A prospective examination of sex differences in posttraumatic autonomic functioning

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2. Introduction

Trauma exposure is very common, with lifetime prevalence rates up to 89% (Kilpatrick et al., 2013). Symptoms of posttraumatic stress disorder (PTSD) affect a substantial proportion of those exposed to trauma and include unwanted re-experiencing of the event, avoidance of trauma reminders, negative changes in thinking and mood, and hyperarousal (APA, 2013). Individuals with PTSD symptoms experience significant functional impairment across multiple domains, and they are at greater risk of having cardiometabolic diseases compared to the general population (Edmondson et al., 2013; Norman et al., 2006; Pacella et al., 2013). One of the proposed mechanisms underlying increased cardiometabolic disease incidence in PTSD is altered functioning of the autonomic nervous system, such as increased heart rate (HR) and blood pressure (BP), and decreased high frequency heart rate variability (HF-HRV); for reviews see Buckley and Kaloupek, 2001 and Michopoulos et al., 2015). While numerous cross-sectional studies have demonstrated that those with PTSD exhibit altered autonomic functioning (reviewed below), there is a paucity of longitudinal studies following individuals in the immediate aftermath of trauma. Further, it is well-established that PTSD rates are twice as high in women compared to men (Kessler et al., 1995), yet sex differences in autonomic functioning are relatively unknown among trauma-exposed populations. There is a long-standing literature supporting an association between PTSD and autonomic deficits. Compared to healthy and trauma-exposed controls, individuals with PTSD demonstrate increased sympathetic...
determine if skin conductance in the immediate post-trauma period was sex differences in HR, HRV, and BP at this 2-week session, as well as to where HR, HRV, and BP were assessed. We sought to identify potential this time. They completed a fear conditioning paradigm two weeks later. Given the study’s aim of examining acute trauma responses, participants were also excluded if they reported ongoing domestic violence. Fear conditioning was completed in a sub-sample of AURORA participants at one of four locations two weeks following the emergency department visit. All participants provided informed consent and the study was approved by each site’s Institutional Review Board. See Fig. 1 for a CONSORT diagram outlining participant flow through the study.

2.2. Measures

PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013). The PCL-5 is a 20-item self-report measure of PTSD symptom severity and was administered eight weeks following the ED visit. Responses are on a scale from 0 (not at all) to 4 (extremely). A total score was used to assess overall PTSD severity. A score of 33 or higher was used to indicate probable PTSD diagnosis (Bovin et al., 2016).

2.3. ED skin conductance response measurement

eSense (Mindfield Biosystems, Inc., Berlin, Germany). Using previously validated procedures (Hinrichs et al., 2017), skin conductance levels were recorded with the eSense system during the initial ED visit. eSense software was downloaded to an iPad and two Velcro electrodes, which were connected to the iPad, were attached to the middle and index finger. Participants were asked to describe the traumatic event that brought them to the ED and eSense was used to continuously measure skin conductance levels during the interview. This method has been used previously in the ED among trauma-exposed adults (Hinrichs et al., 2019).

2.4. 2-Week psychophysiological assessment

Approximately two weeks following the ED visit, participants completed a follow-up session that included a seated BP assessment and a fear-potentiated startle (FPS) paradigm, during which HR and HRV from 22 emergency departments (EDs) across the U.S. immediately following a traumatic event (see McLean et al., 2020 for additional detail). Traumatic events included motor vehicle collisions, physical assault, sexual assault, and serious accidents. Exclusion criteria were intracranial injury, long bone fracture or significant extracranial hemorrhage, pregnancy, and admission due to intentional self-injury or suicide attempt. Given the study’s aim of examining acute trauma responses, participants were also excluded if they reported ongoing domestic violence. Fear conditioning was completed in a sub-sample of AURORA participants at one of four locations two weeks following the emergency department visit. All participants provided informed consent and the study was approved by each site’s Institutional Review Board. See Fig. 1 for a CONSORT diagram outlining participant flow through the study.

2. Methods

2.1. Participants and procedure

As part of the multi-site AURORA study, participants were recruited from 22 emergency departments (EDs) across the U.S. immediately following a traumatic event (see McLean et al., 2020 for additional detail). Traumatic events included motor vehicle collisions, physical assault, sexual assault, and serious accidents. Exclusion criteria were intracranial injury, long bone fracture or significant extracranial hemorrhage, pregnancy, and admission due to intentional self-injury or suicide attempt. Given the study’s aim of examining acute trauma responses, participants were also excluded if they reported ongoing domestic violence. Fear conditioning was completed in a sub-sample of AURORA participants at one of four locations two weeks following the emergency department visit. All participants provided informed consent and the study was approved by each site’s Institutional Review Board. See Fig. 1 for a CONSORT diagram outlining participant flow through the study.

Fig. 1. CONSORT diagram.
were obtained. The FPS paradigm is a Pavlovian fear conditioning paradigm that has been validated in clinical and nonclinical samples (e.g., Glover et al., 2011; Jovanovic et al., 2012; Norroholm et al., 2006; Seligowski et al., 2018). It includes a habituation phase followed by fear acquisition and extinction phases. During habituation, 12 108 dB startle probes were delivered through headphones to assess baseline startle, and eight of these were delivered upon the termination of conditioned stimuli (CS), which were colored shapes presented on a computer screen. During acquisition, one of the shapes (CS+) was paired with an averse unconditioned stimulus (US), while the other was not (CS-).

The US was a 250 ms/140 p.s.i. air blast directed at the larynx. The CS+ and CS- were each presented for 6 s and the startle probe was presented at their termination. During acquisition, the CS+ and startle probe were followed by the US 0.5 s later. Habituation included four trials of each CS (not reinforced with air blasts) and four startle probes alone (noise alone [NA]).

Acquisition included three conditioning blocks with four trials of each type (NA, CS+, CS-) in each block. Extinction included four blocks of four trials of each type (NA, CS+, [unreinforced], and CS-) in each block. All trials were on a fixed schedule and the inter-trial interval was 9–22 s.

Psychophysiological data were acquired using Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA). HR and HF-HRV were continuously measured with Ag/AgCl electrodes in the Lead II sampling rate of 10 Hz and the data were exported using.csv files.

3.2. Data analysis

Eight-week PCL-5 data were available for 192 participants. Using a cutoff score of 33 (Bovin et al., 2016), a dichotomous PTSD variable was created to indicate probable versus no PTSD. Of those with 8-week PCL-5 data, 158 participants had useable BP from the 2-week session, 151 participants had useable HR and HF-HRV data from 2-week fear conditioning, and 141 had useable eSense data from the ED. Reasons for missingness included data quality (e.g., noisy ECG signals) and incomplete data acquisition (e.g., participant did not complete fear conditioning). A chi-square analysis was used to compare the prevalence of hypertension among men versus women. Six univariate analyses of variance (ANOVAs) were used to test the effects of sex and PTSD on systolic and diastolic BP, average HR during acquisition and extinction, and average HF-HRV during acquisition and extinction. These models controlled for age, race, and body mass index (BMI). Bivariate correlations were used to test associations among eSense and BP, HR, and HF-HRV. All analyses were conducted with SPSS v.24 and significance set to \( p < .05 \).

4. Results

Table 1 displays descriptive data among the total sample and by sex, and Table 2 displays bivariate correlations among the total sample. Of the 192 participants with 8-week PCL-5 data \((M_{age} = 35.88, S_D = 13.56, 78 (40.6\%) \) met criteria for probable PTSD per the cutoff score of 33. There were no sex differences in putative PTSD diagnosis \((\chi^2(1,192) = 0.77, p = .389)\). In terms of race, 44.3\% (\( n = 85 \)) identified as Non-Hispanic Black, 33.3\% (\( n = 64 \)) identified as Non-Hispanic White, 17.7\% (\( n = 34 \)) identified as Hispanic, and 4.7\% (\( n = 9 \)) identified as Non-Hispanic “other” racial category.

Men were significantly more likely to meet criteria for hypertension than women, \( \chi^2(1,138) = 10.74, p = .001 \). Results of the first univariate ANOVA indicated a significant main effect of sex on systolic BP, \( F(1,140) = 20.51, p < .001 \), that it was higher in men compared to women (Fig. 2). The PTSD by sex interaction was not significant, \( F(1,140) = 0.34, p = .564 \), and there were no significant findings for diastolic BP.

There was not a significant sex difference in baseline HF-HRV, \( F(1,173) = 0.41, p = .523 \). Further, there were no significant sex differences in eyelink startle to the CS+ or CS- during acquisition or extinction (see Fig. 3), nor any significant PTSD by sex interactions when controlling for age, race, and BMI (\( p > .05 \)).

There was a significant main effect of sex on HR during fear acquisition, \( F(1,138) = 14.80, p < .001 \). The PTSD by sex interaction was not significant. During fear extinction, there was a significant main effect of sex on HR, \( F(1,130) = 9.90, p = .002 \), as well as a significant PTSD by sex interaction, \( F(1,130) = 4.10, p = .045 \). Post-hoc tests for this interaction indicated that HR was significantly different for men versus women only in the PTSD group, \( F(1,123) = 10.94, p = .001 \), whereas there was no significant effect of PTSD within either sex. As depicted in Fig. 4, women demonstrated higher HR compared to men during both fear acquisition and extinction, and this effect was stronger in the PTSD group during extinction, where HR was significantly higher in women \((M = 78.53)\) compared to men \((M = 67.70)\).

There was a significant main effect of sex on HF-HRV during fear acquisition, \( F(1,138) = 4.60, p < .034 \). The PTSD by sex interaction was not significant, \( F(1,138) = 3.41, p = .067 \). During fear extinction, there was a significant PTSD by sex interaction, \( F(1,129) = 5.18, p = .025 \). Post-hoc tests for this interaction indicated that HF-HRV was significantly different for men versus women only in the PTSD group, \( F(1,122) = 7.20, p = .008 \), whereas there was no significant effect of PTSD within either sex. As depicted in Fig. 5, women demonstrated lower HF-HRV compared to men during fear acquisition, and this effect was stronger in the PTSD group during extinction, where HF-HRV was significantly lower in women \((M = 5.41)\) compared to men \((M = 6.49)\).

Next, we examined associations among eSense skin conductance data in the ED and 2-week BP, HR, and HF-HRV. Skin conductance values were significantly and positively associated with HR and negatively associated with HF-HRV only among women who developed PTSD \((p < .05; \) see Table 3\), indicative of increased sympathetic arousal and decreased parasympathetic control during fear conditioning. When controlling for age, race, and BMI using linear regression models, only the association between baseline eSense and extinction HF-HRV in women with PTSD remained significant \((\beta = -0.36, p = .006)\). This suggests that increased sympathetic arousal in the immediate aftermath of trauma was associated with worse parasympathetic responses to fear extinction in women but not men with PTSD. No significant findings were observed in men or in women without PTSD.
most women were pre-menopausal. While prior studies have found that individuals with PTSD demonstrate higher BP than those without PTSD may explain lower rates of hypertension in pre-menopausal women; for age groups and it is thought that decreasing estradiol levels as a result of association, men demonstrated significantly higher BP and rates of hypertension, women. Sex differences were observed and varied by biomarker. While autonomic functioning among a sample of recently traumatized men and

5. Discussion

This study used a prospective design to examine sex differences in autonomic functioning among a sample of recently traumatized men and women. Sex differences were observed and varied by biomarker. While men demonstrated significantly higher BP and rates of hypertension, women demonstrated significantly higher HR and lower HF-HRV, and these effects were strongest among women who subsequently developed PTSD. Further, acute sympathetic arousal (indexed via skin conductance response) associated with HR and HF-HRV during fear conditioning but only among women who developed PTSD.

Our findings regarding BP and hypertension are consistent with what is commonly observed in the general population, such that men are more likely than women to experience hypertension (American Heart Association, heart.org). This sex difference is known to decrease among older age groups and it is thought that decreasing estradiol levels as a result of menopause in women play a role (i.e., estradiol is cardioprotective and may explain lower rates of hypertension in pre-menopausal women; for reviews, see Colafella and Denton, 2018; Regitz-Zagrosek et al., 2016). It is important to note that the average age in our sample was 35 and thus most women were pre-menopausal. While prior studies have found that individuals with PTSD demonstrate higher BP than those without PTSD (for a review, see Buckley and Kaloupek, 2001), we did not observe an effect of PTSD status. One potential explanation is that our sample is not as highly traumatized as comparisons in prior work (e.g., most participants were in motor vehicle collisions). Similarly, BP was assessed with only one measurement and this occurred two weeks following trauma exposure. It is therefore possible that the higher levels of BP observed in prior PTSD studies were a result of more chronic PTSD symptoms and sympathetic hyperarousal, which our study did not capture.

In terms of HR and HF-HRV, our findings indicate that women experienced worse autonomic functioning during fear conditioning compared to men, and this was particularly seen in those women who subsequently developed PTSD. Specifically, trauma-exposed women experienced worse autonomic functioning during extinction. This is consistent with prior literature implicating extinction deficits as a biomarker specific to PTSD (Jovanovic et al., 2012) and further suggests that women may be more likely than men to experience these deficits. Given that HR-HRV has been shown to be higher in healthy women compared to men (for a review, see Koenig and Thayer, 2016), our findings also highlight the importance of trauma and PTSD status in sex differences in autonomic function. The lack of sex

| Table 1 | Descriptive statistics for total sample and by sex. |
|---------|--------------------------------------------------|
|         | Male (n = 61) | Female (n = 131) | Total (N = 192) | Missing values |
|         | n | % | n | % | n | % | n | % |
| Race    |   |   |   |   |   |   |   |   |
| Non-Hispanic Black | 20 | 32.8 | 65 | 49.6 | 85 | 44.3 | – | – |
| Non-Hispanic White | 26 | 42.6 | 38 | 29.0 | 64 | 33.3 | – | – |
| Hispanic | 13 | 21.3 | 21 | 16.0 | 34 | 17.7 | – | – |
| Non-Hispanic other/not listed | 2 | 3.3 | 7 | 5.3 | 9 | 4.7 | – | – |
| Hypertension (2-weeks) | 26 | 42.6 | 21 | 16.0 | 21 | 16.0 | – | – |
| PTSD (8-weeks) | 22 | 36.1 | 56 | 42.7 | 78 | 40.6 | – | – |
| M | SD | M | SD | M | SD | n | % |
| Age | 37.61 | 14.83 | 35.07 | 12.91 | 35.88 | 13.56 | 0 | – |
| BMI | 27.13 | 5.16 | 29.82 | 7.43 | 28.91 | 6.85 | 20 | – |
| eSense Baseline (ED) | 3.78 | 2.90 | 2.71 | 1.86 | 3.09 | 2.33 | 51 | – |
| eSense Start (ED) | 4.33 | 4.21 | 2.93 | 2.07 | 3.43 | 3.06 | 53 | – |
| eSense Max (ED) | 6.18 | 6.08 | 5.02 | 3.49 | 5.43 | 4.59 | 51 | – |
| eSense End (ED) | 4.71 | 5.22 | 3.29 | 2.14 | 3.81 | 3.62 | 69 | – |
| BP – Systolic (2-weeks) | 133.98 | 20.42 | 120.65 | 15.33 | 125.46 | 18.43 | 34 | – |
| BP – Diastolic (2-weeks) | 83.30 | 13.17 | 81.80 | 11.38 | 82.34 | 12.03 | 25 | – |
| HR – Acquisition (2-weeks) | 68.44 | 10.12 | 74.31 | 10.15 | 72.44 | 10.47 | 41 | – |
| HRV – Acquisition (2-weeks) | 6.16 | 1.38 | 6.02 | 1.33 | 6.06 | 1.34 | 41 | – |
| HR – Extinction (2-weeks) | 70.29 | 10.93 | 75.69 | 10.38 | 73.96 | 10.82 | 51 | – |
| HRV – Extinction (2-weeks) | 6.01 | 1.46 | 5.89 | 1.40 | 5.93 | 1.42 | 52 | – |
| PTSD symptoms (8-weeks) | 27.10 | 17.67 | 29.58 | 18.96 | 28.79 | 18.55 | 0 | – |

Note. BMI = body mass index; BP = blood pressure; HR = heart rate; HRV = heart rate variability.

| Table 2 | Descriptive and bivariate correlations among study variables. |
|---------|---------------------------------------------------------------|
|         | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 1. eSense Baseline (ED) | – | – | – | – | – | – | – | – | – | – | – |
| 2. eSense Start (ED) | .947** | – | – | – | – | – | – | – | – | – | – |
| 3. eSense Max (ED) | .782** | .830** | – | – | – | – | – | – | – | – | – |
| 4. eSense End (ED) | .823** | .891** | .947** | – | – | – | – | – | – | – | – |
| 5. BP – Systolic (2-weeks) | −.088 | −.155 | −.134 | −.135 | – | – | – | – | – | – | – |
| 6. BP – Diastolic (2-weeks) | −.048 | −.068 | −.052 | −.083 | −.728** | – | – | – | – | – | – |
| 7. HR – Acquisition (2-weeks) | −.029 | −.111 | −.095 | −.133 | −.133 | −.056 | – | – | – | – | – |
| 8. HRV – Acquisition (2-weeks) | −.081 | −.094 | −.141 | −.062 | −.092 | −.205 | −.539** | – | – | – | – |
| 9. HR – Extinction (2-weeks) | −.039 | −.093 | −.099 | −.137 | −.088 | −.071 | −.967** | −.473** | – | – | – |
| 10. HRV – Extinction (2-weeks) | −.029 | −.083 | −.090 | −.049 | −.192 | −.240* | −.506** | −.924** | −.503** | – | – |
| 11. PTSD symptoms (8-weeks) | −.030 | −.023 | −.067 | −.100 | −.021 | −.041 | −.096 | −.043 | −.103 | −.043 | – |
| Mean | 2.96 | 3.15 | 4.99 | 3.45 | 126.14 | 82.38 | 71.57 | 61.22 | 72.80 | 60.03 | 28.41 |
| SD | 2.14 | 2.27 | 3.43 | 2.22 | 19.52 | 12.58 | 10.69 | 1.28 | 10.95 | 1.38 | 18.50 |
| Minimum | .43 | .44 | .45 | .43 | 96.00 | 54.00 | 48.47 | 3.15 | 49.75 | 2.69 | 0 |
| Maximum | 9.02 | 9.26 | 14.90 | 10.12 | 207.00 | 120.00 | 94.96 | 10.17 | 92.81 | 10.36 | 75 |

Note. *p < .05; **p < .01; BP = blood pressure; HR = heart rate; HRV = heart rate variability.
differences in autonomic functioning may have clinical implications. Specifically, men and women differed in their sympathetic arousal, with men demonstrating higher BP and women demonstrating higher HR. Further, women demonstrated lower parasympathetic function than men. As mentioned above, autonomic deficits have been implicated in the increased risk of cardiovascular disease in PTSD. Our findings suggest that the specific autonomic mechanisms through which cardiovascular disease develops could differ for men versus women with PTSD. For example, there is preliminary evidence that blockade of the renin-angiotensin system (responsible for BP regulation) via ace-inhibitors and angiotensin receptor blockers is associated with decreased likelihood of PTSD diagnosis (Khoury et al., 2012; Seligowski et al., 2021). We recently observed a sex effect such that the protective effects of these medications may be greater among men versus women (Seligowski et al., 2021). Thus, medications targeting BP may be more effective in men versus women with PTSD because men are more likely to experience hypertension and therefore see an effect of such medications. Prospective trials of antihypertensive medications for PTSD are needed to further explore sex differences in their effects. Another possible avenue for future trials is to determine if the autonomic deficits we observed during extinction in women with PTSD translate to clinical outcomes (e.g., do women with PTSD experience less symptom reduction from exposure treatments than men?). Thus far, sex differences in exposure-based treatments have not been reported, but we are not aware of any trials that examined sex differences in autonomic functioning during these treatments.

While capturing acute trauma reactions with a prospective design is a strength of this study, an important limitation is that our sample is not as highly symptomatic as comparisons from the literature. For example, we did not see main effects of PTSD status on BP, HR, of HF-HRV and this may be due to the recency of trauma exposure and the absence of severe PTSD symptoms in this cohort. Another limitation relates to trauma type, such that the index trauma for most participants was a motor vehicle collision and the incidence of PTSD in that population is lower than that of other trauma types, such as interpersonal violence and combat exposure (Kessler et al., 2017). Additionally, while we used a recommended cutoff for provisional PTSD diagnosis (Bovin et al., 2016) at 8-weeks, the current study relied on self-reported symptoms and did not include a structured clinical interview of PTSD. Future studies with more robust PTSD assessment among individuals with a broader range of trauma exposure will be needed to replicate and extend our findings. Despite these limitations, this study adds to a very scant literature regarding both 1) prospective assessments of posttraumatic autonomic functioning and 2) sex differences in posttraumatic autonomic functioning.

The current study identified sex differences in multiple domains of autonomic functioning among a recently traumatized sample. Our findings suggest that men and women demonstrate different patterns of sympathetic arousal, with men exhibiting higher BP and women exhibiting higher HR. Women also exhibited worse parasympathetic function as indicated by lower HF-HRV during fear conditioning, as was particularly seen in women who developed PTSD. Acute sympathetic arousal indexed by skin conductance in the emergency department was associated with HR and HF-HRV among women who developed PTSD, suggesting it may be a useful biomarker of subsequent autonomic functioning in this population. Additional studies examining subsequent sex differences in cardiovascular risk as a result of differential autonomic mechanisms are warranted.

CRediT authorship contribution statement

Antonia V. Seligowski: Data processing, Formal analysis, Data interpretation, Writing – original draft. Elizabeth R. Steuber: Data processing, Formal analysis, Data interpretation, Writing – original draft. Rebecca Hinrichs: Data processing, Formal analysis. Mariam H. Reda: Data processing, Formal analysis. Charis N. Wiltshire: Data processing, Original draft.
processing, Formal analysis. Cassandra P. Wanna: Data processing, Formal analysis. Sterling J. Winters: Data processing, Formal analysis. Karlye A. Phillips: Data processing, Formal analysis. Stacey L. House: Funding acquisition, recruitment, logistics. Francesca L. Beaudoin: Funding acquisition, recruitment, logistics. Xinming An: Funding acquisition, recruitment, logistics. Jennifer S. Stevens: Funding acquisition, recruitment, logistics. Donglin Zeng: Funding acquisition, recruitment, logistics. Thomas C. Neylan: Funding acquisition, recruitment, logistics. Gari D. Clifford: Funding acquisition, recruitment, logistics. Sarah D. Linnstaedt: Funding acquisition, recruitment, logistics. Laura T. Germain: Funding acquisition, recruitment, logistics. Guia Guffanti: Funding acquisition, recruitment, logistics. Scott L. Rauch: Funding acquisition, recruitment, logistics. John P. Haran: Funding acquisition, recruitment, logistics. Alan B. Storrow: Funding acquisition, recruitment, logistics. Christopher Lewandowski: Funding acquisition, recruitment, logistics. Paul I. Musey: Funding acquisition, recruitment, logistics. Sophia Sheikh: Funding acquisition, recruitment, logistics. Christopher W. Jones: Funding acquisition, recruitment, logistics. Britanny E. Punches: Funding acquisition, recruitment, logistics. Michael C. Kurz: Funding acquisition, recruitment, logistics. Vishnu P. Murty: Funding acquisition, recruitment, logistics. Meghan E. McGrath: Funding acquisition, recruitment, logistics. Lauren A. Hudak: Funding acquisition, recruitment, logistics. Jose L. Pascual: Funding acquisition, recruitment, logistics. Mark J. Seamon: Funding acquisition, recruitment, logistics. Elizabeth M. Datner: Funding acquisition, recruitment, logistics. Anna M. Chang: Funding acquisition, recruitment, logistics.

Fig. 3a. FPS by sex during fear acquisition at 2-weeks
Figure 3b. FPS by sex during fear extinction at 2-weeks.
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Declaration of competing interest

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**Fig. 4a.** Sex effect on HR during fear acquisition at 2-weeks

**Figure 4b.** Sex and interaction effects on HR during fear extinction at 2-weeks.
Fig. 5a. Sex effect on HF-HRV during fear acquisition at 2-weeks
Figure 5b. Interaction effect on HF-HRV during fear extinction at 2-weeks.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100384.

Table 3

Descriptives and bivariate correlations of study variables among women with PTSD.

|               | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   |
|---------------|------|------|------|------|------|------|------|------|------|------|------|
| 1. eSense Baseline (ED) |      |      |      |      |      |      |      |      |      |      |      |
| 2. eSense Start (ED) | .918**|      |      |      |      |      |      |      |      |      |      |
| 3. eSense Max (ED) | .698**| .825**|      |      |      |      |      |      |      |      |      |
| 4. eSense End (ED) | .672**| .776**| .863**|      |      |      |      |      |      |      |      |
| 5. BP – Systolic (2-weeks) | .067 | .025 | .056 | .139 |      |      |      |      |      |      |      |
| 6. BP – Diastolic (2-weeks) | -.182 | -.169 | .023 | -.029 |      |      |      |      |      |      |      |
| 7. HR – Acquisition (2-weeks) | .287 | .390* | .339 | .386 | .237 | .256 |      |      |      |      |      |
| 8. HRV – Acquisition (2-weeks) | -.259 | -.232 | -.157 | -.368 | .268 | .327 | -.566*|      |      |      |      |
| 9. HR – Extinction (2-weeks) | .369 | .411* | .417* | .536* | .123 | -.207 | .967**| .460*|      |      |      |
| 10. HRV – Extinction (2-weeks) | -.491* | .341 | .301 | -.530* | .029 | -.401* | .877**| -.339 |      |      |      |
| 11. PTSD symptoms (8-weeks) | -.118 | -.178 | .309 | -.235 | .262 | -.232 | -.331 | .174 | -.387 | .321 |      |
| Mean          | 2.69 | 3.03 | 5.36 | 3.27 | 122.58 | 83.08 | 73.04 | 6.16 | 74.45 | 6.23 | 46.98 |
| SD           | 1.87 | 2.10 | 3.34 | 1.75 | 18.95 | 13.95 | 11.60 | 1.05 | 11.20 | 1.13 | 10.50 |
| Minimum       | .43  | .50  | .62  | .43  | 96.00 | 57.00 | 53.41 | 3.32 | 54.02 | 3.30 | 33   |
| Maximum       | 8.80 | 6.95 | 14.90 | 6.58 | 171.00 | 118.00 | 94.96 | 7.49 | 92.81 | 7.80 | 75   |

Note. *p < .05; **p < .01; BP = blood pressure; HR = heart rate; HRV = heart rate variability.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100384.

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References

American Psychiatric Association. 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
Blechert, J., Michael, T., Friends, N., Margraf, J., Wilhelm, F.H., 2007. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. Behav. Res. Ther. 45, 2019–2033.
Bovin, M.J., Marx, B.P., Westers, F.W., Gallagher, M.W., Rodrigue, P., Schnurr, P.P., Keane, T.M., 2016. Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental disorders—fifth edition (PCL-5) in veterans. Psychol. Assess. 28, 1297.
Buckley, T.C., Kaloupek, D.G., 2001. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. Psychosom. Med. 63, 585–594.
Cohen, H., Korler, M., Matar, M.A., Kaplan, Z., Miodovni, H., Casuto, Y., 1997. Power spectral analysis of heart rate variability in posttraumatic stress disorder patients. Biol. Psychiatr. 41, 627–629.
Colafella, K.M.M., Denton, K.M., 2018. Sex-specific differences in hypertension and associated cardiovascular disease. Nat. Rev. Nephrol. 14, 185.
Edmondson, D., Kronish, I.M., Shaffer, J.A., Falzon, L., Burg, M.M., 2013. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am. Heart J. 166, 806–814.
Ehlers, A., Sauerermann, O., Bellinghausen, I., Vosbeck-Eibeuchus, A., Gamer, M., Briddon, E., Martin, M.W., Glucksman, E., 2010. Heart rate responses to standardized trauma-related pictures in acute posttraumatic stress disorder. Int. J. Psychophysiol. 78, 27–34.
Gerardi, R.J., Keane, T.M., Cahoon, B.J., Klauminzer, G.W., 1994. An in vivo assessment of physiological arousal in posttraumatic stress disorder. J. Abnorm. Psychol. 103, 585–594.
Glover, E.M., Jovanovic, T., Mercer, K.B., Kerley, K., Bradley, B., Ressler, K.J., Norrholm, S.D., 2012. Estrogen levels are associated with extinction deficits in women with posttraumatic stress disorder. Biol. Psychiatr. 72, 19–24.
Glover, E.M., Mercer, K.B., Norrholm, S.D., Davis, M., Duncan, E., Bradley, B., Ressler, K.J., Jovanovic, T., 2013. Inhibition of fear is differentially associated with cycling estrogen levels in women. J. Psychiatry Neurosci. 38, 341.
Glover, E.M., Phifer, J.E., Crain, D.F., Norrholm, S.D., Davis, M., Bradely, F., Ressler, B.K., Jovanovic, T., 2011. Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. Depress. Anxiety 28, 1058–1066.
Hauschmidt, M., Peters, M.J.V., Moritz, S., Jelinek, L., 2011. Heart rate variability in response to affective scenes in posttraumatic stress disorder. Biol. Psychol. 88, 215–222.
Hinrichs, R., Michopoulos, V., Winter, S., Rothbaum, A.O., Rothbaum, B.O., Ressler, K.J., Jovanovic, T., 2017. Mobile assessment of heightened skin conductance in posttraumatic stress disorder. Depress. Anxiety 34, 502–507.
Hinrichs, R., van Rooij, S.J., Michopoulos, V., Schultebrack, K., Winters, S., Maples-Keller, J., Rothbaum, A.O., Stevens, J.S., Galazter-Levy, I., Rothbaum, B.O., Ressler, K.J., 2019. Increased skin conductance response in the immediate aftermath of trauma predicts PTSD risk. Chronic Stress 3, 247057019844441.
Hopfer, J.W., Spinazzola, J., Simpson, W.B., van der Kolk, B.A., 2006. Preliminary evidence of parasympathetic influence on basal heart rate in posttraumatic stress disorder. J. Psychosom. Res. 60, 83–90.
Inslicht, S.S., Metzler, T.J., Garcia, N.M., Pineles, S.L., Milad, M.R., Orr, S.P., et al., 2013. Sex differences in fear conditioning in posttraumatic stress disorder. J. Psychiatr. Res. 47, 64–71.

Irish, L.A., Fischer, B., Fallon, W., Spooner, E., Sledjeski, E.M., Delahanty, D.L., 2011. Gender differences in PTSD symptoms: an exploration of peritraumatic mechanisms. J. Anxiety Disord. 25, 209–216.

Jovanovic, T., Norrholm, S.D., Sakoman, A.J., Esterajsher, S., Kozar-Tatovic, D., 2009. Altered resting psychophysiology and startle response in Croatian combat veterans with PTSD. Int. J. Psychophysiol. 71, 264–268.

Jovanovic, T., Kazama, A., Bechvalner, J., Davis, M., 2012. Impaired safety signal learning may be a biomarker of PTSD. Neuropharmacology 62, 695–704.

Kamkwala, A., Norrholm, S.D., Poole, J.M., Brown, A., Donley, S., Duncan, E., et al., 2012. Dark-enhanced startle responses and heart rate variability in a traumatized civilian sample: putative sex-specific correlates of posttraumatic stress disorder. Psychosom. Med. 74, 153–159.

Keary, T.A., Hughes, J.W., Palmieri, P.A., 2009. Women with posttraumatic stress disorder have larger decreases in heart rate variability during stress tasks. Int. J. Psychophysiol. 73, 257–264.

Kesler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the national comorbidity survey. Arch. Gen. Psychiatr. 52, 1048–1060.

Kesler, R.C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E.J., Cardoso, G., Degenhardt, L., de Girolamo, G., Díonovlova, R.F., Ferry, F., Florencu, S., 2017. Trauma and PTSD in the WHO world mental health surveys. Eur. J. Psychotraumatol. 8, 1353383.

Khoury, N.M., Marvar, P.J., Gillespie, C.F., Wingo, A., Schwartz, A., Bradley, B., Kramer, M., Kesler, K.J., 2012. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. J. Clin. Psychiatr. 73, 849–855.

Kilpatrick, D.G., Resnick, H.S., Milanak, M.E., Miller, M.W., Keyes, K.M., Friedman, M.J., 2013. National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. J. Trauma Stress 26, 537–547.

Klein, B., Willemen, F.H., Glucksman, E., Ehlers, A., 2010. Sex differences in heart rate responses to script-driven imagery soon after trauma and risk of posttraumatic stress disorder. Psychosom. Med. 72, 917–924.

Koenig, J., Thayer, J.F., 2006. Associations between psychological trauma and physical illness in postdeployment posttraumatic stress disorder in active-duty marines. JAMA Psychiatr. 157, 255–261.

Kleim, B., Wilhelm, F.H., Glucksman, E., Ehlers, A., 2010. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Eur. Heart J. 37, 24–34.

Kramer, M., Ressler, K.J., 2012. The renin-angiotensin pathway in posttraumatic stress disorder in women is associated with a block in conversion of progesterone to the GABAergic neurotransmitter allopregnanolone and pregnanolone measured in plasma. Psychoneuroendocrinology 39, 133–141.

Regitz-Zagrosek, V., Oertelt-Prigione, S., Prescott, E., Francioni, F., Gerdtz, E., Fryest-Ludwig, A., Maaz, A.H., Kastner-Willer, A., Knuppe-Wengen, D., 2016. Gender differences in posttraumatic stress in women with posttraumatic stress disorder. Arch. Psychiatr. 49, 637–643.

Seligowski, A.V., Bondy, E., Singleton, P., Orcutt, H.K., Ressler, K.J., Auerbach, R.P., 2018. Testing neurophysiological markers related to fear-potentiated startle. Psychosom. Res. 127, 195–206.

Shalev, A.Y., Peri, T., Ben-Shakhar, G., Orr, S.P., Shalev, A.Y., 2000. Physiopsychologic assessment of aversive conditioning in posttraumatic stress disorder. Biol. Psychiatr. 47, 512–519.

Pineles, S.L., Nilini, Y.I., King, M.W., Patton, S.C., Bauer, M.R., Mostoufi, S.M., et al., 2016. Extinction retention and the menstrual cycle: different associations for women with posttraumatic stress disorder. J. Abnorm. Psychol. 125, 349–355.

Pineles, S.L., Nilini, Y.I., Pinna, G., Irvine, J., Webb, A., Arditte Hall, K.A., et al., 2018. PTSD in women is associated with a block in conversion of progesterone to the GABAergic neurotransmitter allopregnanolone and pregnanolone measured in plasma. Psychoneuroendocrinology 39, 133–141.

Weathers, F., Litz, B., Keane, T., Palmieri, T., Marx, B.P., Schnurr, P., 2013. The PTSD checklist for DSM-5 (PCL-5). Scale available from the national center for PTSD at www.ptsd.va.gov.

A.V. Seligowski et al. Neurobiology of Stress 15 (2021) 100384