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Involvement of the brain-heart axis in the link between PTSD and cardiovascular disease

Antonia V. Seligowski, PhD[1,2], **Theresa K. Webber, BA**[2], **Paul J. Marvar, PhD**[3], **Kerry J. Ressler, MD, PhD**[1,2], **Noah S. Philip, MD**[4,5]

[1]Department of Psychiatry, Harvard Medical School, Boston, MA, USA

[2]McLean Hospital, Belmont, MA, USA

[3]George Washington University, Washington DC, USA

[4]VA RR&D Center for Neurorestoration and Neurotechnology, Providence VA Medical Center, Providence, RI, USA

[5]Department of Psychiatry and Human Behavior, Alpert Medical School, of Brown University, Providence, RI, USA

Abstract

Posttraumatic stress disorder (PTSD) has long been associated with a heightened risk of cardiovascular disease (CVD). A number of mechanisms have been implicated to underlie this brain-heart axis relationship, such as altered functioning of the autonomic nervous system and increased systemic inflammation. While neural alterations have repeatedly been observed in PTSD, they are rarely considered in the PTSD-CVD link. The brain-heart axis is a pathway connecting frontal and limbic brain regions to the brainstem and periphery via the autonomic nervous system, and it may be a promising model for understanding CVD risk in PTSD given its overlap with PTSD neural deficits. We first provide a summary of the primary mechanisms implicated in the association between PTSD and CVD. We then review the brain-heart axis and its relevance to PTSD, as well as findings from PTSD trials demonstrating that a number of PTSD treatments have effects on areas of the brain-heart axis. Finally, we discuss sex considerations in the PTSD-CVD link. A critical next step in this research is to determine if PTSD treatments that affect the brain-heart axis (e.g., brain stimulation that improves autonomic function) also reduce the risk of CVD.

Keywords

PTSD; cardiovascular disease; autonomic; inflammation; sex; brain-heart axis

Corresponding author: Antonia V. Seligowski, PhD, 115 Mill St. Mail Stop 212, Belmont, MA 02478, 617-855-2945, aseligowski@mclean.harvard.edu.

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Introduction

Posttraumatic stress disorder (PTSD) is a debilitating neuropsychiatric disorder associated with a heightened risk of cardiovascular disease (CVD; Edmondson et al., 2013a; Edmondson & von Känel, 2017; Myers, 2017). A number of physiological mechanisms have been purported to link these disease states, including dysfunction of the autonomic nervous system (e.g., increased heart rate [HR], blood pressure [BP]) and neurohumoral systems (e.g., renin-angiotensin system, HPA-axis, cortisol), as well as heightened systemic inflammation, metabolic dysfunction, and maladaptive health behaviors (e.g., cigarette smoking, poor diet). While impaired top-down brain circuitry and brain connectivity have repeatedly been observed in PTSD (e.g., reduced frontal cortical inhibition and heightened amygdala activity), they are rarely considered in the PTSD-CVD link. However, the brain-heart axis, a pathway connecting frontal and limbic brain regions to the brainstem and periphery via the autonomic nervous system, may be a promising model for understanding CVD risk in PTSD given its overlap with brain regions that have established alterations in PTSD.

We review the evidence for several key mechanisms implicated in the PTSD-CVD link, as also discussed in the recent review by O'Donnell et al. (2021). We build upon their recent summary by discussing the brain-heart axis and its relevance to PTSD, as well as evidence that several PTSD treatments have demonstrated effects on areas of the brain-heart axis. Finally, we review sex considerations in PTSD-CVD risk, which are critical in order to better understand the heightened risk of PTSD in women.

The link between PTSD and CVD

Individuals with trauma exposure and PTSD have higher rates of CVD compared to the general population, such that PTSD is associated with a greater risk of myocardial infarction, stroke, heart failure, congestive heart failure, and peripheral vascular disease, as well as CVD risk factors, such as hypertension and poor endothelial function (for reviews, see Edmondson et al., 2013b and O'Donnell et al., 2021). The evidence for this link is so compelling that the NIH recently convened a working group of experts, including the American Heart Association, to identify the state of the literature on the link between PTSD and CVD, titled *"The Cardiovascular Consequences of Post-Traumatic Stress Disorder"* (https://www.nhlbi.nih.gov/events/2018/nhlbi-working-group-cardiovascular-consequences-post-traumatic-stress-disorder). While PTSD is typically considered to be a risk factor for CVD, much of the literature is cross-sectional and does not confirm a causal link (see Koenen et al., 2017). Additionally, PTSD can result from cardiac events (e.g., myocardial infarction), and this may further increase subsequent CVD risk (Edmondson et al., 2011, 2012; von Känel et al., 2011). Better characterization of the possible bidirectional relationship between PTSD and CVD is needed, and this should be considered when evaluating the existing literature on underlying mechanisms. Several mechanisms have been implicated in the PTSD-CVD link and are reviewed below.

Autonomic function and the HPA-axis

An altered stress response is the hallmark characteristic of PTSD, represented by autonomic nervous system and HPA-axis dysfunction (Brudey et al., 2015). Studies have repeatedly demonstrated that individuals with PTSD exhibit elevated sympathetic arousal, indicated by higher HR and BP both at rest and in response to fearful stimuli, compared to controls (Buckley & Kaloupek, 2001; Ehlers et al., 2010; Jovanovic et al., 2009; Keane et al., 1998; Orr et al., 1993). PTSD is also associated with decreased parasympathetic activity, such as lower heart rate variability (HRV) at rest (Chang et al., 2013; Hauschildt et al., 2011; Minassian et al., 2014, 2015) and in response to challenge (Jovanovic et al., 2009; Keary et al., 2009; Park et al., 2017; Sahar et al., 2001). As a biomarker of autonomic activity, increased plasma and urine catecholamine levels have also been reported in PTSD (Pan et al., 2018). In terms of the HPA-axis, individuals with PTSD demonstrate lower basal cortisol levels compared to controls, which is thought to be the result of sensitive glucocorticoid receptors that cause excessive negative feedback of cortisol (Daskalakis et al., 2013; Morris et al., 2012; Yehuda et al., 1993). PTSD is also associated with increased secretion of corticotropin-releasing hormone, which ultimately leads to decreased cortisol release as a result of receptor downregulation (Baker et al., 1999; Heim et al., 2001; Yehuda, 2006) There is some evidence for heightened glucocorticoid receptor sensitivity in PTSD as well, but findings are not consistent (Morris et al., 2016; Yehuda, 2006).

The renin-angiotensin system

A related mechanism that has been implicated in the PTSD-CVD link is the renin-angiotensin system (RAS). The RAS is a hormone system that controls BP, fluid regulation, and sodium balance mainly through activity of the liver and kidneys, and it promotes vasoconstriction and sympathetic activity through the synthesis and release of angiotensin II. Several preclinical studies have found that blockade of the angiotensin II type 1 receptor using angiotensin receptor blockers reduces sympathetic activity and improves fear inhibition (Grassi et al., 2003; Klein et al., 2003; Sueta et al., 2014; Wang et al., 2014; Xia et al., 2009). For example, our group demonstrated that mice treated with losartan, an angiotensin receptor blocker, exhibited significantly less freezing (a threat response in rodents) compared to controls (Marvar et al., 2014). This has also been demonstrated in humans, where losartan has been shown to enhance positive learning and to facilitate fear extinction as indexed with skin conductance (Pulcu et al., 2019; Stout & Risbrough, 2019; Zhou et al., 2019). Cross-sectional research in humans has demonstrated that RAS blockade in humans via ace-inhibitors and angiotensin receptor blockers has been associated with decreased likelihood of a PTSD diagnosis (Khoury et al., 2012; Nylocks et al., 2015; Seligowski et al., 2021a), although a recent randomized controlled trial of losartan did not find evidence for the superiority of losartan over placebo for PTSD symptom reduction (Stein et al., 2021). RAS physiology (e.g., renin level) has also been examined and appears to be altered among trauma-exposed individuals and particularly in those with PTSD (Terock et al., 2019a, 2019b). Taken together, RAS activity and its contributions to autonomic pathophysiology may be an important mechanism in further elucidating CVD risk in PTSD.

Inflammation

It is thought that the chronic HPA-axis and autonomic dysfunction in PTSD also strains the immune system and promotes inflammation. Indeed, individuals with PTSD have elevated levels of proinflammatory cytokines compared to trauma-exposed controls, and this inflammation is linked to CVD (Brudey et al., 2015; Kim et al., 2020; O'Donovan et al., 2012). In addition to serum cytokine levels, there is evidence that PTSD is associated with increased concentrations of C-reactive protein, a biomarker of inflammation that can be predictive of CVD (Brudey et al., 2015; Heath, 2013; Mehta et al., 2020; Michopoulos et al., 2015, 2017; Spitzer et al., 2010). Notably, systemic inflammation has been associated with altered neural functioning, such as decreased connectivity between the vmPFC and striatum, and increased connectivity between the dorsomedial PFC and amygdala (Michopoulos et al., 2017). This inflammation underlies not only PTSD but also metabolic disease, pointing towards metabolic dysregulation as an additional mechanism implicated in the connection between PTSD and CVD (Friend et al., 2020; Lindqvist et al., 2014).

Metabolic dysregulation

Highly comorbid with PTSD, metabolic dysregulation is characterized by the presence of phenotypes including increased abdominal fat mass, disrupted glucose regulation, and increased levels of triglycerides (Michopoulos et al., 2016). Like PTSD, metabolic dysregulation is associated with changes in the HPA axis and inflammation, leading to increased abdominal fat mass and potentially exacerbating hyperglycemia and insulin resistance (Michopoulos et al., 2016). A study by Šagud et al. (2017) reported that people with PTSD had a *near-double risk* for metabolic dysregulation compared to the general population, and metabolic dysregulation is itself a risk factor for CVD (Dedert et al., 2010; Heppner et al., 2009; Kibler et al., 2014; Michopoulos et al., 2016). Stress activates the autonomic nervous system, which triggers the release of catecholamines, thereby increasing the concentration of cholesterol and triglycerides that are integral to metabolic dysregulation (Weiss et al., 2011). It is thus clear that PTSD is related to a high risk of metabolic dysregulation, and to complicate matters, there are multiple health-related behaviors that are linked to both metabolic dysregulation and CVD in people with PTSD (Bartoli et al., 2013).

Health behaviors

Trauma exposure is associated with increased smoking behavior, which is a major CVD risk factor (de Oliveira et al., 2018; Gilsanz et al., 2017; Lopez et al., 2011). Additionally, individuals with PTSD are more likely to resume smoking after quitting and have a lower tolerance for withdrawal symptoms that are experienced when reducing nicotine intake (Burg & Soufer, 2016; Van den Berk-Clark et al., 2018). Supporting the finding that tobacco use is highly prevalent in those with PTSD are other studies that point to a high comorbidity between substance use disorder and PTSD, with alcohol use in particular being another CVD risk behavior (Berg & Soufer, 2016; Mills et al., 2006). Furthermore, individuals with PTSD may engage less in physical activity and may have poorer diet, which are additional risk factors for poor health outcomes, including CVD (Burg & Soufer, 2016; Dedert et al., 2010; Gilsanz et al., 2017; Hoerster et al., 2019; van den Berk-Clark et al., 2018). PTSD is also associated with disruption in social relationships, such as difficulty maintaining social

connection and increased social isolation (Davidson et al., 1991; Platt et al., 2016). Since social isolation is associated with both depression and increased mortality following CVD events, isolation represents an additional health-related behavior that may further increase CVD risk in PTSD (Berkman et al., 1992; Edmondson & Cohen, 2013a).

The confluence of autonomic and RAS dysfunction, as well as inflammation, metabolic dysregulation, and health behaviors, suggests that the PTSD-CVD link is strong but highly complex. It is notable that the mechanisms implicated in the PTSD-CVD link comprise peripheral markers; however, there is a longstanding literature on neural alterations in PTSD. The most-replicated findings are that PTSD is associated with increased activity of the amygdala and dorsal anterior cingulate (dACC), and decreased activity of the ventromedial prefrontal cortex (vmPFC; see Fenster et al., 2018 and Hayes et al., 2012 for reviews). These brain regions affect the peripheral systems mentioned above via innervation of brainstem nuclei that project to the autonomic nervous system. Therefore, the brain-heart axis provides a model of brain-heart interaction that may be useful to apply to the PTSD-CVD link.

The brain-heart axis

The brain-heart axis is a well-established and evolutionarily conserved circuit connecting frontal brain regions to the autonomic nervous system via limbic (i.e., amygdala), hypothalamic, and brainstem structures. Projections from the PFC extend to the insula and cingulate cortex, which project to both the amygdala and hypothalamus, which then project to the solitary nucleus and rostral ventrolateral medulla in the brainstem, regulating HR through sympathetic and parasympathetic projections to the sinoatrial node (the heart's endogenous pacemaker; Kingma, Simard, & Rouleau, 2018). The solitary nucleus is also a critical hub for integrating bottom up (afferent) inputs from baroreceptors within the carotid bodies and vagal afferents. Thus, the brain-heart axis is directly implicated in cardiovascular and autonomic functioning. No prior studies that we are aware of have directly probed these connections among individuals with PTSD symptoms, but the brain-heart axis clearly has particular relevance to PTSD and trauma-related pathophysiology (see Figure 1 for a depiction of the brain-heart axis and areas implicated in PTSD).

PTSD is a disorder characterized by poor top-down regulation (e.g., low vmPFC activity) of exaggerated sympathetic responses (e.g., high amygdala, and dACC activity, high HR and BP). In the characteristic fear response, threat perceived by sensory systems stimulates the amygdala and promotes fear learning, and this information is sent to the hypothalamus and brainstem, which contribute to the physiological and cardiovascular response to threat (e.g., increased HR, BP). The hippocampus encodes contextual information about the threat and the vmPFC regulates the response by inhibiting amygdala activation when threat is no longer present. In PTSD, the fear response is typically altered as indicated by hyperactivation of the amygdala combined with hypoactivation of the hippocampus and vmPFC, and these neural deficits may contribute to the peripheral autonomic dysfunction observed in PTSD via the brain-heart axis (for a review, see Ross et al., 2017). Some PTSD symptoms may have greater relevance to this axis than others. For example, a study by Jovanovic et al. (2012) reported that only re-experiencing symptoms of PTSD (e.g., intrusive memories, nightmares) were associated with eye blink startle (a brainstem-mediated reflex) during

fear conditioning. Re-experiencing has also been associated with increased amygdala and hippocampus activity (Akiki et al., 2017; Stevens et al., 2017), lower connectivity in the default mode network (Sheynin et al., 2020), decreased cortical thickness in the temporal gyrus (Crombie et al., 2021), and shorter event-related brain potential latencies for safety signals (i.e., decreased processing of safety signals; Seligowski et al., 2021b). Additionally, re-experiencing symptoms have been associated with increased risk for hypertension (Sumner et al., 2020) and plasma-based markers of endothelial dysfunction (von Känel et al., 2008). Thus, re-experiencing symptoms of PTSD may have particular relevance to the brain-heart axis and the link between PTSD and CVD. Studying the connections between central and peripheral aspects of the nervous system may provide greater insight into the PTSD-CVD link, as well as inform newer treatment approaches. For example, better understanding of how established cortical deficits in PTSD contribute to CVD risk via autonomic innervation may suggest that treatments directly targeting cortical function (i.e., neurostimulation) could show promise for reducing CVD risk in PTSD. While the efficacy of PTSD treatments for reducing CVD risk remains unknown, a number of PTSD treatments have already demonstrated effects on the brain-heart axis.

PTSD treatments that affect the brain-heart axis

Psychotherapy

The first-line treatment for PTSD is cognitive behavioral therapy, and in particular, Prolonged Exposure and Cognitive Processing Therapy (APA, 2020). There is emerging evidence that cognitive behavioral therapy has effects on areas of the brain-heart axis. Findings from a randomized controlled trial of Prolonged Exposure and Virtual Reality Exposure (versus waitlist control) for PTSD suggested that resting HR and BP were reduced following treatment (Bourassa et al., 2020). Lindauer et al. (2006) reported reduced HR and BP following a randomized controlled trial of Brief Eclectic Psychotherapy for PTSD. Other randomized controlled trials have reported reduced HR in response to trauma-related stressors, such as listening to a script relating to a personal traumatic experience, seeing trauma-related pictures, or interacting with virtual-reality-based trauma cues, following various forms of cognitive behavioral therapy for PTSD (Dunne et al., 2012; Fecteau & Nicki, 1999; Rabe et al., 2006; Wells et al., 2015). Similar findings have been reported from single-arm trials (Griffin et al., 2012; Loucks et al., 2019; Maples-Keller et al., 2019; Wangelin & Tuerk, 2015). In terms of brain-based findings, a systematic review by Manthey et al. (2021) found significant differences in the mPFC, rACC, and amygdala activity following a number of forms of cognitive behavioral therapies. Thus, there is growing support for the potential of psychotherapy to improve aspects of the brain-heart axis. A crucial next step is to determine if CVD risk can be reduced among individuals with PTSD by using these existing gold-standard treatments, as well as by using novel but promising approaches (e.g., TMS, VNS).

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a rapidly-evolving form of neurostimulation that uses magnetic pulses to stimulate the cortex. TMS protocols have demonstrated efficacy in reducing PTSD symptoms using a broad range of targets and frequencies,

with consistent results indicating efficacy from both randomized controlled/sham-controlled trials (Boggio et al., 2010; Cohen et al., 2004; Watts et al., 2012) and single-arm unblinded trials (Carpenter et al., 2018). Brain-based markers such as network connectivity (including PFC, cingulate, amygdala, insula, hippocampus; Philip et al., 2018; unblinded trial), electroencephalography frequency coherence (Zandvakili et al., 2019; Zandvakili et al., 2020; randomized controlled trial), and white matter tracts (Barredo et al., 2019; sub-analysis from randomized controlled trial) have been implicated in TMS response among those with PTSD. A newer, more rapid TMS protocol is intermittent theta-burst stimulation (iTBS), which provides short bursts of 50 Hz stimulation repeated at 5 Hz (200 ms interval). iTBS is brief (<10 minutes/treatment), highly tolerable, and has recently demonstrated efficacy for PTSD (Philip et al., 2019; randomized controlled/sham-controlled trial) with clinical benefit for up to one year (Petrosino et al., 2020).

There is evidence that TMS and iTBS may improve autonomic functioning (see Makovac et al., 2017 for a review). Among healthy participants, increased HRV has been demonstrated using both TMS (Remue et al., 2016; Yoshida et al., 2001) and iTBS (Poppa et al., 2020) in randomized controlled/sham-controlled trials, and decreased pulse rate and BP have been demonstrated using TMS (Jenkins et al., 2002; non-sham-controlled). In depressed populations, TMS has been associated with reduced sympathetic-to-parasympathetic ratios (Udupa et al., 2007; unblinded trial) and iTBS has been associated with decreased HR and BP, and increased HRV (Iseger et al., 2020; randomized controlled/sham-controlled trial). This circuit has been broadly proposed as a way to optimize TMS treatment for depression (Iseger et al., 2020). Given that autonomic functioning is a proposed mechanism linking PTSD with increased CVD risk, there is reason to suggest that neurostimulation may be appropriate to address CVD risk in PTSD. However, only one study to date has tested the effects of TMS or iTBS on autonomic functioning among individuals with PTSD. In a sample of 50 Veterans with PTSD, we recently demonstrated that those with higher autonomic function exhibited greater PTSD improvement following a randomized controlled/sham-controlled trial of iTBS (Cosmo et al., 2021), suggesting that autonomic function may be a useful biomarker of iTBS response.

Vagal nerve stimulation

While TMS may be considered a top-down neurostimulation approach, a bottom-up approach is non-invasive vagus nerve stimulation (VNS), which involves electrical stimulation of the vagus nerve. There is evidence to show that VNS has an anti-inflammatory effect, modulating the brain-gut axis, and that it can facilitate extinction of the conditioned fear response (Breit et al., 2018; Noble et al., 2017). Further, VNS modulates cardiovascular activity by improving vagal tone (HRV) and reducing heart rate (Koek et al., 2019; Lamb et al., 2017). Few studies have examined VNS in PTSD. In a single-visit pilot study, Lamb et al. (2017) found that Veterans randomized to VNS (versus sham) demonstrated increased HRV and reduced skin conductance response to auditory startle. Using a randomized controlled/sham-controlled design, VNS has also been shown to improve PTSD symptoms, reduce HR, improve vascular function, increase anterior cingulate and hippocampus activity, reduce limbic activity, and reduce inflammatory reactivity during a trauma script (Bremner et al., 2020, 2021; Gurel et al., 2020; Wittbrodt et al., 2020,

2021). VNS may therefore be a highly promising treatment for PTSD and related autonomic deficits, and new devices are currently being developed (e.g., https://www.evrenvns.com/provenresults).

Psychiatric medications

While there are two FDA-approved medications for PTSD (sertraline and paroxetine), different medication classes have demonstrated efficacy for PTSD and impact areas of the brain-heart axis. For example, beta-blockers (e.g., propranolol) impair memory reconsolidation, thus reducing the strength of the conditioned fear response controlled by the autonomic nervous system and brainstem nuclei (for reviews, see McCleery & Harvey, 2004; Noble et al., 2017; Steckler & Risbrough, 2012). Beta-blockers are thought to reduce PTSD symptoms by suppressing the effects of adrenaline and noradrenaline. While the results of one randomized controlled trial suggested that propranolol reduced HR during script-driven imagery (Brunet et al., 2008), findings are generally mixed (Burbiel, 2015; Steckler & Risbrough, 2012). Randomized controlled trials of prazosin, an α1-adrenoreceptor antagonist with efficacy for hypertension, have yielded more mixed outcomes for PTSD (and nightmares, specifically). That said, prazosin has been shown to reduce BP in PTSD populations (Raskind et al., 2018; Reist et al., 2021). SSRIs have demonstrated efficacy in reducing PTSD symptoms and preventing relapse, and multiple classes of antidepressants appear to normalize the HPA axis response to stress, which may be a common mechanism of action among these types of psychiatric medications (Steckler & Risbrough, 2012). They have also been shown to reduce levels of C-reactive protein and interleukin-6, which may result in cardiovascular benefits (Pizzi et al., 2009). While any psychiatric medication may cause unintended side effects, SSRIs generally do not seem to pose serious cardiovascular risk (Andrade et al., 2013) and appear to be safe and effective for patients with acute myocardial infection and unstable angina (Glassman et al., 2002).

Other treatments—Several other treatment approaches have demonstrated efficacy for PTSD, though evidence supporting their use is less strong or in earlier stages of study. For example, acupuncture can reduce PTSD symptoms and improve physical health composite scores in randomized controlled trials, but with mixed findings in terms of long-term benefits (Engel et al., 2014; Hollifield et al., 2007; for a review, see Grant et al., 2018). There is also some evidence that acupuncture may be associated with lower CVD risk, but replication and larger clinical trials are needed (Hao et al., 2014). Another treatment that has been tested in PTSD is stellate ganglion blockade (Rae Olmsted et al., 2020). However, the evidence for its efficacy is mixed and has to date relied on case reports (for a review, see Lipov & Richie, 2015). A review by Krediet et al. (2020) found some support for the efficacy of psychedelics for PTSD (e.g., MDMA, psilocybin, LSD). While there are current trials underway to examine the treatment potential for psychedelics in PTSD, more research is needed to better understand the effects that these drugs might have on the cardiovascular system (Siegel et al., 2021). Given the psychomimetic effects of these compounds, it is reasonable to anticipate some involvement of the cardiovascular system that may have important implications for treatment development.

Consideration of sex

A consistent finding in PTSD is that its prevalence is approximately two times greater in women compared to men (Kilpatrick et al., 2013; Tolin & Foa, 2006); however, few studies have examined mechanisms underlying sex differences in PTSD (for reviews, see Fonkoue et al., 2020; Seligowski et al., 2020). The most robust findings are that women exhibit heightened skin conductance responses to conditioned stimuli compared to men (Inslicht et al., 2013) and that gonadal hormones moderate these responses (e.g., higher progesterone in women with PTSD confers worse extinction retention; Pineles et al., 2016). Other conditioning studies have shown that women with PTSD demonstrate higher HR and lower HRV, but lower BP compared to men, and that women with PTSD and low estradiol (the most common circulating estrogen) demonstrate worse fear inhibition (indexed by acoustic startle paradigms) compared to those with PTSD and high estradiol (Glover et al., 2012, 2013; Seligowski et al., 2021b). Thus, gonadal hormones, in particular estradiol levels, may partially explain differences in PTSD phenomenology among men versus women.

Estradiol is well-established as protective against CVD, such that it is associated with lower BP, lower cholesterol, and better endothelial function (Charkoudian et al., 2017; Hashimoto et al., 1995, 2002; Mendelsohn & Karas, 1999). The primary explanation for the decreased incidence of CVD in pre-menopausal women (compared to men) is that they have higher circulating levels of estradiol, as this sex difference no longer exists in older age groups with post-menopausal women (Kannel et al., 1976; Vitale et al., 2009). Further, sex differences within the RAS in the context of cardiovascular regulation are well studied (see Medina et al., 2020 for a review). The RAS consists of two axes: one that leads to vasoconstriction and sympathetic activation, and one that leads to vasodilation and sympathoinhibition. Estradiol shifts the balance towards the vasodilation axis by lowering the production of renin, which subsequently decreases sympathetic activity, and by reducing angiotensin II activity (the primary vasoconstrictive peptide in the RAS; Medina et al., 2020). In contrast, testosterone shifts the balance towards the vasoconstriction axis. Much less is known about how sex differences in the RAS impact fear learning in PTSD, however, a recent pre-clinical study found that female rats with low estradiol exhibited worse fear extinction compared to those with high estradiol (Parrish et al., 2019). This could suggest that RAS-estradiol interactions are relevant to fear learning and that low estradiol in humans confers increased PTSD risk through impaired RAS regulation.

The effect of estradiol on metabolic and inflammatory indices is unknown among women with PTSD, however, there is research supporting a protective role of estradiol on these systems in other populations (for a review, see Taylor & Sullivan, 2016). Considering that CVD is the leading cause of death among women and that women are more likely to have PTSD, determining the role of estradiol on the mechanisms implicated in the PTSD-CVD link will be an essential step in identifying and reducing CVD risk in women with PTSD.

Conclusions

The brain-heart axis is a well-established neural pathway connecting frontal and limbic brain regions to the autonomic nervous system via brainstem projections. Given that it

connects several brain regions and peripheral systems implicated in both PTSD and CVD, the brain-heart axis offers a model to study the link between these sets of diseases and better understand their interrelations. Further, as PTSD treatments have demonstrated effects on multiple areas of the brain-heart axis, an area for future research will be to test whether such treatments reduce the risk of CVD in PTSD populations. Clinical trials that would be particularly useful are those that test the effects of PTSD treatments (e.g., TMS) on subsequent CVD development among those with pre-existing risk, such as individuals with elevated BP, heightened RAS activity, and/or poor endothelial function. Further, the established effects of estradiol on the RAS and fear learning necessitate that future trials account for sex as a biological variable.

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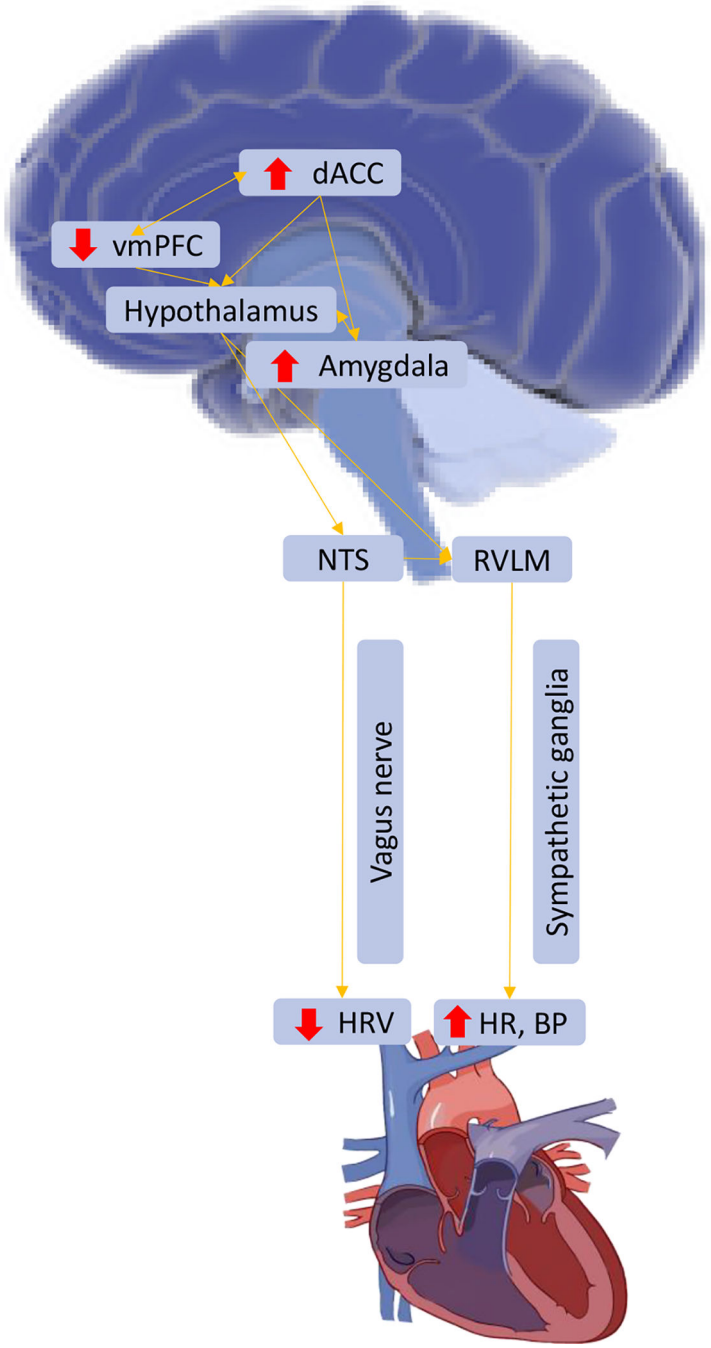

Figure 1. The brain-heart axis and PTSD

Note. Red arrows indicate areas over- and under-active in PTSD; vmPFC = ventromedial prefrontal cortex; dACC = dorsal anterior cingulate; NTS = nucleus of the solitary tract; RVLM = rostral ventrolateral medulla; HRV = heart rate variability; HR = heart rate; BP = blood pressure.