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Estradiol, Stress Reactivity, and Daily Affective Experiences in Trauma-Exposed Women

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Objective: Women experience higher risk for PTSD following trauma compared with men. Fluctuations in ovarian hormones might contribute to this greater vulnerability, given that estradiol is associated with affect and stress reactivity. Our objective was to test the relations between menstrual cycle-related changes in estradiol, affect, stress reactivity, and trauma-related symptoms. ***Method:*** We assessed trauma-related symptoms in ethnically diverse naturally cycling women with a history of trauma during a clinical interview. Participants also completed a 10-day ecological momentary assessment (EMA) that included lower- and higher-estradiol phases. We tested associations between estradiol and PTSD symptoms and stress reactivity to a trauma reminder using Spearman correlation and Wilcoxon rank-sum tests. We tested the effect of menstrual cycle day on daily affect using multilevel modeling. ***Results:*** Estradiol was negatively associated with symptom severity ($r_s = -.36$), and participants in low- versus high-estradiol cycle phases at interview had higher sympathetic ($r = .35$) and lower hypothalamic-pituitary-adrenal axis ($r = .41$) reactivity. Across the EMA period, participants showed a decrease in daily PTSD symptoms ($b = -.39$), negative ($b = -.11$) and positive ($b = -.24$) affect, and variability in daily valence ($b = -.07$) and arousal ($b = -.08$), from the low- to high-estradiol phase. ***Conclusions:*** Consistent with prior evidence of more aversive affective experiences in low-estradiol states, lower estradiol was associated with higher trauma-related symptoms. In addition, trauma-exposed women showed a discordant pattern of stress reactivity to a trauma reminder, higher daily symptoms, and greater affective lability in a low-estradiol phase. Given that our sample consisted of high-functioning trauma-exposed women, these results should be replicated in women with PTSD.

Clinical Impact Statement
We show that lower estradiol is associated with greater number and severity of self-reported PTSD symptoms in naturally cycling women with a history of trauma exposure. In addition, trauma-exposed women in low- versus high-estradiol menstrual cycle phases show greater sympathetic and lower hypothalamic-pituitary-adrenal axis reactivity to a trauma reminder, more severe daily PTSD symptoms, and more variable daily affect. These results have potential implications for clinical assessment, as menstrual cycle phase at the time of assessment could influence PTSD diagnosis. Additionally, clinicians working with women with PTSD might anticipate greater affective lability and increased symptoms during low-estradiol menstrual cycle phases.

Keywords: ecological momentary assessment, estradiol, menstrual cycle, trauma, stress reactivity

People who experience trauma can develop enduring trauma-related symptoms that are triggered in daily life by cues that act as trauma reminders. Trauma-related symptoms include (a) reexperiencing of the traumatic event through intrusive thoughts, memories, or

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Jenna K. Rieder conceived of the idea for the manuscript, designed the study, collected and analyzed data, and drafted the manuscript; Olena Kleshchova conducted statistical analyses and interpreted results, created visuals, and drafted the manuscript; Mariann R. Weierich contributed to the study design, supervised the project, acquired grant funding for the study, and contributed to the writing and editing of the manuscript.

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nightmares; (b) avoidance of trauma-related memories, people, or situations; (3) negative alterations in cognition and mood; and (4) heightened physiological arousal. Women are twice as likely to develop posttraumatic stress disorder (PTSD) following trauma than men (e.g., Perrin et al., 2014), and women often experience more severe symptoms (e.g., Seedat et al., 2005). Fluctuations in gonadal hormones might contribute to sex differences in symptoms. Estradiol (17β-estradiol), the most prevalent and biologically potent estrogen in nonpregnant premenopausal women, is broadly associated with affective responses. Thus, estradiol fluctuations might confer risk for aversive affective experiences such as trauma-related symptoms.

Estradiol and Affect

Throughout the life span, dramatic changes in circulating estradiol levels are associated with changes in affect, regardless of trauma exposure (e.g., Hickey et al., 2012). Risk for affective disorders increases when estradiol steeply declines during the perimenopause, menopause, and postpartum periods (e.g., Freeman et al., 2006; Vesga-López et al., 2008). In naturally cycling women, estradiol fluctuates more gradually across the menstrual cycle, and these smaller fluctuations are also associated with affect. Women generally report greater negative affect during lower-estradiol menstrual cycle phases (e.g., Gonda et al., 2008; Kanojia et al., 2013). During processing of affective information, lower estradiol is associated with heightened activation in affect-related limbic areas and reduced activation in prefrontal regulatory areas (e.g., Zeidan et al., 2011), which together fit a characteristic profile of elevated stress and anxiety states. Consistent with these differences in affective brain response, lower estradiol has been associated with greater fear responses, such as persistent fear following extinction (e.g., Milad et al., 2010; Zeidan et al., 2011), impaired fear inhibition in the presence of safety cues (e.g., Glover et al., 2013), and intrusive memories following exposure to unpleasant content (e.g., Wegerer et al., 2014). Lower-estradiol portions of the menstrual cycle have been associated with a variety of clinical symptoms, such as premenstrual dysphoric disorder symptoms and heightened physiological reactivity (Epperson et al., 2007), eating disorder symptoms (e.g., Edler et al., 2007), and risk for suicide attempts (e.g., Sein Anand et al., 2005). In daily life, trauma-related cues can evoke maladaptive fear responses in trauma survivors. Associations between lower estradiol and maladaptive fear suggest that trauma-exposed women might be more prone to symptoms during low-estradiol phases of the menstrual cycle. Accordingly, trauma-exposed women experience greater general psychological distress during low-estradiol menstrual cycle phases (e.g., Nillni et al., 2015). However, less is known about the influence of menstrual cycle-related variation in estradiol on variation in trauma-related symptoms. Thus, there is a need to better understand how PTSD symptoms might differ between low- and high-estradiol phases and whether these effects are stronger for particular symptom clusters.

Estradiol and Stress Reactivity

Stress reactivity is one form of affective responding that could contribute to increased trauma-related symptoms during low-estradiol menstrual cycle phases. Trauma exposure has been associated with greater self-reported anxiety in response to acute stressors (e.g., Regehr et al., 2007). Additionally, trauma exposure has been associated with heightened sympathetic nervous system (SNS) reactivity to aversive or trauma-related stimuli (e.g., Ali & Pruessner, 2012) and differences in hypothalamic-pituitary-adrenal (HPA) axis reactivity in both directions, with heightened reactivity reported in some studies (e.g., Inslicht et al., 2006) and blunted reactivity in other studies (e.g., Carpenter et al., 2011). In normative samples, both stress systems are modulated by estradiol, such that lower estradiol is associated with greater SNS (e.g., McFetridge & Sherwood, 2000) and lower HPA axis (e.g., Roche et al., 2013) reactivity to stressors. Suppression of the HPA axis is associated with heightened SNS reactivity (e.g., Andrews et al., 2012), suggesting that menstrual variation in one system might drive changes in the other. This is an important consideration, as the ratio of SNS to HPA activity predicts stress and depression in trauma survivors (e.g., Ali & Pruessner, 2012). Therefore, lower estradiol might be associated with greater SNS and lower HPA reactivity to trauma reminders, and this reactivity profile might contribute to increased symptoms.

The Present Study

Much of the existing research on menstrual cycle variability in affect has relied on data from a small number of laboratory sessions or has focused on comparisons between the early follicular and midluteal phases, as the low- and high-estradiol phases, respectively. Whereas the early follicular phase is characterized by low levels of ovarian hormones (i.e., estradiol and progesterone), the midluteal phase includes not only high estradiol, but also high progesterone. However, because progesterone also can influence affect (e.g., Ertman et al., 2011), the unique effect of estradiol on affective experiences in trauma-exposed women is currently unknown. To address this gap in knowledge, we tested the relations between estradiol and daily affect, trauma-related symptoms, and stress reactivity in naturally cycling women with a history of trauma. We utilized a multimethod approach that included cross-sectional assessments and longitudinal experience sampling methods. We assessed trauma-related symptoms over the past month and measured physiological stress reactivity to a trauma reminder during a clinical interview. In addition, we assessed daily affective experiences, including trauma-related symptoms, over a 10-day ecological momentary assessment (EMA) which spanned the early follicular phase (lower estradiol, lower progesterone) and the late follicular phase (higher estradiol, lower progesterone). We selected these phases to better understand the influence of estradiol fluctuations without the confound of high progesterone. We hypothesized that (Hypothesis 1) lower estradiol would be associated with greater number and severity of trauma-related symptoms, and (Hypothesis 2) a stress response profile of greater SNS reactivity, indexed by salivary alpha-amylase (sAA), and lower HPA axis reactivity, indexed by salivary cortisol, to a trauma reminder. We also hypothesized that (Hypothesis 3) women would report more frequent aversive affective experiences (i.e., unpleasant, high arousal states), including trauma-related symptoms, during a low- versus high-estradiol menstrual cycle phase.

Method

Participants

We recruited 40 naturally cycling women with a history of trauma exposure from an urban university in the northeastern United States. We recruited participants according to self-reported

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exposure to potentially traumatic events, and trauma exposure was subsequently confirmed during a clinical interview. Exclusion criteria for the study included: (a) hormonal contraceptive use in the past six months, (b) pregnancy or lactation within the past year, (c) use of psychotropic or steroid medications known to influence stress system function, (d) habitual cigarette smoking, (e) current major psychiatric disorders other than PTSD, (f) age outside of the 18–35 range, and (g) irregular menstrual cycles.

Procedure

The study included two parts: a laboratory visit and a 10-day EMA spanning the early and late follicular menstrual cycle phases. All study procedures were approved by Institutional Review Board and conducted in accordance with The Code of Ethics of the World Medical Association and the APA ethical standards. Prior to the study, participants provided informed consent after study procedures were thoroughly explained to them by an experimenter and outlined in written form.

Laboratory Visit

Clinical Interview. All participants completed a structured clinical interview to verify the presence of trauma exposure and to assess symptoms of PTSD and other major psychiatric disorders. The interview included the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM–IV*)[1] Disorders (SCID; First et al., 1996), which we used to assess symptoms of major psychiatric disorders, general health, and medication and substance use, and the Clinician-Administered PTSD Scale for *DSM–5* (CAPS-5; Weathers, Blake, et al., 2013), which we used to assess PTSD symptoms over the past month. We verified trauma exposure using Criterion A of the CAPS (that is, exposure to actual or threatened death, serious injury, or sexual violence through direct exposure, witnessing, learning that it happened to a relative or close friend, or indirect exposure to aversive details of the trauma, as is the case with first responders). During the interview, participants described the traumatic event, and this description also served as a trauma reminder.

Saliva Collection. During the lab visit, participants provided saliva samples at three timepoints using passive drool via Salimetrics saliva collection aids (Salimetrics, LLC). We used the saliva samples to measure: (a) salivary alpha-amylase (sAA), a surrogate marker of SNS function (e.g., Ditzen et al., 2014; Warren et al., 2017); (b) cortisol, an index of HPA axis function; and (c) estradiol. All lab visits began at 10 a.m., and all participants had been awake for at least one hour prior to the study, ensuring that our timepoints did not overlap with the cortisol or estradiol awakening response. Participants refrained from eating or drinking, except for water, for one hour prior to the study session. The first saliva sample (T1), which served as a study baseline, was collected in the resting period following informed consent at approximately 10:05 a.m. We collected the first sample at the same time for all participants to control for diurnal variation in hormone levels (e.g., Nater et al., 2007). The second sample (T2) was collected immediately following the description of the traumatic event during the interview. The third sample (T3) was collected exactly 20 minutes after the second sample. The samples were aliquoted into cryovials for later assays and stored in a −20 °C freezer. Salivary alpha-amylase levels at each timepoint indexed SNS activity at that timepoint, as this enzyme increases almost immediately poststressor onset (Rohleder et al., 2004). Given that cortisol peaks approximately 20 minutes following a stressor (Kirschbaum & Hellhammer, 2000), cortisol levels at each timepoint indexed HPA axis activity approximately 20 minutes prior to sample collection.

EMA Phase

EMA Procedure. The EMA comprised 10 days spanning the early follicular (lower estradiol) and late follicular (higher estradiol) phases. The EMA began on day 2 following the onset of menstruation and continued through day 11 of the cycle. The early follicular phase (low estradiol and progesterone) was operationalized as menstrual cycle days 2–6. The late follicular phase (higher estradiol and low progesterone) was operationalized as days 7–11. Participants completed questionnaires at five daily assessment points using a provided electronic device (i.e., Android phone): after waking, before bed, and at three variable daytime assessment points. The three daytime assessment points were programmed to occur semirandomly at approximately three-hour intervals within the participant's waking hours. At each daytime assessment point, a text message instructed the participant to complete a questionnaire within 30 minutes. All completed assessments were automatically time-stamped and uploaded to the laboratory server.

We confirmed that participants showed an expected increase in estradiol during EMA by measuring estradiol in two at-home saliva samples, which participants collected on the first and last days of the EMA. We also measured levels of progesterone in the second at-home sample to verify that participants remained in the follicular phase. To minimize the impact of diurnal fluctuations in ovarian hormones, both at-home samples were collected immediately postwaking. On the mornings of saliva collection, the participants received a text message reminder to collect the saliva samples. We instructed participants to collect the samples via passive drool immediately upon waking, store them in a freezer, and later transport them to the lab in insulated containers. Samples were then stored in a −20 °C lab freezer.

EMA Measures. At all assessment points, participants rated current affect (i.e., valence and arousal). Valence was rated on a scale of 1–9, where 1 was *extremely unpleasant*, 5 was *neutral*, and 9 was *extremely pleasant*. Arousal was also rated on a scale of 1–9, where 1 was *extremely nonstimulated or activated*, 5 was *moderately stimulated or activated*, and 9 was *extremely stimulated or activated*. These rating anchors were thoroughly explained at the end of the lab visit. The morning and evening questionnaires also included the Positive and Negative Affect Schedule (PANAS-SF; Watson et al., 1988), a 10-item measure of current positive and negative affect. For each item, participants indicated the extent to which they were currently feeling that affective state on a scale of 1 (*very slightly or not at all*) to 5 (*extremely*). We assessed trauma-related symptoms in the evening questionnaires using the PTSD Checklist for *DSM–5* (PCL-5; Weathers, Litz, et al., 2013), a 20-item measure that assesses *DSM–5* symptoms of PTSD. For each symptom, participants reported the extent to which they were bothered by the symptom that day on a scale of 0 (*not at all*) to 4

[1] The SCID-5 was not yet available when data collection began; therefore, for consistency we used the SCID-IV for all disorders except PTSD, for which we used the CAPS-5.

(*extremely*) in relation to the traumatic event discussed during the interview.

Salivary Biomarker Assays. Saliva assays were conducted in house, and all samples were processed in duplicate. We conducted alpha-amylase assays using Salimetrics kinetic reaction assay kits (Salimetrics, LLC). The procedure uses a chromogenic substrate, 2-chloro-p-nitrophenol, linked to maltotriose. The amount of alpha-amylase present in each sample is directly proportional to the increase in absorbance, measured spectrophotometrically by a standard plate reader at 405 nm. The kits' intra- and interassay coefficients of variation (CVs) are <7.5% and 6%, respectively. We conducted cortisol, estradiol, and progesterone assays using Salimetrics enzyme immunoassay kits, which use microtiter plates coated with hormone-specific monoclonal antibodies. Hormones in samples and standards compete with hormones conjugated to horseradish peroxidase for the antibody binding sites. The amount of hormone-enzyme conjugate detected is inversely proportional to the amount of hormone present in the sample, measured spectrophotometrically by a standard plate reader at 450 nm. The kits' intra- and interassay CVs are, respectively: <7% and 10% for cortisol, <8.5 and 9% for estradiol, and <8.5% and 10% for progesterone.

Data Analysis

Estradiol and PTSD Symptoms

Because symptom data were not normally distributed, we used Spearman rank-order correlations to test associations between estradiol and PTSD symptom count and severity over the past month, as reported during the clinical interview.

Estradiol and Stress Reactivity

Given that salivary biomarker data were skewed, we used nonparametric statistical tests to avoid transforming the data. We tested associations between estradiol and SNS and HPA axis reactivity to the trauma reminder using Spearman rank-order correlations. SNS reactivity was indexed by the difference in sAA between T1 and T2. HPA axis reactivity was indexed by the difference in cortisol between T2 and T3. We also tested associations between stress reactivity and menstrual cycle phase on the day of the interview, which we determined using the dates of their three most recent menstrual cycles and average cycle length. We categorized participants into two groups: low-estradiol phase (early follicular, early luteal, and late luteal) and high-estradiol phase (late follicular/peri-ovulatory and midluteal). We tested group differences in sAA and cortisol reactivity between participants in the lower- versus higher-estradiol phases using nonparametric Wilcoxon rank-sum tests.

Menstrual Cycle Phase and Daily Affect

We used multilevel modeling (MLM) to test the effect of menstrual cycle day on daily valence, arousal, negative and positive affect, and trauma-related symptoms over the 10-day EMA. Because valence and arousal were assessed five times a day, we calculated daily means and standard deviations for valence and arousal only for days without any missing assessments. For each outcome of interest, we tested mixed models with two levels (Level 1: day, Level 2: participant) and participant-specific random intercepts. We specified the first-order autoregressive error structure and used the restricted maximum likelihood method. MLM analyses were performed in R (Version 4.3) using the *nlme* package.

Results

Descriptive Data

Participants (see Table 1) were an ethnically diverse sample of women between the ages of 18 and 33 (n = 40; M = 21.9, SD = 4.3). All participants had regular menstrual cycles with average cycle length between 26 and 35 days (M = 30.1, SD = 2.5). Eight participants (20%) met criteria for a provisional PTSD diagnosis. However, consistent with many high-functioning undergraduate samples, these participants scored at the lower end of the symptom severity range. Three participants had estradiol levels in the at-home samples that were inconsistent with the expected menstrual cycle phase and were therefore excluded from EMA data analyses. For the remaining participants, progesterone values at the end of the EMA phase had a median of 66.42 (IQR = 42.09), which is within the normative range for the follicular phase (Soni et al., 2013). Seven participants had insufficient EMA questionnaire data (>50% of day forms missing or completed at times inconsistent with the prompts) and were excluded from EMA analyses. For the remaining participants, the overall compliance was high (morning forms: 98.5%, daytime forms: 84.9%, evening forms: 96.7%). The final sample size for lab visit data analyses was n = 40, and the final sample size for EMA data analyses was n = 30.

Estradiol and PTSD Symptoms Over the Past Month

Lower estradiol was associated with higher total number of symptoms (r_s = −.36, p = .023), reported during the interview (see Figure 1). Lower estradiol was also associated with more (r_s = −.32, p = .046) but not more severe (r_s = −.15, p = .350)

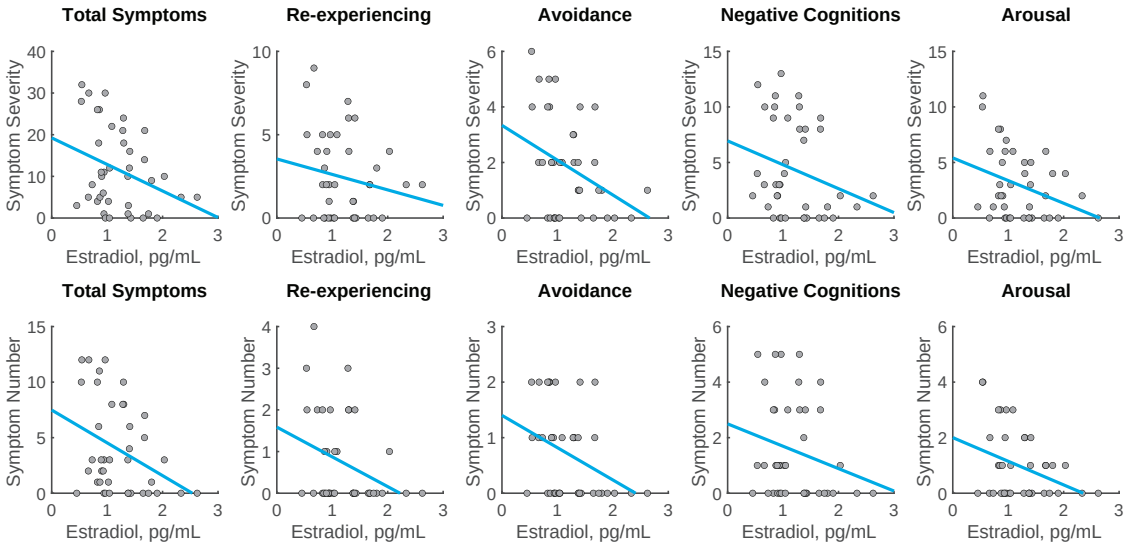
Table 1
Participants

Variable	Statistic
Age in years, *M* (*SD*), range	21.9 (4.3), 18−33
Race/ethnicity, *n* (%)	
Asian/Pacific Islander	8.0 (20.0)
Black, non-Hispanic	6.0 (15.0)
Hispanic	10.0 (25.0)
White, non-Hispanic	11.0 (27.5)
Multiple	3.0 (7.5)
Other	2.0 (5.0)
Total number of symptoms (CAPS-5), median (IQR), range	3.0 (7.5), 0−12
Number of re-experiencing symptoms	0.0 (1.5), 0−4
Number of avoidance symptoms	0.5 (1.0), 0−2
Number of negative cognitions and mood symptoms	1.0 (3.0), 0−5
Number of arousal symptoms	0.5 (2.0), 0−4
Total severity of symptoms (CAPS-5), median (IQR), range	10.0 (16.0), 0−32
Severity of re-experiencing symptoms	2.0 (4.0), 0−9
Severity of avoidance symptoms	2.0 (3.0), 0−6
Severity of negative cognitions and mood symptoms	3.0 (8.0), 0−13
Severity of arousal symptoms	2.0 (5.0), 0−11

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Figure 1

Estradiol at Clinical Interview and Self-Reported Posttraumatic Stress Disorder (PTSD) Symptoms Over the Past Month



Note. Lower estradiol at the time of the clinical interview was associated with more severe avoidance symptoms over the past month (top). Lower estradiol during the interview was also associated with more trauma-related symptoms, as well as more re-experiencing and avoidance symptoms over the past month (bottom). See the online article for the color version of this figure.

reexperiencing symptoms, and more ($r_s = -.40$, $p = .010$) and more severe ($r_s = -.34$, $p = .034$) avoidance symptoms. Estradiol was not associated with total symptom severity ($r_s = -.30$, $p = .057$), the number ($r_s = -.25$, $p = .113$) or severity ($r_s = -.30$, $p = .057$) of arousal symptoms, or the number ($r_s = -.25$, $p = .114$) or severity ($r_s = -.31$, $p = .051$) of negative alterations in cognitions and mood symptoms.

Estradiol and Stress Reactivity to the Trauma Reminder

Estradiol and salivary stress biomarker levels are shown in Table 2. Overall, sAA increased ($Z = 2.66$, $p = .008$, Wilcoxon effect size $r = .42$) whereas cortisol decreased ($Z = -2.06$, $p = .040$, $r = -.33$) in response to the trauma reminder. Estradiol was not associated with either sAA ($r = .05$, $p = .775$) or cortisol ($r = -.01$, $p = .972$) reactivity to the trauma reminder. However, stress response profiles differed between participants who were in lower- versus higher-estradiol phases at the time of the interview (see Figure 2). Compared with participants in high-estradiol phases ($n = 17$), participants in low-estradiol phases ($n = 23$) had greater sAA reactivity ($Z = 2.19$, $p = .029$, $r = .35$) but lower cortisol reactivity ($Z = 2.57$, $p = .010$, $r = .41$).

Menstrual Cycle Phase Effects on Affect

Estradiol, daily affect, and trauma-related symptoms by menstrual cycle phase are shown in Table 3. Mean self-reported daily affect, as measured via EMA, did not change as a function of cycle day from the early to late follicular phase (valence: $b = -.01$, $SE = .03$, $p = .878$; arousal: $b = -.01$, $SE = .03$, $p = .839$). However, the variability of daily affect, as indexed by standard deviations, decreased as a function of cycle day from the early to late follicular phase (valence: $b = -.07$, $SE = .02$, $p < .001$; arousal: $b = -.08$, $SE = .02$, $p < .001$; Figure 3). Positive and negative affect, as indexed by PANAS scores, did not change as a function of cycle day for the morning assessments (positive affect: $b = -.12$, $SE = .07$, $p = .099$; negative affect: $b = -.01$, $SE = .05$, $p = .845$). However, for the evening assessments, both negative ($b = -.11$, $SE = .05$, $p = .034$) and positive ($b = -.24$, $SE = .07$, $p = .001$) affect decreased from the early to late follicular phase.

Menstrual Cycle Phase Effects on PTSD Symptoms

Overall symptom severity, as indexed by EMA PCL scores, decreased as a function of cycle day from the early to late follicular phase ($b = -.39$, $SE = .19$, $p = .039$; Figure 3). Additionally, the severity of negative cognitions and mood ($b = -.19$, $SE = .08$,

Table 2

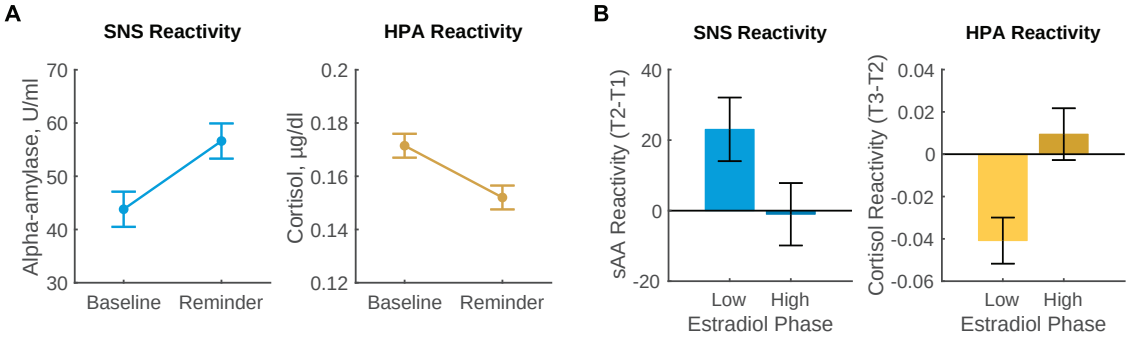
Salivary Estradiol and Stress Biomarkers

Analyte	Median	IQR	Range
Laboratory visit estradiol (pg/mL)	1.04	0.55	0.45–2.62
Low-estradiol phase group estradiol ($n = 23$)	0.97	0.52	0.45–2.33
High-estradiol phase group estradiol ($n = 17$)	1.38	0.81	0.54–2.62
Baseline α-amylase (U/ml)	36.45	38.91	6.72–159.98
Poststressor α-amylase (U/ml)	45.22	57.42	2.29–227.07
α-amylase reactivity (delta)	8.03	22.36	−96.50–187.26
Baseline cortisol (μg/dl)	0.15	0.10	0.06–0.50
Poststressor cortisol (μg/dl)	0.14	0.10	0.02–0.36
Cortisol reactivity (delta)	−0.02	0.06	−0.14 to 0.10

Note. IQR = interquartile range.

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Figure 2
Estradiol and Stress System Reactivity to a Trauma Reminder



Note. Participants showed an increase in sympathetic nervous system (SNS) activity and a decrease in hypothalamic-pituitary-adrenal (HPA) activity to a trauma reminder (A). Participants who were in a low-estradiol menstrual cycle phase showed higher SNS and lower HPA reactivity to the trauma reminder compared with participants in a high-estradiol phase (B). Bars and circles represent means; error bars represent standard errors. See the online article for the color version of this figure.

p = .012) and arousal (b = −.14, SE = .07, p = .043) symptoms decreased from the early to late follicular phase. However, reexperiencing (b = −.06, SE = .05, p = .195) and avoidance (b = −.01, SE = .02, p = .694) symptom severity did not change as function of cycle day.

Discussion

Our results suggest a considerable influence of fluctuations in gonadal hormones on women's vulnerability for symptoms posttrauma. The relation between estradiol and symptoms measured cross-sectionally, as well as menstrual cycle-driven differences in daily affect and symptoms measured over time, demonstrate the key role of estradiol in the expression of trauma symptoms in women. Consistent with our first hypothesis, lower estradiol during the laboratory visit was associated with more trauma-related symptoms reported during the clinical interview. This association was driven by two symptom clusters: reexperiencing symptoms and avoidance symptoms. Report of more symptoms in lower-estradiol states aligns with the existing evidence for a protective effect of estradiol on intrusive thoughts and memories, which characterize reexperiencing symptoms (e.g., Soni et al., 2013; Wegerer et al., 2014). Estradiol levels at the time of assessment might influence current affective state and color the perception of episodic trauma symptoms over the past month, consistent with prior evidence for biased retrospective reports of affect (e.g., Mill et al., 2015).

Table 3
Estradiol, Daily Affect, and Trauma-Related Symptoms by Menstrual Cycle Phase

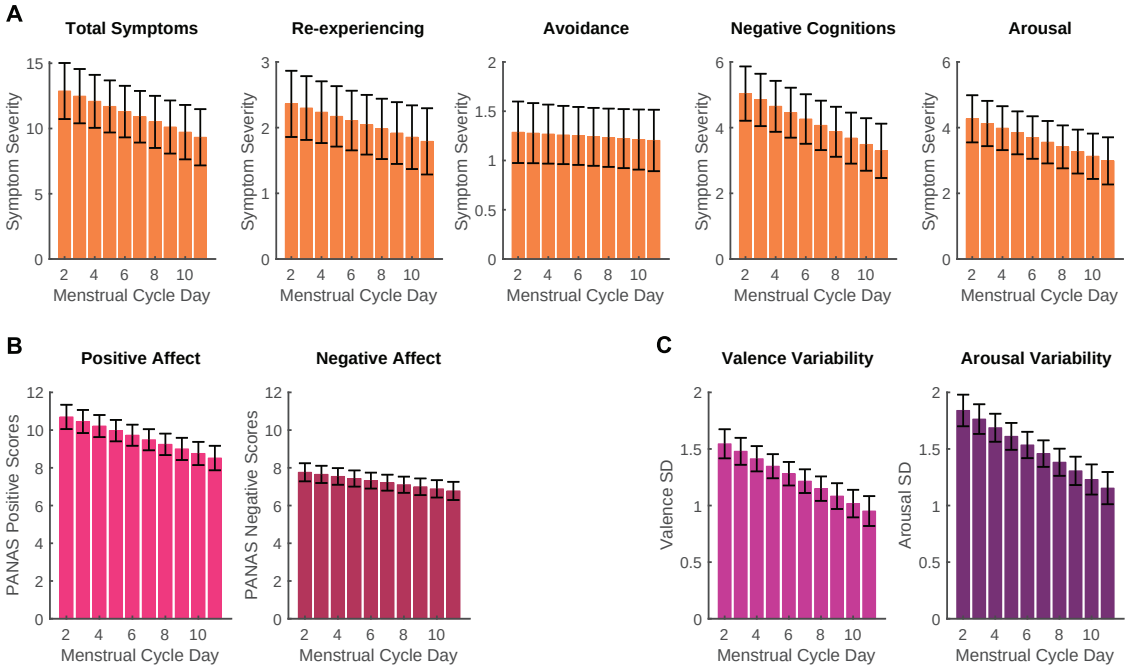
Variable	Early Follicular Phase (Cycle Days 2–6) Mdn	IQR	Range	Late Follicular Phase (Cycle Days 7–11) Mdn	IQR	Range	b	SE
Estradiol, pg/mL	0.88	0.42	0.51−1.78	1.30	0.96	0.67−5.85		
			Trauma-related symptoms across the five days of each phase (PCL-5)					
Total symptoms	9.5	14.6	0.0–47.2	6.2	13.0	0.0–50.0	−0.39*	0.19
Re-experiencing	1.7	3.0	0.0–8.2	0.4	2.6	0.0–10.4	−0.06	0.05
Avoidance	0.8	1.8	0.0–7.6	0.4	1.8	0.0–7.4	−0.01	0.02
Negative cognitions	3.4	6.8	0.0–15.0	2.2	5.2	0.0–15.8	−0.19*	0.08
Arousal	3.3	4.4	0.0–16.4	2.2	4.0	0.0–16.4	−0.14*	0.07
			Daily affect scores across the five days of each phase					
Valence (*M*)	6.1	1.3	2.7–7.5	6.1	1.8	2.0–8.3	−0.01	0.03
Arousal (*M*)	4.8	1.7	1.4–7.3	4.6	2.2	1.1–8.1	−0.01	0.03
Valence (*SD*)	1.8	0.9	0.8–2.9	1.5	1.0	0.3–2.7	−0.07***	0.02
Arousal (*SD*)	1.9	0.7	0.6–3.0	1.8	0.9	0.0–3.1	−0.08***	0.02
PANAS Negative (AM)	6.6	2.1	5.0–13.4	6.1	3.3	5.0–13.8	−0.01	0.05
PANAS Negative (PM)	6.8	4.0	5.0–14.0	6.0	2.2	5.0–14.0	−0.11*	0.05
PANAS Positive (AM)	9.8	3.8	6.2–15.8	9.2	3.8	5.2–15.4	−0.12	0.07
PANAS Positive (PM)	9.3	5.8	5.0–17.4	8.7	5.2	5.0–16.4	−0.24**	0.07

Note. Mdn = median; IQR = interquartile range; PCL-5 = the Posttraumatic Stress Disorder Checklist for *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; AM = morning assessments; PM = evening assessments. The b and SE correspond to the fixed effect of cycle day in multilevel models.
*$p < .05$. **$p < .01$. ***$p < .001$.

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Figure 3

Menstrual Cycle Phase Differences in Posttraumatic Stress Disorder (PTSD) Symptoms and Affect



Note. Total PTSD symptom severity decreased as function of cycle day from the early (days 2–6, lower estradiol) to late (days 7–11, higher estradiol) follicular phase. This effect was driven by negative cognitions and arousal symptoms (A). Positive and negative affect on evening assessments also decreased from the early to late follicular phase (B). Finally, variability in daily valence and arousal ratings also decreased from the early to late follicular phase (C). The graphs represent the fixed effect of menstrual cycle day, as estimated by the random-intercepts models. Bars represent model fit; error bars represent standard errors. See the online article for the color version of this figure.

We also demonstrate differences in stress reactivity by menstrual cycle phase. Consistent with previous work in trauma-exposed populations (e.g., Carpenter et al., 2011), our sample as a whole showed SNS reactivity, but blunted HPA axis reactivity, to a trauma reminder. Counter to our second hypothesis, however, individual variation in estradiol was not associated with stress reactivity to a trauma reminder. However, when we divided the sample into two groups according to menstrual cycle phase at the time of the interview, group differences emerged. Participants in lower-estradiol phases (i.e., early follicular, early luteal, late luteal) had higher SNS and lower HPA reactivity than participants in higher-estradiol phases (i.e., late follicular, midcycle, midluteal). These data are consistent with evidence that links the stress response profile of higher SNS and lower HPA axis activity with more affective symptoms in trauma-exposed populations (e.g., Ali & Pruessner, 2012). Further, our results support the importance of accounting for menstrual cycle phase in research on stress reactivity in trauma survivors.

Consistent with our third hypothesis, daily affective experiences differed by menstrual cycle phase. Variability in self-reported affect decreased linearly from the early follicular (low estradiol) to the late follicular (high estradiol) phase. These data suggest that affective lability during low-estradiol phases might contribute to greater subjective distress, which is consistent with evidence that affective variability contributes to perceived negative affect (e.g., Wichers et al., 2010). During the early follicular phase, participants also more strongly endorsed positive and negative affective states, although this effect only applied to evening reports. Reporting of higher-frequency positive and negative affect provides additional evidence for more variable, rather than strictly negative, affect during low-estradiol states.

In addition to self-reported affect, the severity of daily trauma-related symptoms also decreased from the early to late follicular phase. This effect was primarily driven by negative alterations in cognitions and mood, which encompass persistent negative affect and cognitions, such as inappropriate self-blame and exaggerated negative beliefs. The severity of arousal symptoms, which encompass heightened physiological arousal, both tonically and in response to external stimuli, also decreased from the early to late follicular phase. These data are consistent with evidence for poorer psychological well-being (e.g., Nillni et al., 2015) and increased physiological arousal (e.g., Kanojia et al., 2013) during low-estradiol phases of the cycle. To our knowledge, however, our study is the first to demonstrate greater negative cognitions in trauma-exposed women during a low- compared with high-estradiol phase. Our results suggest that lower estradiol might render women more prone to negative affective states and thus negative thoughts or feelings about past events (including past trauma).

Consistent with previous evidence for differences between interview and experience-sampling methods (e.g., Solhan et al.,

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2009), we show that estradiol might have distinct effects on recall of symptoms during a clinical interview and the experience of symptoms in daily life. Lower estradiol was associated with greater recall of reexperiencing and avoidance symptoms during the clinical interview. This result suggests that recall of past-month episodic symptoms is colored by current affective state, which is in turn impacted by estradiol levels. In contrast, the lower-estradiol menstrual cycle phase was characterized by greater self-reported severity of daily arousal and negative cognition and mood symptoms. This result suggests that EMA reports provide a more sensitive measure of phase-related differences in the more generalized symptom clusters.

There are several limitations to our study that warrant attention in future work. We timed the EMA portion of the study to occur at a specific point in the menstrual cycle, and we verified menstrual cycle phase during EMA using gonadal hormone measurement. However, we did not preassign lab visit timing based on menstrual cycle phase, and thus we had to estimate menstrual cycle phase during the clinical interview based on participants' recent cycles. We therefore were not able to directly test the effect of cycle phase on stress reactivity. To better address this issue, researchers might assess all participants during a specific cycle phase and subsequently test associations between estradiol and stress reactivity. In addition, despite our confidence that a dimensional approach to trauma-related symptoms allows robust measurement of the phenomena of interest, as large effects should be observable even in subclinical groups, our EMA results nonetheless should be replicated in clinical (e.g., PTSD) populations. Although our observed differences in affect by menstrual cycle phase might be more evident in clinical populations, it is also possible that women with PTSD experience symptoms more consistently across the cycle, with no alleviation of symptoms during high-estradiol phases.

Taken together, our results suggest that lower-estradiol states are associated with higher risk for trauma-related symptoms and greater affective lability in trauma-exposed women. Client report of more trauma-related symptoms in response to assessment in low- versus high-estradiol phases could influence diagnostic status or assessed PTSD severity. Low-estradiol portions of the cycle might be the time window where interviews would be most sensitive to any current PTSD symptoms and when the reported symptoms might be most severe. Clinicians might improve diagnostic accuracy by accounting for client menstrual cycle phase at the time of assessment. In addition to symptoms, our results also demonstrate differential stress reactivity between lower- and higher-estradiol phases and suggest that studies of stress reactivity in trauma-exposed women should control for menstrual cycle phase. Better knowledge of menstrual cycle variability in affect can also inform treatment. Clinicians who work with PTSD populations could gather information about clients' recent menstrual cycles to predict when clients might experience more frequent aversive daily experiences, including symptoms. Clinicians could also potentially tailor treatments and schedule interventions at specific points in the menstrual cycle. During higher-estradiol states, women show better extinction learning and better overall mood, and these differences might enhance the efficacy of cognitive behavior therapies (e.g., exposure therapy). The degree to which some treatments might be more effective during some menstrual phases is an exciting avenue for future clinical trials. Finally, clinicians might provide psychoeducation to help their clients better anticipate changes in symptoms that might occur across the menstrual cycle.

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