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Exploring the mutual regulation between oxytocin and cortisol as a marker of resilience

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ABSTRACT

Early trauma can increase the risk for developing posttraumatic stress disorder (PTSD) in adulthood. Early trauma has also been associated with the dysregulation between the hypothalamic-pituitary-adrenal (HPA) and oxytocin systems and may influence the co-regulation between these two systems. But whether the mutual regulation of the two systems represents a sign of resilience and/or mutual dysregulation could be a sign of vulnerability to PTSD and the dissociative subtype of PTSD (PTSD-D) is unknown. The study aims to synthesize and conduct a preliminary test of a conceptual model of the mutual regulation between these two systems as a marker of resilience. We analyzed a pilot data with 22 pregnant women in 3 groups (PTSD only, PTSD-D, and trauma-exposed resilient controls) and repeated measures of plasma oxytocin and cortisol. Oxytocin and cortisol seemed reciprocal in all three groups, but both levels were relatively high in women with PTSD-D and low in those with PTSD compared with controls. This suggests that both hormones in women with PTSD-D and PTSD only are dysregulated, but not lacking in reciprocity.

Introduction

A substantial amount of research has focused on alteration in the hypothalamic-pituitary-adrenal (HPA) axis as a potential underpinning for posttraumatic stress disorder (PTSD; Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012; Meewisse, Reitsma, Vries, Gersons, & Olff, 2007). Many of the most chronic and complex cases of PTSD are those with roots in childhood maltreatment trauma. Cascade theory posited that there are three pillars of stress response dysregulated as consequences of attachment trauma in early development: cortisol, catecholamines, and oxytocin (Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Those stress response hormones might be associated with psychopathological vulnerabilities, including PTSD and other manifestations of early developmental trauma, including dissociation and the dissociative subtype of PTSD (PTSD-D; Delahanty, Nugent, Christopher, & Walsh, 2005; Olff et al., 2013; Seng et al., 2013; Simeon et al., 2007).

Oxytocin as a neuropeptide hormone, can not only regulate the smooth muscle contractility for reproductive and lactation processes, but also plays a role in attachment and social affiliation such as mother-child interaction and parenting (Feldman, 2012; Galbally, Lewis, Ijzendoorn, & Permezel, 2011; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010; Orsucci, Paoloni, Conti, Reda, & Fulcheri, 2013). Oxytocin has also received increasing attention for its role in stress regulation and related psychopathology, including PTSD. The oxytocin and HPA systems are mutually regulating (Dabrowska et al., 2011). Oxytocin can inhibit the stress-induced activity of the HPA axis to promote the return of cortisol levels to normal levels after stress is experienced (Neumann, Kromer, Toschi, & Ebner, 2000; Neumann, Torner, & Wigger, 2000; Pierrehumbert, Torrisi, Ansermet, Borghini, & Halfon, 2012). A variety of stressors could induce oxytocin secretion in both blood and brain. Brain oxytocin plays a role in the control of neuroendocrine stress responses by inhibiting the secretion of adrenocorticotropic hormone (ACTH) and thus decreasing the production and release of cortisol. Oxytocin release, oxytocin receptor expression, and oxytocin binding exist in many brain regions that are rich in glucocorticoid receptors and thus oxytocin can have an effect on the inhibition of neuroendocrine stress responses. Maltreated children have been reported to have decreased urinary oxytocin levels (Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005) and women with a history of childhood abuse showed reduced cerebrospinal fluid oxytocin concentrations (Heim et al., 2009). Childhood trauma may alter the development of the oxytocin system as well as the connectivity with other systems (Buisman-Pijlman et al., 2014). A study found increased cortisol

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reactivity in subjects with early life stress while attenuated cortisol reactivity in subjects without early life stress after oxytocin administration (Grimm et al., 2014). Early parental separation stress has been studied to decrease the suppressing effect of oxytocin on cortisol levels (Meinlschmidt & Heim, 2007). These findings suggest that oxytocin and cortisol systems may be mutually dysregulated as a consequence of traumatic stress.

There is a growing consensus that altered reactivity of the oxytocin system can contribute to enhanced vulnerability to the development of psychiatric disorders and reduced resilience to stress (Buisman-Pijlman et al., 2014; Ozbay, Fitterling, Charney, & Southwick, 2008). Mutual dysregulation between oxytocin and cortisol as a consequence of traumatic stress could contribute to individual vulnerability to the psychopathologic effects of stress (e.g., PTSD). Conversely, the mutual regulation between these two hormones may be a sign of resilience to stress (Meinlschmidt & Heim, 2007). This hypothesis has not been considered; there is not yet a theoretical basis or empirical evidence to support mutual dysregulation between these two hormones as a sign of the susceptibility to PTSD and PTSD-D or conversely mutual regulation as a sign of resilience.

The concept of resilience

Resilience is a dynamic, interactive concept that refers to the overcoming of traumatic stress, decreased vulnerability to environmental risk experiences, and maintenance of relatively normal physical and psychological function (Rutter, 2006). In contrast, vulnerable individuals can be defined as exhibiting detrimental physiological and psychological consequences as a result of trauma exposure, including serious stress-related psychiatric disorders (e.g., PTSD). Thus, from the resilience perspective, the development of psychopathology such as PTSD can be explained by individual variability in stress vulnerability (Liberzon & Knox, 2012). Studies have established models of resilience to stress from a psychosocial perspective (Agaibi & Wilson, 2005; Sandler, Wolchik, & Ayers, 2008; Woodgate, 1999). For example, in the resiliency model proposed by Woodgate (1999) for adolescent cancer patients, whether adolescent cancer patients adapt successfully to their stressors (e.g., cancer diagnosis, hair loss) depends on the interaction between vulnerability (e.g., disabling) and protective (e.g., self-understanding) factors on stress response.

Increasing attention has also been paid to the neurobiological features of resilience (Rutter, 2013). Individuals who successfully adapt to traumatic stress may exhibit changes in biological processes that differ from those found in stress-vulnerable individuals (Liberzon & Knox, 2012). Many biomarkers, including oxytocin and cortisol typically considered separately, have been suggested to represent the biological basis for resilience to stress (Osorio, Probert, Jones, Young, & Robbins, 2016; Ozbay et al., 2008). For example, among police officers routinely exposed to potentially traumatic events and routine life stressors, those who followed trajectories of resilience and recovery over 4 years had significantly increased cortisol levels in response to the experimental stressor, while those following a trajectory of chronic increasing distress had a blunted cortisol response to the challenge (Galatzer-Levy et al., 2014). This finding suggests that individual differences in cortisol stress response may be related to the development and long-term course of stress pathology and resilience. The anxiolytic effects of oxytocin have been seen through reducing anxiety and increasing the effects of social support in individuals exposed to psychosocial stress (Heinrichs & Domes, 2008). Dysregulated oxytocin system may be a biological underpinning for the elevated risk for psychiatric disorders and decreased resilience to stress (Buisman-Pijlman et al., 2014; Ozbay et al., 2008).

It has been noted that resilience to stress cannot be fully accounted for by a single neurobiological marker, but rather the interaction of multiple biomarkers (Osorio et al., 2016; Ozbay et al., 2008). Tops, van Peer, Korf, Wijers, and Tucker (2007) suggested that stress-related health outcomes might rely on the balance between oxytocin and cortisol stress responses (Tops et al., 2007). This is biologically plausible because oxytocin could inhibit the stress-induced cortisol levels that play a protective role in maintaining normal HPA stress regulation (Neumann, Kromer, et al., 2000; Neumann, Torner, & Wigger, 2000; Pierrehumbert et al., 2012). The fight/flight system—HPA axis and the stress-buffering oxytocin system, tends to operate in balance, reaching a homeostasis state (Moberg, 2003). But when the oxytocin system is affected by early attachment trauma, the connectivity with the HPA axis may also be influenced (Buisman-Pijlman et al., 2014). This could affect the stress response activity of the HPA axis, contributing to HPA dysregulation. Thus, the mutual regulation between oxytocin and cortisol may play a significant role in an individual's resilience to stress, while the mutual dysregulation between these two hormones may reflect the susceptibility to PTSD. The resilience concept can serve as a conceptual basis for understanding the balance between oxytocin and cortisol stress responses as a sign of resilience to stress and the imbalance between these two systems as a marker of susceptibility to PTSD.

Despite a growing body of research on the neurobiological underpinnings of resilience, no resilience models have been constructed that focuses on the reciprocal relationship between oxytocin and cortisol. Therefore, it is essential to build a conceptual model with oxytocin and cortisol and their mutual regulation and/or dysregulation as a potential biological pathway for resilience to stress and/or vulnerability to the development of PTSD. We posit that, in addition to individual variability in oxytocin and cortisol levels, their interactions can affect resilience to stress. The purpose of this paper is to propose a conceptual model that can be considered as a guide for future research on the neurobiological mechanism of PTSD and to put it to a very preliminary test-of-concept using archived data from a small clinical study.

Literature on oxytocin and cortisol in relation to PTSD and its dissociative subtype

Numerous studies have investigated cortisol in relation to PTSD, but the findings have been varied. Two meta-analyses indicated that PTSD was not associated with basal cortisol levels (Klaassens et al., 2012; Meewisse et al., 2007), while the other two meta-analyses found lower daily cortisol output in relation to PTSD (Miller, Chen, & Zhou, 2007; Morris, Compas, & Garber, 2012). Oxytocin administration has been recently suggested as a potential therapeutic intervention for alleviating psychiatric disorders (Macdonald & Feifel, 2013). However, high oxytocin levels are not always associated with the beneficial conditions. In a study with 26 adults exposed to child abuse, 25 adult survivors of childhood cancer and 39 healthy controls, the adults who experienced life-threatening illnesses in childhood had higher oxytocin secretion in response to the psychosocial stress test compared to the other two groups (Pierrehumbert et al., 2010). A study with a highly traumatized sample in Atlanta reported the highest basal levels in those who had a history of childhood maltreatment as well as a current PTSD diagnosis while the lowest levels of oxytocin in individuals without child maltreatment and current PTSD (Olff et al., 2013). Given the mixed the findings, studies are still needed to test the direction of the relationships between cortisol, oxytocin and PTSD.

PTSD-D, as included in the DSM-5, is defined primarily by symptoms of derealization and depersonalization (APA, 2013). This subtype of PTSD has been associated with emotional over-modulation, while PTSD has been associated with emotional under-modulation (Lanius et al., 2010). A review of the PTSD neuroimaging literature found individuals with PTSD-D had a different pattern of neurobiological response to symptom provocation compared to those with PTSD diagnosis only (Lanius, Bluhm, Lanius, & Pain, 2006). Thus, the dissociative subtype of PTSD and PTSD diagnosis only may have a distinct biological basis. Although recent studies have tested whether oxytocin can be considered as a potential biomarker of PTSD, more research is needed to determine if oxytocin could be a biomarker for PTSD-D and whether

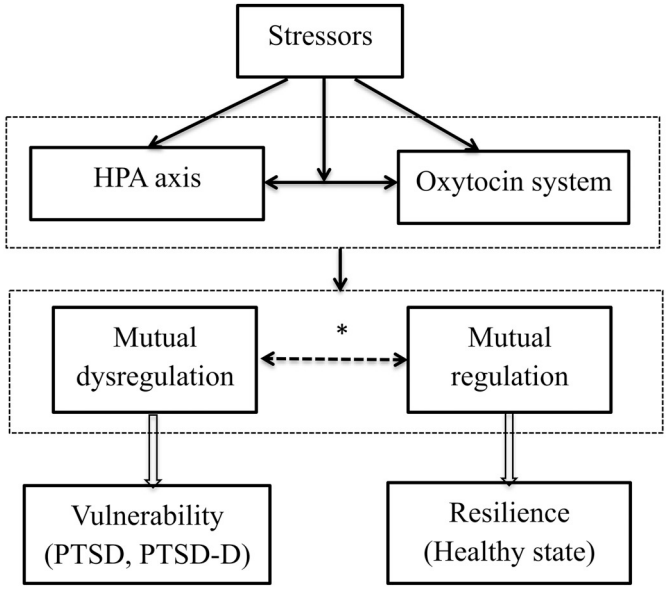

Fig. 1. The bio-behavioral resilience model for understanding the mutual regulation between oxytocin and cortisol as a marker of resilience.
Note. * The dashed line indicates a continuum of mutual regulation and dysregulation. HPA = hypothalamic-pituitary-adrenal; PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD.

it could distinguish between PTSD-D and PTSD only. In a small pilot study of oxytocin in relation to nausea and vomiting of pregnancy among women with PTSD, levels of oxytocin were highest among those with both dissociation and PTSD and lowest among those with PTSD only (Seng et al., 2013). Limited studies have found the association of cortisol with the dissociative disorder (Simeon et al., 2007), but no studies have explored whether cortisol is related to PTSD-D. Neither is it known whether the direction of the correlation between oxytocin and cortisol distinguishes individuals with PTSD-D from those with PTSD only or healthy individuals. Although both PTSD and PTSD-D are consequences of traumatic stress, they may significantly differ in terms of the relationship between oxytocin and cortisol. Therefore, it is important to consider the subtype of PTSD in constructing the resilience model.

Explication of the conceptual model

The conceptual model was constructed by synthesizing the resilience concept, the resilience model by Woodgate (1999), and evidence from the literature (Fig. 1). The model posits that when stressors occur, the activity of the HPA axis is initiated, which produces cortisol in response to stress. Oxytocin exerts stress-buffering effects to inhibit the stress-induced HPA activity and decrease cortisol levels. When cortisol stress responses and the protective stress-buffering effects of oxytocin reach a balance, homeostasis is preserved. Oxytocin level and its connectivity with the HPA axis might be affected by severe or chronic stressors, including early trauma in attachment relationships. Severe or chronic stressors could also cause dysregulation of the HPA axis, including abnormal basal cortisol levels and/or elevated or weak cortisol stress reactivity. The mutual regulation between these two systems would thus be considered as a sign of resilience to stress, while the mutual dysregulation between these two systems would be a sign of vulnerability to PTSD and especially PTSD-D. There likely would be a continuum or dynamic process from the mutual regulation to the mutual dysregulation.

The main components of the model are stressors, HPA axis, oxytocin system, mutual regulation, mutual dysregulation, resilience, and vulnerability. Stressors include acute (e.g., traumatic life events, catastrophic events) and chronic (e.g., childhood maltreatment and sociodemographic and environmental) stressors, with stressors to attachments plausibly taking both acute and chronic forms. Cortisol and oxytocin are primary physiological indicators of the HPA axis and oxytocin system, respectively. The mutual regulation is defined as a homeostasis state in which HPA axis and oxytocin reach a balance within their normal range. The mutual dysregulation can be classified into three types: both oxytocin and cortisol in extremely high levels; both hormones in extremely low levels; and the ratio of these two hormones out of proportion (one in extremely high levels and the other in extremely low levels). For the first two types of dysregulation, the two hormones may lack reciprocity, while they are still reciprocal for the last type. Resilience refers to a healthy state in which an individual remains after exposure to stressors, while vulnerability is more specific to the risk for developing PTSD and PTSD-D.

The test-of-concept

To provide a very preliminary test of this bio-behavioral resilience model, we conducted secondary analysis of data to answer the question: Do differences in mutual regulation of oxytocin and cortisol (a) distinguish women with posttraumatic psychopathology from trauma-exposed resilient controls and (b) distinguish PTSD-D from women with PTSD only? Based on the results of the analysis, we would revise or refine the model to advance it toward further testing.

Methods

Study design and data suitability

To conduct a theory-testing secondary analysis, we needed, at a minimum, repeated measures of oxytocin and cortisol in a sample well-characterized in terms of PTSD and dissociation. We used the archived data from the co-author's pilot study of oxytocin and the severe vomiting of pregnancy, PTSD, and dissociation. The original study was a test of concept about the extent to which PTSD-related oxytocin dysregulation might be a mechanism of hyperemesis via its role in smooth muscle peristalsis (Seng, 2010; Seng et al., 2013). That study demonstrated oxytocin differences in PTSD and PTSD-D but did not examine relationship with cortisol or consider their mutual regulation. Thus, this dataset was well-suited to being extended into this resilience theory test-of-concept purpose. It contained the necessary series of repeated measures of both oxytocin and cortisol collected under a strict in-patient research protocol. It characterized the women with standardized measures of PTSD and dissociation. As oxytocin is sexually dimorphic, testing the concept in a sample of females only is a reasonable starting point. However, there were some shortcomings, including small sample size and the fact that all are pregnant and affected to a greater or lesser extent by nausea and vomiting. The previously published pilot report contains descriptions of the study sample recruitment, data collection, and assay methods (Seng et al., 2013). Here we present an overview of those methods and our analysis plan for the test-of-concept.

Sample and setting

In the pilot study, pregnant women who met diagnostic criteria for the severe nausea and vomiting of pregnancy (hyperemesis gravidarum) were recruited during their first emergency department visit, and pregnant women with more normal levels of pregnancy nausea and vomiting were recruited via community fliers. Exclusion criteria were smoking, non-English speaking, more than sixteen weeks of gestational age, histories of psychotic disorder, acute illness, molar pregnancy or multiple gestations, both of which raise oxytocin levels. A total of twenty-five pregnant women were included in the pilot study.

Participants completed data collection in the inpatient General Clinical Research Center at the medical center of the University of

Michigan with approval of the Institutional Review Board, a confidentiality certificate, and written informed consent. In the original protocol ("24-h protocol"), fifteen participants had blood specimens for oxytocin and cortisol collected every four hours for 24 h. No diurnal pattern for oxytocin was observed, so 10 more women were enrolled in a revised protocol ("90-min protocol") and had blood specimens for oxytocin drawn every 10 min between 10:30 am and noon, based on Nyquist's Sampling Theorem (Nyquist, 1928) to detect pulsatility; cortisol was measured in the first, fifth, and last of these specimens.

In this secondary analysis of the data, the PTSD diagnosis and a dissociative symptom score cutoff were used to classify participants into three groups: the PTSD-D group who had the dissociative symptoms as well as PTSD, the PTSD only group who met the diagnosis for PTSD but did not have dissociative symptoms, and trauma-exposed resilient controls with neither dissociative symptoms nor PTSD. Three women in the 90-min protocol had dissociative symptoms but did not meet the PTSD diagnosis and were excluded because of the small group size and because this study focused on PTSD-D rather than the dissociation per se. Thus, the total sample size included in the present study is twenty-two, with fifteen women in the 24-h protocol and seven women in the 90-min protocol. The participant flow is shown in Fig. 2.

Measures

The Life Stressor Checklist was used to assess lifetime exposure to 30 potentially traumatic events with a yes/no response format (Wolfe & Kimerling, 1997). The 30 traumatic events includes disasters, accidents, being sent to jail, parental separation or divorce, physical or mental illness, emotional abuse or neglect, physical neglect, physical abuse, sexual assault, and other events. Respondents are asked to provide ages when events occurred and when they ended. The questionnaire has shown high sensitivity to trauma among women (Norris & Hamblen, 2004). In this study, child abuse was defined as any "yes" response to physical abuse, physical neglect, emotional abuse or neglect, and sexual assault before age 16. Adult abuse was defined as any "yes" response to physical abuse, physical neglect, emotional abuse or neglect, and sexual assault after age 16. The sum of lifetime trauma exposures was the total number of "yes" responses to the 30 traumatic events.

The National Women's Study PTSD Module was used to yield a 0–17 count of symptoms and a current PTSD case variable based on the DSM-IV symptom clusters criteria. The measure had sensitivity of 0.99 and specificity of 0.79 compared to the Structured Clinical Interview for DSM-III-R (Kilpatrick et al., 1998; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993).

The 8-item taxon version of the Dissociative Experiences Scale (DES-T) was used to measure dissociative symptoms (Waller, Putnam, & Carlson, 1996). In clinical and community samples, test-retest reliability was 0.84 to 0.96, alpha was 0.95, sensitivity was 0.80, and specificity was 0.80 (Bernstein & Putnam, 1986; Waller et al., 1996). The 75th percentile of the DES-T score was used as the cutoff to make the dissociation cases.

The Pregnancy Unique Quantification of Emesis (PUQE) includes 3 questions to assess the severity of nausea and vomiting (Koren et al., 2002). The number of hours of nausea and the number of times of vomiting and retching/dry heaves were asked on a 1 to 5 scale. The nausea and vomiting severity score was computed by summing up the scores of the 3 questions, ranging from 3 to 15.

Statistical analysis

The demographic characteristics, gestational weeks, nausea and vomiting severity score, trauma history, PSTD symptom count, DES-T score and group membership were compared for the total, 24-h protocol, and 90-mi protocol samples using chi-squares and ANOVAs. Due to the small sample size in each protocol, and the availability of noon oxytocin and cortisol in both protocols, we combined the samples and used the noon blood specimens. Moreover, we calculated the mean of the repeated measures for oxytocin in the 24-h protocol, as well as the area under the curve (AUC) for the cortisol levels across the 24-h protocol since there was a diurnal pattern for cortisol. However, the 90-min protocol for this pilot has only 7 women. Given this small sample size in the 90-min protocol, we did not conduct any inferential statistical analysis, but we did depict their levels in the graphs.

We analyzed the hormone patterns with descriptive statistical and basic visualizing approaches. Although the sample size is small, we used independent samples *t*-tests and ANOVAs to describe group differences in terms of noon oxytocin and cortisol levels for both protocols combined, mean oxytocin levels for the 24-h protocol, and cortisol AUC for the 24-h protocol. These statistical methods were used to test hypothesis 1a, that oxytocin and cortisol patterns among women with PTSD would differ from healthy controls and to test hypothesis 1b that patterns would also differ between women with PTSD and PTSD-D. We interpreted the tests to be statistically significant if P was < 0.05 (two-tailed), which is stringent for this sample size. Linear regressions were done to estimate effect size of significant relationships in terms of variance explained. When oxytocin and cortisol levels were not log-

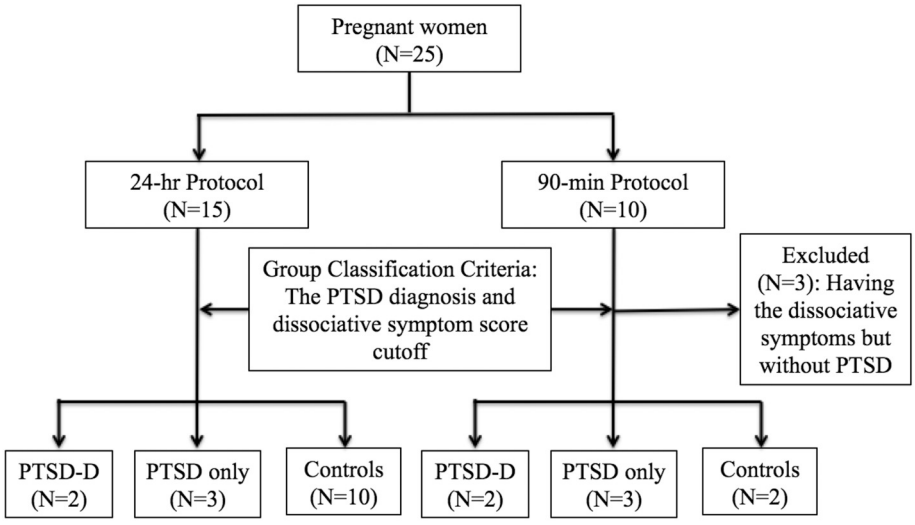

Fig. 2. Participant flow chart.
Note. PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD.

Table 1
Sample characteristics.

Characteristic	Total Sample (n = 22)	24-h protocol (n = 15)	90-min protocol (n = 7)
Demographics, *n*			
African American race	8	6	2
Pregnant as a teen (20 years old or less)	4	2	2
Living in poverty (income < $15,000)	3	3	0
High school education or less	15	11	4
Gestational Weeks, *M (SD)*	12.27 (2.51)	11.67 (2.74)	13.57 (1.27)
Nausea and vomiting severity, *M (SD)*	8.07 (3.66)	8.20 (4.07)	7.79 (2.84)
Trauma History			
Childhood abuse/neglect, *n*	7	5	2
Adult abuse/assault, *n*	9	5	4
Trauma exposure sum, *M (SD)*	6.27 (3.59)	6.86 (4.74)	6.00 (3.07)
Mental Health, *M (SD)*			
PTSD symptom count	5.55 (4.95)	5.07 (4.98)	6.57 (5.13)
DES-T score	9.64 (2.92)	9.27 (2.58)	10.43 (3.64)
Group Membership, *n*			
PTSD-D	4	2	2
PTSD only	6	3	3
Resilient controls	12	10	2

PTSD = posttraumatic stress disorder; DES-T = the taxon version of the Dissociative Experiences Scale; PTSD-D = the dissociative subtype of PTSD.

transformed, the ANOVA and linear regression results were similar with the results with oxytocin and cortisol levels log-transformed. Thus, the non- transformed oxytocin and cortisol levels were used for analysis to show the natural units of oxytocin and cortisol. To test hypothesis 2, Pearson's correlations were used to examine the correlations between oxytocin and cortisol levels within the three groups. We graphically depicted hormone levels by group for each hormone separately. Then we juxtaposed the oxytocin and cortisol levels within each group to explore the appearance of reciprocity. SPSS v.22 was used for all analyses.

Results

Sample characteristics

There were no significant differences in the demographic characteristics, gestational weeks, nausea and vomiting severity, trauma history, PTSD symptom count, DES-T score, or group membership across the total, 24-h protocol, and 90-min protocol samples ($P > .05$). The results can be seen in Table 1.

Oxytocin and cortisol levels across groups

Independent samples t-tests showed no significant differences between PTSD group and resilient controls in noon oxytocin and cortisol levels from both protocols combined and mean oxytocin and cortisol AUC from the 24-h protocol ($P > .05$).

ANOVA tests showed that there were significant differences in noon oxytocin levels and mean oxytocin levels for the 24-h protocol among the three groups (F (2, 19) = 18.74, $P < .001$, partial $\eta^2 = 0.66$; F (2, 12) = 4.34, $P = .038$, partial $\eta^2 = 0.42$). Post hoc analyses revealed that the significant difference was between the PTSD-D group compared to both the PTSD only group and resilient controls ($P < .05$). No significant group differences were observed for either noon cortisol levels or cortisol AUC from the 24-h protocol ($P > .05$). The results can be seen in Table 2 and Fig. 3. Following up this finding with linear regression showed that the PTSD-D group's higher noon oxytocin levels and mean oxytocin levels ($\beta = 0.79$; $\beta = 0.62$) explained 66% of the noon oxytocin variance and 42% of the mean oxytocin levels. However, there were no significant associations of group with noon cortisol levels and cortisol AUC from the 24-h protocol ($P > .05$). No significant associations of PTSD only with any oxytocin and cortisol levels were detected ($P > .05$). The results can be seen in Table 3.

Correlation and reciprocity between oxytocin and cortisol levels among the three groups

Coefficients for correlations between the hormones within groups were weak, ranging from −0.26 to 0.06, and none were statistically significant.

Fig. 4 depicts the inter-relationships between oxytocin and cortisol levels across time for each group. Fig. 4A, B, and C described changes in oxytocin and cortisol levels across 24 h for PTSD-D, PTSD only and resilient controls. In the PTSD-D group, oxytocin levels decrease as cortisol levels increase before 8 AM and then oxytocin levels rise as cortisol levels go down. The oxytocin and cortisol levels seem reciprocal, but both levels are relatively high. In the PTSD-only group, both hormones are at relatively low levels and appear to be consistently lower than resilient controls. Fig. 4D, E, and F depict changes in oxytocin and cortisol levels across 90 min for PTSD-D, PTSD only and controls. The oxytocin and cortisol levels seem reciprocal among all three groups. The PTSD-D group exhibited the most obvious reciprocity, but both hormones are at relatively high levels. The revised bio-behavioral resilience model based on the preliminary test (Fig. 5) aligns with the specific finding that patterns of cortisol and oxytocin appear to distinguish the PTSD-D group from those with PTSD only.

Discussion

This study developed a conceptual model to guide future research on the mutual dysregulation between oxytocin and cortisol as a potential sign of the susceptibility to PTSD and PTSD-D, as well as tested the model via secondary analysis of data from a small sample of pregnant women. The test-of-concept graphic analysis partially supported the conceptual model that oxytocin and cortisol co-varied in higher patterns with the PTSD-D group and lower patterns with the PTSD only group and appeared to be especially dysregulated (significantly higher oxytocin levels) in women with PTSD-D. However, this co-variance suggests that reciprocity is maintained.

Table 2
Means and standard deviations of the oxytocin (pg/mL) and cortisol levels (ug/dL) among the three groups.

	PTSD-D[a]	PTSD only[b]	Resilient controls[c]	F	P	η^2	Post hoc comparison
Noon oxytocin for both protocols combined, n = 22	619.75 (290.00)	72.00 (41.78)	118.67 (130.08)	18.74	< 0.001	0.66	a > b a > c
Mean oxytocin for 24-h protocol, n = 15	477.50 (423.09)	78.28 (52.90)	125.10 (124.02)	4.34	0.038	0.42	a > b a > c
Noon cortisol for both protocols combined, n = 22	9.58 (2.41)	9.12 (3.68)	11.78 (4.68)	1.00	0.388	0.10	–
Cortisol AUC for 24-h protocol, n = 15	51.65 (15.56)	35.83 (3.62)	49.68 (15.91)	1.15	0.349	0.16	–

PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD; AUC = Area under the curve.

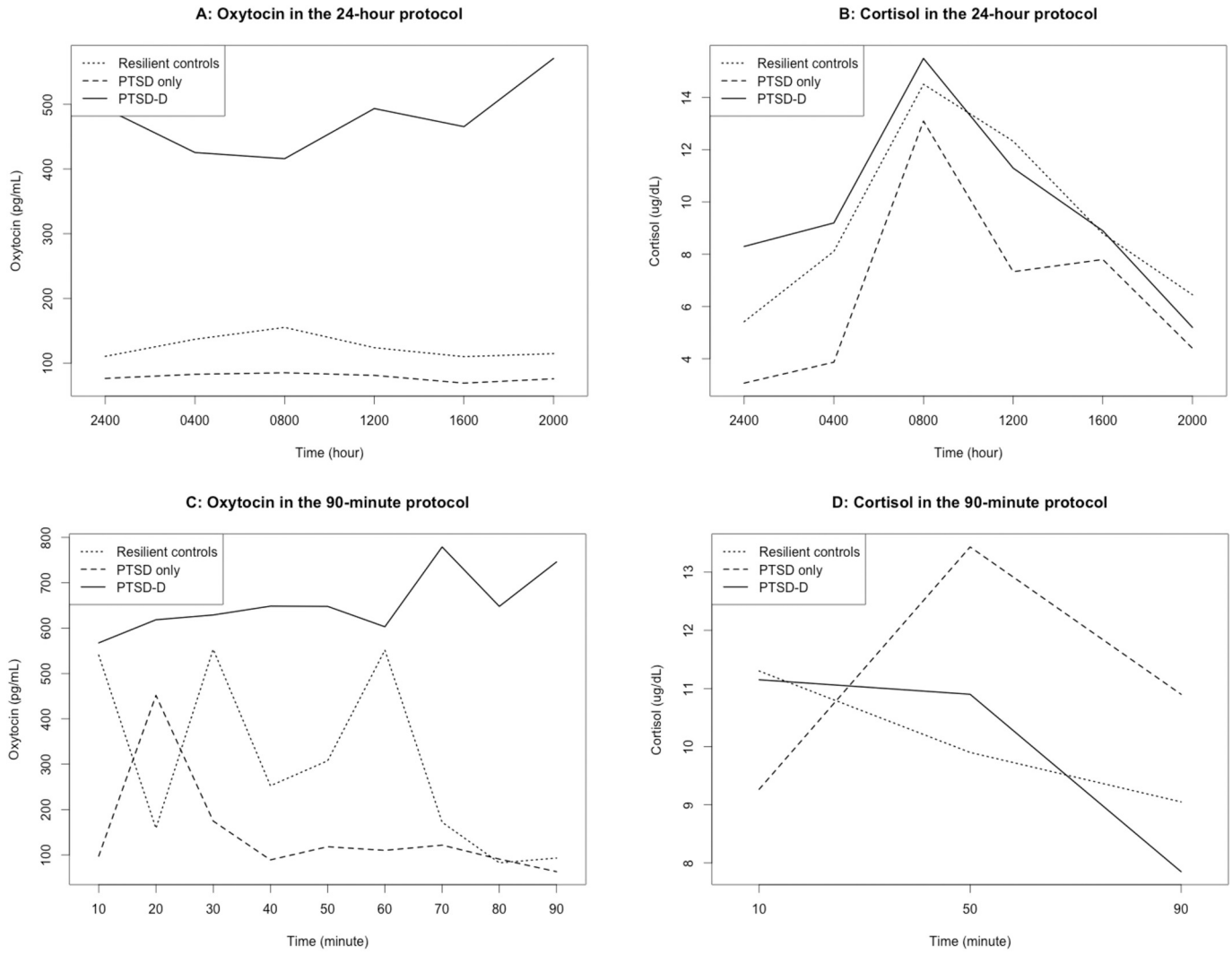

Fig. 3. Changes in oxytocin and cortisol levels across time by group.
Note. PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD.

Table 3
Linear regressions for the associations of oxytocin and cortisol levels with the dissociative subtype of PTSD and PTSD only.

	Predictor [a]	β	F	P	R^2
Noon oxytocin for both protocols combined			18.74	< 0.001	0.66
	PTSD-D	0.79***			
	PTSD only	−0.09			
Mean oxytocin for 24-h protocol			4.34	0.038	0.42
	PTSD-D	0.62*			
	PTSD only	−0.10			
Noon cortisol for both protocols combined			1.00	0.388	0.10
	PTSD-D	−0.21			
	PTSD only	−0.29			
Blood cortisol AUC for 24-h protocol			1.15	0.349	0.16
	PTSD-D	0.05			
	PTSD only	−0.39			

PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD; AUC = Area under the curve.
[a] The reference group is the resilient controls.
* $P < .05$.
*** $P < .001$.

As reported in relation to the parent study, PTSD-D was found in relation to higher oxytocin levels, indicating that elevated oxytocin concentrations may be a marker for the subtype of PTSD. This is consistent with another pilot study including 15 women, where the presence of dissociative symptoms was correlated with higher oxytocin levels in response to a laboratory provocation (Munro et al., 2013). Although oxytocin administration has been demonstrated to have treatment effects on psychiatric disorders such as anxiety (Macdonald & Feifel, 2013), our finding suggests that it may not be effective in treating individuals with PTSD-D as those individuals already have high basal oxytocin levels. The overall lower levels of oxytocin in pregnant women with PTSD only compared to resilient controls was not statistically significant, but it may still suggest that PTSD-D and PTSD diagnosis only may have a distinct biological basis in the oxytocin regulation system. In individuals with PTSD-D, the enhanced oxytocin levels may serve as a signal for a need to seek social affiliation (Olff et al., 2013). However, the lower levels of oxytocin in those with PTSD diagnosis only are in line with the understanding of PTSD as an anxiety disorder since it appears in these data that they have low plasma oxytocin levels. An experiment study demonstrated greater anxiety-related behavior in transgenic mice that lacked oxytocin (Amico, Mantella, Vollmer, & Li, 2004).

We did not find significant differences in cortisol levels among the three groups, which is inconsistent with studies reporting the associations of cortisol levels with PTSD or dissociation (Bremner, Vermetten, & Kelley, 2007; Luecken, Dausch, Gulla, Hong, & Compas, 2004; Simeon et al., 2007). No correlations between oxytocin and cortisol

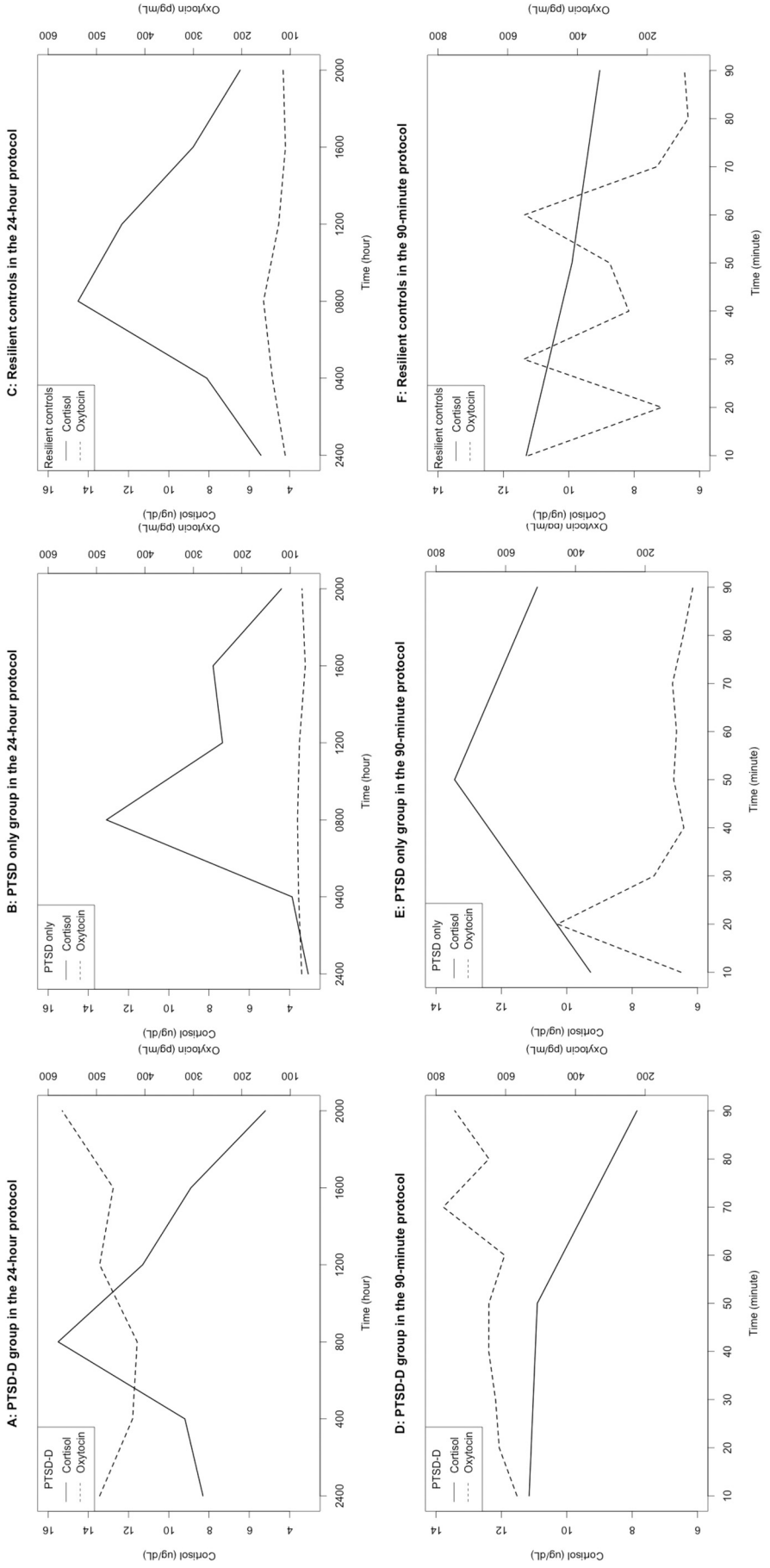

Fig. 4. The inter-relationships between oxytocin and cortisol levels across time within each group.
Note. PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD.

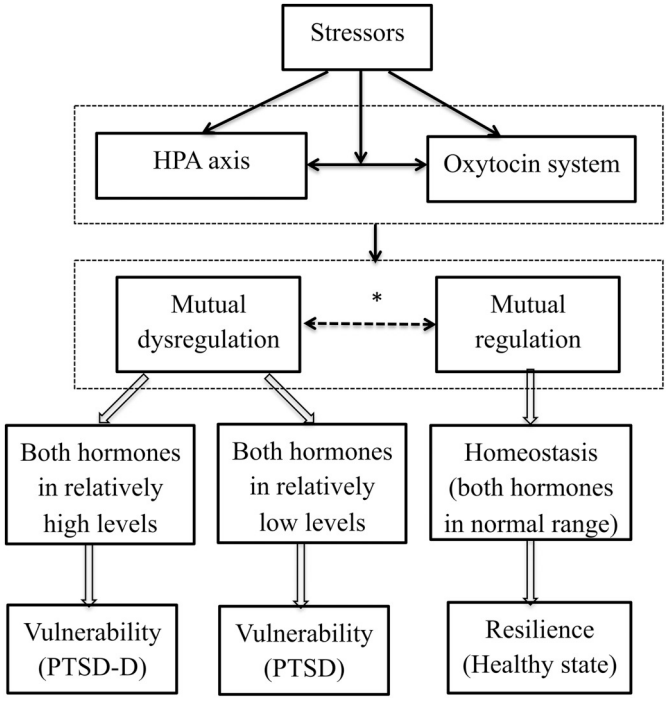

Fig. 5. The revised bio-behavioral resilience model.
Note. * The dashed line indicates a continuum of mutual regulation and dysregulation. HPA = hypothalamic-pituitary-adrenal; PTSD = posttraumatic stress disorder; PTSD-D = the dissociative subtype of PTSD.

were observed for any group. Among women with PTSD-D, the higher levels of oxytocin might inhibit the stress response and thus the release of cortisol is decreased. Such a process may explain our finding that cortisol levels in women with PTSD-D were not significantly higher than the other two groups. But the small sample size used in the pilot study makes it challenging to determine whether the non-significant findings are also not clinically significant. Another possible explanation for the non-significant findings is that study subjects included pregnant women with nausea and vomiting. Since numerous physiological changes occur throughout pregnancy (de Weerth & Buitelaar, 2005) and nausea and vomiting have been reported in relation to higher cortisol levels (Jewell & Young, 2003), it may lead to the non-significant associations between cortisol levels and PTSD or dissociation, as well as between oxytocin and cortisol levels.

Despite our hypothesis was that mutual regulation of oxytocin and cortisol would be a sign of resilience to stress, the graphs revealed that all three groups exhibited reciprocity. But oxytocin levels were the highest in women with PTSD-D. Although no statistical significances were reached, women with PTSD-D had slightly higher cortisol levels and women with PTSD diagnosis only had relatively lower oxytocin and cortisol levels compared to resilient controls. Thus, the most succinct statement of the findings might be that both hormones in women with PTSD-D and PTSD only are mutually dysregulated, but not lacking in reciprocity. To some extent, the findings support our conceptual model that the two forms of mutual dysregulation (i.e., both hormones in extremely high levels or low levels) can be considered as a sign of vulnerability to PTSD and PTSD-D.

Based on the findings, we revised the proposed conceptual model. The first type of mutual dysregulation we defined is that both oxytocin and cortisol are at very high levels compared to the healthy group, which may be associated with the vulnerability to developing PTSD-D. The second type of mutual dysregulation is that both hormones are lower than healthy group levels, which may be the biological basis for the risk of developing PTSD. But for these two types of dysregulations, the two hormones still remain reciprocal, which is opposite to our initial hypothesis. The regulating functions of each hormone system may be impaired by chronic or severe stress, but the inhibiting effect of oxytocin on cortisol levels is not influenced. We initially defined the ratio of these two hormones being out of proportion (one in extremely high levels and the other in extremely low levels) as the last type of mutual dysregulation. Although our findings did not identify this type, it did not mean this type does not exist. Future studies need to explore if this type of mutual dysregulation is associated with other trauma-related psychopathology (e.g., depression, anxiety).

This test-of-concept secondary analysis had several limitations inherent in the pilot study database available for the purpose. First, the sample size is relatively small, limiting the power to detect significant differences in cortisol levels among the three groups, as well as significant correlations between oxytocin and cortisol levels. Second, as our sample size was small, we were unable to control for confounding factors such as demographic characteristics, gestational weeks, nausea and vomiting severity, trauma history, and comorbid depression that may influence our main findings. Third, our sample included pregnant women who had 16 weeks or less gestation, as well as had hyperemesis gravidarum, nausea, or vomiting. Pregnancy physiological changes and hyperemesis gravidarum, nausea, and vomiting may influence our findings. Fourth, PTSD-D was measured based on the self-rating DES-T score. The lack of clinical diagnosis may underestimate the severity of the dissociative symptoms. Fifth, due to the small sample size, the numbers of participants who reported child maltreatment was very small. Thus, we did not examine the effects of child maltreatment as the attachment trauma on the risk for PTSD and PTSD-D as well as the mutual regulation between oxytocin and cortisol. Lastly, the study lacked attachment measures, as well as a stress provocation test specific to attachment trauma during the blood specimen collection. Measuring attachment and oxytocin and cortisol levels in response to attachment trauma would contribute to better understanding of the oxytocin and cortisol regulating mechanisms for PTSD-D and PTSD diagnosis only.

Implications for research and clinical practice

The study has implications for future research. Since the conceptual model was tested based on a secondary analysis of data from a pilot study with some limitations, the model needs to be further developed and tested to better understand the mutual regulation between oxytocin and cortisol as a potential sign of resilience to stress. Future studies need to have a larger female representative or clinical sample, attachment measures, and a stress-provocation test specific to attachment trauma. Oxytocin and cortisol need to be collected multiple times using a protocol to detect the pulsatility. The different oxytocin and cortisol patterns for the PTSD only and the dissociative subtype of PTSD suggest that researchers need to pay attention to this subtype of PTSD and further investigate the specific biological basis for the subtype. These findings may also have implications for psychiatric nursing practice. The bio-behavioral model may help psychiatric nurses better understand the neurobiological role in vulnerability to trauma-related psychopathology, as well as the neurobiological mechanisms for resilience to stressful life events, which could promote nursing care for patients with trauma exposures. Additionally, interventions that could facilitate the mutual regulation of oxytocin and cortisol may be effective treatment strategies to enhance resilience to stress. Identifying biomarkers of trauma-related psychopathology could assist in recognizing at–risk populations.

Conclusion

This study is the first to explore a conceptual model that considers the mutual dysregulation of oxytocin and cortisol as a sign of vulnerability to PTSD and PTSD-D. Our study filled a gap in exploring Cascade theory's view that more than one stress response system is dysregulated by childhood maltreatment trauma. The parent pilot study had already

shown that oxytocin levels were elevated in the presence of high levels of dissociation (Seng et al., 2013); and this test-of-concept extends that finding by focusing on the relationship between the two systems to show that reciprocity appears to be maintained, but that both oxytocin and HPA systems appear to be similarly dysregulated – either both are elevated or diminished. Future studies are still needed to modify and validate the conceptual model to better understand the biological basis for the vulnerability to PTSD and its dissociative subtype.

Declarations of interest

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