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Probing the neurocardiac circuit in trauma and posttraumatic stress

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ABSTRACT

The neurocardiac circuit is integral to physiological regulation of threat and trauma-related responses. However, few direct investigations of brain-behavior associations with replicable physiological markers of PTSD have been conducted. The current study probed the neurocardiac circuit by examining associations among its core regions in the brain (e.g., insula, hypothalamus) and the periphery (heart rate [HR], high frequency heart rate variability [HF-HRV], and blood pressure [BP]). We sought to characterize these associations and to determine whether there were differences by PTSD status. Participants were $N = 315$ (64.1 % female) trauma-exposed adults enrolled from emergency departments as part of the prospective AURORA study. Participants completed a deep phenotyping session (e.g., fear conditioning, magnetic resonance imaging) two weeks after emergency department admission. Voxelwise analyses revealed several significant interactions between PTSD severity 8-weeks posttrauma and psychophysiological recordings on hypothalamic connectivity to the prefrontal cortex (PFC), insula, superior temporal sulcus, and temporoparietaloccipital junction. Among those with PTSD, diastolic BP was directly correlated with right insula-hypothalamic connectivity, whereas the reverse was found for those without PTSD. PTSD status moderated the association between systolic BP, HR, and HF-HRV and hypothalamic connectivity in the same direction. While preliminary, our findings may suggest that individuals with higher PTSD severity exhibit compensatory neural mechanisms to down-regulate autonomic imbalance. Additional study is warranted to determine how underlying mechanisms (e.g., inflammation) may disrupt the neurocardiac circuit and increase cardiometabolic disease risk in PTSD.

Trauma exposure is extremely common, affecting approximately 90% of the U.S. population (Kilpatrick et al., 2013). While many individuals recover from its effects, approximately 8% of the general U.S. population develop debilitating symptoms of posttraumatic stress disorder (PTSD), which includes intrusive re-experiencing, avoidance of trauma reminders, negative affect and cognition, and hyperarousal (APA, 2013). Prevalence rates are higher among certain populations, such as military and first responder personnel, individuals exposed to interpersonal and sexual violence, and individuals chronically exposed to violence in underserved communities (Fulton et al., 2015). Research has increasingly focused on biomarkers that may predict the onset of PTSD, though most suffer from a lack of prospective designs due to the retrospective nature of most trauma research. Nevertheless, there are consistent findings that suggest negative alterations in the brain (e.g., low PFC activity) and periphery (e.g., high blood pressure) are associated with PTSD. Most of this research has been conducted separately, such that the brain *or* the periphery have been studied, but given that these systems are connected through the neurocardiac circuit (described below), their associations with one another may provide additional clues into the neurobiological effects of PTSD.

The neurocardiac circuit refers to a system of connections between the brain and the periphery that includes frontal (e.g., ventromedial PFC [vmPFC]) and limbic (e.g., amygdala, insula) structures, the hypothalamus, and several areas of the brainstem (e.g., solitary nucleus). Through numerous ganglia, these structures connect to the autonomic nervous system and regulate heart rate (HR), heart rate variability (HRV), and blood pressure (BP) (Berntson et al., 1997; Mather and Thayer, 2018; Thayer et al., 2009). As described above, PTSD is associated with functional variability across all areas of the neurocardiac circuit (e.g., low vmPFC activity, high amygdala and dorsal anterior cingulate [dACC] activity, high HR and BP). While some studies have examined this circuit in other populations (Osborne et al., 2019, 2020; Radfar et al., 2021; Tawakol et al., 2017), few have examined the brain-periphery association as an indicator of dysfunction in PTSD. Given that existing treatments for PTSD have effects on both the brain (Manthey et al., 2021) and the periphery (Bourassa et al., 2020), better characterization of neurocardiac circuit deficits in PTSD may have relevance to treatment.

Neuroimaging-based biomarkers of PTSD have largely implicated core regions of the neurocardiac circuit. Trauma exposure directly affects neural reactivity of the dACC during fear conditioning (Harnett et al., 2018). Emergency department (ED) studies with neuroimaging conducted within a few weeks of trauma exposure suggest threat-related activity within the vmPFC, amygdala, and hippocampus is associated with vulnerability to adverse neuropsychiatric sequalae (Stevens et al., 2021; Tanriverdi et al., 2022). Similarly, post-trauma amygdala/-hippocampal connectivity at rest is predictive of future PTSD symptoms (Belleau et al., 2020; Fitzgerald et al., 2022; Harnett et al., 2021). These findings are consistent with imaging studies conducted in other acute trauma populations that suggest neurobiology of the PFC, hippocampus, and amygdala is associated with the development of PTSD (Ben-Zion et al., 2020; Koch et al., 2021). Limited functional imaging research of the hypothalamus in trauma/PTSD has been conducted to date, however, white matter tracts interconnecting the amygdala and hippocampus with the hypothalamus (e.g., fornix and stria terminalis) are associated with PTSD symptoms and recovery (Harnett et al., 2020, 2021; Kennis et al., 2015). Few studies have examined how these neural alterations associated with trauma/PTSD may interact with peripheral physiology, although prior research has demonstrated that dACC activity was associated with BP changes to stress (Gianaros et al., 2008). The extant literature thus suggests that key nodes of the neurocardiac circuit play a role in PTSD vulnerability.

Alterations in peripheral psychophysiology (which is mediated by neurocardiac circuitry) have been documented in individuals with PTSD compared to trauma-exposed and healthy controls. In terms of the sympathetic nervous system, higher levels of BP and HR at rest and in response to conditioned stimuli have been found in those with PTSD (Blechert et al., 2007; Gerardi et al., 1994; Jovanovic et al., 2009; Milad

et al., 2009; Seligowski et al., 2020). Our recent work suggests that systolic BP is predictive of future PTSD differences between men and women (Seligowski et al., 2021). Deficits in parasympathetic function have also been documented, with lower rates of high frequency heart rate variability (HF-HRV) at rest and under stress in individuals with PTSD compared to healthy and trauma-exposed controls (Chang et al., 2013; Hauschildt et al., 2011; Keary et al., 2009; Minassian et al., 2014). Further, skin conductance response (SCR) and HF-HRV have been prospectively associated with PTSD (Hinrichs et al., 2019; Minassian et al., 2015; Shalev, 2000; Shalev et al., 1998). Taken together, peripheral biomarkers of PTSD reflect impairments in sympathetic and parasympathetic function. However, limited work has investigated how expression of autonomic activity may interact with regions of the neurocardiac circuit in the early aftermath of trauma to contribute to PTSD symptoms.

The current study probed the neurocardiac circuit by examining associations among core regions within the circuit (e.g., PFC, insula, hypothalamus) and peripheral psychophysiology measures (e.g., HR, BP) implicated in PTSD. Our sample included men and women with a recent trauma exposure as part of the prospective AURORA study (McLean et al., 2020). We sought to characterize these associations and to determine whether there were differences by PTSD status. We hypothesized that PTSD would be associated with alterations in the relationship between neural connectivity and peripheral psychophysiology, indicative of decreased regulatory capacity (i.e., top-down control).

1. Methods

1.1. Participants

Participants included $N = 315$ (64.1 % female) adults recruited from 22 emergency departments (ED) in the United States as part of the multisite longitudinal AURORA study (McLean et al., 2020). Trauma exposure in the AURORA sample included motor vehicle accidents, physical and sexual assault, fall greater than 10 feet, mass casualty incidents, or other events that threatened or resulted in injury, violence, or death. Individuals were excluded from participation based on intracranial injury, long bone fracture or significant extracranial hemorrhage, pregnancy, ongoing domestic violence, and ED admission due to self-injury or attempted suicide. Participants completed a BP measurement, fear conditioning, and magnetic resonance imaging (MRI) two weeks after ED admission. All study procedures were approved by each site's Institutional Review Board. All participants provided informed consent.

1.2. PTSD symptoms

PTSD Checklist for DSM-5 (PCL-5). The PCL-5 is a 20-item measure of PTSD symptoms (Weathers et al., 2013b) that was administered eight weeks after ED admission. Items refer to the four DSM-5 symptom clusters of PTSD: Re-experiencing, Avoidance, Negative Alterations in Cognition and Mood, and Alterations in Arousal and Reactivity. Responses range from 0 (not at all) to 4 (extremely). A total score was used to assess overall PTSD symptom severity. As previously reported, the PCL-5 demonstrated high internal consistency in this study, $\alpha = 0.96$ (Kessler et al., 2021).

1.3. Week-2 laboratory visit

Fear Conditioning and Psychophysiology. The fear conditioning paradigm has been well-validated in several different populations (e.g., Glover et al., 2012; Jovanovic et al., 2012; Norrholm et al., 2006; Seligowski et al., 2019). The paradigm consists of three phases: habituation, acquisition, and extinction, on a fixed schedule. Conditioned stimuli (CS) include colored shapes presented on a computer screen that are paired with audio startle probes. During habituation, baseline startle was assessed via 12 108 dB white noise startle probes delivered via headphones. This phase consisted of four trials of each CS followed by a startle probe, and four startle probes alone without presentation of the CS (noise alone [NA]). During acquisition, a 250 ms/140 p.s.i. air blast directed at the larynx served as the unconditioned stimulus (US) which was paired with one of the shapes (CS+); the other shape was not paired with an airblast (CS-). Acquisition consisted of three conditioning blocks, with four trials of each type of stimuli (i.e., NA, CS+, CS-) in each block. All CS were presented for 6 s and followed by a startle probe. For the CS + trials, following the termination of the CS+ and startle probe, the US was presented 0.5 s later. There was a 10-min break between acquisition and extinction phases. The extinction phase consisted of four blocks, each block including four trials of each type (CS+, CS-, NA), but without US presentation. Inter-trial interval was 9–22 s for all trials.

During the fear conditioning paradigm, HR and HF-HRV were collected. HR was collected continuously using Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA). Two Ag/AgCl electrodes were placed in the Lead II position using the electrocardiogram (ECG) module. MindWare software was used to process the HR and HF-HRV data using R-waves and R–R intervals. Data artifacts detected through MindWare were visually inspected and corrected (Mindware, Inc.). Spectral analysis and log transformation of 1-min epochs with a Hamming windowing function were used to derive HR and HR-HRV. Standard recommendations for the high frequency band for the HF-HRV were used (i.e., 0.12–0.40 Hz; Task Force, 1996). Averaged HR and HF-HRV values across acquisition and extinction blocks were used for analyses. All psychophysiological data was exported to SPSS following processing.

1.4. Magnetic resonance imaging

Magnetic resonance imaging data was collected from participants within approximately 2-weeks after trauma exposure, within 1–2 days of fear conditioning. Detailed information on acquisition parameters by site and imaging processing are available in the supplement. Briefly, FMRIPREP was used to preprocess task and resting-state fMRI data. The rs-fMRI data were further processed within the Analysis for Functional NeuroImages (AFNI) program 3dTproject to perform linear detrending, censoring of non-steady state volumes identified by FMRIPREP, bandpass filtering (0.01–0.1 Hz), and regression of white matter, corticospinal fluid, and global signal to account for potential physiological noise. Functional connectivity of the entire neurocardiac circuit was assessed by correlating the mean fMRI signal time-course from the left and right dACC, ventral ACC (vACC, used to indicate PFC), insula, hippocampus, and amygdala defined by the Desikan-Killainy atlas (Desikan et al., 2006). The hypothalamus ROI was derived from the CIT168 atlas using a 95% probability threshold (Pauli et al., 2018). To reduce the number of comparisons, connectivity values for each hemisphere were averaged (i.e., combining left and right for each seed region). Given our primary interest in the hypothalamus, we also generated whole-brain voxelwise functional connectivity maps using the hypothalamus ROI for each participant. Whole-brain connectivity maps were entered into voxelwise linear models to assess the association between hypothalamus connectivity, psychophysiological recordings, and

PTSD status. All connectivity values were Fisher Z transformed prior to statistical analysis.

1.5. Data analysis

All analyses were conducted in SPSS v.24, using a significance level of $p < 0.05$. Voxelwise group-level models were completed using 3dMVM in AFNI that included tested effects of psychophysiological variable (e.g., HF-HRV during acquisition), PTSD symptoms at 8-weeks, and the interaction between the psychophysiological variable and PTSD symptoms. Additional covariates in the group level models were participant sex, age, and site. A gray matter mask that included subcortical areas and the cerebellum was applied to the data. Cluster-based methods for multiple comparison correction were applied to determine the voxel extent *k* needed at a cluster forming threshold of p = .005 to maintain α = 0.05. Specifically, 3dFWHMx was applied to the 1st-level contrasts of the preprocessed rs-fMRI data to derive the auto-correlation function parameters for 3dClustSim (10 000 iterations). The minimum *k* for analyses of the rs-fMRI data was 99 voxels.

2. Results

Demographic data on the present sample are provided in Table S1. We first assessed bivariate associations between rs-fMRI connectivity of our a priori regions of interests (i.e., the neurocardiac circuit) and physiological measures (Table 1). We observed significant bivariate correlations between functional connectivity of several brain regions and peripheral psychophysiology measures. Higher functional connectivity of the hypothalamus-PFC at 2 weeks was associated with higher HR during fear acquisition ($r = 0.21$, $p = 0.017$) and fear extinction ($r = 0.23$, $p = 0.015$). When controlling for age and sex, these correlations remained significant. No significant correlations were observed for hypothalamic connectivity with BP or HF-HRV.

We next completed voxelwise analyses to better probe associations between hypothalamic connectivity, physiological measures, and later PTSD symptoms. Voxelwise analyses revealed several significant interactions between PTSD symptom severity at 8-weeks posttrauma and psychophysiological recordings on hypothalamic connectivity to the PFC, insula, superior temporal sulcus (STS), and temporoparietaloccipital junction (Table S2). The largest effects were observed for PTSD symptoms moderating associations between diastolic BP and hypothalamic connectivity to regions including the PFC, insula, and temporoparietal junction. Among those with PTSD, lower diastolic BP was associated with lower right insula-hypothalamic connectivity and higher diastolic BP was associated with higher connectivity, whereas the reverse was found for those without PTSD (i.e., lower BP was associated with higher connectivity; Fig. 1). Similarly, lower diastolic BP was associated with lower hypothalamic connectivity with the right post-central gyrus, right central sulcus, and right middle temporal gyrus among those with PTSD, while higher diastolic BP was associated with higher connectivity of the hypothalamus with these regions (Supplemental Fig. 1).

PTSD status also moderated the association between systolic BP, HR, and HF-HRV and hypothalamic connectivity (Table S2). Lower systolic BP among those with PTSD was associated with lower right middle temporal gyrus-hypothalamic connectivity while higher systolic BP was associated with higher connectivity in PTSD (and the reverse was found for those without PTSD; Fig. 2). Among those with PTSD, lower HR during acquisition and extinction was associated with lower PFC-hypothalamic connectivity and higher HR was associated with higher connectivity, whereas the reverse was found for those without PTSD (Fig. 3). Finally, those with PTSD and lower HF-HRV demonstrated higher superior temporal sulcus-hypothalamic connectivity, while those with PTSD and higher HF-HRV demonstrated lower connectivity (and

Table 1
Bivariate correlations among neurocardiac rs-fMRI connectivity and physiological variables.

	1	2	3	4	5	6	7	8	9
1. Systolic BP	–								
2. Diastolic BP	0.68**	–							
3. HR Acquisition	0.07	0.24**	–						
4. HR Extinction	0.07	0.21**	0.96**	–					
5. HRV Acquision	−0.21**	−0.25**	−0.49**	−0.47**	–				
6. HRV Extinction	−0.23**	−0.25**	−0.56**	−0.57**	0.87**	–			
7. Insula- PFC	−0.11	−0.13	−0.02	−0.08	−0.07	0.04	–		
8. Hypothalamus-PFC	0.12	0.10	0.21*	0.23*	−0.08	−0.11	0.05	–	
9. Hypothalamus-Insula	−0.02	0.08	−0.06	−0.05	0.04	0.00	0.01	0.35**	–

Note. **$p < 0.01$; *$p < 0.05$. BP = blood pressure; HR = heart rate; HRV = heart rate variability; PFC = prefrontal cortex.

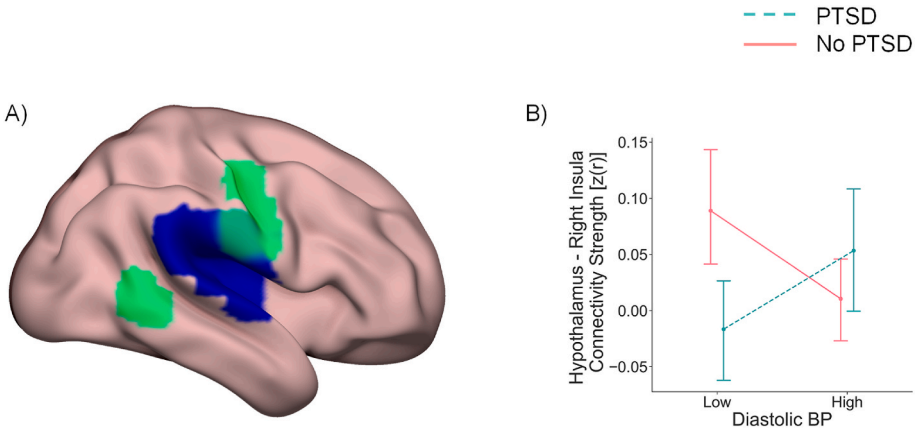

Fig. 1. PTSD moderates the association between diastolic BP and hypothalamic connectivity. *Note.* A) PTSD status significantly moderated the association between diastolic BP and hypothalamus connectivity to several brain regions including the insula (dark blue). B) Simple slopes analyses revealed participants with PTSD (cyan) showed a positive association between Diastolic BP and connectivity whereas participants without PTSD (red) showed an inverse relationship. BP = blood pressure.

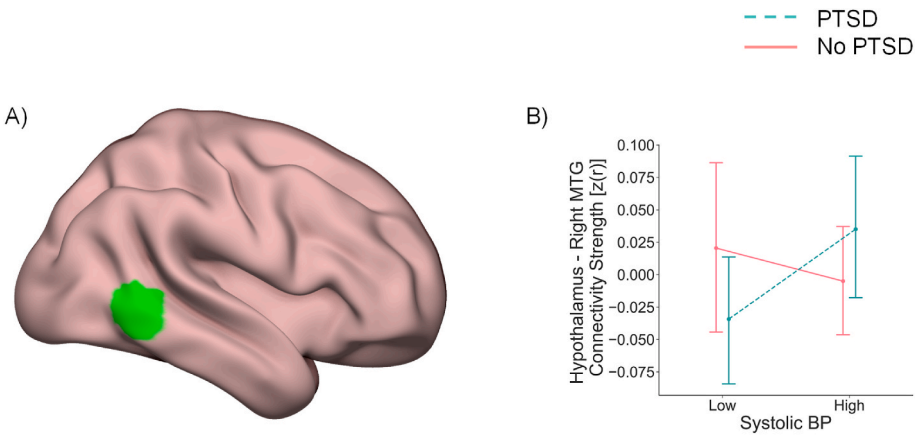

Fig. 2. PTSD moderates the association between systolic BP and hypothalamic connectivity. *Note.* A) PTSD status significantly moderated the association between diastolic BP and hypothalamus connectivity to several brain regions including the MTG (green). B) Simple slopes analyses revealed participants with PTSD (cyan) showed a positive association between Systolic BP and connectivity whereas participants without PTSD (red) showed an orthogonal relationship. BP = blood pressure; MTG = middle temporal gyrus.

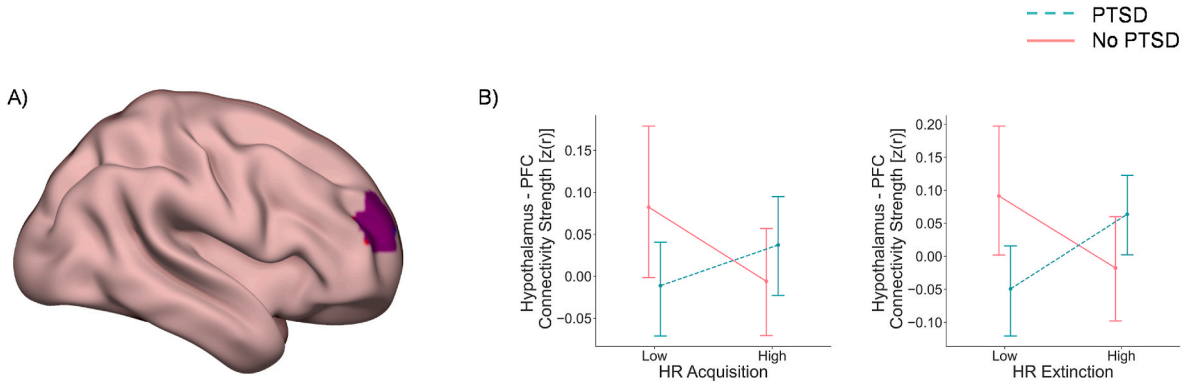

Fig. 3. PTSD moderates the association between HR and hypothalamic connectivity. *Note.* A) PTSD status significantly moderated the association between HR during acquisition (red) and extinction (blue) of conditioned fear and hypothalamus connectivity to the PFC (overlap shown in purple). B) Simple slopes analyses revealed participants with PTSD (cyan) showed a positive association between HR (acquisition and extinction) and connectivity whereas participants without PTSD (red) showed an inverse relationship. HR = heart rate; PFC = prefrontal cortex.

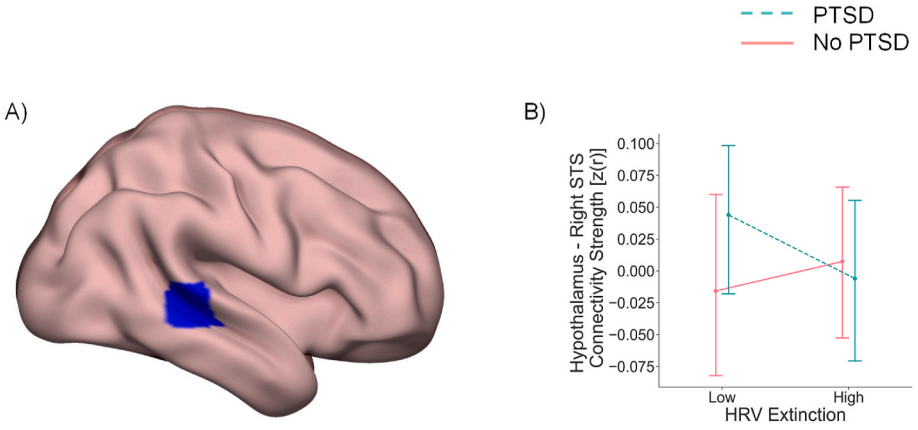

Fig. 4. PTSD moderates the association between HRV and hypothalamic connectivity. *Note.* A) PTSD status significantly moderated the association between HRV during extinction of conditioned fear and hypothalamus connectivity to the STS (dark blue). B) Simple slopes analyses revealed participants with PTSD (cyan) showed a negative association between HRV and connectivity whereas participants without PTSD (red) showed an orthogonal relationship. HRV = heart rate variability; STS = superior temporal sulcus.

the reverse was found for those without PTSD; Fig. 4).

3. Discussion

In a sample of recently trauma-exposed adults, we observed that neurocardiac circuit connectivity was associated with several physiological indicators and that these associations were moderated by PTSD status. Specifically, PTSD moderated associations between BP, HR, and HF-HRV and hypothalamic connectivity to multiple brain regions. These findings may indicate that PTSD is associated with compensatory neural

mechanisms to down-regulate autonomic imbalance. Further, these findings provide additional support for the concept of an ecophenotype, such that trauma and PTSD may confer neural alterations that represent a unique biological subtype (Meneguzzo et al., 2022; Staginnus et al., 2023; Teicher and Samson, 2013).

We found multiple indicators of sympathetic nervous system activity that were significantly associated with hypothalamic connectivity. Two weeks after trauma exposure, higher HR during fear conditioning and extinction was associated with higher hypothalamic-PFC connectivity. This provides further validation that peripheral measures of sympathetic function are relevant to neural biomarkers of threat circuitry in an acutely trauma-exposed sample. Additionally, these findings are consistent with prior research suggesting a link between threat circuitry (e.g., hypothalamus, insula), stress, and cardiovascular autonomic function (e.g., HR) (Schaeuble and Myers, 2022). An important next step in this work is to identify whether alterations in these circuits predict adverse outcomes in trauma-exposed populations. Specifically, trauma and PTSD are associated with increased risk for cardiometabolic disease (Koenen et al., 2017; Wentworth et al., 2013), but underlying pathways have yet to be clarified. It has been suggested that high stress and its associated neural circuitry triggers peripheral inflammation (via sympathetic nervous system activation), which is a major contributor to cardiovascular disease. Thus, it is critical to determine if alterations in the neurocardiac circuit predict cardiometabolic disease in trauma-exposed individuals.

Associations between peripheral physiology and hypothalamic connectivity were moderated by PTSD status. Generally speaking, hypothalamic connectivity with several brain regions was lower among those with PTSD and low BP/HR, but higher among those with PTSD and high BP/HR (i.e., autonomic imbalance). Similarly, connectivity was lower among those with PTSD and high HF-HRV, but higher among those with PTSD and lower HF-HRV. The reverse was consistently observed for those without PTSD. This suggests that individuals who are more symptomatic and have higher autonomic imbalance experience greater neural activation in specific regions (e.g., insula). This pattern of findings is consistent with a prior study that demonstrated high connectivity between vmPFC and insula were associated with high HRV among healthy controls (Thome et al., 2017). However, the same study did not find an association between HRV and connectivity among those with PTSD (Desikan et al., 2006). During the presentation of trauma-related stimuli, another study found that the association between insula activity and HF-HRV was negatively correlated with PTSD severity, and the association between dorsolateral PFC activity and HF-HRV was positively correlated with PTSD severity (Rabellino et al., 2017). Altogether, our findings are consistent with prior literature, and while preliminary, they could indicate that increased recruitment of neural activity (particularly the hypothalamus) represents a compensatory mechanism for autonomic imbalance among those with more PTSD symptoms. It is also worth considering that the inherent link between these systems is the sole reason for this finding and that neural activity will always parallel that of the periphery. However, we found that these associations were moderated by PTSD status, suggesting that they may differ as a result of posttraumatic dysfunction.

A limitation of this study is that neural and peripheral markers were assessed separately, such that psychophysiological measures were assessed outside of the MRI scanner and in some cases, on separate days. While the measures included in this study have demonstrated reliability (Esteban et al., 2019; Klingelhöfer-Jens et al., 2022), there are a number of factors that could have increased variability (e.g., circadian timing, menstrual phase). Future studies would benefit from concurrent brain-periphery measurement. An additional limitation is our use of a self-report PTSD measure as opposed to a clinical interview (e.g., Clinician Administered PTSD Scale; Weathers et al., 2013a). While the PCL-5 has demonstrated strong psychometric properties and associations with CAPS-5 scores (Geier et al., 2019; Lee et al., 2022; Weathers et al., 2018), a clinical interview would increase confidence in our PTSD assessment. Relatedly, while a strength of this study is our inclusion of an acutely trauma-exposed sample, it is not a clinical or treatment-seeking sample and thus we did not observe high PTSD severity. Replication in more severe PTSD samples is necessary to determine if our observations are truly reflective of PTSD-based differences or if they are more akin to peritraumatic responses.

The current study demonstrated associations among well-known neural and peripheral markers of risk in a trauma-exposed sample. We also found that connectivity between certain brain regions (e.g., hypothalamus, PFC) and psychophysiological indices (e.g., BP) differed based on PTSD symptom severity. While preliminary, our findings could suggest that individuals with higher PTSD severity exhibit compensatory neural mechanisms to down-regulate autonomic imbalance. Additionally, they may provide support for the relevance of ecophenotypes that represent unique neural alterations indicative of biological subtypes (Meneguzzo et al., 2022; Staginnus et al., 2023; Teicher and Samson, 2013). Further study is warranted to determine mechanisms (e.g., inflammation) by which disruptions in the neurocardiac circuit confer cardiometabolic disease risk in PTSD.

CRediT authorship contribution statement

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Declaration of competing interest

Dr. Neylan reports consultation for Jazz Pharmaceuticals; Dr. Rauch reports royalties from Oxford University Press, the American Psychiatric Publishing Inc., and Springer Publishing royalties; Dr. McLean reports consultation for Walter Reed Army Institute for Research and for Arbor Medical Innovations; Dr. Kessler reports consultation for Cambridge Health Alliance, Canandaigua VA Medical Center, Holmusk, Partners Healthcare, INC Mirah, PYM, and Roga Sciences; Dr. Koenen reports royalties from Guilford Press and Oxford University Press; Dr. Ressler reports consultation for Bioxcel, Bionomics, Acer, and Jazz Pharma; All other authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.06.009.

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