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Changes in Salivary Cortisol During Psychotherapy for Posttraumatic Stress Disorder:
A Pilot Study in 30 Veterans

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ABSTRACT

Background: Convergent evidence suggests that the hypothalamic-pituitary-adrenal (HPA) axis is disrupted in posttraumatic stress disorder (PTSD) and that HPA axis normalization may be associated with symptom improvement. Thus, the current study was designed to test the association between HPA axis reactivity and treatment response in psychotherapy for PTSD.

Methods: Thirty returning veterans with *DSM-IV-TR* PTSD were randomly assigned to receive 10 sessions of prolonged exposure therapy or present-centered therapy as part of a previously published randomized clinical trial (2008–2010). Treatment groups were collapsed for the current analyses. Salivary cortisol was collected 3 times during 3 therapy sessions. Cortisol reactivity was calculated by area under the curve with respect to ground. Hierarchical linear modeling was used to measure longitudinal change in salivary cortisol nested within patients and to test the effects of treatment responder status at both levels.

Results: Session number was significant in the final model, indicating linear increases in cortisol output across sessions ($\beta = 1.06$, $P = .02$). In addition, responder status significantly predicted slope of cortisol reactivity across sessions ($\beta = 1.35$, $P = .04$). Compared to high responders, low responders exhibited a 1.35 (μg/dL) mean increase in cortisol reactivity between sessions. Responder status accounted for 6% of the previously unexplained variance in cortisol reactivity.

Conclusions: As compared to high treatment responders, low treatment responders showed greater increases in salivary cortisol output over the course of treatment. These results indicate that increases in HPA axis reactivity over the course of psychotherapy may be associated with worse treatment response. Future work is needed to investigate how modulation of HPA axis reactivity may be targeted in order to optimize PTSD treatment outcomes.

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Posttraumatic stress disorder (PTSD) is a major public health challenge. Soldiers returning from Afghanistan and Iraq show rates of PTSD between 12% to 20%[1] and have significant psychological, physical, and economic burdens. While effective treatments for PTSD such as prolonged exposure therapy (PE) have been developed,[2] many veterans remain symptomatic or are unable to utilize these treatments to their full potential and continue to suffer with symptoms of PTSD.[2] Optimization of these treatments is essential if the substantial personal and social costs of PTSD are to be reduced. However, treatment optimization requires better understanding of the underlying processes implicated in treatment change in order to improve efficacy and efficiency of treatment. Specifically, understanding key biological processes involved in treatment-related change can inform treatment planning, increase efficiency and efficacy, and improve acceptability as we apply what we learn to clinical care.

Optimizing PTSD treatment to make it both more efficacious and more efficient, however, constitutes a formidable challenge. Accumulating evidence suggests that key biological mechanisms of change in PTSD treatment involve the neuroendocrine system. PTSD is associated with abnormalities in hypothalamic-pituitary-adrenal (HPA) axis activity, specifically enhanced HPA axis negative feedback[3] and attenuated cortisol awakening response.[4–6] In addition, increased HPA reactivity to traumatic cues prior to treatment predicts response to PTSD treatment, and both pretreatment reactivity and change in negative self-perceptions independently contribute to treatment outcome.[6] However, little research has examined how HPA axis function changes over the course of treatment, and no research to date has examined how HPA axis reactivity during the actual exposure treatment session is related to outcome. If cortisol levels or stress reactivity during treatment is associated with treatment outcomes, such insight may provide direction for efforts to further improve treatment efficacy.

Preliminary studies with cortisol administration in the acute period following trauma suggest that cortisol can, itself, impact recovery, with reduced PTSD rates in those receiving cortisol compared to those who received placebo,[7,8] although not in all cases.[9] Indeed, 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.[10] Consistent with these findings, Bentz et al[11] proposed that glucocorticoids may enhance inhibitory learning or specifically enhance non–fear responding in feared situations and inhibit retrieval of aversive learning. One naturalistic examination of cortisol in panic disorder found that those with higher cortisol levels during exposure therapy had the most reduction in symptoms.[12] In addition, Meuret et al[13] found that higher absolute cortisol during exposure moderated treatment outcomes. As such, altering exposure procedures to tap into

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Clinical Points

- Cortisol and function of the hypothalamic-pituitary-adrenal (HPA) axis in posttraumatic stress disorder (PTSD) are complex and highly relevant to the development and effective treatment of PTSD. Evidence is highly conflicting, and few studies have examined HPA axis measures during intervention sessions. The current study aimed to fill this gap.
- More research is needed to examine the function of the HPA axis during exposure therapy.

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. In our previous analysis of cortisol reactivity across PTSD treatment in the script-driven imagery paradigm, high responders showed increased reactivity at pretreatment and midtreatment, but no difference was found between low and high responders at posttreatment.[6]

To address this critical gap in knowledge, we examined salivary cortisol during 3 key sessions (third, sixth, and tenth) for all patients engaged in PTSD treatment as part of a randomized clinical trial (RCT) of mechanisms (see Rauch et al[6]). We analyzed salivary cortisol reactivity within therapy sessions to examine patterns of change over the course of treatment. Analyses were conducted using hierarchical linear modeling (HLM), a multilevel modeling technique that accounts for the inherent nested nature of data generated by treatment studies. In the current study, we modeled longitudinal change in salivary cortisol reactivity (level 1) nested within patients (level 2). We then tested the effects of treatment responder status at both levels. Based on our script-driven imagery results, we hypothesized that high treatment responders would show greater reduction in within-session cortisol reactivity/cortisol output over the course of treatment.

METHODS

Sample and Treatment Setting

The current analyses were conducted as part of an RCT of PTSD treatment mechanisms. For a full description of study procedures and the sample, see Rauch et al.[6] Thirty-six veterans participated in the treatment study between January 2008 and July 2010 (8% female [n = 3], 14% African American [n = 5], 83% white [n = 30], 3% other race [n = 1]). Of those 36 veterans, 30 provided at least 1 cortisol sample, enabling inclusion in the current analyses. Mean age was 32 years (standard deviation [SD] = 7.6 years). With regard to combat location, 86% served in Iraq and 22% served in Afghanistan. As reported in the primary outcome article, comorbidity was representative of the Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn population: 47% had depression (n = 17), 6% had alcohol abuse (n = 2), and 36% met criteria for another anxiety disorder at intake (n = 13). To enhance generalizability, exclusion criteria were minimized and included only contraindications for PTSD treatment and factors that would interfere with cortisol assessment. Exclusion criteria were (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. Eligible veterans reviewed consent with the first author who also served as the study therapist. Those who were interested signed consent forms and were randomly assigned to receive 80-minute sessions of PE or present-centered therapy (PCT). Treatment groups were collapsed for the current analyses. Data were collected with approval from the Institutional Review Board for the VA Ann Arbor Healthcare System, Ann Arbor, Michigan.

Measures

Clinician-Administered PTSD Scale (CAPS). The CAPS is an interview measure of PTSD severity with excellent psychometric properties.[14] Cronbach α for this sample was 0.95. We used a stringent classification of responders, such that patients were characterized as high responders only if they experienced a 50% or greater reduction in CAPS over the course of therapy. All other patients were classified as low responders.

Salivary cortisol. Salivary cortisol was collected during each of 3 therapy sessions (3, 6, and 10). These sessions were chosen because they included the first imaginal exposure (session 3), an imaginal exposure session in the middle of the protocol (session 6), and a late/last imaginal exposure session (session 10) for patients that received PE. Patients received up to 2 additional sessions (12 total) if they had not remitted from PTSD (Posttraumatic Diagnostic Scale[15]; PDS < 10); however, we chose to measure cortisol at session 10 for every patient in order to standardize the interval between cortisol measurements. All sessions were started between 12 PM and 2 PM in order to provide at least minimal control of diurnal cortisol variation. Cortisol collections occurred at the start of the session, 30 minutes into the session, and the end of the session. Saliva was collected into Salivettes via passive drool, and cortisol levels were determined by chemiluminescent enzyme immunoassay (IMMULITE) according to the manufacturer's directions (Siemens Healthcare Diagnostics Inc, Tarrytown, New York). Cortisol responsivity was calculated by area under the curve with respect to ground (AUCG).[16]

Interventions

PE[17] 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 veterans and other trauma-exposed population.[18,19] PCT[20] is an active control treatment that matches PE for number and length of sessions. The first 2 sessions provide psychoeducation about PTSD, and the remaining sessions focus on the patient's current experience of PTSD symptoms

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and coping mechanisms. One author (S.A.M.R.) served as the only study therapist.

Data Analysis

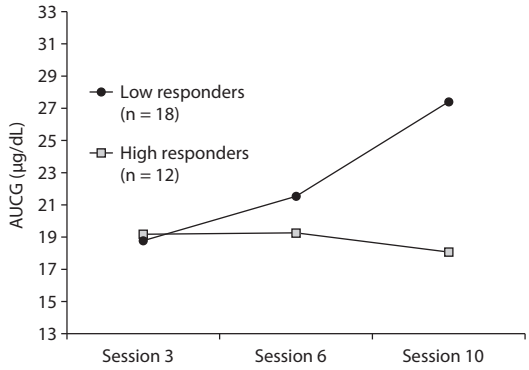
Two-level hierarchical linear modeling (HLM) was used to characterize patterns of cortisol change and to investigate the potential associations between these patterns and treatment responder status. HLM is a practical strategy for analyzing clinical data because the method does not assume fixed time points of measurement or equal numbers of observations.[21] In the current study, HLM was used to investigate longitudinal cortisol reactivity measurements (level 1) nested within patients (level 2).

We used a sequential approach to fitting the models. In step 1, an unconditional model was fitted, and intraclass correlations were calculated to assess the variance in cortisol attributable to each level of the data. Session number (ie, "session dose") was added in step 2 as a level-1, within-patient predictor. In step 3, responder status (ie, high or low responder) was added to the model as a level-2, patient-level predictor. The variances of random errors at level 1 and random effects at level 2 were estimated. Statistically significant outcomes were qualified using R^2-type effect sizes in a manner consistent with recommended guidelines.[22] Hierarchical linear modeling analyses were conducted using HLM software.[23]

Table 1. Longitudinal Cortisol Responsivity During Prolonged Exposure Therapy

Fixed effect	Coefficient	Standard Error	*t*	*P*
Intercept	18.16	3.08	5.90	<.001
Responder status	1.81	4.88	0.037	.71
Session number	1.06	0.43	2.45	.02
Session × responder	1.35	0.64	2.10	.04
Random effect		Variance Component	χ^2	*P*
Intercept, μ_0		123.86	181.79	<.001
Level 1, *r*		54.14		

Figure 1. Within-Session Cortisol Reactivity Over Treatment by Responder Status Interaction



Abbreviation: AUCG = area under the curve with respect to ground.

RESULTS

Descriptive Statistics

Thirty patients were included in the final sample. Based on a cutoff of at least 50% CAPS reduction, 12 participants were classified as high responders (high: PE = 7, PCT = 5; low: PE = 7; PCT = 11). As previously reported, PE resulted in significantly more symptom reduction than PCT, although both treatment groups demonstrated significant symptom reduction at posttreatment (pretreatment to posttreatment Cohen *d*, PE = 3.16; PCT = 1.08). With regard to retention, 87% of randomized patients who attended intake (n = 26) completed treatment. Detailed results are reported in the parent study.[6] Of the 30 participants providing saliva samples, 77% of participants (n = 23) provided saliva during at least 2 treatment sessions, and 70% of participants (n = 21) provided saliva at all 3 treatment sessions. One additional data point was dropped because only 2 of the 3 required saliva samples were collected during the treatment session. Since calculating AUC requires 3 time points, an AUC could not be calculated for this time point.

HLM Results

Models of longitudinal cortisol responsivity were based on 66 points of measurement (level 1) nested within 30 patients (level 2). The unconditional model estimated variance components for level 1 ($\sigma^2 = 57.91$) and level 2 units ($\tau = 124.87$). The value of τ was significantly different from zero ($\chi^2_{29} = 177.73$, $P < .001$), indicating the presence of patient-level effects on outcomes. The intraclass correlation (ICC) for between-patient variability was 0.68, indicating that 68% of variance in cortisol could be accounted for by factors associated with the patient (R^2-between). The remaining variance (32%) could be attributed to within-patient effects such as time in treatment or to other factors not included in the model.

In step 2, session number (session dose) was added to the model. Session dose did not significantly predict cortisol outcomes ($t_{41} = 1.15$, $P = .26$). In step 3, a main effect for treatment responder status was added to the model to explore potential associations with overall cortisol reactivity. Treatment responder status did not significantly predict overall cortisol reactivity within therapy session ($t = -0.41$, $P = .69$), and the effect of session dose remained nonsignificant. In step 4, the interaction between treatment responder status and session number was computed to test the association between responder status and cortisol change over the course of treatment. In the resulting model, the effect of session number was rendered significant ($t_{40} = 2.45$ $P = .02$; Table 1). The modeled coefficient indicated linear increases in cortisol reactivity over the course of treatment (across sessions). In addition, responder status significantly predicted slope of cortisol AUCG across sessions ($t_{40} = 2.10$, $P = .04$) but not overall cortisol reactivity, indicating that responder status was specifically related to change in cortisol over the course of treatment. Compared to high responders, low responders exhibited a mean 1.35 µg/dL (standard error = 0.64) increase in cortisol AUCG, on average, between each therapy session. Responder status accounted for 6% of the previously unexplained variance in cortisol AUCG (Figure 1).

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To address the concern that observed differences in cortisol response could be related to anticipatory anxiety instead of session content, we reran the model using only the first cortisol sample for each session. Results of this model were not significant, indicating that the observed differences were in fact related to response to the session itself.

DISCUSSION

In the current study, we tested the association between HPA axis reactivity and treatment response in veterans undergoing PTSD treatment and found that veterans who demonstrated less reduction in PTSD with treatment showed greater increases in salivary cortisol output over the course of treatment compared to those with larger reductions in PTSD. However, the absolute level of cortisol reactivity during each session across all patients was not related to magnitude of treatment response. As such, contrary to Meuret et al[13] and contrary to our hypothesis that high treatment responders would show greater reduction in reactivity, change was not related to absolute level of cortisol reactivity or to the overall system state but instead to specific increases in cortisol system response to therapy across sessions. Specifically, those veterans in the low treatment-response group showed an increase in cortisol reactivity during imaginal exposure across treatment. This pattern suggests a possible HPA–axis mediated mechanism involved in lower treatment response. These results add to a growing body of evidence elucidating the complexity of the HPA system and response and dysfunction in PTSD with several studies reporting that low cortisol during treatment is a poor prognostic factor.[12,24,25] While experimental studies clearly support the idea that pharmacologic administration of cortisol (producing very high circulating levels) enhances extinction learning in animals and humans,[26–28] how this translates to the physiological system response during therapy sessions is less clear. The current study suggests that HPA response to psychotherapy may be a dynamic process and that greater HPA response may have different implications at different points in treatment. Whereas previous research supports that having higher levels of cortisol reactivity may facilitate the therapeutic process early on in exposure therapy, our data suggest that higher levels of cortisol reactivity in the mid and late sessions are associated with less optimal response.

While differences in treatment model and study design do not allow parallel comparison across studies, a recent study[29] of a brief (4 week) mindfulness intervention for PTSD in primary care found that patients in the mindfulness intervention showed a reduction in cortisol awakening response (CAR), a general measure of HPA axis function, compared to treatment as usual. This very interesting finding contrasts somewhat to previous findings that PTSD is associated with relatively decreased CAR compared to healthy people[5] and findings that CAR shows a negative correlation with PTSD symptoms.[4,6] However, the reported decrease in CAR was not related to PTSD or other comorbid symptom change,[29] suggesting that it may not necessarily be relevant to symptom remission. In a study[30] examining cortisol response during a virtual reality trauma-potentiated startle task for patients receiving virtual reality exposure therapy randomized to D-cycloserine, alprazolam, or placebo, only patients who received D-cycloserine showed lower cortisol response to the fear-potentiated startle task over treatment. Given that research so far provides inconsistent results suggesting that biomarker predictors and biomarkers of response may differ, additional, more specific studies are warranted. Specifically, data from the same patients in our previous analyses showed that increased reactivity to specific brief trauma cues predicts better response to PE and cortisol awakening response is normalized in responders to PE.[6] However, in the current analysis, when examining biomarkers of change in treatment, increased cortisol reactivity during imaginal exposure sessions was related to low response.

Our previously published cortisol data show that veterans who had larger cortisol response to a brief, 1-minute personal trauma script prior to PTSD treatment were more likely to respond to PTSD treatment.[6] We interpreted this reactivity to trauma scripts as reflecting willingness/readiness to engage with the emotional content of the memory prior to starting treatment. Consistent with Emotional Processing Theory[31] and previous research showing that increased physiological reactivity at pretreatment predicts better outcome,[31–33] pretreatment cortisol reactivity seems to reflect this activation and engagement. Thus, an initial activation of cortisol to a brief but specific trauma trigger suggests an openness to experience emotion in high responders. However, the current study found that during the process of therapy, low treatment responders demonstrate increases in cortisol reactivity over the course of therapy compared to high treatment responders who show little change across sessions. Therefore, increased cortisol reactivity over the course of treatment may reflect or give rise to processes that are not beneficial to treatment response. Indeed, this may be an indicator of sensitization rather than extinction in these patients. While one might think that this is due to worsening of PTSD, symptom data from our sample do not support this assumption.

Providing cortisol data from within PTSD therapy sessions is a novel contribution, but limitations must be noted. First, the small sample size requires replication and extension in larger samples. In addition, the sample was all veterans and also mostly male. As such, replication in larger samples with more variable trauma types and demographics is warranted. Cortisol is easily influenced by many factors, including diurnal variations, food, smoking, etc. While we provided direction not to eat within an hour of our session or smoke prior to session, we did not have a control within therapy sessions to ensure that veterans were compliant. As such, we maintained session time between 12 PM and 2 PM but did not have other controls in place. The current analyses collapsed across 2 very different treatment types that may have differing mechanisms of efficacy. Since this study was a pilot and not powered for the comparison of responders and nonresponders across treatments, presentation of these results would not represent a valid analysis and may mislead.

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As such, we have not presented these comparisons, but examination of the effect of treatment type in a larger study that is able to examine those differences would be a critical next step. Indeed, it may be that HPA axis changes that are related to lower PTSD symptoms and better function are not specific to a given treatment type but rather to a general change that is nonspecific to treatment type. The current analyses show that differential cortisol response during imaginal exposure explains about 6% of the variance in our models. This may be a reflection of the high rates of treatment response overall in the sample but is noteworthy as we are accounting for a significant, though not large, amount of variance. Finally, our sample had high rates of comorbid depression, as is common with PTSD. Given that the influences of depression and PTSD on HPA function are complex and often opposing, examination of the influence of depression in a larger sample is also warranted. Future work is needed to investigate how modulation of HPA axis reactivity may be targeted in order to optimize PTSD treatment outcome through designs that more specifically pull apart the process of treatment change and examine HPA axis function in real time across PTSD treatments that purport different mechanisms of change.

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