Research Article

BIOLOGICAL AND SYMPTOM CHANGES IN POSTTRAUMATIC STRESS DISORDER TREATMENT: A RANDOMIZED CLINICAL TRIAL

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Background: *Understanding cognitive and biological mechanisms of PTSD treatment can help refine treatments and increase rates of response.* **Methods:** *Thirty-six veterans with PTSD were randomly assigned to receive Prolonged exposure therapy (PE) or Present-Centered therapy (PCT). We examined symptoms, trauma-related cognitions, and two indices of HPA axis function (cortisol awakening response and cortisol response to a script-driven imagery task).* **Results:** *Thirty veterans started treatment and 26 completed. PE resulted in significantly more symptom reduction than PCT (P = .008). High treatment responders collapsed across treatments showed nominally higher cortisol levels measured at pretreatment 30 min after trauma script exposure compared to low responders (P = .08). At midtreatment, high treatment responders showed higher cortisol levels throughout the imagery task (Ps = .03–.04). There were no differences between high and low treatment responders at posttreatment. Thoughts of incompetence (F (1.6, 35.8) = 16.8, P = .000) and a dangerous world (F (1.3, 29.9) = 8.2, P = .004) significantly improved over time in high treatment responders but showed no change in low responders. Script-associated cortisol response prior to treatment and reductions in thoughts of incompetence accounted for 83% of the variance in reductions in PTSD severity with PE.* **Conclusions:** *Both increased cortisol response to personal trauma script prior to PTSD therapy and reductions in cognitive symptoms of PTSD were significantly and uniquely related to reductions in the core symptoms of PTSD in PE. However, contrary to our hypotheses, cortisol measures were not related to cognitive changes. Depression and Anxiety 32:204–212, 2015.* *© 2014 Wiley Periodicals, Inc.*

Key words: *PTSD; cortisol; treatment; exposure therapy; cognitive behavioral therapy; veteran*

Mechanistic research examining the biological and psychological factors involved in effective PTSD treatment is a critical area of developing research. Understanding these mechanisms can help to refine treatments, improve efficacy and efficiency, and increase rates of response. Among the most studied biological systems involved in PTSD is the hypothalamic–pituitary–adrenal (HPA) axis with significant focus on cortisol.

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Patients with PTSD have been consistently shown to have HPA axis abnormalities, primarily enhanced glucocorticoid receptor sensitivity leading to enhanced negative feedback and, less consistently, hypocortisolemia[1–3] and flattened diurnal cortisol rhythms.[4] There is evidence that glucocorticoids can influence the course of illness in PTSD. However, it remains unclear as to whether HPA axis dysregulation is an etiologic/pathophysiologic factor in PTSD, a biomarker of trait vulnerability, or an active agent shaping illness manifestation and perhaps recovery by promoting plasticity of specific brain circuits.

Although Prolonged Exposure therapy (PE) is a highly effective treatment[5], many patients drop out of PE or do not remit from PTSD,[6] suggesting that greater understanding of the processes involved could direct us toward better outcomes. The components of PE include exposure and emotional processing. Repeated exposures to the memory itself and cues in life (imaginal and in vivo exposure) lead to extinction/desensitization of emotional responses possibly through inhibitory learning. Emotional processing occurs as a result of these exposures and changes in cognitions, such as increasing sense of self-competence and self-control over negative affect and emotional difficulty (i.e., "I can handle bad things that happen") and enhancing the experience of social support (i.e., "other people think I am a good person").[7–9]

Research supports that trauma survivors who have lower cortisol in the acute aftermath of trauma exposure may be at a higher risk of PTSD at long-term followup.[10,11]. This effect may be moderated by prior trauma exposure, and preliminary studies with cortisol administration in the acute period following trauma suggest reduced PTSD rates in those receiving cortisol compared to those who received placebo.[10–12] These data suggest that adequate levels of cortisol in the aftermath of trauma exposure may facilitate recovery, and that cortisol levels may predict or even influence outcomes. If cortisol levels or stress reactivity at entry into treatment can similarly shape treatment outcomes, efforts to enhance levels or reactivity in conjunction with exposure therapy might further improve PE efficacy.

Several studies have shown that administration of cortisol prior to exposure exercises has resulted in significantly larger reductions in phobic avoidance and less increased skin conductance on exposure to phobic situations than placebo.[13,14] Consistent with these findings, Bentz et al.[15] proposed that glucocorticoids may enhance inhibitory learning, or specifically enhance the consolidation of nonfear responding in feared situations and inhibit retrieval of aversive learning. Altering exposure procedures to tap into processes that enhance inhibitory learning and/or recall, not simply tolerating distress, may enhance treatment outcome; and cortisol may be a salient "player" in these processes. Few studies have examined endogenous cortisol secretion or reactivity over a full course of treatment in PTSD patients.

We know that the HPA axis is highly reactive to novelty and habituates readily to repeated exposure.[16] This system is specifically sensitive to social support and to cognitive sets associated with sense of competence, control, and mastery.[16–18] It is possible that HPA axis dysregulation is tightly tied to symptom manifestations in PTSD and that PE may be effective partially because it addresses phenomena that are "salient" to the HPA axis. Activity within the HPA axis may be able to predict treatment response, may be a marker of successful recovery, or may actively influence emotional/cognitive processing in ways that influence recovery.

We studied the effects of PTSD treatment on PTSD severity among veterans randomly assigned to PE or an active comparator (Present-centered Therapy [PCT]), examining two indices of HPA axis function (cortisol awakening response [CAR] and cortisol response to trauma cues [using script-driven imagery]). CAR is a readily accessible and commonly used HPA axis measure. Alterations in CAR are associated with perceived stress,[19,20] and with both PTSD[21] and depressive symptoms.[22] Script-driven imagery[23] taps into trauma-related reactivity and has been shown to elevate plasma cortisol levels in combat veterans with PTSD.[24,25] We expected greater symptom and cognition improvement in PE relative to PCT and hypothesized that higher CAR and higher cortisol response to trauma scripts (prior to treatment) would be associated with better treatment responses across treatments. We predicted that high treatment responders compared to low responders would show higher CAR and lower cortisol response at the end of treatment. Since we expected potential differences in magnitude of relationship of factors by treatment, we examined within each treatment changes in trauma-related cognitions and predicted that reductions in negative thoughts about the self and world would be linked to changes in HPA measures and to symptom change.

MATERIALS AND METHODS

Thirty-six military veterans with significant PTSD (CAPS $\geq$ 50) and reported impairment of at least 3 months duration who presented to the VAAAHS PTSD Clinical Team were consented. Informed consent was obtained following explanation of all procedures. Assessment included the Mini International Neuropsychiatric Interview (MINI[26]), and the Clinician-administered PTSD Scale (CAPS[27]). Evaluators were blind to veteran assignment. To enhance generalizability, exclusion criteria were minimized and included only contraindications for PTSD treatment and factors that would interfere with the mechanisms under study. Exclusion criteria were the following: (1) level of self-harm risk that requires immediate, focused intervention; (2) unmanaged psychosis or bipolar disorder; (3) alcohol or substance dependence in the past 3 months; (4) working night-shifts; (5) changes to psychoactive medications in the past 4 weeks; or (6) taking medication that makes HPA axis measures difficult to interpret. Veterans were randomly assigned to receive 10 to 12, 80-min sessions of PE or PCT. In session 10, all veterans were assessed using the Posttraumatic Diagnostic Scale[28] and those who scored 10 or higher continued for 12 total sessions. The protocol was approved by the VA Ann

Arbor Healthcare System Human Subjects Committee and complies with the Code of Ethics of the World Medical Association.

Assessments occurred at pre-, mid-, and posttreatment. Each assessment included evaluation of symptoms and biological factors. This report focuses on HPA measures and primary symptom outcomes. Prior to the first major assessment, veterans attended an acclimation and interview visit in order to reduce novelty response to the laboratory environment, create 1-min personal neutral and trauma scripts in accordance with a standardized script presentation paradigm,[1,23] and introduce the salivary CAR collection.

On the morning of each assessment, veterans used salivettes to collect saliva samples at awakening and 30 and 45 min post awakening and brought samples to the laboratory that day. In the lab, they heard neutral and personal trauma scripts followed by a 45-min colored block task to prevent napping. Salivary cortisol collections occurred prior to the script and 15, 30, and 45 min following each script. Independent evaluators completed CAPS interview and veterans completed self-report forms.

INTERVENTIONS

PE. PE (see manual[29]) includes psychoeducation, exposure to trauma memories (imaginal exposure), in vivo exposure to trauma-related avoided situations (in vivo exposure), and emotional processing. PE has extensive support for its efficacy with combat veteran and other trauma populations.[5,30]

PCT. PCT followed the Shea manual.[31] PCT matched PE for number and length of sessions. The first two sessions provide psychoeducation about PTSD and the remaining sessions focused on discussion of current experience of PTSD symptoms and coping. The first author served as the only study therapist.

OUTCOME MEASURES

CAPS. CAPS[27] is a standard interview for PTSD severity. Current PTSD was assessed in relation to the war-zone trauma that was currently most upsetting. For PTSD diagnosis, a symptom was rated as present if the sum of frequency and severity was 4.[32] The CAPS has excellent psychometrics. Clinically significant reduction in PTSD was defined as reduction in total CAPS of at least 10 points compared to baseline.[31] For responder status, a more conservative measure of response was used to better differentiate the groups for detection of biological differences. We required a 50% reduction in CAPS score from pre- to posttreatment to be considered a high responder. Average number of sessions did not differ between responders ($M = 10.3$, $SD = 1.9$) and nonresponders ($M = 10.8$, $SD = 2.5$; F (1, 24) = 0.3, ns).

CAR. CAR measures HPA response axis upon awakening. Saliva was collected using salivettes placed in his/her mouth for 30–60 s for each collection. Veterans were instructed to refrain from eating, drinking, brushing their teeth, or smoking for at least an hour before sampling. Cortisol was assayed using the Diagnostic Products Corporation (DPC) Coat-a-Count cortisol radioimmunoassay (RIA; Los Angeles, CA) kit. This 125I RIA method has an intra-assay and inter-variability of <5%. CAR was calculated as area under the curve (AUC) produced by the samples taken at awakening, 30 and 45 min after awakening.

Cortisol Response to Script-Driven Imagery. Cortisol response to script-driven imagery is a measure of trauma-specific stress reactivity. Cortisol level for each of the assays collected during script-driven imagery was examined. In addition, for total cortisol response we used the area under the curve above preexposure baseline.

Posttraumatic Cognitions Inventory (PTCI). PTCI[33] has 36 items assessing negative thoughts about the self, negative thoughts about the world, and self-blame. Only the negative thoughts about the self and world scales are presented here. The scale has good psychometrics.[8]

ANALYTIC PLAN

Our study focused on biological factors related to treatment response, therefore only subjects who received an active dose of therapy (at least seven sessions and mid- or posttreatment assessment) were included in the final analyses of treatment associated mechanisms of change. Given the small sample size and hypothesis directed tests, cortisol levels were examined with planned independent *t*-tests as comparisons of PE versus PCT and low and high treatment responders within each assay and time point. Separate repeated measures ANOVAs with Greenhouse–Geisser corrections and post hoc *t*-tests examined the impact of treatment (PE vs. PCT) on PTSD severity. A similar series of ANOVAs with follow-up *t*-tests were conducted comparing high and low treatment responders on cognitions. In addition, standardized residuals of all of the symptom and mechanisms measures were calculated to examine magnitude of change in each variable while controlling for the multiple assessments.[34] Standardized residuals of these measures were correlated to examine whether changes in cortisol response to scripts, CAR, and cognitions were related to symptom change. A series of regression analyses were conducted within PE and PCT to examine the relationships between these change measures and change in PTSD.

RESULTS

STUDY POPULATION

Thirty-six veterans were consented (PE, $n = 18$; PCT, $n = 18$; see CONSORT Flowchart and Checklist). Six of these veterans did not return for any study visit and no data is available. Twenty-six veterans completed treatment (PE, $n = 11$, PCT, $n = 15$; 87% retention). Table 1 presents sample demographics.

EFFECTS OF TREATMENT

Clinically significant reductions (>10-point reduction in CAPS) were seen in 91% of PE and 60% of PCT patients. Examining conservatively defined high- and low-responder groups, 64% of PE and 33% of PCT patients were high responders. PE resulted in significantly more symptom reduction than PCT, though both treatment groups demonstrated significant symptom reduction at posttreatment (Table 2). Trauma-related negative cognitions (PTCI) showed significant reductions over the course of treatment with no differences between treatment groups (pretreatment data are missing for one veteran, $n = 25$).

A series of planned *t*-tests comparing PE and PCT revealed no group difference in CAR at pre ($t\,(24) = .03$, ns) or midtreatment ($t\,(17) = -1.23$, ns). However, at posttreatment, veterans who received PE showed significantly higher CAR compared to those who received PCT ($t\,(15) = -3.4$, $P = .004$, $d = 1.7$). A series of planned *t*-tests comparing PE and PCT in cortisol level and response during script-driven imagery revealed no significant differences between groups.

TABLE 1. Sample demographics

Variable	Total ($N = 36$)	High responders ($n = 12$)	Low responders ($n = 14$)
Age			
M (*SD*)	31.9 (7.6)	31.9 (7.3)	31.36 (7.0)
Gender, *n*			
Male	33	10	14
Female	3	2	0
Race, *n* (%)			
Black	5 (13.9)	1	4
White	30 (83.3)	11	9
Other	1 (2.8)	0	1
Relationship, *n* (%)			
Married	16 (44.4)	4 (33.3)	9 (64.3)
Remarried	4 (11.1)	1 (8.3)	1 (7.1)
Divorced/separated	8 (22.3)	4 (33.3)	1 (7.1)
Never married	5 (13.9)	2 (16.7)	2 (14.3)
Missing	3 (8.3)	1 (8.3)	1 (7.1)
Deployment, *n* (%)			
Afghanistan	8 (22.2)	3 (25.0)	4 (28.6)
Iraq	31 (86.1)	10 (83.3)	11 (78.6)
Service connection, *n* (%)			
PTSD	5 (13.9)	1 (8.3)	3 (21.4)
Medical	10 (27.8)	2 (16.7)	5 (35.7)
Comorbid diagnoses, *n* (%)			
Major depressive episode	17 (47.2)	8 (66.7)*	2 (14.3)*
Panic disorder	5 (13.9)	1 (7.1)	3 (25.0)
Agoraphobia	3 (8.3)	0	2 (16.7)
Social phobia	3 (8.3)	0	2 (16.7)
Alcohol abuse	2 (5.6)	2 (14.3)	0
Generalized anxiety disorder	2 (5.6)	1 (7.1)	0

*High and low responders differ (χ^2 (1, $N = 26$) = 7.5, $P = .009$).

RESPONDER ANALYSES

A series of planned *t*-tests were conducted comparing high and low treatment responders on cortisol levels during the script-driven imagery paradigm within each assessment. These showed that at pretreatment, high treatment responders showed a trend toward increased cortisol level at 30 min post trauma script when compared to low responders (t (24) = −1.8, $P = .08$ [see Fig. 1A]). At midtreatment, high treatment responders showed higher cortisol levels throughout the imagery task, with significant elevations as compared to low responders at initiation of the trauma script and 15, 30, and 45 min later (t (22) = −2.4, $P = .03$; 15 min, t (22) = −2.3, $P = .03$; 30 min, t (22) = −2.6, $P = .02$; 45 min, t (22) = −2.2, $P = .04$ [see Fig. 1B]). At posttreatment, no differences between high and low treatment responders were detected in cortisol response to the trauma script task and no difference in levels during the task (see Fig. 1C). There were no differences between high and low treatment responders in CAR at any time point.

High and low responders differed significantly in cognitive changes (PTCI) over the course of treatment. Thoughts of incompetence to handle negative affect and thoughts of a generally dangerous world significantly improved over time in high responders but showed no change in low responders (see Table 2).

TREATMENT CHANGE IN SYMPTOMS, COGNITIONS, AND CORTISOL

Prior to treatment, higher CAPS PTSD symptom severity was associated with higher cortisol total response to the trauma script task (r (26) = .39, $P = .05$) and with lower CAR (r (31) = −.40, $P = .03$). These relationships were lost at mid- and posttreatment. Higher cortisol responses to the trauma script exposure prior to treatment significantly predicted enhanced treatment symptom improvement (r (26) = −.40, $P < .05$); and treatment response was significantly associated with reductions in negative thoughts about the self (r (21) = .70, $P = .001$). Other cortisol measures did not predict symptom change.

To further examine the role of outcome predictors within each treatment, two separate series of multiple regressions (PE and PCT) investigated relationships among cognitive changes, pretreatment cortisol measures, and symptom change (see Table 3). Each treatment was examined in three models including just the factor by itself (script-associated cortisol response, CAR, and change in negative thoughts about the self) predicting symptom change. In PCT, treatment change was predicted only by change in negative thoughts about the self. As such, no additional models were conducted. In PE, all three factors showed significant relationship to symptom change. Thus, we analyzed the two cortisol measures together to see their contributions to symptom change. This analysis suggested a suppression effect where both factors were nonsignificant predictors when included together. To clarify, we then examined each cortisol measure combined with change in negative thoughts about the self predicting symptom change, to isolate a unique cortisol effect while controlling for important cognitions. Script-associated cortisol response prior to treatment and reductions in negative thoughts about the self over treatment each made significant, unique, and large contributions to prediction of PTSD symptom change. The final model accounted for 83% of the variance in PTSD symptom change, with both cognitive change (43% unique variance) and cortisol levels (22% unique variance) contributing significantly to outcome variance. When CAR was combined in a multiple regression with change in negative thoughts about the self, cognitive change predicted improvement but CAR did not.

DISCUSSION

The current study is unique in its examination of changes in HPA axis function over PTSD treatment and inclusion of trauma-related cognitions and PTSD symptoms. High treatment responders showed a trend toward higher cortisol level to their personal trauma script at pretreatment. Further, in regression analyses predicting

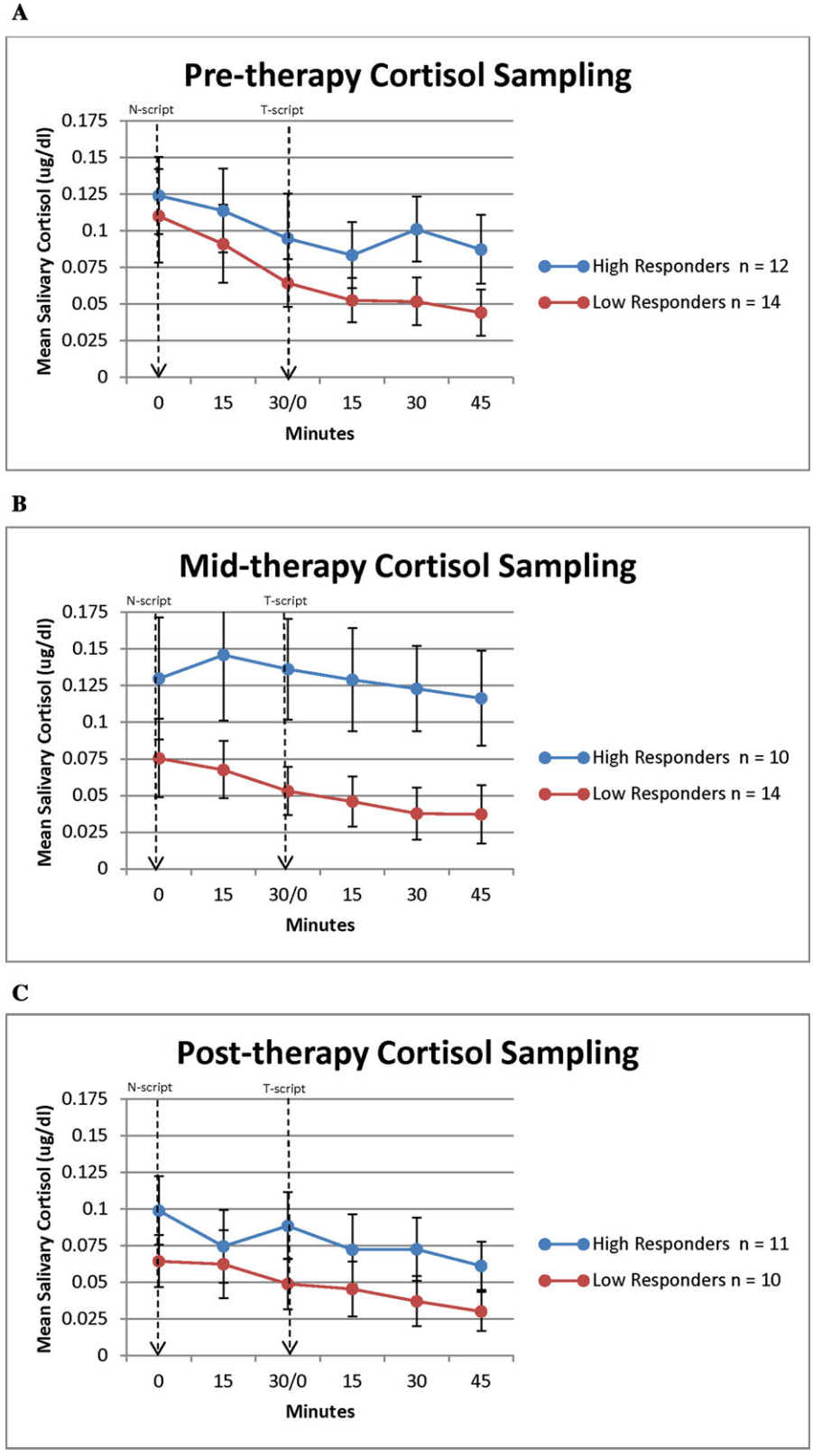

Figure 1. (A) Cortisol response to trauma scripts by posttreatment responder status at pretreatment. (B) Cortisol response to trauma scripts by posttreatment responder status at midtreatment. (C) Cortisol response to trauma scripts by posttreatment responder status at posttreatment.

TABLE 2. Means (and *SD*) for completers and responders samples by time point and condition

	Assessment					
	Pre		Mid		Post	
Condition	PE	PCT	PE	PCT	PE	PCT
CAPS						
CAPS Total score*						
M (*SD*)	79.2 (12.1)	77.4 (12.1)	50.5 (20.0)	65.5 (20.0)	30.0 (18.4)	53.6 (28.7)
n	11	15	11	15	11	15
Posttraumatic Cognitions Inventory						
PTCI Total**						
M (*SD*)	121.9 (27.2)	117.4 (32.3)	106.8 (32.9)	110.2 (35.0)	91.3 (41.9)	97.1 (45.6)
n	11	14	11	14	11	14
PTCI Self[a]						
M (*SD*)	3.7 (1.0)	3.5 (1.2)	3.0 (1.2)	3.3 (1.2)	2.5 (1.4)	2.8 (1.4)
n	11	14	11	14	11	14
PTCI World[b]						
M (*SD*)	5.3 (1.0)	4.9 (1.2)	5.1 (1.4)	4.6 (1.3)	4.6 (2.1)	4.1 (1.8)
n	11	14	11	14	11	14
	Pre		Mid		Post	
Treatment response	High	Low	High	Low	High	Low
PTCI Total†						
M (*SD*)	118.3 (35.0)	120.4 (25.1)	89.1 (28.5)	126.8 (27.3)	61.0 (24.4)	125.5 (31.9)
n	12	13	12	13	12	13
PTCI Self††						
M (*SD*)	3.6 (1.3)	3.5 (0.9)	2.5 (1.0)	3.8 (1.0)	1.5 (0.5)	3.7 (1.1)
n	12	13	12	13	12	13
PTCI World†††						
M (*SD*)	4.9 (1.7)	5.1 (0.9)	4.4 (1.5)	5.2 (1.0)	3.4 (2.2)	5.1 (1.2)
n	12	13	12	13	12	13

Note: Intent to treat analysis with CAPS, Time × Treatment, $F(2, 56) = 2.6$, $P = .08$.

*CAPS, Time × Treatment, $F(1.5, 36.4) = 6.4$, $P = .008$. Follow-up *t*-tests, midtreatment ($t(24) = 1.9$, $P = .07$, $d = .75$) and posttreatment ($t(24) = 2.4$, $P = .03$, $d = .98$). Pre to post Cohen's *d*, PE = 3.16; PCT = 1.08.

**PTCI Total, Time main effect, $F(1.3, 29.0) = 6.5$, $P = .01$, $d = 0.67$.

[a]PTCI, negative thoughts about the self, Time main effect, $F(1.3, 30.5) = 6.4$, $P = .01$, $d = .79$.

[b]PTCI, negative thoughts about world, Time main effect, $F(1.2, 28.0) = 5.8$, $P = .02$, $d = .45$.

†PTCI, Total, Time × responder, $F(1.4, 33.3) = 16.8$, $P = .000$. Pre to post Cohen's *d*, high = 1.9; low = −0.18. Follow-up *t*-tests, pre = ns; mid, $t(24) = 3.1$, $P = .004$, $d = 1.3$; post, $t(24) = 5.4$, $P = .000$, $d = 2.27$.

††PTCI, negative thoughts about the self, Time × Responder, $F(1.6, 35.8) = 16.8$, $P = .000$. Pre to Post Cohen's *d*, high = 2.13; low = −0.30. Follow-up *t*-tests, pre = ns; mid, $t(24) = 3.0$, $P = .006$, $d = 1.3$; post, $t(24) = 6.0$, $P = .000$, $d = 2.49$.

†††PTCI, negative thoughts about the world, Time × Responder, $F(1.3, 29.9) = 8.2$, $P = .004$. Pre to post Cohen's *d*, high = 1.9; low = 0.17.

reductions in PTSD severity with PE, pretreatment cortisol response to personal trauma script predicted 40% of the variance in change in PTSD severity. Although change in negative thoughts about the self was a significant predictor of change in PTSD with both treatments, this cortisol response to trauma script was specific in predicting PTSD change in PE only. As such, increased self-efficacy is related to treatment response across these different treatment models, but the HPA axis was specifically relevant to response in PE. Thus, our data support the idea that during PE activation of cortisol response may open a window of plasticity that then allows inhibitory learning and changes in trauma-related cognitions to occur resulting in reductions in PTSD.

Consistent with previous studies suggesting that trauma survivors who are able to mount a cortisol response may be more likely to recover (either naturally or with treatment), our results illustrate how this may occur. In high treatment responders, at pretreatment, we see initial cortisol level elevation at 30 min post script, and in contrast, no cortisol response in the low-responder group. This finding is apparent despite the brief nature of the trauma cue (1-min audio script). At midtreatment, this separation between high and low responders becomes more pronounced with groups separating in their cortisol levels throughout the research session. One can speculate that this separation is potentially a function of the degree of emotional engagement in the imaginal and in vivo exposures in therapy. As they are more engaged in the work of therapy, their HPA axis is more activated. However, this is preliminary given the small sample size in the current study. Finally, at

TABLE 3. Prediction of change in CAPS from cognitions, script-driven cortisol, and CAR in PCT and PE

Model and variable	*R*	*β*	*SE*	*F/t*	*P*
PCT					
Model 1 ($n = 14$)	0.10	–	–	0.14	ns
SA-Cort	–	−0.10	195.8	−0.37	ns
Model 2 ($n = 14$)	0.28	–	–	5.56	ns
CAR	–	0.28	15.4	1.05	ns
Model 3 ($n = 12$)	0.70	–	–	10.26	.01
ΔSelf	–	−0.70	5.56	−3.20	.01
PE					
Model 1 ($n = 10$)	0.63	–	–	6.00	.04
SA-Cort	–	0.63	75.54	2.45	.04
Model 2 ($n = 10$)	0.64	–	–	6.30	.03
CAR	–	−0.64	12.02	−2.51	.03
Model 3 ($n = 7$)	0.78	–	–	9.26	.02
ΔSelf	–	−0.78	4.54	−3.04	.02
Model 4 ($n = 10$)	0.80	–	–	5.45	.03
SA-Cort	–	0.45	73.73	1.76	.12
CAR	–	−0.46	11.85	−1.83	.11
Model 5 ($n = 7$)	0.91	–	–	11.73	.01
SA-Cort	–	0.49	45.61	2.49	.05
ΔSelf	–	−0.63	3.49	−3.21	.02
Model 6 ($n = 7$)	0.81	–	–	4.64	.07
CAR	–	−0.21	15.34	−.78	ns
ΔSelf	–	−0.73	4.80	−2.71	.04

ns, any *P*-values of .15 or higher. Script-Associated Cortisol (SA-Cort).

posttreatment, again there are no differences between the groups and both groups appear to have overall minimal cortisol levels. At this point, for those veterans who have highly responded to treatment, trauma cues no longer evoke a cortisol response, whereas the low-responder group maintains the same pattern of continued low cortisol levels. If, indeed, the absence of cortisol level increase at pre and midtreatment reflects a biomarker of absence of emotional engagement, it could be important to explore whether the low treatment responders are showing a conscious avoidance and pushing away of the emotional memory content, or a less voluntary "dissociation-like" response when confronted with the memory content. On the other hand, it is possible that it represents a physiological inability to mount cortisol response during the memory task. Additional study is needed to replicate and clarify these results in a larger sample.

This observed lack of cortisol response to trauma cues may represent a preexisting risk factor for PTSD or an alteration in function that occurs posttrauma. Such a distinction has implications for how and if it can be modified with intervention. However, if it is possible to use a pretreatment script-driven imagery paradigm to identify those who are likely to become low treatment responders and use augmentation to "jump start" their cortisol response to cues while providing PTSD treatment, more patients may respond to effective treatment. Such increased effectiveness may come through higher retention as response comes more quickly or larger reductions in symptoms for previous partial responders. Indeed, in trauma-focused therapies emotional engagement with the memory has been put forward as a critical element for efficacy.[29] However, research examining this mechanism has been largely reliant on self-report of distress from the patient and results have been inconsistent. Cortisol response to the trauma script may be a biomarker of this process mechanism.

In addition, our data replicate the association between pretreatment PTSD severity and CAR and cortisol response to personal trauma script at pretreatment, validating the representativeness of our sample, and potential generalizability of our findings. Specifically, as demonstrated in other samples of trauma survivors, PTSD is related to a flattening of CAR[35] and increased responsiveness to personal trauma script.[1] Although these findings might be consistent with the notion that PTSD is associated with less pronounced HPA diurnal response, they do not suggest overall decreased HPA responsivity, as evidenced by the increased cortisol response to a trauma specific challenge task.

With regard to treatment-type analyses, both treatments showed significant reduction in PTSD symptoms from pre- to posttreatment. However, changes related to PE were significantly larger than PCT, with 91% of the PE group showing clinically significant reduction in PTSD and only 60% in the PCT condition meeting that criterion. Further, the PE group showed significantly larger CAR response at posttreatment than the PCT group. Thus, PE may impact a PTSD-related HPA axis–associated dysfunction. Recently, PTSD patients randomized to receive D-cycloserine (DCS) prior to PE evidenced a lower cortisol and startle response to a fear potentiated startle paradigm at posttreatment than those who did not get DCS,[36] also demonstrating alteration in HPA axis function with PE.

Several caveats are warranted. The current sample is small and effects may not have been detected. Our sample is composed wholly of veterans and whether these results generalize to other PTSD treatment samples is unclear. With regard to CAR, based on patient burden and study budget, we were limited to assessment of CAR on a single morning. Replication with assessment on three consecutive mornings may increase confidence in the effect.[37]

CONCLUSIONS

Specific alterations in HPA axis response to diurnal processes (CAR) and specific trauma cues are related to PTSD treatment response within PE. In addition, reductions in negative thoughts about the self and world are related to reductions in PTSD symptoms in both PE and PCT. As the neurobiological mechanisms are characterized, therapeutic techniques can be targeted and more efficiently delivered, allowing more patients access as treated cases respond in fewer sessions and allowing reduction in drop out as patient burden is reduced.

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