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Conditioned Physiological Reactivity and PTSD Symptoms Across the Menstrual Cycle: Anxiety Sensitivity as a Moderator

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Objective: Posttraumatic stress disorder (PTSD) is often associated with heightened physiological reactivity during fear conditioning procedures, but results vary across studies. This study examined whether anxiety sensitivity (AS), or the fear of arousal-related sensations, strengthens the relationship between PTSD symptoms and skin conductance responses (SCR) during fear conditioning and extinction. Because gonadal hormones implicated in fear learning fluctuate across the menstrual cycle, the stability of these relationships in women was examined in 2 distinct menstrual cycle phases. ***Method:*** Thirty-two trauma-exposed women, half of whom had PTSD, completed the Clinician-Administered PTSD Scale, Anxiety Sensitivity Inventory, and a fear conditioning and extinction paradigm during the midluteal (mLP) and early-follicular (eFP) menstrual cycle phases. ***Results:*** In the mLP, stronger SCR to stimuli paired with shock (CS+) during fear acquisition significantly predicted greater PTSD symptoms only when AS was high and after removing an outlier. This appeared driven by effects on Numbing and Hyperarousal symptom clusters. Other hypothesized interactions between AS and CS responses were not significant. However, in the eFP, differential SCR between the CS+ and CS- during extinction predicted significantly greater PTSD symptoms, and there was a trend for this effect being stronger as AS increased. ***Conclusions:*** Results offer preliminary evidence that high AS contributes to a stronger relationship between SCR during fear acquisition and PTSD symptoms, at least among women in the mLP. Further research investigating the impact of individual differences in traits such as AS on the relationship between conditioned fear responses and PTSD symptoms is warranted.

Clinical Impact Statement

Fear conditioning serves as a model for the development of Posttraumatic stress disorder (PTSD). However not all individuals with PTSD show strong conditioned fear responses. This study's findings suggest that the link between conditioned fear responses and PTSD symptoms may be strongest for individuals with high levels of anxiety sensitivity, or "fear of fear."

Keywords: posttraumatic stress disorder, fear conditioning, anxiety sensitivity, menstrual cycle, moderation

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Posttraumatic stress disorder (PTSD) is characterized by heightened physiological and emotional reactivity to stimuli that trigger memories or emotions associated with a traumatic event. The development of PTSD therefore parallels the processes modeled in fear conditioning experiments, in which a previously neutral stimulus becomes associated with threat through repeated pairings with an aversive unconditioned stimulus (UCS; Lissek & van Meurs, 2015). The neutral stimulus then becomes a conditioned stimulus (CS+) that triggers a conditioned fear response even in the absence of the UCS. Recovery from PTSD can similarly be modeled in conditioning experiments. Specifically, repeated presentations of the CS+ in the absence of the UCS during extinction typically lead to a gradual decline in conditioned fear, much in the same way that PTSD treatment involves approaching trauma-related situations, memories and emotions to learn they are in fact safe (Zuj & Norrholm, 2019). Deficits in extinction learning, however, may impede new learning about the absence of imminent threat, and contribute to sustained PTSD symptoms (Zuj et al., 2016).

Studying how individuals with and without PTSD characteristically respond to conditioning procedures can help to identify differences in associative learning processes potentially contributing

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to the development, maintenance and recovery from the disorder (VanElzakker et al., 2014). Consistent with theoretical predictions, individuals with PTSD typically demonstrate slower extinction learning compared to those without PTSD, as demonstrated by heightened reactivity to the CS+ during extinction trials (Blechert et al., 2007; Duits et al., 2015; Norrholm et al., 2011; Norrholm et al., 2015). With regard to fear acquisition, on the other hand, a meta-analysis by Duits and colleagues (2015) found no significant difference between PTSD and control groups in response to the CS+, nor to differential reactivity between the CS+ and a control stimulus never paired with shock (i.e., the CS-). Rather, PTSD has most consistently been found to be associated with heightened reactivity to the CS- (Duits et al., 2015; Glover et al., 2011; Norrholm et al., 2011), which may reflect overgeneralization from danger cues (i.e., the CS+), as well as deficits in fear inhibition (Jovanovic & Norrholm, 2011).

Despite a general pattern of support for the above findings, there is substantial variability in results among individual studies. For instance, not all studies show heightened reactivity to the CS- during acquisition in PTSD (Blechert et al., 2007; Jovanovic et al., 2013; Miller et al., 2011), and a number of studies have shown PTSD to be associated with greater reactivity to the CS+ during acquisition (Blechert et al., 2007; Glover et al., 2011; Orr et al., 2000; Lissek et al., 2005; Norrholm et al., 2011), particularly when comparing PTSD groups to trauma-exposed controls (Duits et al., 2015). One factor potentially influencing variability in results is the use of skin conductance response (SCR) versus fear-potentiated startle (FPS) as an indicator of conditioned responding, as direct comparisons of the two measures indicate FPS may be more sensitive to differences between those with and without PTSD (Glover et al., 2011). Nonetheless, discrepant findings regarding the association of PTSD with CS+ and CS- responding can be seen when comparing results from studies only using FPS measures (e.g., Miller et al., 2011; Norrholm et al., 2011) as well as studies examining SCR (e.g., Glover et al., 2011; Orr et al., 2000). Therefore, an examination of participant-level characteristics that may explain such discrepant results is needed to better illuminate the role of associative learning processes in PTSD.

One participant-level characteristic that may influence the relationship between reactivity to a CS and PTSD symptoms is anxiety sensitivity (AS), or the fear of arousal-related sensations (Taylor et al., 2007). Beliefs about the aversiveness and negative consequences of physiological fear responses, which are characteristic of individuals high in AS, can amplify reactions to trauma-related stimuli, thereby playing a role in the development and maintenance of PTSD (Boffa et al., 2016; Marshall et al., 2010). In fear conditioning studies, AS has been shown to predict self-reported anxiety responses to conditioned stimuli, but not physiological reactivity (Harrison et al., 2015; Melzig et al., 2011), suggesting high AS is associated with greater subjective fear in the context of similar physiological responses. Moreover, AS has been shown to amplify the relationship between fear responses and avoidance behavior, a hallmark of PTSD, in both fear conditioning (Hunt et al., 2019) and clinical studies (Lebowitz et al., 2015). Accordingly, those with strong conditioned physiological responses to trauma-related stimuli may be particularly likely to develop and maintain PTSD symptoms if such physiological responses are seen as highly aversive and dangerous (i.e., AS is high). In contrast, conditioned reactions to trauma-related stimuli may be less likely to be associated with PTSD symptom severity if such physiological fear responses are viewed as less bothersome or concerning, as would be expected in individuals with low AS.

The present study examined whether the relationship between PTSD symptoms and physiological reactivity (measured via SCR) to conditioned stimuli during fear acquisition and extinction is moderated by anxiety sensitivity. During acquisition, it was expected that higher levels of AS would be associated with a stronger relationship between PTSD symptoms and SCR to both the CS+ and CS-, but not differential CS reactivity. This was based on the premise that greater reactivity to the CS+ and CS- reflects strong excitatory fear learning processes and weak fear inhibition (for the CS-), both of which are sources of vulnerability to PTSD (Lissek et al., 2005; Duits et al., 2015), whereas differential CS reactivity may be more reflective of adaptive levels of associative learning (Grillon, 2002). Moreover, PTSD tends to be associated with a stronger response to the CS- (Duits et al., 2015), which could in fact decrease differential CS scores. During extinction, however, CS- reactivity is less relevant given that the UCS is now completely absent. Sustained high reactivity to the CS+ in the absence of the UCS, on the other hand, is most likely to reflect a deficit in fear inhibition reflective of PTSD symptoms, a relationship that could be particularly strong in the context of high AS. Thus, we expected that during extinction elevated AS would be associated with a stronger relationship between PTSD symptoms and CS+ reactivity (and consequently differential CS), but would not moderate the relationship with the CS-.

To examine these hypotheses, the present research used data from a parent study (Pineles et al., 2016) in which trauma-exposed female participants underwent fear conditioning and extinction procedures twice: once during the midluteal phase (mLP) and once during the early follicular phase (eFP). Menstrual phase is an oft-neglected but important variable to consider in fear conditioning studies, as gonadal hormones that fluctuate over the course of the menstrual cycle (i.e., estradiol and progesterone) are implicated in fear learning processes and may impact vulnerability to PTSD (see Garcia et al., 2018 for a review). The most robust findings in this area have focused on extinction recall, but some studies have shown lower levels of estradiol to be associated with increased fear responding during acquisition (Li & Graham, 2016) and impaired fear inhibition in the presence of safety cues (Glover et al., 2013). Furthermore, individuals high in AS exhibit particularly strong physiological and cognitive responses to laboratory stressors during the premenstrual phase of their cycle when levels of estradiol and progesterone are rapidly declining (Nillni et al., 2012). In consideration of possible influences of menstrual phase, the present study examined AS as a moderator of the relationship between conditioned physiological reactivity and PTSD symptoms during both the eFP (i.e., when estradiol and progesterone are both relatively low) and mLP (i.e., when estradiol and progesterone are relatively high and stable). Given the nascence of research examining menstrual phase effects on the relationship between fear conditioning and PTSD symptom severity (Garcia et al., 2018), we did not have a priori hypotheses about menstrual phase effects. Instead, we sought to conduct a preliminary examination of possible menstrual phase differences that could inform future research.

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Method

Participants

Study participants included 32 trauma-exposed women (*M* Age = 28.81, *SD* = 7.96) who met criteria for a parent study (Pineles et al., 2016) by being eligible for one of two groups: a PTSD group (*n* = 16) or a trauma control group (*n* = 16). Participants in the PTSD group met *DSM–IV* criteria for PTSD as assessed by the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) and scored at least 40 on the CAPS. The trauma control group included participants who were exposed to a Criterion A traumatic event but did not meet criteria for lifetime, partial, or current PTSD, lifetime recurrent major depressive disorder, or any other current psychological disorder (except for a single participant with public-speaking phobia). *M* CAPS score for the sample was 32.60 (*SD* = 27.70). See Pineles et al. (2016) for full demographic information.

Additional exclusion criteria for all participants were: psychotic disorder, bipolar I disorder, current substance or alcohol use disorder, infectious illness, organic brain disorder, major neurological problem, endocrine disorder, irregular menstrual cycle (i.e., cycle length outside of 25 to 35 days, missed periods, vaginal bleeding between periods), current trauma-focused psychotherapy, use of psychotropic or other medications that might influence hormone levels or psychophysiological measures (e.g., beta blockers), or use of hormonal contraceptives. Absence of pregnancy and substance use was biochemically verified at each study session.

Because the primary outcome for the current study was SCR, participants were excluded from analysis if they failed to show SCR to the UCS during fear conditioning (further details in Measures section below). Nineteen participants from the original sample of 51 study completers (37%) were excluded from data analysis for these reasons. The sample's racial composition may have contributed to this relatively high nonresponse rate. Increased rates of SCR nonresponse have been found in African Americans (Kredlow et al., 2017), and 28% of SC responders and 71% of nonresponders in this sample were African American (Pineles et al., 2016).

Procedures

After providing informed consent, the CAPS was administered as part of a screening visit. Eligible participants then completed the conditioning task and the Anxiety Sensitivity Inventory (ASI; Reiss et al., 1986) during their eFP and mLP. Order of menstrual phase was determined by random assignment. For testing during the eFP, the first session occurred 1 to 5 days from the start of menses. For testing during the mLP, the first session occurred 6 to 10 days after the luteinizing hormone surge was detected using a home ovulation kit. Prior to psychophysiological testing, plasma level progesterone and estradiol samples were collected to confirm menstrual cycle phase. All study procedures were approved by the VA Boston Health care System institutional review board.

Conditioning Procedures

To avoid potential morning adrenal neurosteroid spikes, study sessions were scheduled during the afternoon. Further, in order to limit HPA axis activation, participants were instructed to eat 2–3 hr prior to session and abstain from caffeine 4 hr and nicotine 1 hr prior to session. Participants were also required to abstain from illicit drugs and alcohol for 2 weeks and 1 week before each session, respectively.

The standard differential conditioning paradigm followed the procedure previously outlined by Pineles et al (2016). A Coulbourn Modular Instrument System (Allentown, PA) was used to administer the procedure. The UCS was a 500-ms electric pulse delivered via electrodes attached to the second and third fingers of the left hand. This level was previously rated by participants to be "highly annoying but not painful." Distinct colored shapes were presented for 8-s (intertrial interval = 20 $\pm$5 s) in pseudorandom order to represent the different CSs. These shapes were 16 cm in size and were presented on a monitor 4 feet from the participant. In the acquisition phase, the CS+ consisted of a colored shape paired with the UCS, and the CS- consisted of a different colored shape presented in the absence of the UCS. Different colors and shapes were used during each menstrual phase the participant completed the conditioning task.

Participants were given instructions explaining that there were three phases of the task, each involving presentation of two different colored shapes. They were also told that an electrical shock would be administered during the second phase. The presence or absence of the electrical stimulus during the extinction phase was not specified. After a 5-min baseline period, participants completed the habituation, acquisition, and extinction phases of the task. The habituation phase consisted of five presentations each of the to-be CS+ and CS- shapes in the absence of a shock. Next, the acquisition phase was comprised of five presentations each of the CS+ and CS-; the 500 ms shock occurred immediately after each CS+ offset. Finally, the extinction phase was comprised of 10 presentations of the CS+ and CS- in the absence of shock.

Measures

Skin Conductance Response (SCR)

Skin conductance (SC) was measured with an isolated skin conductance coupler using a .5-V constant DC through 8-mm Ag/AgCl surface electrodes filled with isotonic paste and placed on the hypothenar surface of the nondominant hand. Before calculating SCR scores, data were examined for recording errors and outliers. Data were then screened to exclude participants who did not show an adequate SCR to the unconditioned stimulus (UCS). To demonstrate adequate SCR, participants had to demonstrate an average unconditioned response to the five shock presentations during acquisition of $>.1$ μS in at least one of the two conditioning sessions (i.e., during mLP or eFP).

For each CS presentation, SCR was calculated by subtracting the mean SC level during the 2-s immediately prior to CS onset from the highest SC level recorded during the 8-s presentation of the CS. SCR values were then square-root-transformed to reduce skewness and kurtosis. The percentage of missing SCR values for each participant ranged from 0% to 16% (*M* = 4.3%, *SD* = 5.0). Missing values were replaced using multivariate imputation by chained equations based on random forest recursive partitioning (Shah et al., 2014). Reported analyses reflect pooled outcomes from five imputed data sets.

For the acquisition phase, SCR values for the CS+ and CS- were calculated using the mean of the last two trials of each type. For the extinction phase, we followed the convention of separating early extinction (i.e., the first half of the extinction trials) from late extinction (i.e., the second half; Ney et al., 2020). Analysis was restricted to the early extinction because of the relative speed with which most participants extinguished the conditioned response (Pineles et al., 2016), a pattern that is consistent with prior literature (e.g., Zuj et al., 2017). Specifically, SCR values for extinction were calculated based on the mean response to the CS+ or CS- across Trials 2 to 5 (trial 1 was not used because participants had not yet observed the nonoccurrence of shock following the CS+). For both acquisition and extinction, differential conditioned response scores (CSdiff) were derived by subtracting mean values for the CS- from the CS+.

Anxiety Sensitivity Index (ASI)

The ASI (Reiss et al., 1986) is a 16-item self-report measure of anxiety sensitivity, that is, fear of arousal-related symptoms. For the current study, the 16 items were summed to form a total score. This measure has been shown to have good internal and external validity (Reiss et al., 1986). In the present study, reliability was excellent (α = .92-.93). In our previous work from the same parent study, we demonstrated that anxiety sensitivity did not vary across the menstrual cycle (Nillni et al., 2020).

Clinician-Administered PTSD Scale (CAPS)

The CAPS (Blake et al., 1995) is a reliable and valid structured interview that assesses *DSM–IV* PTSD diagnosis and severity. A clinician rates the severity and frequency of each symptom and ratings are combined to form a total PTSD severity score. Internal consistency for the full scale in this study was excellent (α = .96). Symptom cluster scores were calculated for the PTSD symptom clusters defined by King et al (1998), as they map on more closely to *DSM–5* clusters and have shown superior factor structure to the traditional three-factor solution (Elhai & Palmieri, 2011). Internal consistency in this study for the symptom clusters was excellent: reexperiencing (α = .89), avoidance (α = .93), numbing (α = .87), and hyperarousal (α = .86).

Data Analytic Plan

Data were analyzed in SPSS v.26 using hierarchical linear regression, entering ASI and each SCR measure as predictors of CAPS in Step 1 and their interaction in Step 2. We examined CAPS scores rather than PTSD diagnosis as the dependent variable to capture the continuous nature of PTSD (Kotov et al., 2017) and to afford more statistical power. Although participants were selected based on inclusion in a PTSD and trauma-exposed control group, CAPS scores were distributed relatively evenly across the scale (median = 25.5, IQR = 10.0 to 58.5), and skewness and kurtosis values did not indicate violations of normality. To control for any potential order effects on SCR-PTSD relationships, a categorical variable indicating whether the fear conditioning paradigm was administered first during eFP or mLP was also entered in Step 1, and its interaction with the selected SCR measure was entered in Step 2. Given that no order by SCR interactions were significant we elected to use the more parsimonious model with such variables removed. Separate models examining CS+, CS- and CSdiff were conducted for mLP and eFP, and during acquisition and extinction.

In the case of significant ASI by SCR interactions, predicted values at the mean, +1 *SD* and −1 *SD* of the predictor and moderator variables were graphed to characterize the nature of the interaction. In addition, the Johnson–Neyman technique (Bauer & Curran, 2005) was utilized via the CAHOST workbook (Carden et al., 2017) in Microsoft Excel, which estimates the range of values of a continuous moderator at which the effect of the predictor on the dependent variable is statistically significant.

Tests of normality, homoscedasticity, independence of residuals, and multicollinearity indicated the data were suitable for linear regression. To analyze for potential outliers, centered leverage and Cook's distance *(D)* values were inspected graphically. Following recommendations by Cook (2011) for identifying and dealing with highly influential observations, cases where Cook's *D* was > .5 and substantially larger than the rest of the sample were examined for possible data entry errors and experimental abnormalities. In the absence of these, the effect of deleting that case was examined, and results with and without possible outliers are reported when discrepancies arose. The squared semipartial correlation coefficient (sr^2), representing the unique portion of variance explained by the predictor, was used as an indicator of effect size.

Results

See Table 1 for means, standard deviations and bivariate correlations for study variables.

Acquisition

Results of regression analyses predicting CAPS scores by ASI, SCR to conditioned stimuli during acquisition, and their interaction during the mLP and eFP are shown in Table 2. Across analyses, ASI significantly predicted CAPS scores in the positive direction.

Mid-Luteal Phase

In the mLP, there was no significant main effect of SCR to the CS+, CS-, or CSdiff, nor any significant interactions between the CS reactivity indices and ASI. However, inspection of possible influential observations revealed the model examining SCR to the CS+ may have been impacted by an outlier (Cook's Distance value of .78; next highest value = .26; mean Cook's *D* = .06).[1] When removing this case from analyses, the main effect of SCR to the CS+ remained nonsignificant and the ASI by CS+ interaction emerged as a significant predictor of CAPS scores. This interaction indicated that the positive association between SCR to the CS+ and CAPS scores became stronger as ASI increased (see Figure 1). As shown in Figure 2, the Johnson-Neyman test for regions of significance estimated that the association of CS+ SCR and

[1] Further inspection of this case revealed a low ASI score (12th percentile) and very high SCR to the CS+ (91st percentile). The high leverage value of 0.51 (*M* leverage = 0.09, *SD* = 0.12) indicated the combination of values for this case (including the interaction term) was unusual, in addition to being disproportionately influential (as indicated by Cook's *D*). A scatter plot illustrating the outlier can be seen in online supplementary materials.

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Table 1
Means, SDs, and Bivariate Correlations of PTSD Severity, Anxiety Sensitivity, and SCR Values

Variable	Mid-Luteal phase *M (SD)*	Mid-Luteal phase Range	*r* CAPS	*r* ASI	Early-Follicular phase *M (SD)*	Early-Follicular phase Range	*r* CAPS	*r* ASI
Acquisition								
CS+ SCR	0.33 (0.32)	−0.08 – 1.10	.11	−.11	0.34 (0.41)	−0.11–1.52	−.30	−.28
CS− SCR	0.20 (0.23)	−0.15 – 0.96	.11	.10	0.17 (0.25)	−0.20 – 0.91	.03	.01
CSdiff SCR	0.12 (0.33)	−0.42 – 1.06	.04	−.17	0.18 (0.40)	−0.35 – 1.32	−.34	−.31
Extinction								
CS+ SCR	0.15 (0.18)	−0.16 – 0.71	−.34	−.12	0.15 (0.20)	−0.06 – 0.85	.09	.14
CS− SCR	0.12 (0.17)	−0.18 – 0.67	.00	.11	0.15 (0.18)	−0.07 – 0.73	−.10	.38*
CSdiff SCR	0.02 (0.19)	−0.28 – 0.65	−.32	−.23	0.00 (0.16)	−0.31 – 0.50	.22	−.26
Clinical Variables								
ASI	14.01 (11.81)	0 – 53	.36*	—	16.41 (12.02)	0 – 47	.56**	—
CAPS[a]			*M(SD)* = 32.59 (27.70) Range = 0 – 85					

Note. ASI = Anxiety Sensitivity Index; CAPS = Clinician Administered PTSD Scale; SCR = skin conductance responses. SCR data reflect square-root transformed values.
[a] reflects past-month PTSD symptoms.
* $p < .05$. ** $p < .01$.

CAPS during acquisition was significant for values of ASI > 15.30 (upper 38.5% of the sample).

Analyses of CAPS subscales showed this interaction was strongest in predicting Numbing symptoms, $B = 2.42$, $SE = .81$, $p = .006$, $sr^2 = .25$, followed by Hyperarousal symptoms, $B = 1.92$, $SE = .93$, $p = .048$, $sr^2 = .14$. Effects on Avoidance, $B = .79$, $SE = .59$, $p = .20$, $sr^2 = .06$, and Reexperiencing symptoms, $B = 1.35$, $SE = .87$, $p = .14$, $sr^2 = .08$, were nonsignificant.

Early Follicular Phase

Similar to the mLP, there was no significant main effect in the eFP of SCR to the CS+, CS- or CSdiff on CAPS scores, nor were there any significant interactions between CS SCR and ASI. Inspection of outliers revealed that for the model examining CSdiff, one participant had an abnormally high Cook's *D* value equal to 3.08 (next highest Cook's $D = .20$).[2] With this outlier removed, the main effect of SCR to CSdiff remained nonsignificant, $B = -14.74$, $SE = 10.79$, $p = .18$, $sr^2 = .06$, whereas the ASI by CSdiff interaction approached significance, $B = -4.44$, $SE = 2.44$, $p = .08$, $sr^2 = .07$. Visual inspection of this interaction indicated the negative association between CSdiff and CAPS scores emerged as values of ASI increased. However, the Johnson-Neyman test estimated that this effect only reached significance for values of ASI > 8.30 and < 10.39, (capturing the 22nd to 41st percentile), with confidence intervals indicating low precision of this estimate for higher levels of ASI.

Extinction

Results of regression analyses predicting CAPS scores by ASI, SCR to conditioned stimuli during extinction, and their interaction during the mLP and eFP can be seen in Table 3.

Mid-Luteal Phase

During the mLP, the main effect of ASI on CAPS score was significant or approached significance depending on which CS variable was in the model. There was no significant main effect of SCR to the CS+, CS- or CSdiff, nor were any of the ASI by CS SCR interactions significant. The main effect of SCR to the CS+ approached significance ($p = .08$) and was associated with a medium effect size ($sr^2 = .10$), such that greater SCR to the CS+ during extinction was associated with greater CAPS scores.

Early-Follicular Phase

The main effect of ASI on CAPS scores was significant across analyses in the positive direction. No main effect of SCR to the CS+ was present, but there was a significant main effect of SCR to the CS- such that greater SCR to the CS- was associated with lower CAPS scores. The main effect of CSdiff was also significant such that greater differential SCR to the CS+ versus CS- during extinction was associated with greater CAPS severity scores. Neither of the interactions between ASI and CS+ or CS- were significant, though the interaction with CSdiff approached significance ($p = .07$), a result associated with a medium effect size ($sr^2 = .11$). Visual inspection of this interaction indicated that the positive association between CSdiff during extinction and CAPS scores was stronger as ASI scores increased. The Johnson-Neyman test for regions of significance estimated that this positive effect was significant for participants with values of ASI > 7.73 (upper 78% of sample).

Discussion

The primary aim of this paper was to examine whether the relationship between physiological reactivity (measured via SCR) during fear conditioning and PTSD symptoms would be strengthened in the context of high AS, or fear of arousal-related sensations. Our results show partial support for this hypothesis. When tested in the mLP of the menstrual cycle and after removing an outlier, AS significantly moderated the relationship between CS+ reactivity during fear acquisition and PTSD symptoms, such that this relationship became significant in the context of higher levels of

[2] Further inspection of this case revealed a very high ASI score (97th percentile) and very low differential CSR (6th percentile), resulting in an interaction term > 3 SD below the mean. The high leverage value of 0.68 (mean leverage = 0.09, SD = 0.14) indicated that this combination of values was highly unusual. A scatter plot illustrating the outlier can be seen in online supplementary materials.

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Table 2
Prediction of PTSD Severity by SCR to Conditioned Stimuli, Anxiety Sensitivity, and Their Interaction During Fear Acquisition

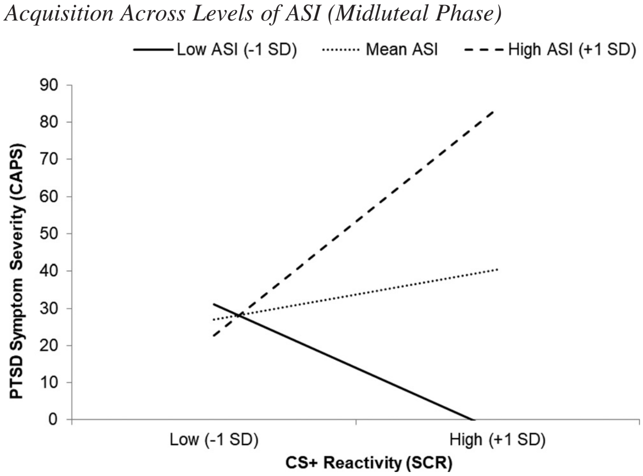
			Mid-Luteal phase				Early-Follicular phase			
Model	Step	Predictor	B	*SE* B	*p*	sr^2	B	*SE* B	*p*	sr^2
CS+	1.	SCR to CS+	11.73	15.66	.46	.02	−10.31	10.58	.34	.03
		ASI	**0.89**	**0.40**	**.04**	**.14**	**1.20**	**0.36**	**.002**	**.28**
	2.	ASI × CS+	**6.48**	**2.80**	**.03**[a]	**.17**	−2.54	2.31	.28	.04
CS−	1.	SCR to CS−	8.78	20.84	.68	.01	2.92	17.20	.87	.001
		ASI	0.86	0.41	.05	.12	**1.30**	**0.35**	**.001**	**.31**
	2.	ASI × CS−	−2.45	1.87	.20	.04	−1.44	1.45	.33	.03
CSdiff	1.	CSdiff	9.00	14.71	.54	.01	−12.58	10.98	.26	.04
		ASI	**0.93**	**0.42**	**.04**	**.14**	**1.18**	**0.36**	**.003**	**.26**
	2.	ASI × CSdiff	2.32	1.43	.12	.08	−4.44	2.44	.08[a]	.07

Note. ASI = Anxiety Sensitivity Index; SCR = skin conductance responses. Bolded values represent significance $p < .05$. For model examining CS+ in the mLP, including the outlier did not change significance of Step 1 predictors, whereas effect of ASI × CS+ was no longer significant, $B = 3.22$, $SE = 2.21$, $p = .16$, $sr^2 = .07$. For the model examining CSdiff in the eLP, including the outlier similarly did not meaningfully change Step 1 predictors, but the effect of ASI × CSdiff no longer approach significance, $B = -4.44$, $SE = 1.61$, $p = .86$, $sr^2 = .001$.
[a] Results reported are with outlier removed.

AS. Such a relationship was not seen in the eFP, nor did hypothesized interactions with the CS- during acquisition emerge. During extinction, there was a trend toward greater differential conditioned responding to be more strongly related to PTSD symptoms in the context of high AS during the eFP, though no significant moderation was found to the CS+ individually, nor to any stimuli during the mLP.

The evidence supporting AS as a moderator of the relationship between SCR to the CS+ and PTSD symptoms during acquisition is notable considering that on average individuals with PTSD do not show stronger reactivity to the CS+ than controls (Duits et al., 2015). Heightened SCRs to the CS+ during acquisition is considered an indicator of strong excitatory fear responses (Lissek et al., 2005), but may also reflect adaptive levels of associative learning (Grillon, 2002). In this study, SCR to the CS+ emerged as a significant predictor of PTSD symptoms for individuals with AS scores in the upper 38.5% of the sample, indicating AS may be

Figure 1
Predicted Values of CAPS Scores by CS+ Reactivity During Acquisition Across Levels of ASI (Midluteal Phase)



Note. Figure reflects data with outlier removed. CAPS = Clinician Administered PTSD Scale; ASI = Anxiety Sensitivity Index; SCR = skin conductance reactivity.

one factor that can influence whether strong conditioned responses are associated with negative outcomes.

Notably, this result was found only in the mLP of the menstrual cycle, highlighting gonadal hormones that fluctuate across the menstrual phase as another potential factor in the discrepant results on CS+ reactivity and PTSD. Although the high levels of estradiol and progesterone seen in the mLP are generally associated with adaptive fear learning (Garcia et al., 2018), in the context of PTSD this may be a period of vulnerability. For example, work from the parent study indicates that individuals with PTSD exhibit worse recall of inhibitory learning during the mLP (Pineles et al., 2016), which is at least partly a result of decreased capacity to convert progesterone into its anxiolytic GABAergic metabolites (i.e., allopregnanolone and pregnanolone, or Allo+PA) (Pineles et al., 2018; Pineles et al., 2020). Accordingly, it is possible that AS emerged as a moderator only during this period of relative vulnerability, but not in the eFP when progesterone and Allo+PA levels are lower and other neurobiological factors may be more important in facilitating inhibitory learning (Pineles et al., 2018).

Examination of PTSD symptom clusters showed that the significant interaction of AS and CS+ reactivity during acquisition specifically predicted greater scores on the CAPS Numbing and Hyperarousal clusters. Prior investigations examining fear-potentiated startle have found mixed evidence regarding associations between CS+ reactivity and hyperarousal (Glover et al., 2011; Norrholm et al., 2011). Present results add to these findings by demonstrating associations with CS+ reactivity as measured by SCR, but only among those who report strong fear of anxiety-related sensations. For those high in AS, the association between strong conditioned responses and sustained vigilance and physiological arousal may be a result of such responses being viewed as highly aversive. In contrast to hyperarousal, numbing symptoms have not been found to be associated with CS+ reactivity in past studies (Glover et al., 2011; Norrholm et al., 2011). However, numbing has been conceptualized as an inhibition of emotional expression resulting from hyperreactivity to negative emotional stimuli (Litz & Gray, 2002). Such emotional inhibition may be most likely to occur for individuals who exhibit both heightened conditioned responses and a strong aversion to arousal-related

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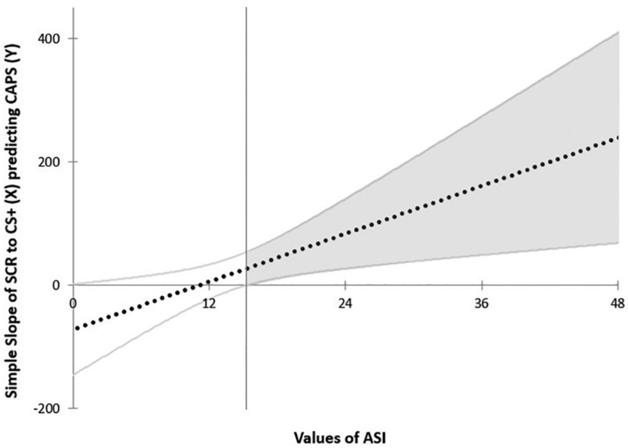
Figure 2
Slope of CS+ SCR as a Predictor of CAPS Scores (i.e., PTSD Severity) Across Values of ASI During the Midluteal Phase



Note. Gray lines represent 95% confidence intervals. The vertical line indicates the point (ASI = 15.30) at which the confidence interval no longer overlaps with 0, indicating that the effect of CS+ SCR on CAPS is significant for all values greater than that point (i.e., shaded area). Mean ASI for the sample = 14.43 (*SD* = 11.76). Figure reflects analyses with outlier removed. CAPS = Clinician Administered PTSD Scale; ASI = Anxiety Sensitivity Index; SCR = skin conductance reactivity.

sensations (i.e., high AS). This interpretation is supported by research showing that AS amplifies the relationship been self-reported arousal and numbing symptoms (Stephenson et al., 2009).

Regarding findings from the extinction phase of the study, results indicated a significant positive association between PTSD symptoms and differential conditioned responding during extinction in eFP, and a trend for this association being stronger in the context of high AS. Although the direction of these results is consistent with our hypotheses, interpretation is complicated by the significant negative association between SCR to the CS- and PTSD symptoms and absence of an effect of SCR to the CS+. Rather than reflecting greater reactivity to the CS+ during extinction, it appears that the positive association between differential CS reactivity and PTSD severity was driven by lower reactivity to the CS- among those with greater PTSD symptoms and greater reactivity to the CS- among those with less PTSD. This is an unusual finding and may reflect a statistical artifact impacted by the moderate correlation between AS and CS- reactivity during extinction in the eFP (absent in all other relationships between AS and CS variables). Notably, bivariate correlations between SCR to the CS- and PTSD symptoms without AS in the model were not significant (see Table 1).

Given the cross-sectional nature of this study, conclusions cannot be made about causal effects of AS and conditionability on the development or maintenance of PTSD. However, longitudinal research has shown pretrauma AS (Boffa et al., 2016) and conditioned physiological reactivity (Orr et al., 2012; Sijbrandij et al., 2013) to predict greater PTSD symptoms after a traumatic event, though the latter effect has largely been found in regards to poorer extinction rather than acquisition. Furthermore, Olatunji and Fan (2015) found that physiological reactivity to trauma film clips interacted with AS to lead to greater subsequent intrusion symptoms. Thus, the interaction of AS and physiological reactivity during fear acquisition represents a plausible risk factor for development or worsening of PTSD symptoms worthy of further investigation. However, PTSD symptoms have also been shown to predict subsequent increases in AS (Marshall et al., 2010), potentially due to development of associations between physiological arousal and trauma reminders. Regardless of directionality, present results provide preliminary evidence that AS plays a role in linking heightened excitatory fear learning with PTSD symptoms, adding to existing evidence (Allan et al., 2015) that AS is a meaningful target for trauma treatment.

This study has several limitations. First, the sample size was relatively small. Though associated with a medium-to-large effect size, the fact that moderator findings during acquisition only emerged as significant with an outlier removed and were not consistent across the menstrual cycle indicates that findings should be interpreted with caution and need replication. Generalizability to male samples should also be investigated. Another limitation is that PTSD severity was assessed using the CAPS-IV rather than the updated CAPS-5 reflecting *DSM–5* criteria. Although total scores for the two versions of the CAPS are highly correlated ($r = .83$) (Weathers et al., 2018), scoring methods and some individual items differ between CAPS-IV to CAPS-5, limiting generalizability of the results. In addition, this study used the original version of the ASI (Reiss et al., 1986), which has since been updated to better capture the multidimensional nature of the AS construct (Taylor et al., 2007).

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Table 3
Prediction of PTSD Severity by SCR to Conditioned Stimuli, Anxiety Sensitivity, and Their Interaction During Extinction

			Mid-Luteal phase				Early-Follicular phase			
Model	Step	Predictor	B	*SE* B	*p*	sr^2	B	*SE* B	*p*	sr^2
CS+	1.	SCR to CS+	−47.23	25.90	.08	.10	1.16	21.76	.96	.001
		ASI	0.76	0.39	.06	.12	**1.30**	**0.36**	**.001**	**.31**
	2.	ASI × CS+	−3.13	5.49	.57	.01	−2.41	2.38	.32	.04
CS−	1.	SCR to CS−	−6.68	27.79	.81	.002	**−55.83**	**22.88**	**.02**	**.17**
		ASI	**0.85**	**0.41**	**.04**	**.13**	**1.62**	**0.35**	**<.001**	**.44**
	2.	ASI × CS−	−1.87	2.74	.50	.02	−1.37	1.35	.33	.02
CSdiff	1.	CSdiff	−37.43	25.59	.15	.07	**66.29**	**24.14**	**.01**	**.21**
		ASI	0.71	.40	.09	.10	**1.53**	**0.33**	**<.001**	**.32**
	2.	ASI × CSdiff	3.79	2.73	.18	.06	3.95	2.07	.07	.11

Note. ASI = Anxiety Sensitivity Index; SCR = skin conductance reactivity. Bolded values represent significance $p < .05$.

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Despite the above limitations, the present study offers relevant insights into the role of AS as a moderator of the relationship between conditioned physiological reactivity and PTSD symptoms. Furthermore, by examining such relationships at different phases of the menstrual cycle, this study illustrates the possible influence of gonadal hormones on physiological predictors of PTSD symptoms, an oft-neglected factor influencing fear learning in women (Peyrot et al., 2020). Results provide tentative evidence that among trauma-exposed women in the mLP of the menstrual cycle, heightened SCR to a conditioned stimulus (CS+) during fear acquisition predicts greater PTSD symptoms among individuals high in AS. Future research replicating these findings in larger samples, and investigating such relationships longitudinally would be beneficial for better understanding the role of associative learning processes and AS in PTSD.

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