanced Agency under Contract No. W911QY-07-C-0002 awarded to MJT.

REFERENCES

1. Institute of Medicine: Treatment for posttraumatic stress disorder in military and veteran populations: final assessment. Mil Med 2014; 179(12): 1401–3. doi:10.7205/MILMED-D-14-00418.
2. Ginzburg K, Ein-Dor T, Solomon Z: Comorbidity of posttraumatic stress disorder, anxiety and depression: a 20-year longitudinal study of war veterans. J Affect Disord 2010; 123(1–3): 249–57. doi:10.1016/j.jad.2009.08.006.
3. Belmaker RH, Agam G: Major depressive disorder. N Engl J Med 2008; 358(1): 55–68. doi:10.1056/NEJMra073096.
4. Sullivan PF, Neale MC, Kendler KS: Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000; 157(10): 1552–62. doi:10.1176/appi.ajp.157.10.1552.
5. Hammen C: Stress and depression. Annu Rev Clin Psychol 2005; 1(1): 293–319. doi:10.1146/annurev.clinpsy.1.102803.143938.
6. Mazure CM: Life stressors as risk factors in depression. Clin Psychol 1998; 5(3): 291–313. doi:10.1111/j.1468-2850.1998.tb00151.x.
7. Monroe SM, Simons AD: Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. Psychol Bull 1991; 110(3): 406–25. doi:10.1037//0033-2909.110.3.406.
8. Monroe SM, Harkness KL: Life stress, the "kindling" hypothesis, and the recurrence of depression: considerations from a life stress perspective. Psychol Rev 2005; 112(2): 417–45. doi:10.1037/0033-295×0.112.2.417.
9. Kendler KS, Thornton LM, Gardner CO: Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry 2000; 157(8): 1243–51. doi:10.1176/appi.ajp.157.8.1243.
10. Kendler KS, Thornton LM, Gardner CO: Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 2001; 158(4): 582–6. doi:10.1176/appi.ajp.158.4.582.
11. Patten SB: Major depression epidemiology from a diathesis-stress conceptualization. BMC Psychiatry 2013; 13(1): 19. doi:10.1186/1471-244×-13-19.
12. Herbert J: Cortisol and depression: three questions for psychiatry. Psychol Med 2013; 43(3): 449–69. doi:10.1017/S0033291712000955.
13. Knorr U, Vinberg M, Kessing LV, Wetterslev J: Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. Psychoneuroendocrinology 2010; 35(9): 1275–86. doi:10.1016/j.psyneuen.2010.04.001.
14. Burke HM, Davis MC, Otte C, Mohr DC: Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 2005; 30(9): 846–56. doi:10.1016/j.psyneuen.2005.02.010.

15. McHenry J, Carrier N, Hull E, Kabbaj M: Sex differences in anxiety and depression: role of testosterone. Front Neuroendocrinol 2014; 35 (1): 42–57. doi:10.1016/j.yfrne.2013.09.001.
16. Amiaz R, Seidman SN: Testosterone and depression in men. Curr Opin Endocrinol, Diabetes Obes 2008; 15(3): 278–83. doi:10.1097/MED .0b013e3282fc27eb.
17. Shores MM, Moceri VM, Gruenewald DA, Brodkin KI, Matsumoto AM, Kivlahan DR: Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men in a geriatric rehabilitation unit. J Am Geriatr Soc 2004; 52(12): 2077–2081. doi:10.1111/j.1532-5415.2004.52562.x.
18. Joshi D, van Schoor NM, de Ronde W, et al: Low free testosterone levels are associated with prevalence and incidence of depressive symptoms in older men. Clin Endocrinol (Oxf) 2010; 72(2): 232–40. doi:10. 1111/j.1365-2265.2009.03641.x.
19. Schweiger U, Deuschle M, Weber B, et al: Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. Psychosom Med 1999; 61(3): 292–6. doi:10.1097/00006842-199905000-00007.
20. Almeida OP, Yeap BB, Hankey GJ, Jamrozik K, Flicker L: Low free testosterone concentration as a potentially treatable cause of depressive symptoms in older men. Arch Gen Psychiatry 2008; 65(3): 283–9. doi:10.1001/archgenpsychiatry.2007.33.
21. Oitzl MS, Champagne DL, van der Veen R, de Kloet ER: Brain development under stress: hypotheses of glucocorticoid actions revisited. Neurosci Biobehav Rev 2010; 34(6): 853–66. doi:10.1016/j.neubiorev. 2009.07.006.
22. McEwen BS, Eiland L, Hunter RG, Miller MM: Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology 2012; 62(1): 3–12. doi:10.1016/j.neuropharm.2011.07.014.
23. Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC: The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. NeuroImage 2009; 47(3): 864–71. doi:10.1016/j .neuroimage.2009.05.074.
24. Mehta PH, Josephs RA: Testosterone change after losing predicts the decision to compete again. Horm Behav 2006; 50(5): 684–92. doi:10. 1016/j.yhbeh.2006.07.001.
25. Josephs RA, Sellers JG, Newman ML, Mehta PH: The mismatch effect: when testosterone and status are at odds. J Pers Soc Psychol 2006; 90 (6): 999–1013. doi:10.1037/0022-3514.90.6.999.
26. Josephs RA, Cobb AR, Lancaster CL, Lee H-J, Telch MJ: Dual-hormone stress reactivity predicts downstream war-zone stress-evoked PTSD. Psychoneuroendocrinology 2017; 78: 76–84. doi:10.1016/j .psyneuen.2017.01.013.
27. Viau V: Functional cross-talk between the hypothalamic-pituitary-gonadal and -adrenal axes. J Neuroendocrinol 2002; 14(6): 506–13. doi:10.1046/j.1365-2826.2002.00798.x.
28. Disner SG, Beevers CG, Lee H-J, Ferrell RE, Hariri AR, Telch MJ: War zone stress interacts with the 5-HTTLPR polymorphism to predict the development of sustained attention for negative emotion stimuli in soldiers returning from Iraq. Clin Psychol Sci 2013; 1(4): 413–25. doi:10.1177/2167702613485564.
29. Telch MJ, Beevers CG, Rosenfield D, et al: 5-HTTLPR genotype potentiates the effects of war zone stressors on the emergence of PTSD, depressive and anxiety symptoms in soldiers deployed to iraq. World Psychiatry 2015; 14(2): 198–206. doi:10.1002/wps.20215.
30. Perna G, Gabriele A, Caldirola D, Bellodi L: Hypersensitivity to inhalation of carbon dioxide and panic attacks. Psychiatry Res 1995; 57(3): 267–73. doi:10.1016/0165-1781(95)02723-A.
31. Telch MJ, Harrington PJ, Smits JAJ, Powers MB: Unexpected arousal, anxiety sensitivity, and their interaction on CO_2-induced panic: further evidence for the context-sensitivity vulnerability model. J Anxiety Disord 2011; 25(5): 645–53. doi:10.1016/j.janxdis.2011.02.005.
32. Harrington PJ, Schmidt NB, Telch MJ: Prospective evaluation of panic potentiation following 35% CO2 challenge in nonclinical subjects. Am J Psychiatry 1996; 153(6): 823–5. doi:10.1176/ajp.153.6.823.
33. Schmidt NB, Maner JK, Zvolensky MJ: Reactivity to challenge with carbon dioxide as a prospective predictor of panic attacks. Psychiatry Res 2007; 151(1–2): 173–6. doi:10.1016/j.psychres.2006.11.006.
34. Telch MJ, Smits JAJ, Brown M, et al: Effects of threat context and cardiac sensitivity on fear responding to a 35% CO_2 challenge: a test of the context-sensitivity panic vulnerability model. J Behav Ther Exp Psychiatry 2010; 41(4): 365–72. doi:10.1016/j.jbtep.2010.03.008.
35. Amanatkar HR, Chibnall JT, Seo B-W, Manepalli JN, Grossberg GT: Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. Ann Clin Psychiatry 2014; 26(1): 19–32.
36. Morris MC, Rao U, Garber J: Cortisol responses to psychosocial stress predict depression trajectories: social-evaluative threat and prior depressive episodes as moderators. J Affective Disord 2012; 143(1–3): 223–30. doi:10.1016/j.jad.2012.05.059.
37. Roozendaal B, Okuda S, de Quervain DJF, McGaugh JL: Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. Neuroscience 2006; 138(3): 901–10. doi:10. 1016/j.neuroscience.2005.07.049.
38. Macoveanu J, Henningsson S, Pinborg A, et al: Sex-steroid hormone manipulation reduces brain response to reward. Neuropsychopharmacology 2016; 41(4): 1057–65. doi:10.1038/npp.2015.236.
39. First MB, Spitzer RL, Gibbon M, Williams JBW: Structured Clinical Interview for DSM-IV® Axis I Disorders (SCID-I), Clinician Version.. New York, NY, American Psychiatric Pub, 2012doi:10.1002/cpp.693/full.
40. Radloff LS: The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1(3): 385–401. doi:10.1177/014662167700100306.
41. Lee H-J, Goudarzi K, Baldwin B, Rosenfield D, Telch MJ: The combat experience log: a web-based system for the in theater assessment of war zone stress. J Anxiety Disord 2011; 25(6): 794–800. doi:10.1016/j. janxdis.2011.03.018.
42. King LA, King DW, Vogt DS, Knight J, Samper RE: Deployment risk and resilience inventory: a collection of measures for studying deployment-related experiences of military personnel and veterans. Mil Psychol 2006; 18(2): 89–120. doi:10.1207/s15327876mp1802_1.
43. Andresen EM, Malmgren JA, Carter WB, Patrick DL: Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 1994; 10(2): 77–84.
44. Irwin M, Artin KH, Oxman MN: Screening for depression in the older adult: Criterion Validity of the 10-Item Center for Epidemiological Studies Depression Scale (CES-D). Arch Intern Med 1999; 159(15): 1701–4. doi:10.1001/archinte.159.15.1701.
45. Zhang W, O'Brien N, Forrest JI, et al: Validating a shortened depression scale (10 item CES-D) among HIV-positive people in British Columbia, Canada. PLoS One 2012; 7(7): e40793. doi:10.1371/journal. pone.0040793.
46. Kenward MG, Roger JH: Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53(3): 983. doi:10. 2307/2533558.
47. Fitzmaurice GM, Laird NM, Ware JH: Applied Longitudinal Analysis, 2nd ed, Hoboken, NJ, John Wiley & Sons, 2011doi:10. 1111/biom.12572.
48. Hoffman L, Stawski RS: Persons as contexts: evaluating between-person and within-person effects in longitudinal analysis. Res Hum Dev 2009; 6(2–3): 97–120. doi:10.1080/15427600902911189.
49. Aiken LS, West SG, Reno RR: Multiple Regression: Testing and Interpreting Interactions.. Thousand Oaks, CA, SAGE Publications, Inc, 1991.
50. Telch MJ, Rosenfield D, Lee H-J, Pai A: Emotional reactivity to a single inhalation of 35% carbon dioxide and its association with later symptoms of posttraumatic stress disorder and anxiety in soldiers deployed to Iraq. Arch Gen Psychiatry 2012; 69(11): 1161–8. doi:10. 1001/archgenpsychiatry.2012.8.

51. Adlercreutz H, Härkönen M, Kuoppasalmi K, Kosunen K, Näveri H, Rehunen S: Physical activity and hormones 1. Phys Act Coron Heart Dis 1976; 18(0): 144–57. doi:10.1159/000399520.
52. Tegelman R, Carlström K, Pousette Å: Hormone levels in male ice hockey players during a 26-hour cup tournament. Int J Androl 1988; 11 (5): 361–8. doi:10.1111/j.1365-2605.1988.tb01009.x.
53. Kumar RC, Thakur MK: Androgen receptor mRNA is inversely regulated by testosterone and estradiol in adult mouse brain. Neurobiol Aging 2004; 25(7): 925–33. doi:10.1016/j.neurobiolaging.2003.10.011.
54. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS: Hippocampal volume reduction in major depression. AJP 2000; 157(1): 115–7.
55. Santarelli L, Saxe M, Gross C, et al: Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003; 301(5634): 805–9. doi:10.1126/science.1083328.
56. Spritzer MD, Galea LAM: Testosterone and dihydrotestosterone, but not estradiol, enhance survival of new hippocampal neurons in adult male rats. Dev Neurobiol 2007; 67(10): 1321–33. doi:10.1002/dneu.20457.
57. Carrier N, Kabbaj M: Extracellular signal-regulated kinase 2 signaling in the hippocampal dentate gyrus mediates the antidepressant effects of testosterone. Biol Psychiatry 2012; 71(7): 642–51. doi:10.1016/j.biopsych .2011.11.028.
58. Hamson DK, Wainwright SR, Taylor JR, Jones BA, Watson NV, Galea LAM: Androgens increase survival of adult-born neurons in the dentate gyrus by an androgen receptor-dependent mechanism in male rats. Endocrinology 2013; 154(9): 3294–304. doi:10.1210/en.2013-1129.
59. Spritzer MD, Ibler E, Inglis W, Curtis MG: Testosterone and social isolation influence adult neurogenesis in the dentate gyrus of male rats. Neuroscience 2011; 195: 180–90. doi:10.1016/j.neuroscience.2011.08.034.
60. Brännvall K, Bogdanovic N, Korhonen L, Lindholm D: 19-Nortestosterone influences neural stem cell proliferation and neurogenesis in the rat brain. Eur J Neurosci 2005; 21(4): 871–8. doi:10.1111/j.1460-9568.2005.03942.x.
61. Bockting CLH, Lok A, Visser I, et al: Lower cortisol levels predict recurrence in remitted patients with recurrent depression: a 5.5 year prospective study. Psychiatry Res 2012; 200(2–3): 281–7. doi:10.1016/j. psychres.2012.03.044.