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Trauma Characteristics Moderate the Relation Between Estradiol and Trauma-Related Symptoms

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Abstract

Women are more likely to develop posttraumatic stress disorder (PTSD) than men, and fluctuations in gonadal hormones might contribute to this vulnerability. Low-estradiol states are associated with aversive affective experiences, including trauma-related symptoms. However, the impact of trauma characteristics on the relation between estradiol and trauma-related symptoms is unknown. We used a clinical interview and 10-day ecological momentary assessment (EMA) that spanned low- and high-estradiol menstrual cycle phases to test trauma type, chronicity, and timing as moderators of the association between estradiol and trauma-related symptoms in 40 naturally cycling young women. We tested interactions between trauma characteristics and (a) estradiol on self-reported symptoms and (b) menstrual cycle-related change in estradiol on change in symptoms. Sexual, chronic, and earlier trauma was associated with more severe symptoms as reported during the interview, $r_s = .51-.33$, but not mean symptoms across the EMA. Estradiol at the time of the interview was inversely associated with symptoms in women with sexual, but not nonsexual, trauma, interaction: $B = -12.62$ ($SE = 5.28$), $p = .022$. Menstrual cycle-related change in estradiol was inversely associated with change in symptoms in women with chronic trauma, $B = -9.65$ ($SE = 3.49$), $p = .006$, and earlier trauma, $B = 0.71$ ($SE = 0.34$), $p = .036$, but not discrete or later trauma. Sexual, chronic, or early trauma exposure might confer greater vulnerability for symptoms in low-estradiol states. Clinicians who work with women with particular trauma histories might anticipate menstrual cycle-related variation in symptoms.

Trauma Characteristics Moderate the Relation Between Estradiol and Trauma-Related Symptoms

In women, trauma exposure is associated with a higher risk for posttraumatic stress disorder (PTSD; e.g., Perrin et al., 2014) and greater symptom severity (e.g., Seedat et al., 2005) and symptom persistence (e.g., Holbrook et al., 2002) compared with men. Fluctuations in ovarian hormones, such as estradiol, might contribute to women's greater susceptibility to trauma-related symptoms. For example, low-estradiol states are broadly associated with an increased risk of aversive affective experiences, such as elevated psychological symptoms (e.g., Gonda et al., 2008). In addition, lower estradiol has been associated with maladaptive fear responses, such as persistent fear following extinction (e.g., Milad et al., 2010), reduced fear inhibition in the presence of safety cues (Glover et al., 2013), and intrusive memories after viewing unpleasant content (Wegerer et al., 2014). Lower estradiol has also been associated with heightened stress reactivity, including higher sympathetic and lower parasympathetic activity (e.g., Kanojia et al., 2013) and greater activation of stress-relevant circuitry during aversive image processing (e.g., Goldstein et al., 2005). Maladaptive fear responses and heightened stress reactivity in low-estradiol states could respectively contribute to reexperiencing and arousal symptoms following trauma exposure. Accordingly, trauma-exposed women experience greater psychological distress in low-estradiol menstrual cycle phases (Nillni et al., 2015).

Thus, accumulating evidence suggests that low-estradiol states might contribute to the risk of more severe trauma-related symptoms. However, much of the previous research has focused on comparisons between the early follicular and mid-luteal phases. Given that the mid-luteal phase includes high progesterone as well as high estradiol, these comparisons make it difficult to isolate the effects of estradiol. Additionally, less is known about the interaction between estradiol and other risk

factors for PTSD, such as characteristics of the traumatic event. Trauma characteristics, such as the type, chronicity, and timing (i.e., the age at which the exposure occurred) of the traumatic event, can confer greater susceptibility to adverse posttrauma mental health outcomes. For example, compared with other trauma types, sexual trauma has been associated with a higher risk of PTSD (McCutcheon et al., 2010) and higher symptom counts (Smith et al., 2016), severity (Dworkin et al., 2017), and persistence (Müller et al., 2018). In addition, chronic trauma has been associated with more symptoms, particularly higher levels of guilt and shame, compared to single-event traumatic events (Hagenaars et al., 2011). Finally, trauma exposure at a younger age has also been associated with a greater risk of PTSD (McCutcheon et al., 2010), more severe symptoms (Schoedl et al., 2010), and greater symptom persistence (Müller et al., 2018). In addition to an increased risk of a higher total PTSD symptom count, specific trauma characteristics have been related to specific symptom clusters in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* PTSD diagnostic criteria. For example, sexual trauma has been associated with more severe symptoms in the avoidance and negative alterations in cognitions and mood clusters compared with nonsexual trauma (Guina et al., 2018).

Although there is a robust literature on the impact of trauma characteristics, such as trauma type, chronicity, and timing, on symptom severity, less is known about the interactions between trauma characteristics and physiological factors that are unique to women, such as ovarian hormone fluctuations. To date, most research on PTSD has focused on men, and most studies that have included women have not controlled for hormonal status or menstrual cycle phase. Although women are more likely to experience trauma types that are associated with a higher risk of PTSD, trauma type alone does not account for women's increased risk (Tolin & Foa, 2006). Rather, characteristics of the traumatic event might modulate the impact of biological factors, such as

fluctuations in ovarian hormones, on mental health outcomes in trauma-exposed women. For example, sensitivity to cyclic variation in ovarian hormones differs by trauma type (Eisenlohr-Moul et al., 2016). In particular, exposure to physical abuse has been associated with a greater effect of progesterone fluctuations on mood and interpersonal difficulties (e.g., interpersonal conflicts, rejection sensitivity). In contrast, exposure to sexual abuse has been associated with a greater effect of estradiol fluctuations on anxiety symptoms. Sexual abuse also has been associated with an elevated risk of premenstrual dysphoric disorder (PMDD), which is characterized by cognitive, affective, and physical symptoms that co-occur with menstrual cycle-related hormonal changes (Girdler et al., 2003). The higher prevalence of sexual trauma in women with PMDD compared to the general population (Golding et al., 2000) suggests that sexual trauma might increase women's sensitivity to fluctuations in ovarian hormones (e.g., estradiol).

Together, preliminary evidence suggests that low-estradiol states might contribute to women's vulnerability to symptoms, and trauma characteristics might moderate this vulnerability. Women with a history of traumatic events that are associated with poorer outcomes (e.g., sexual, chronic, or early-life trauma exposure) might be more sensitive to the deleterious effects of lower estradiol and/or the protective effects of higher estradiol. To test this hypothesis, we assessed trauma characteristics, including type, chronicity, and timing, as moderators of the relation between estradiol and trauma-related symptoms in a nonclinical sample of naturally cycling young women. We used a mixed cross-sectional and longitudinal design to assess trauma-related symptoms over the past month, using a structured clinical interview, and during the early (i.e., low estradiol) and late (i.e., high estradiol) follicular phase, using a 10-day ecological momentary assessment (EMA). The EMA approach allowed us to track menstrual

cycle changes in daily symptoms within a naturalistic context (i.e., participants' daily-life environments). We focused on the follicular phase of the menstrual cycle (i.e., cycle days 2–11) for the EMA because estradiol increases markedly from the early to late follicular phase, whereas progesterone levels remain low. We hypothesized that sexual, chronic, and/or earlier-life trauma exposure would be associated with greater severity of self-reported symptoms compared with nonsexual, discrete, and later-life trauma, respectively. We also hypothesized that women with a history of sexual, chronic, and/or earlier-life trauma would demonstrate stronger associations between (a) estradiol and symptoms, as measured during the clinical interview and (b) change in estradiol and change in symptoms from the early to late follicular phase.

Method

Participants

We recruited 40 naturally cycling trauma-exposed women aged 18–33 years ($M = 21.85$ years, $SD = 4.25$) from an urban university in the northeastern United States (Table 1).

Participants were recruited based on their responses on a self-report screening measure for exposure to potentially traumatic life events (Weathers, Blake, et al., 2013). We recruited participants who reported having a regular menstrual cycle, defined as an average cycle length between 25 and 36 days and no missed periods within the past 6 months. The exclusion criteria were: (a) hormonal contraceptive use in the past 6 months; (b) pregnancy or lactation within the past year; (c) the use of beta-blockers, corticosteroids, or anxiolytic medications; (d) habitual cigarette smoking; and (e) current psychiatric disorder other than PTSD.

More than half of the sample (55.0%) reported having experienced sexual trauma, and half of the participants reported having experienced chronic trauma. Eleven participants (27.5%) reported both sexual and chronic trauma. The timing of participants' index traumatic events

ranged from childhood (37.5%) and adolescence (37.5%) to emerging adulthood (25.0%). All participants had regular menstrual cycles, with an average cycle length of 26–35 days ($M = 30.27$ days, $SD = 2.46$). Participants' progesterone values at the end of the EMA phase had a median of 66.40 pg/mL, interquartile range (IQR) = 41.38, which is within the normative range for the follicular phase (Soni et al., 2013). The results of a Wilcoxon signed-rank test showed that estradiol increased from cycle day 2 to cycle day 11, as expected, $Z = 4.47$, $p < .001$, $r = .83$.

The counts and severity of trauma-related symptoms over the past month and during the EMA are presented in Table 2. Participants reported a range of symptoms, and eight women (20.0%) met the criteria for a provisional PTSD diagnosis. Age was not associated with symptoms, $ps = .357-.933$. Average symptom severity was higher during the early versus late follicular phase, $Z = 2.28$, $p = .023$, $r = .42$.

Procedure

The study consisted of two parts. First, participants completed a laboratory visit, where they were administered a structured clinical interview and provided a saliva sample. Next, the women completed a 10-day EMA, which spanned the early and late follicular menstrual cycle phases. All study procedures were approved by the Institutional Review Board of the City University of New York. Before the study began, participants provided informed consent once study procedures were thoroughly explained by an experimenter and outlined in written form.

Clinical Interview

After providing informed consent, participants completed a clinical interview to verify trauma exposure and assess clinical symptoms. We also assessed characteristics of the index trauma (i.e., the participant's self-reported most distressing traumatic event), including trauma type (i.e., sexual vs. nonsexual), chronicity (i.e., chronic vs. discrete), and timing (i.e., age at

trauma exposure). Chronic trauma was defined as (a) an event that lasted several weeks or longer or (b) a series of repeated events that occurred in the same overall context over the course of weeks or longer (e.g., repeated sexual abuse by a family member). Discrete trauma was defined as (a) a single event with a clear beginning and end or (b) multiple unrelated events with a clear beginning and end that occurred in different contexts. Participants also reported the dates of their last three menstrual cycles, which we used to determine menstrual cycle length and menstrual phase at the time of the interview.

Saliva Collection

On the morning of the lab visit, after consent, we collected saliva samples to measure estradiol; to control for diurnal variation in estradiol, this collection occurred at approximately 10:05 a.m. We collected saliva samples using passive drool via Salimetrics saliva collection aids (Salimetrics, LLC; State College, PA). All participants had been awake for at least 1 hr before the study began such that saliva collection did not overlap with the estradiol awakening response. Participants refrained from eating or drinking, except for water, for 1 hr before the study. The samples were stored in cryovials in a -20 °C freezer.

EMA

The EMA began on day 2 of participants' menstrual cycle and comprised 10 days spanning the early follicular (i.e., cycle days 2–6, marked by lower estradiol and lower progesterone) and late follicular (i.e., cycle days 7–11, marked by higher estradiol and lower progesterone) phases. The study design ensured that even participants with shorter cycles would remain in the follicular phase. We also confirmed that participants were in the expected menstrual cycle phases by measuring levels of ovarian hormones in two at-home saliva samples. Participants collected at-home saliva samples on the first and last days of the EMA, which

correspond to cycle day 2 (i.e., early follicular phase) and cycle day 11 (i.e., late follicular phase). Participants were instructed to collect the saliva samples via passive drool immediately upon waking and received text message reminders on the appropriate mornings. At-home samples were stored in participants' home freezers and later transported to the lab in insulated containers. Samples were then stored in a -20 °C laboratory freezer.

We provided each participant with a handheld device (i.e., an Android phone) for the duration of the EMA. On the first day of her menstrual cycle, each participant contacted an experimenter to report that her cycle had started, and the EMA prompts were programmed to start the following day. During the 10 days of the EMA, participants received daily text messages instructing them to complete questionnaires. Trauma-related symptoms were assessed before bedtime.

Measures

Trauma-Related Symptoms

During the clinical interview, we assessed lifetime trauma exposure and past-month PTSD symptoms using the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5; Weathers, Blake, et al., 2013a; in our sample Cronbach's $\alpha = .88$). The CAPS is a widely used and validated measure used to assess the severity of each *DSM-5* PTSD symptom on a scale ranging from 0 (*absent*) to 4 (*extreme/incapacitating*).

During the EMA phase, we measured daily symptoms using the PTSD Checklist for *DSM-5* (PCL-5; Weathers, Litz, et al., 2013; in our sample Cronbach's $\alpha = .93$). Participants reported the extent to which they were bothered by each symptom that day on a scale ranging from 0 (*not at all*) to 4 (*extremely*).

Psychiatric Diagnoses

Current symptoms of other major psychiatric disorders were assessed using the Structured Clinical Interview for *DSM-IV* Disorders (SCID; First et al., 1996).

Hormone Assays

Hormone assays were conducted in-house by lab personnel. We used Salimetrics enzyme immunoassay kits to measure estradiol on the morning of the lab visit and both estradiol and progesterone in the at-home saliva samples. All samples were processed in duplicate. Any samples with a coefficient of variation (CV) exceeding 15% were redone. The mean CVs for our samples were 5.13% for estradiol and 7.02% for progesterone.

Data Analysis

One participant did not provide the chronicity of her trauma and was excluded from the relevant analyses. Four participants were excluded from the EMA analyses due to invalid estradiol values in the at-home saliva samples (i.e., estradiol values that were inconsistent with the expected menstrual cycle phase, $n = 3$; change in estradiol from the early to late follicular phase more than 3 standard deviations above the group mean, $n = 1$). Seven participants had invalid or insufficient EMA data (i.e., more than 50.0% of their assessments were missing or had been completed at inappropriate times) and were excluded from EMA analyses. For the remaining sample, the overall compliance was 96.7%.

We tested the effects of trauma type (sexual vs. nonsexual), chronicity (chronic vs. discrete), and timing (age at trauma exposure) on (a) trauma-related symptoms over the past month, as reported during the clinical interview, and (b) trauma-related symptoms averaged over the 10-day EMA period. Because symptom data were not normally distributed, we used Wilcoxon rank-sum tests to test group differences in symptoms by trauma type and chronicity and Spearman rank-order correlations to test the relation between symptoms and trauma timing.

We also tested trauma type, chronicity, and timing as moderators of the relation between estradiol on the morning of the lab visit and trauma-related symptoms over the past month, as reported during the clinical interview. We used separate linear regression models for each trauma characteristic and included the following predictors of symptom severity in each model: estradiol, trauma characteristic (i.e., type, chronicity, or timing), and their two-way interaction. Statistically significant interaction terms were interpreted as evidence of moderation. Finally, we used multilevel modeling (MLM) to test trauma type, chronicity, and timing as moderators of the relation between change in estradiol from cycle day 2 to cycle day 11 and change in trauma-related symptoms from the early follicular phase (i.e., cycle days 2–6) to the late follicular phase (i.e., cycle days 7–11). For each trauma characteristic, we tested a separate random-intercept model that included cycle phase (Level 1), change in estradiol (Level 2), trauma characteristics (Level 2), and their three-way interaction. We also included cycle day as a Level 1 predictor and specified the first-order autoregressive error structure to account for autocorrelation between consecutive days. MLM analyses were performed in R (Version 4.0.2) using the *nlme* package. The details of each model are presented in Supplementary Information.

Results

Trauma Characteristics and Trauma-Related Symptoms

During the interview, women who had experienced sexual trauma reported greater symptom severity over the past month compared with women who had experienced nonsexual trauma (Figure 1, Panel A), $Z = 3.17, p = .002, r = .50$ for total symptoms; $Z = 2.96, p = .003, r = .47$ for reexperiencing symptoms; $Z = 2.41, p = .016, r = .38$ for avoidance symptoms; $Z = 2.38, p = .017, r = .38$ for negative alterations in cognitions and mood symptoms; and $Z = 2.70, p = .007, r = .43$ for arousal symptoms. There was no difference between women with sexual versus

nonsexual trauma in symptoms averaged across the 10-day EMA period, $Z = 0.64$, $p = .521$, $r = .12$ for total symptoms; $Z = 1.02$, $p = .308$, $r = .19$ for reexperiencing symptoms; $Z = 0.93$, $p = .350$, $r = .17$ for avoidance symptoms; $Z = 0.13$, $p = .894$, $r = .02$ for negative alterations in cognitions and mood symptoms; and $Z = 0.55$, $p = .579$, $r = .10$ for arousal symptoms.

During the interview, women who had experienced chronic trauma reported more severe total symptoms, $Z = 2.99$, $p = .003$, $r = .47$ (Figure 1 Panel B); and more severe symptoms of avoidance, $Z = 2.11$, $p = .035$, $r = .33$; negative alterations in cognitions and mood, $Z = 3.22$, $p = .001$, $r = .51$; and arousal, $Z = 2.43$, $p = .015$, $r = .38$; but not reexperiencing, $Z = 1.77$, $p = .078$, $r = .28$, compared with women who had experienced a single traumatic event or multiple discrete traumatic events (i.e., discrete trauma). Women with chronic trauma also reported more severe avoidance symptoms averaged across the 10-day EMA compared to women with discrete trauma, $Z = 2.01$, $p = .044$, $r = .37$. However, there was no difference between women with chronic versus discrete trauma in total symptoms, $Z = 1.66$, $p = .097$, $r = .31$; or symptoms of reexperiencing, $Z = 1.61$, $p = .107$, $r = .30$; negative alterations in cognitions and mood, $Z = 1.34$, $p = .182$, $r = .25$; or arousal, $Z = 1.22$, $p = .221$, $r = .23$, averaged across the EMA.

Age at trauma was inversely associated with the severity of negative alterations in cognitions and mood symptoms reported during the interview (Figure 1, Panel C), $r_s = -.36$, $p = .023$. Age at trauma was not associated with the severity of total symptoms, $r_s = -.26$, $p = .099$; reexperiencing symptoms, $r_s = -.08$, $p = .630$; avoidance symptoms, $r_s = -.12$, $p = .454$; or arousal symptoms, $r_s = -.24$, $p = .136$. Trauma timing was also not associated with symptoms averaged across the EMA: $r_s = -.29$, $p = .126$ for total symptoms; $r_s = -.16$, $p = .403$ for reexperiencing symptoms; $r_s = -.24$, $p = .210$ for avoidance symptoms; $r_s = -.29$, $p = .129$ for negative alterations in cognitions and mood symptoms; and $r_s = -.28$, $p = .140$ for arousal symptoms.

Trauma Characteristics and the Relation Between Estradiol and Symptoms

There was an interaction between trauma type and estradiol on the morning of the clinical interview on self-reported trauma-related symptoms over the past month. Estradiol was inversely associated with total symptom severity, $B = -12.62$, $SE = 5.28$, $p = .022$; avoidance symptom severity, $B = -2.27$, $SE = 1.02$, $p = .032$; and arousal symptom severity, $B = -4.93$, $SE = 1.61$, $p = .004$, in women with sexual but not nonsexual trauma (Figure 2). The interaction between trauma type and estradiol on reexperiencing symptom severity was not significant, $B = -2.78$, $SE = 1.46$, $p = .065$. There was no interaction between trauma type and estradiol on the severity of negative alterations in cognitions and mood symptoms, $p = .186$; however, sexual trauma was associated with greater symptom severity after controlling for estradiol, $B = 3.34$, $SE = 1.23$, $p = .010$.

There were no interactions between trauma chronicity and estradiol on the morning of the clinical interview on self-reported symptom severity over the past month, $ps = .506$ —.918. However, chronic trauma was associated with greater total symptom severity, $B = 7.11$, $SE = 2.99$, $p = .023$, and greater severity of negative alterations in cognitions and mood symptoms, $B = 3.78$, $SE = 1.25$, $p = .005$, after controlling for estradiol. In addition, estradiol showed a nonsignificant inverse association with avoidance, $B = -1.06$, $SE = 0.57$, $p = .072$, and arousal symptom severity, $B = -1.86$, $SE = 0.99$, $p = .068$, after controlling for trauma chronicity.

There were no interactions between trauma timing and estradiol on the morning of the clinical interview on self-reported symptoms over the past month, $ps = .651$ —.752. However, age at trauma was inversely associated with the severity of negative alterations in cognitions and mood symptoms after controlling for estradiol, $B = -0.27$, $SE = 0.11$, $p = .018$. In addition, estradiol was inversely associated with the severity of total symptoms, $B = -6.17$, $SE = 3.03$, $p = .049$; avoidance symptoms, $B = -1.24$, $SE = 0.55$, $p = .030$, model $F(1, 37) = 2.7$, $p = .080$,

adjusted $R^2 = .08$; and arousal symptoms, $B = -1.99$, $SE = 0.95$, $p = .043$, model $F(1, 37) = 3.07$, $p = .058$, adjusted $R^2 = .10$; after controlling for trauma timing.

Trauma Characteristics and the Relation Between Menstrual Cycle–Related Change in Estradiol and Change in Symptoms

There were no interactions between trauma type, menstrual cycle phase, and change in estradiol from cycle day 2 to cycle day 11 on total symptom severity or on any of the symptom clusters separately, as measured during the EMA, $ps = .097$ —.549. There was an interaction between trauma chronicity, menstrual cycle phase, and change in estradiol on total symptoms, $B = -9.65$, $SE = 3.49$, $p = .006$; reexperiencing symptoms, $B = -1.95$, $SE = 0.92$, $p = .035$; negative alterations in cognitions and mood symptoms, $B = -3.25$, $SE = 1.43$, $p = .024$; and arousal symptoms, $B = -2.81$, $SE = 1.23$, $p = .023$, but not avoidance symptoms, $B = -0.85$, $SE = 0.46$, $p = .066$. An increase in estradiol from cycle day 2 to cycle day 11 was associated with a decrease in symptom severity from the early to late follicular phase in women with chronic trauma, whereas women with discrete trauma showed the opposite relation (Figure 3, Panel A). There was also an interaction between trauma timing, menstrual cycle phase, and change in estradiol from cycle day 2 to cycle day 11 on total symptoms, $B = 0.71$, $SE = 0.34$, $p = .036$; avoidance symptoms, $B = 0.09$, $SE = 0.04$, $p = .029$; and negative alterations in cognitions and mood symptoms, $B = 0.27$, $SE = 0.13$, $p = .047$, but not reexperiencing symptoms, $B = 0.12$, $SE = 0.09$, $p = .187$; or arousal symptoms, $B = 0.17$, $SE = 0.12$, $p = .176$. An increase in estradiol from cycle day 2 to cycle day 11 was associated with a decrease in symptom severity from the early to late follicular phase in women with earlier but not later trauma (Figure 3, Panel B).

Discussion

We tested trauma characteristics as moderators of the relation between trauma-related symptoms and estradiol in a sample of naturally cycling young women during a lab visit and across a 10-day EMA period that included low- and high-estradiol menstrual cycle phases. Consistent with our first hypothesis, trauma characteristics were associated with greater severity of retrospectively reported symptoms over the past month. Women with a history of sexual compared to nonsexual trauma reported more severe trauma-related symptoms across all symptom clusters. Similarly, women with a history of chronic compared to discrete traumatic events reported greater total symptom severity and greater severity of avoidance, arousal, and negative alterations in cognitions and mood symptoms. These results are consistent with prior evidence of more severe and persistent trauma-related symptoms in survivors of sexual and chronic trauma (Ehring & Quack, 2010; Müller et al., 2018). In addition, younger age at trauma was associated with greater severity of negative alterations in cognitions and mood symptoms, but not other symptom clusters. This result suggests that exposure to traumatic events early in life might have long-lasting effects on a person's view of the world and affective processing (Ogle et al., 2013). In contrast, the disproportionate negative impact of early-life events on more episodic symptoms, such as reexperiencing or avoidance, might diminish over time. Together, these results suggest that specific trauma characteristics are associated with distinct trauma-related symptoms.

Consistent with our second hypothesis, there was an interaction between trauma type and estradiol during the clinical interview on retrospective self-report of symptoms over the past month. Lower estradiol was associated with greater severity of total, avoidance, and arousal symptoms but only in women who reported sexual trauma. Compared with women who reported nonsexual trauma, women with sexual trauma reported greater symptom severity in low-estradiol

states and similar symptom severity in high-estradiol states. In contrast, there was no interaction between trauma type and estradiol on negative alterations in cognitions and mood symptoms. Rather, sexual trauma was associated with more severe negative alterations in cognitions and mood symptoms even after controlling for estradiol. These results suggest that women with a history of sexual trauma might be particularly sensitive to the effects of cyclic estradiol fluctuations, especially the deleterious effects of low estradiol. However, the moderating effect of estradiol appears to be symptom-specific and might be more pronounced for symptoms that are episodic (e.g., avoidance) or physiological (e.g., arousal). These results are consistent with previous reports of maladaptive fear responses (e.g., Glover et al., 2013) and increased sympathetic activity (e.g., Kanojia et al., 2013) in low-estradiol states. Conversely, symptoms that are more pervasive or cognitive (e.g., negative alterations in cognitions and mood) were not moderated by estradiol and were consistently reported as being more severe by women with sexual versus nonsexual trauma.

In contrast to trauma type, there were no interactions between trauma chronicity and estradiol on self-reported symptoms over the past month. However, compared with women who reported discrete traumatic events, women exposed to chronic trauma reported greater total symptom severity and more severe negative alterations in cognitions and mood symptoms after controlling for estradiol. There also were no interactions between trauma timing and estradiol on symptoms reported during the interview. However, younger age at trauma was associated with more severe negative alterations in cognitions and mood symptoms after controlling for estradiol. Lower estradiol was associated with greater severity of total, arousal, and avoidance symptoms after controlling for trauma timing. Together, these results suggest that only some trauma characteristics moderate the relation between estradiol and retrospective symptom report

and that this moderation is specific to symptoms that are episodic or have a strong physiological component (e.g., arousal, avoidance). In contrast, symptoms that are more stable or cognitive (e.g., negative alterations in cognitions and mood) are more closely tied to specific trauma characteristics (e.g., sexual, chronic, and early-life trauma).

In contrast to the retrospective assessment of symptoms during the clinical interview, experience sampling using EMA allowed us to longitudinally track changes in daily symptoms during low- and high-estradiol phases, which revealed a different pattern of relations among trauma characteristics, estradiol, and symptoms. Whereas sexual trauma was associated with greater severity of retrospectively reported symptoms over the past month, there were no differences between women with sexual versus nonsexual trauma in mean symptom severity across the 10-day EMA period. Similarly, whereas chronic trauma was associated with greater severity of retrospectively reported symptoms, the only difference across the EMA period between women who reported chronic versus discrete traumatic events was in avoidance symptoms. Likewise, whereas younger age at trauma was associated with greater severity of retrospectively reported negative alterations in cognitions and mood symptoms, there were no associations between trauma timing and mean symptom severity across the EMA period. One possible explanation for this discrepancy between the interview and the EMA is that during the interview, participants reported symptoms that occurred across the past month (i.e., the entire menstrual cycle), whereas the EMA spanned only the follicular phase. Future studies might measure symptom trajectories across the menstrual cycle.

The interactions between trauma characteristics and estradiol on trauma-related symptoms also differed between the clinical interview and the EMA. Whereas trauma type (sexual vs. nonsexual) moderated the association between estradiol and retrospectively reported

symptoms, trauma type did not moderate the relation between change in estradiol and change in symptoms from the early to late follicular phase. These results are consistent with previous evidence that symptoms assessed via retrospective self-report differ from ambulatory reports of symptoms in daily life (e.g., Solhan et al., 2009). Our data also suggest that estradiol levels at the time of clinical assessment might influence the respondent's current affective state and color their perception of trauma-related symptoms and distress over the past month. A potential explanation for greater self-reported symptom severity during the clinical interview compared to daily sampling in women with sexual, chronic, and early-life trauma is that the interview serves as a trauma reminder, which could induce a negative affective state and increase report of recent symptoms. Our data also suggest that estradiol had a greater impact on self-reported symptoms in survivors of sexual trauma, for whom disclosure of the traumatic event might be particularly distressing, given the associated stigma (e.g., Delker et al., 2020). We speculate that in sexual trauma survivors, low estradiol coupled with an aversive affective state during the clinical interview (i.e., during the trauma description) might lead to greater self-reported severity of past-month symptoms. Despite the observed discrepancy between retrospective symptom recall and daily symptom severity, the trauma disclosure portion of the clinical interview might capture the real-world experience of prompted trauma disclosure or trauma reminders.

Whereas trauma chronicity and timing did not moderate the relation between estradiol and retrospectively reported symptoms, trauma chronicity and timing did moderate the relation between change in estradiol and change in symptoms from the early to late follicular phase. In women with a history of chronic versus discrete trauma, a greater increase in estradiol from the early to late follicular phase was associated with a decrease in total symptom severity as well as in the severity of reexperiencing, negative alterations in cognitions and mood, and arousal

symptoms. Similarly, in women with earlier versus later trauma, a greater increase in estradiol from the early to late follicular phase was associated with a decrease in total symptom severity as well as in the severity of avoidance and negative alterations in cognitions and mood symptoms. These results are consistent with our third hypothesis and suggest that survivors of chronic and early-onset trauma are more sensitive to the effects of menstrual cycle–related hormone fluctuations, such as large increases in estradiol levels from the early to late follicular phase, compared with survivors of discrete and later-onset trauma, respectively. These results also suggest that the disproportionate risk for symptoms in women with a history of chronic and early-onset trauma is most pronounced in low-estradiol states. Although our results suggest that low estradiol might be a marker of increased vulnerability for symptoms, we acknowledge that changes in estradiol do not occur in isolation. Changes in symptoms from low- to high-estradiol phases might reflect co-occurring interactions between estradiol and other hormones (e.g., progesterone) or their metabolites. Clarifying these interactions is an important avenue for future work. Future studies might also incorporate ovulation tests to capture the full range of estradiol change during the follicular phase.

Given our relatively small sample size, we were unable to disentangle the unique contributions of different trauma characteristics and test interactions among them. For example, previous studies have demonstrated that early-life trauma can lead to greater vulnerability to symptoms following later traumatic events. Accordingly, people who are exposed to violence at an earlier age show a stronger association between lifetime exposure to violence and hyperarousal symptoms as adults (Miller-Graff et al., 2016). Additionally, although sexual trauma is consistently associated with a greater risk of PTSD development compared with other trauma types, the elevated risk is most pronounced in survivors of early-life sexual abuse

(McCutcheon et al., 2010). We were also unable to probe the nonlinear effects of trauma timing. Despite the general pattern of earlier trauma being associated with poorer clinical outcomes, there is also evidence of heightened risk in adolescence (Schoedl et al., 2010) and middle childhood (Dunn et al., 2018). Finally, given that our participants were at the lower end of the symptom severity spectrum and free of comorbidities, these relations should be tested in a more heterogeneous clinical trauma sample.

The identification of the role of estradiol fluctuations and their interactions with trauma characteristics on symptoms might help explain gender differences in PTSD risk and improve treatment tailoring for women with PTSD. Our results suggest that trauma characteristics moderate the relation between estradiol and trauma-related symptoms such that vulnerability to symptoms in survivors of sexual, chronic, and early-life trauma is most pronounced during lower-estradiol states. We demonstrate that (a) trauma type moderates the relation between estradiol levels during the clinical interview and retrospective self-report of symptoms in the past month and (b) trauma chronicity and timing moderate the relation between menstrual cycle-related change in estradiol and symptoms. These results have implications for diagnosis and treatment. Single timepoint assessments can be influenced by current affective states, and the present results suggest that estradiol levels at the time of assessment might also influence women's retrospective self-report of symptoms, particularly for sexual trauma survivors. Additionally, clinicians who work with women whose trauma history includes sexual, chronic, or early-life trauma might anticipate increased symptom severity during low-estradiol phases of the menstrual cycle. Moreover, our results suggest that symptoms that are more episodic or physiological are more likely to be influenced by estradiol fluctuations, whereas symptoms that are more stable or cognitive are more closely tied to specific trauma characteristics. Finally, our

results highlight the discrepancy between experience sampling techniques and retrospective, single-timepoint assessments and demonstrate the unique interactions between estradiol and trauma characteristics on symptom report with each assessment strategy.

Open Practices Statement

The study reported in this article was not formally preregistered. Neither the data nor the materials have been made available on a permanent third-party archive; requests for the data or materials can be sent via email to the lead author at jenna.rieder@jefferson.edu.

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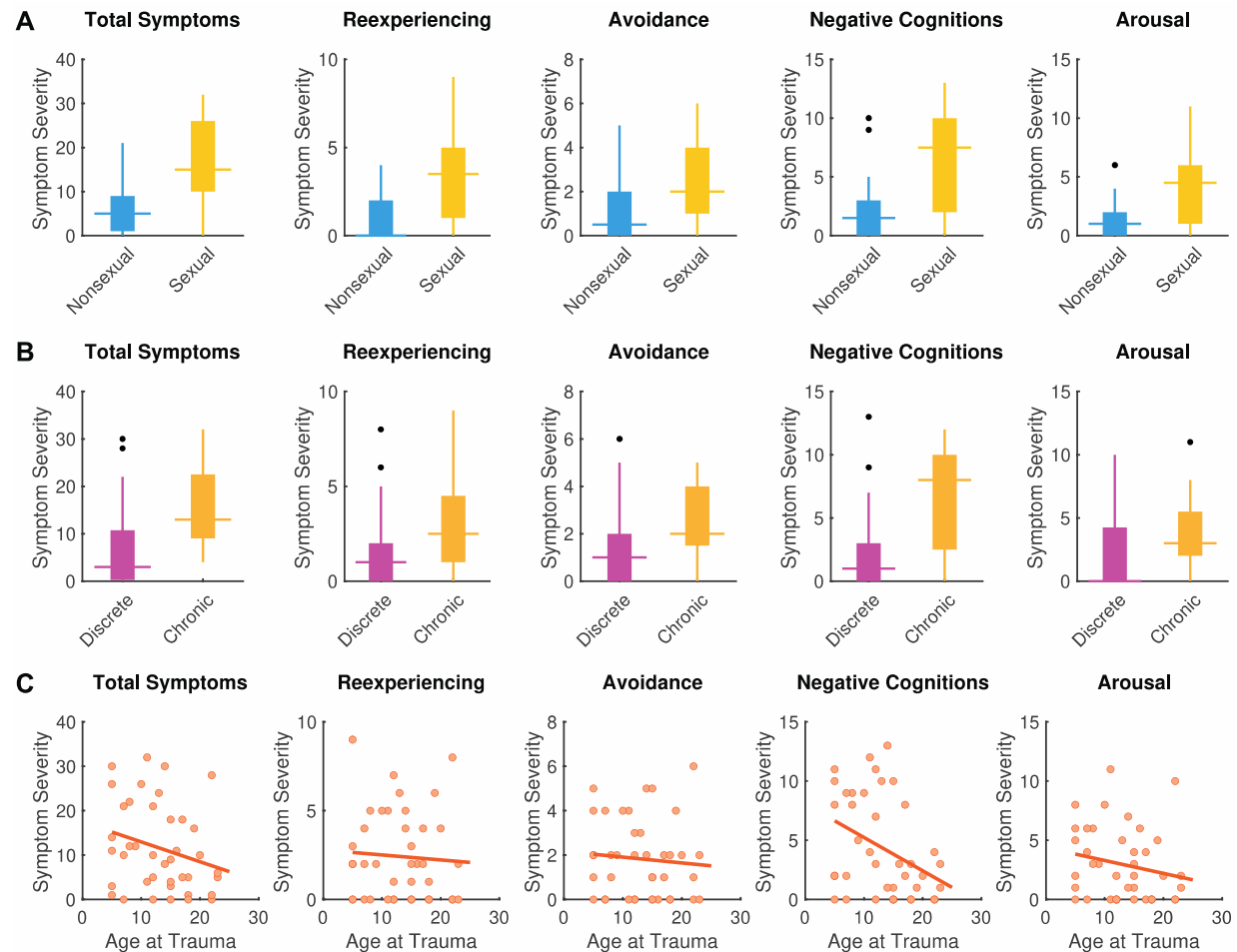
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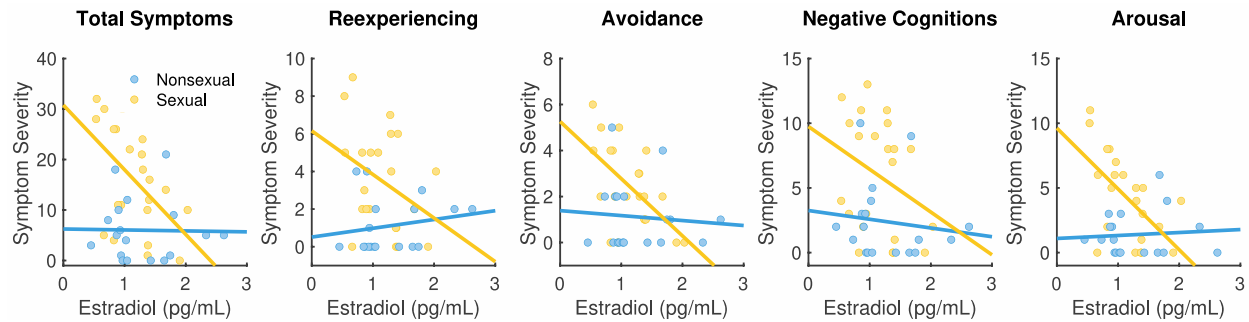
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Figure 1*Trauma Characteristics and Trauma-Related Symptoms Over the Past Month as Reported**During the Clinical Interview*

Note. Compared with nonsexual trauma, sexual trauma was associated with more severe symptoms across all symptom clusters (Panel A). Compared with discrete trauma, chronic trauma was associated with greater total symptom severity and more severe avoidance, negative alterations in cognitions and mood, and arousal symptoms (Panel B). Age at trauma was inversely associated with the severity of negative alterations in cognitions and mood symptoms (Panel C). In Panels A and B, horizontal bars represent medians, box boundaries represent the first and third quartiles, and black circles represent outliers.

Figure 2

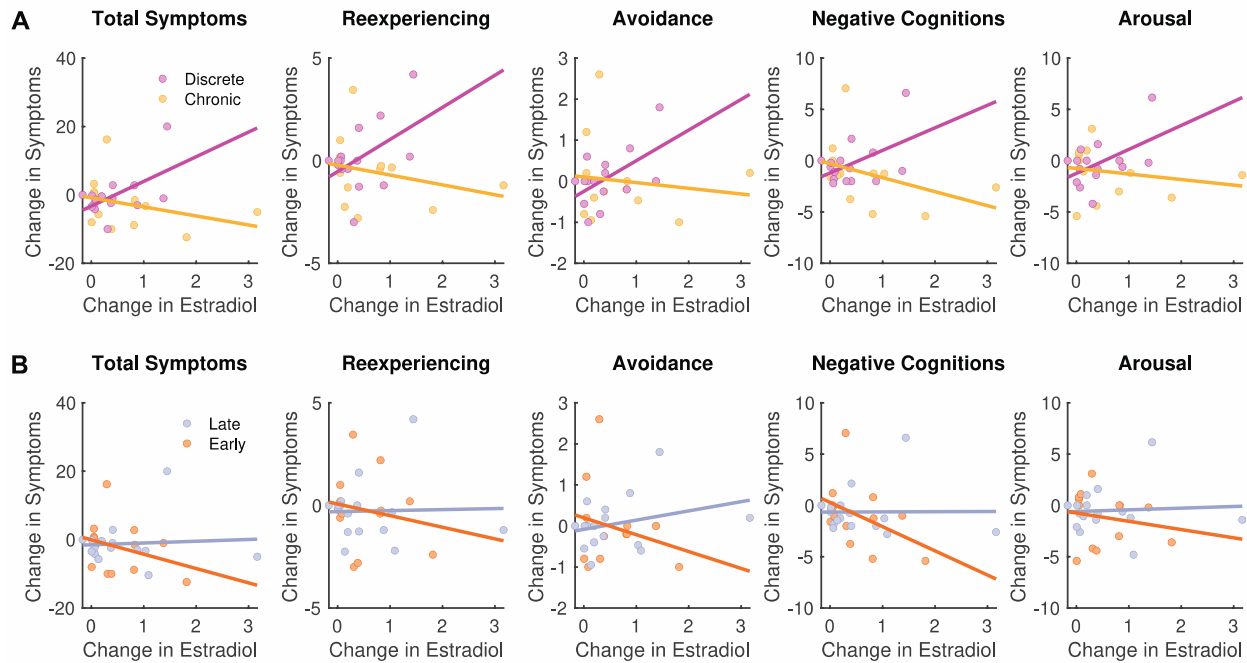
Trauma Type Moderates the Relation Between Estradiol at the Time of the Clinical Interview and Self-Reported Symptoms Over the Past Month



Note. In women with sexual trauma, estradiol was inversely associated with avoidance, arousal, and total symptom severity. In women with nonsexual trauma, estradiol was not associated with trauma-related symptoms.

Figure 3

Trauma Chronicity and Timing Moderate the Relation Between Change in Estradiol and Change in Symptoms From the Early to Late Follicular Phase



Note. In women with chronic trauma, change in estradiol from day 2 to day 11 of their menstrual cycle was inversely associated with the change in symptom severity (i.e., total, reexperiencing, negative alterations in cognitions and mood, and arousal symptoms) from the early to late follicular phase (Panel A). Similarly, in women with earlier trauma, change in estradiol from menstrual cycle day 2 to day 11 was inversely associated with the change in avoidance, negative alterations in cognitions and mood, and total symptom severity from the early to late follicular phase (Panel B). For visualization purposes only, we performed a median split and defined early trauma as trauma exposure before age 15 years and late trauma as trauma exposure at age 15 or older. To simplify the visualization of three-way interactions between cycle phase, estradiol change, and trauma characteristics, cycle-related symptom change is shown as a composite variable.

Table 1*Participant Characteristics*

Variable	<i>M</i>	<i>SD</i>	<i>n</i>	%	<i>Mdn</i>	IQR
Demographics						
Age (years)	21.85	4.25				
Race/ethnicity						
Asian/Pacific Islander			8	20.0		
Black, non-Hispanic			6	15.0		
Hispanic			10	25.0		
White, non-Hispanic			11	27.5		
Multiple			3	7.5		
Other			2	5.0		
Trauma characteristics						
Sexual trauma			22	55.0		
Chronic trauma			20	50.0		
Age at index trauma (years)	13.18	5.65				
Before 12 years old			15	37.5		
12–18 years old			15	37.5		
Older than 18 years			10	25.0		
Years since the most recent trauma	5.67	5.85				
Years since the index trauma	8.68	7.04				
Number of discrete traumatic events	1.33	0.62				

Menstrual cycle and estradiol

Estradiol during interview (pg/mL)	1.04	0.55
Day 2 estradiol (pg/mL)	0.87	0.43
Day 11 estradiol (pg/mL)	1.26	0.96

Note. IQR = interquartile range.

Table 2*Trauma-Related Symptoms*

Variable	<i>Mdn</i>	IQR	Range
Past-month symptoms reported during clinical interview (CAPS-5)			
Total symptom severity	10.00	16.00	0–32
Total symptom count	3.00	7.50	0–12
Reexperiencing symptom severity	2.00	4.00	0–9
Reexperiencing symptom count	0.00	1.50	0–4
Avoidance symptom severity	2.00	3.00	0–6
Avoidance symptom count	0.50	1.00	0–2
NACM symptom severity	3.00	8.00	0–13
NACM symptom count	1.00	3.00	0–5
Arousal symptom severity	2.00	5.00	0–11
Arousal symptom count	0.50	2.00	0–4
Symptoms reported during EMA (PCL-5)			
Early follicular phase ^a			
Total symptoms	9.80	14.25	0.0-47.2
Reexperiencing symptoms	1.80	2.94	0.0-8.2
Avoidance symptoms	0.80	1.62	0.0-7.6
NACM symptoms	3.40	6.90	0.0-15.0
Arousal symptoms	3.80	4.40	0.0-16.4
Late follicular phase ^b			

Total symptoms	6.50	13.05	0.0-50.0
Reexperiencing symptoms	0.40	2.65	0.0-10.4
Avoidance symptoms	0.60	1.85	0.0-7.4
NACM symptoms	2.33	5.35	0.0-15.8
Arousal symptoms	2.40	3.85	0.0-16.4

Note. IQR = interquartile range; CAPS-5 = Clinician-Administered Posttraumatic Stress

Disorder (PTSD) Scale for *DSM-5*; NACM = negative alterations in cognitions and mood; EMA = ecological momentary assessment; PCL-5 = PTSD Checklist for *DSM-5*.

^aAveraged across days 2–6 of the menstrual cycle. ^bAveraged across days 7–11 of the menstrual cycle.