New recognition of heart-brain axis and its implication in the pathogenesis and treatment of PTSD

Haipeng Li\textsuperscript{1}, Zhengrong Zhang\textsuperscript{1}, Keke Ding\textsuperscript{1}, Yang Zhang\textsuperscript{1}, Fang Gao\textsuperscript{1}, and Guoqi Zhu\textsuperscript{1}

\textsuperscript{1}Anhui University of Chinese Medicine

May 14, 2024

Abstract

Post-traumatic stress disorder (PTSD) is a complex psychological disorder provoked by distressing experiences, and it remains without highly effective intervention strategies. The exploration of PTSD’s underlying mechanisms is crucial for advancing diagnostic and therapeutic approaches. Current studies primarily explore PTSD through the lens of the CNS, investigating concrete molecular alterations in the cerebral area and neural circuit irregularities. However, the body’s response to external stressors, particularly the changes in cardiovascular function, is often pronounced, evidenced by notable cardiac dysfunction. Consequently, examining PTSD with a focus on cardiac function is vital for the early prevention and targeted management of the disorder. This review undertakes a comprehensive literature analysis to detail the alterations in brain and heart structures and functions associated with PTSD. It also synthesizes potential mechanisms of heart-brain axis interactions relevant to PTSD’s development. Ultimately, by considering cardiac function, this review proposes novel perspectives for PTSD’s prophylaxis and therapy.

KEYWORDS: Posttraumatic stress disorder; Cardiovascular disease; Heart-brain axis; Drug therapy;
1 INTRODUCTION

Posttraumatic stress disorder (PTSD) is a persistent psychological disorder usually precipitated by distressing experiences. As delineated in the latest version of The Diagnostic and Statistical Manual of Mental Disorders by the American Psychiatric Association, the primary clinical symptoms of PTSD consist of recurring intrusive thoughts, active avoidance of reminders, pervasive negative emotions and cognitions, heightened vigilance, and irritability (Lotfinia et al., 2023). Individuals with co-occurring mental and cardiac conditions are particularly more vulnerable to the emotional strains intensified by the COVID-19 pandemic, with emotional states frequently marked by fear, panic, anger, and frustration (Mazza et al., 2021). Currently, the treatment of PTSD is mainly focused on targeted therapy in specific brain regions, while relatively few are from systemic therapeutic approaches.

PTSD has been acknowledged as a potential cause of cardiovascular disease (CVD). A study utilizing the Swedish national registry revealed that individuals with Stress-induced conditions, including PTSD, adjustment disorders, acute stress reaction, and other stress reactions, have a larger potential for developing new-onset CVD compared to the non-PTSD population (Shen et al., 2023). Research by Freiberger et al. indicated that approximately 20% of adults suffering from congenital heart disease exhibit symptoms of post-traumatic stress, a frequency 5 to 7 times greater than that observed in the average population (Freiberger et al., 2023). Additionally, research focusing on survivors of out-of-hospital cardiac arrests reported that these individuals commonly experience symptoms of anxiety and PTSD (Grand et al., 2023). A deeper understanding of the potential two-way association between PTSD and CVD is crucial and is expected to be a pivotal consideration in the evaluation of studies addressing their underlying mechanisms.

This article comprehensively compiles and examines the literature on the association between PTSD and cardiac dysfunction, providing insights into the updated mechanisms of the heart-brain axis interaction in the context of PTSD and CVD. It encapsulates the pathogenesis of PTSD with a focus on cardiac function, aiming to enhance clinical management strategies at the crossroads of PTSD and cardiovascular disease.

2 RECOGNITIONS OF THE HEART-BRAIN AXIS

The heart-brain axis constitutes a communication network that links the frontal and limbic brain areas to the brainstem and peripheral body systems via the autonomic nervous system. The interactions between the heart and brain are intricate and multidimensional, characterized by a bidirectional flow of information. Various biological processes have been suggested to bridge the comorbidities observed between PTSD and heart diseases. These include imbalance of the autonomic nervous system, changes in the hypothalamic-pituitary-adrenal (HPA) axis, modifications in brain-derived neurotrophic factor (BDNF) levels, elevated systemic inflammation, and the activity of exosomes, as depicted in Figure 1.

2.1 Traditional viewpoint

2.1.1 Autonomic nervous system

PTSD is a highly prevalent mental health condition that is characterized by increased sympathetic nervous system activity, decreased parasympathetic nervous system activity, and baroreflex sensitivity (BRS), which accelerates the development of CVD. Studies have shown that PTSD usually coexists with elevated resting blood pressure because patients with PTSD have higher resting heart rate (HR) and blood pressure (BP) compared to the general population. Moreover, elevated resting blood pressure increases autonomic imbalance in patients with PTSD (Fonkoue et al., 2018). Among the various factors implicated in the development of PTSD, there is a theory that the myelinated branches of the vagus nerve, through the parasympathetic branch of the autonomic nervous system, apply a moderating effect on cardiac activity at the heart’s sinus node (Sahar et al., 2001). Notably, both heightened neurocirculatory reactivity and reduced baroreflex sensitivity are independently linked with the development of hypertension and cardiovascular disease. Severe PTSD is the main contributor to impaired cardiomyocardial baroreflex sensitivity, while those with moderate PTSD maintain intact cardiomyocardial BRS (Fonkoue et al., 2020). The intensity of PTSD symptoms correlates with more pronounced dysfunction in arterial pressure reflex sensitivity and an elevated resting heart rate.
This could mechanistically elucidate the epidemiological finding that more severe psychological symptoms in PTSD are tied to an elevated susceptibility to cardiovascular disorders.

### 2.1.2 HPA axis

In humans and most mammals, it is primarily the autonomic nervous system (ANS) and the HPA axis that are involved in stress behavior. The ANS is responsible for the fast response, while the HPA axis is responsible for the slow response. Upon exposure to stress, the HPA axis becomes activated, leading to the secretion of steroids (such as hydrocortisone) from the suprarenal glands. There is a growing recognition of the relationship between stress and cardiac dysfunction, with evidence linking it to increased mortality rates in patients suffering from cardiometabolic diseases (Chauvet-Gelinier & Bonin, 2017; Levine, 2022). PTSD patients, unlike other stressed individuals, exhibit reduced basal glucocorticoid levels and enhanced negative feedback in the HPA axis. The HPA axis is believed to act as a conduit between the brain and heart, indicated by the expression of mineralocorticoid receptors predominantly in limbic structures and glucocorticoid receptors throughout the brain, with both types of receptors also present in cardiac muscle cells (Fernández-Ruiz, 2022; Liu et al., 2023). Glucocorticoids exert their effects primarily through glucocorticoid receptors (GR), which are encoded by the Nrs3c1 gene. These receptors are present in cardiomyocytes and are critical for direct glucocorticoid signaling within the heart. Experiments with genetically modified mice have shown that the absence of specific GR in cardiomyocytes leads to spontaneous cardiac disease and premature death due to heart failure (HF). This indicates that glucocorticoid signaling via cardiomyocyte-specific GR is vital for preserving normal heart structure and functionality (Oakley et al., 2013).

The glucocorticoid-induced tumor necrosis factor receptor family-related protein is implicated in atherosclerosis progression in mice and correlates with unstable plaque characteristics and abnormalities in the human cerebrovascular system (Shami et al., 2020). Studies exploring genetic variations in GR highlight a link between GR alterations and the intensity of PTSD symptoms, suggesting that glucocorticoid signaling may be disrupted in PTSD patients even before encountering stress (Danan et al., 2021; Gultig et al., 2023). The heightened arousal from trauma triggers activation of the HPA axis, resulting in elevated cortisol production that typically serves to dampen the stress response. Nevertheless, persistent stress may attenuate this response, culminating in decreased cortisol levels. Beyond this, dysregulation of the HPA axis can precipitate HF, which, in turn, may contribute to aberrant brain function and the onset of mental disorders. These findings collectively suggest a close relationship between HF and PTSD, emphasizing the significant role that glucocorticoids and their receptors play in mediating the interaction between cardiac health and PTSD. Thus, the HPA axis is a critical link and regulatory conduit between cardiac and cerebral functions, providing innovative opportunities for the comprehensive care of mental health conditions.

### 2.1.3 BDNF

The dysregulation of nerve growth factors, such as BDNF, is implicated in the pathogenesis of CVDs, as well as in depressive and fatigue symptoms. BDNF, primarily located in the brain, can traverse the cerebral vascular barrier and enter peripheral circulation under certain conditions. By acting both centrally and peripherally, BDNF enhances insulin sensitivity and augments parasympathetic nervous system activity (Marosi & Mattson, 2014). Diminished BDNF levels may lead to dysfunctions in both cardiac and cerebral systems, potentially triggering the emergence of related health issues. Research indicates that BDNF, released by activated platelets, might regulate the inverse relationship observed between platelet activation and cognitive functions (Bélanger et al., 2021). Overactive platelets are a notable factor in the onset of coronary artery disease, which often correlates with cognitive decline. Additionally, BDNF acts protectively against ischemia-induced apoptosis and the resultant dysfunction in cardiac cells by binding to its high-affinity receptor, TrkB (Cannavo et al., 2023). During the initial phases of myocardial infarction, BDNF concentrations significantly rise in heart muscle cells within the ischemic and perilesional regions, conferring protection against ischemic damage (Hong et al., 2014). Furthermore, BDNF expression has been seen to increase due to neural signals from the heart post-myocardial infarction in animal models (Okada et al., 2012).

Reduced serum BDNF levels may act as an important biomarker for the enduring nature of mood disorder.
symptoms in individuals with coronary heart disease (CHD) who are also experiencing depression (Kuhlmann et al., 2017). Notably, CHD patients diagnosed with depression display lower levels of BDNF compared to their non-depressed counterparts, with a noted association between lower BDNF intensities and the persistence of mood disorder among the CHD patient group (Tschorn et al., 2021). Moreover, low-dose BDNF therapy has demonstrated efficacy in lessening the frequency and recurrence of arrhythmic events, such as atrial fibrillation. Considering PTSD, the extinction of disturbing memories—a central element of the most effective PTSD therapies—has been linked to the secretion levels of BDNF (Domitrovic Spudic et al., 2022; Antolasic et al., 2023). BDNF has been identified as one of the proteins with the most pronounced changes in PTSD models induced by single prolonged stress (SPS) (Aksu et al., 2018). Prior research conducted by our team also supports the pivotal involvement of BDNF in PTSD-related phenotypes and synaptic anomalies (Zhang et al., 2021; Wang et al., 2022). These findings collectively underscore the crucial role of BDNF in both CVD and PTSD, positioning it as a key molecular agent in the interconnected heart-brain axis.

2.1.4 Inflammatory

Interleukins are capable of inducing cytokine expression that furthers inflammation, drawing monocytes and neutrophils to the heart where they release reactive oxygen species (ROS). This release contributes to an increased oxidative load and subsequent cardiac damage (Tang et al., 2022). Furthermore, interleukins have been implicated in promoting cardiomyocyte hypertrophy, fibrosis, and impaired diastolic function by disrupting the extracellular matrix (ECM), all of which may result in the emergence and exacerbation of HF (Chirinos et al., 2020; Perestrelo et al., 2021). These pro-inflammatory molecules can also enter the bloodstream and compromise the completeness of the blood-brain barrier (BBB) (Ribeiro et al., 2021), resulting in brain inflammation that may disrupt normal physiological functions and potentially give rise to neuropsychiatric disorders. For instance, IL-6 is known to stimulate cardiomyocyte hypertrophy and promote apoptosis, which impairs cardiac contractility (Kumar et al., 2019). For those in the younger or middle-aged demographic who have suffered an MI—particularly among Black patients—each unit increase in baseline IL-6 resulted in a 2.59-point rise in post-event PTSD symptoms (Buto et al., 2023). In rat models of PTSD, indicators of cardiac injury were noted alongside increased amounts of IL-21 and reduced amounts of IL-6 (Manukhina et al., 2021).

In the context of hypoxic-ischemic encephalopathy, research conducted with a rat model of hypoxic cardiac arrest has shown an upsurge in hypoxia-inducible factor-1α (HIF-1α) expression within the hippocampus following resuscitation (Liu et al., 2016). After cardiac arrest, downstream signaling molecules such as Caspase-3, VEGFR-2, and NF-κB were detected in the hippocampus one day after the occurrence. Acute myocardial infarction (AMI) triggers local and systemic inflammatory responses, expedites atherosclerosis, stimulates the autonomic nervous system, fosters left ventricular remodeling (Renner et al., 2022a), and activates microglia (Renner et al., 2022b). Moreover, pro-inflammatory cytokines released from microglia can lead to axonal damage and degeneration. Among patients with PTSD and acute coronary syndrome, those who had myocardial infarction concurrent with PTSD exhibited heightened amounts of IL-6, particularly during the existence of psychosocial stress (Nie et al., 2021). These findings indicate the involvement of inflammatory pathways in myocardial injury related to PTSD and highlight the significance of inflammatory factors as pivotal mediators impacting both brain and heart functions.

2.2 Frontier viewpoint

2.2.1 Cerebral metabolism

In HF patients with hyponatremia and moderately impaired left ventricular function, there is a reported decrease in cerebral metabolism across the entire brain (Yun et al., 2022). Despite variations in cardiac output, cerebral blood flow is often maintained due to the central nervous system’s complex autoregulation capabilities (Paulson et al., 1990). This autoregulatory mechanism ensures relatively constant cerebral perfusion, thereby supporting cerebral neuron/neurovascular function across a broad blood pressure range. However, brain magnetic resonance imaging studies have noted diminished blood circulation in the brain and
loss of cortical tissue in patients with HF (Roy et al., 2017; Wang et al., 2023a). These particular changes in perfusion and glucose metabolism are closely associated with the diverse neurophysiological symptoms observed in PTSD (Kim et al., 2012). Research indicates that regional brain glucose metabolism can differentiate between trauma-exposed individuals at risk and those not at risk for PTSD, with higher heart and vascular risk linked to the extent of brain glucose metabolism (Ramage et al., 2016; Ishii, 2023; Tristão-Pereira et al., 2023). Consequently, it is suggested that, under persistent severe cardiac function impairment, cerebrovascular autoregulation might become compromised, leading to insufficient cerebral blood flow and metabolic irregularities. There is also a notable parallel between the heart and brain in terms of energy and lipid metabolism (Taegtmeyer, 2016). The use of ketone bodies a small-molecule lipid metabolite has a critical function in the energy metabolism homeostasis of both organs. In HF, there is a shift in energy reliance towards an increased use of ketone bodies. This shift is accompanied by an upregulation in the hepatic production of ketone bodies, indicative of metabolic remodeling in response to cardiac insufficiency.

2.2.2 Exosomes

Exosomes, as a subset of extracellular vesicles, play a role in the heart-brain axis. Research in mice models of MI has shown that high levels of microRNA-1 are produced in the ischemic and limbic regions of the heart and then taken to the hippocampus through exosomes (Duan et al., 2018). This transfer results in a reduced expression of proteins that promote the polymerization of microtubules, ultimately affecting the microscopic stability of neurons. Additionally, some studies have linked elevated levels of exosomes and plasma neurofilament light chain with conditions such as mild traumatic brain injury (mTBI) and chronic manifestations of PTSD and depression (Guedes et al., 2020; Guedes et al., 2021). These results imply that exosomes might function as a molecular conduit, facilitating the impact of cardiac events on brain function and potentially influencing the development of neuropsychiatric symptoms.

Increased levels of neurofilament light (NfL), which is an indicator of axonal damage in neurons, have been documented among individuals who have experienced mTBI. Furthermore, these elevated exosome and plasma NfL levels show a relationship with the extent of PTSD and depressive symptoms (Guedes et al., 2020). CD63, a protein that is abundant in the membranes of exosomes, is used as a marker for these vesicles. Research has shown that the delivery of interleukin-8 (IL-8) via plasma-derived extracellular vesicles (EVs) can impact anxiety and depression-related behaviors in mouse models of PTSD. This is attributed to CD63’s role in facilitating IL-8 delivery, which enhances astrocyte-neuron communication, potentially triggering PTSD onset. Moreover, EVs sourced from the blood plasma of individuals suffering from PTSD have been shown to worsen anxiety and behaviors resembling depression in mice with PTSD (Guo et al., 2023). These findings underscore the complex interplay between exosomes, neuroinflammation, and neuropsychiatric disorders, highlighting the potential of EVs as both biomarkers and mediators in the pathophysiology of PTSD.

MicroRNAs (miRNAs) serve as pervasive gene regulators, with specific variants like miR-124 and miR-153 playing crucial roles in modifying cell morphology, decreasing apoptosis, and reducing levels of inflammatory cytokines in the hippocampus of rats subjected to SPS, which helps mitigate PTSD-like behaviors (Chen et al., 2022a; Chen et al., 2022b). In the context of cardiac events, myocardial infarction activates miR-124, and the targeted manipulation of miR-124 through intramyocardial injection of an antagonist can influence apoptosis and the extent of myocardial infarction in mice. Significantly, elevated levels of circulating miR-124 have also been detected in patients with AMI and are linked to myocardial damage and heart function (Han et al., 2019). Furthermore, miR-124, which is enriched in the brain, has been studied as a predictor of neurological prognosis post-cardiac arrest. Its presence in plasma is indicative of neurologic outcomes in individuals receiving cold therapy following a heart attack (Devaux et al., 2016). These findings position miRNA as a potentially valuable biomarker with significant implications in the pathogenesis of heart-brain axis conditions.

2.2.3 Metabolic syndrome (MetSyn)

MetSyn encompasses a collection of hazard elements that elevate the likelihood of cardiometabolic diseases,
such as dyslipidemia, abdominal obesity, impaired fasting glucose, and hypertension. For firefighters, sudden cardiac arrest and PTSD are the primary causes of death while on duty. Research by Jung et al. has shown that firefighters who have MetSyn, as opposed to their counterparts without it, exhibit poorer physical and cognitive functions. This is marked by higher surrogate markers of insulin resistance, such as triglyceride to high-density lipoprotein cholesterol ratio (HDL-C) and the triglyceride-glucose (TyG) index, along with a diminished response in working memory tasks (Seo et al., 2023). These findings highlight the impact of metabolic health on cognitive and physical performance, particularly in high-stress occupations with increased cardiovascular and psychological demands.

Insulin resistance is a condition that can lead to elevated blood sugar levels, abnormal lipid profiles, and increased blood pressure, all of which contribute to a higher risk of CHD (Basheer et al., 2023). It may also impact the cardiovascular system by fostering the development of atherosclerotic plaques within arteries and triggering inflammatory responses (Jia et al., 2023). The association between cerebral blood flow and cognitive impairments—such as in memory, attention, and behavior may illuminate the link between insulin resistance and cognitive function (Levine et al., 2014). Furthermore, research by Willmann et al. suggests that insulin resistance independently affects cognitive function (Willette et al., 2015), indicating that individuals with impaired insulin sensitivity are at an elevated risk of cognitive decline (Neergaard et al., 2017). Insulin resistance is also tied to disturbances in cerebral glucose metabolism (Dai et al., 2023). Normally, insulin facilitates the uptake and utilization of glucose by brain cells, thereby providing a critical energy source. When insulin resistance occurs, it hampers this glucose uptake, leading to disruptions in the brain's energy metabolism, which could adversely affect memory functions due to the brain's reliance on glucose for memory formation and retention.

3 PTSD PATIENTS DISPLAY BOTH NEUROLOGICAL CHANGES AND HEART DYS-FUNCTION

An increasing body of neuroimaging research reveals clear variations in brain structure between adults with PTSD and those without. Diffusion tensor imaging analysis has been employed to track a five-year course of amygdala structural connections with crucial brain areas (Ho et al., 2019). In the PTSD model, the association between sensory stimuli and strong emotional experiences is formed through traumatic events. In this view, the sensory input to the basal lateral amygdala becomes stronger, and the insula conveys information about visceral states to the amygdala, while the amygdala predicts feedback to lower sensory areas such as the insula. A clinical study on changes in the connection between the amygdala and the insula after post-traumatic stress disorder psychotherapy showed that the amygdala and insula displayed widespread patterns of primarily subregion-uniform intrinsic connectivity change, including increased connectivity between amygdala and insula.

Higher amygdala-prefrontal cortical connectivity has been linked to lower PTSD symptom severity (Morell & Norton, 1980). Patients with PTSD could reduce amygdala activation during trauma provocation, a response that persisted in the absence of neurofeedback during a transfer run. The reduction of amygdalar activation throughout neurofeedback sessions correlated with increased stimulation within prefrontal cortex areas responsible for emotional control and heightened activity-oriented linkage with the prefrontal cortex (PFC) (Nicholson et al., 2017).

PTSD may result in tachycardia, disruptions in circadian HR rhythms, and behavioral deficits. Particularly affecting systolic blood pressure (SBP) and pulse wave velocity (PWV) (Sumner et al., 2021; Dyball et al., 2023). Individuals with PTSD often exhibit a hypoactive medial prefrontal cortex (mPFC) alongside a hyperactive amygdala, with the extent of fear reduction being reliant on the connectivity between these brain regions. Neuroimaging research on military personnel with PTSD has revealed diminished circulation of blood in the ventromedial prefrontal cortex (vmPFC) during trauma-related stimulus exposure (Sun et al., 2020). In younger adults, there’s a notable inverse relationship between heart rate variability (HRV) and the functional connectivity of the amygdala-mPFC, where higher HRV during tasks is linked to more fragile amygdala-mPFC coupling. This suggests that some physiological signal generated by heart rate variability establishes a direct link with the cerebral cortex, creating a conditioned reflex to control the function of the
Clinical research has determined that patients with PTSD exhibit heightened stress reactivity within the sympathetic nervous system (Bedford et al., 2022). These patients also have elevated HR at rest and increased HR responsiveness in comparison to individuals not afflicted with PTSD (Bourassa et al., 2021). For people suffering from PTSD, continuous hyperarousal could result in long-term elevated tonic cardiovascular activity, potentially perpetuated by symptoms of avoidance. For example, studies have identified increased platelet reactivity in veterans with PTSD (Vidović et al., 2011). Therefore, increased cardiovascular reactivity (CVR) and sustained cardiovascular activity have been suggested as potential processes that could lead to the heightened likelihood of premature mortality noted in veterans with PTSD.

Vascular \( \alpha_1 \)-adrenergic receptor sensitivity is markedly elevated in PTSD patients compared to those without the condition (Hartwig et al., 2020). Studies have indicated that people with PTSD exhibit significantly higher HR. When subjected to stress, these individuals not only display increased HR but also experience reduced HRV, heightened cardiovascular sympathetic activation, and diminished respiratory sinus arrhythmias (Schneider & Schwerdtfeger, 2020) (Campbell et al., 2019). SBP corresponds to the pressure in the arteries during cardiac systole, whereas diastolic blood pressure reflects the pressure during cardiac diastole; PTSD has been linked with elevated resting SBP and diastolic blood pressure (Schubert et al., 2019). Young individuals with PTSD have been found to have impaired microvascular function in their arms and thighs (Weggen et al., 2021).

### 4 PATHOGENESIS OF PTSD BASED ON THE HEART-BRAIN AXIS

The insular cortex (InsCtx) is recognized for its role in integrating forecasted sensory and internal body signals to produce nuanced and mutual signals that regulate the annihilation of fear and ensure the maintenance of fear within a functional balance (Klein et al., 2021). The vagus nerve serves as the principal conduit for interoceptive information—internal body sensations—from the body to the brain (Berthoud & Neuhuber, 2000) and is believed to transmit these signals to the visceral InsCtx via a multi-synaptic pathway. The inhibition of InsCtx affects extinction learning and fear expression in a bidirectional manner, influencing HR and InsCtx activity (Klein et al., 2021). Research has observed that InsCtx activity is heightened in low-fear animals upon exposure to the conditioned stimulus (CS+), whereas, in high-fear animals, InsCtx activity decreases—a starkly contrasting response. This prompts the question: What mechanism underlies the diminished InsCtx response to CS+ in high-fear animals compared to low-fear ones? Further studies have noted that fear conditioning elicits marked HR fluctuations, which intensify with repeated pairings of CS+ and the unconditioned stimulus (US).

Fear is actively regulated by the InsCtx, and this regulation is closely linked to HR decelerations. These HR changes are conveyed to the InsCtx via the vagus nerve, leading to a reduction in its responsiveness to aversive stimuli (Roelofs, 2017) (Zych & Gogolla, 2021) (Fig. 3). These findings shed light on a neural mechanism through which the “freezing” response serves as a coping mechanism, as it mitigates the impact of aversive signals on the InsCtx through physiological feedback. Future research should investigate how various forms of physiological feedback to the InsCtx, such as hunger, cravings, and signals related to the gastrointestinal or respiratory systems influence the InsCtx’s role in regulating emotional states. As a result, ongoing research is exploring whether interventions targeting the InsCtx brain regions could mitigate the risk of CVD in individuals with PTSD.

Modern correlational studies have revealed that the insular cortex plays a pivotal role in processing physiological signals and regulating emotions (Hsueh et al., 2023) (Gogolla, 2017). This is further supported by a robust association between cardiac changes and the regulation of emotions, including correlations between cardiac interoception and fear, and anxiety, as well as functional changes in the insular cortex (Oppenheimer & Cecchetto, 2016). To gain a deeper understanding of the implications on the insular cortex in the context of PTSD and CVD, additional research is needed, particularly in conjunction with clinical evidence.

The biological underpinnings of PTSD increasingly suggest a connection with inflammatory processes (Yang et al., 2023), dysregulation of the autonomic nervous system (Cosmo et al., 2022; Fu, 2022), and a
compromised coronary blood flow capacity that increases the susceptibility to myocardial ischemia (Vaccarino et al., 2022). Additionally, there exists a potential for reciprocal interactions and feedback loops that intertwine behavioral and biological elements. Cardiac positron emission tomography (PET) scans have revealed reduced myocardial circulation in those suffering from PTSD. Computed tomography scans in another study showed that individuals with PTSD exhibited elevated amounts of calcium in the coronary arteries, indicative of atherosclerosis (Ahmadi et al., 2011). Regarding myocardial ischemia, PTSD patients were more likely to show signs of ischemia during exercise treadmill tests (Turner et al., 2013). Although these biological and behavioral mechanisms are plausible, the evidence is not uniform across studies, leaving unanswered questions about which mechanisms most accurately explain the correlation between PTSD and increased cardiovascular disease risk.

Sleep disturbances, prevalent in PTSD, may contribute to this dysregulation (Rajachandran et al., 2023). Research suggests that while PTSD severity is inversely correlated with HRV, this relationship becomes non-significant when sleep disturbances are accounted for. This implies that sleep disorders might be a fundamental factor linking PTSD symptoms with autonomic dysregulation (Cox et al., 2023). Inflammation, which can also be exacerbated by sleep disturbances, is another proposed pathway connecting PTSD, sleep, and CVD risk. Studies indicate that disturbed sleep can promote endothelial inflammation and the progression of atherosclerosis by lowering the levels of exosome miR-182-5p (Li et al., 2023). Furthermore, addressing sleep disturbances post-trauma may attenuate inflammation, thereby potentially reducing cardiovascular risk (Barr et al., 2015). Moving forward, it’s imperative for mental health professionals and physicians working with PTSD-CVD intersections to screen patients with PTSD for sleep disturbances and cardiovascular risk factors. Providing behavioral recommendations or referrals for sleep interventions could be pivotal in enhancing cardiovascular health outcomes. This integrated approach recognizes the complex interplay between psychological health, sleep quality, and cardiovascular risk, aiming to offer a more holistic care strategy for those affected by PTSD.

5 TREATMENT PTSD FROM THE CARDIOVASCULAR SYSTEM

The Food and Drug Administration (FDA) has sanctioned paroxetine and sertraline as treatments for PTSD (Raut et al., 2022b), and various classes of medications are effective for PTSD, also influencing the heart-brain axis. Propranolol, a beta-blocker, reduces myocardial contractility, autoregulation, conduction, and excitability. It also slows HR, diminishes cardiac output, and lowers myocardial oxygen consumption (Lin et al., 2020; Ibrahim et al., 2021; Peltenburg et al., 2022). The noradrenergic system plays a significant role in the consolidation of contextual fear memories (Fan et al., 2022), and propranolol is a widely studied drug for memory reconsolidation therapy in clinical settings. Research indicates that propranolol significantly reduces HR following the recall of traumatic memories compared to a placebo (Raut et al., 2022a) and alleviates the severity of nightmares in PTSD patients (Mallet et al., 2022). Intriguingly, it is low doses of propranolol that have been found to induce PTSD-like memory impairments (Zhu et al., 2018). In a PTSD mouse model, sotalol, another beta-blocker, seemed to lessen traumatic memories and anxiety-like behavior, likely through a reduction in peripheral adrenergic activity that affects traumatic memory processing (Martinhoet et al., 2021). However, the substantial heterogeneity and variation in the dosages of propranolol used in studies necessitate a careful interpretation of the effects of beta-blockers on PTSD.

During acute coronary syndromes (ACS), benzodiazepines and morphine are administered to mitigate anxiety and pain. Clinical and experimental studies suggest that benzodiazepines might impede the process of relearning necessary for recovery from trauma, potentially heightening the likelihood of posttraumatic behaviors in response to stress and trauma-related cues (von Kane et al., 2021). There is a significant correlation between benzodiazepine use and the total severity score of the Clinician-Administered PTSD Scale, as well as the reexperiencing subscore (Guina et al., 2015). Benzodiazepines may also exert favorable cardiovascular effects, either directly or indirectly through the reduction of anxiety. These effects include vasodilation, anti-ischemic and antiarrhythmic properties, platelet inhibition, and the reduction of catecholamine levels (Huffman & Stern, 2003; Herlitz et al., 2011). However, there are alternative approaches to managing anxiety in ACS patients, such as reassurance, which is important considering that ACS-induced PTSD is
linked to a higher risk of recurrent cardiac events and increased all-cause mortality (Edmondson et al., 2012). Clinicians should be cognizant of these associations and the potential impacts of benzodiazepine use in the context of ACS and PTSD.

Prazosin, an α1-adrenergic receptor antagonist, is primarily used as an antihypertensive medication. It functions by dilating both arteries and veins, which leads to a reduction in both cardiac preload and afterload, a decrease in left ventricular end-diastolic pressure, and an overall improvement in cardiac function (Jiang et al., 2023). Beyond its cardiovascular applications, prazosin is also utilized to treat sleep disturbances associated with PTSD (Laitman et al., 2014; Sartor et al., 2023). It can cross the BBB and is present in brain regions such as the frontal cortex, hippocampus, and amygdala (Aykac et al., 2020; Ketenci et al., 2020). The postsynaptic adrenergic α1 receptors, which prazosin targets, are implicated in the fear response and regulate both startle and sleep responses. Recent research indicates that oral prazosin can significantly lessen the intensity and to a lesser extent the frequency of PTSD-related nightmares in individuals with bulimia nervosa. However, it did not seem to impact subjective sleep efficiency, quality, cortisol levels, or the pattern of diurnal cortisol secretion (Mahr et al., 2023). Additionally, clinical case reports have noted a sustained remission of PTSD symptoms following the discontinuation of prazosin. Based on these findings, it is hypothesized that prazosin’s therapeutic effects in PTSD may be mediated via the heart-brain axis, with its action starting through oral absorption impacting the heart and subsequently influencing cognitive function in the brain through its presence in the bloodstream and penetration of the BBB.

Disruptions in the BDNF and its receptor, TrkB, signaling pathways are implicated in both brain and heart diseases. The natural flavonoid 7,8-dihydroxyflavone (7,8-DHF) is capable of crossing the BBB and can mimic the action of BDNF within the brain. By selectively activating the TrkB receptor’s downstream signaling pathways, 7,8-DHF provides neuroprotective benefits and improves cardiac function (Yang & Zhu, 2022). It protects against cardiomyocyte cytotoxicity by preventing mitochondrial dysfunction in these cells and promoting the nuclear translocation of phosphorylated STAT (Hang et al., 2023). In previous research, 7,8-DHF was found to counteract deficits in astrocytes and synapses within the hippocampus by targeting TrkB. This led to a reduction in PTSD-like symptoms, such as generalized fear and anxiety-like behaviors (Wang et al., 2022). Additionally, 7,8-DHF has been shown to inhibit cardiac hypertrophy and mitochondrial dysfunction via the activation of AMP-activated protein kinase signaling (Hang et al., 2022). Given these properties, 7,8-DHF emerges as a promising pharmacological agent for treating cardiac dysfunction associated with PTSD.

The endocannabinoid (eCB) system has been identified as a potential target for the treatment of CVD. Through liquid chromatography-mass spectrometry (LC-MS) analyses, components of the eCB system are distributed throughout various body tissues, including the heart and blood vessels. The endogenous and exogenous ligands of this system, particularly phytocannabinoids, play a pivotal role in a range of pathological conditions (Gunduz-Cinar et al., 2023). The eCB system has also garnered significant interest in the field of mental health, especially for its potential in treating PTSD and facilitating fear extinction (Mayo et al., 2022). Preclinical studies suggest that enhancing eCB signaling correlates with a decrease in PTSD symptoms and dysregulation of the HPA axis. This indicates that targeting eCB signaling could represent a promising pharmacological treatment strategy (Sbarski & Akirav, 2020). Cannabidiol (CBD), a non-psychoactive component of cannabis, has been shown to alleviate cognitive impairments during the recall of traumatic events in patients with PTSD (Bolsoni et al., 2022), highlighting the therapeutic potential of modulating the eCB system in managing both mental and cardiovascular health challenges.

CBD is a non-psychoactive constituent of cannabis noted for its anti-fibrotic properties. It has been observed that CBD administration can lead to a reduction in plasma levels of NT-proBNP, a biomarker for cardiac stress and HF. Additionally, CBD has been shown to decrease the size of cardiomyocytes, reduce the area of fibrosis, and lower the expression of fibronectin and fibroblasts, thereby alleviating right ventricular fibrosis (Krzyżewska et al., 2023). CBD also mitigates cardiomyocyte apoptosis that is induced by perfluorooctanesulfonic acid (Wang et al., 2023b), showcasing its potential as a therapeutic agent in the treatment of cardiac-related conditions.
A new oral cannabinoid formulation has been found to significantly lower diastolic blood pressure and mean arterial pressure in patients with hypertension (Batinic et al., 2023). Furthermore, transcriptome-wide analyses have indicated that agonists of the cannabinoid type II receptor may confer a protective effect against cardiac injuries resulting from chronic psychological stress (Qin et al., 2022). Notably, the direct injection of cannabinoid receptors into the lateral ventricles of rats subjected to cecum ligation and puncture has been shown to reverse impairments in fear memory extinction (Matias et al., 2023). Given these findings, future research should concentrate on determining whether cannabinoids can modulate cardiac function via the heart-brain axis and whether this could contribute to the amelioration of cognitive deficits associated with PTSD (Table 1).

The mechanism of drug action on PTSD and Cardiovascular system

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiovascular system</th>
<th>PTSD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Decreases myocardial contractility, autoregulation, conduction, and excitability, slows HR, and reduces cardiac output and myocardial oxygen consumption</td>
<td>Reduces nightmare severity in patients with PTSD</td>
<td>(Mallet et al., 2022; Raut et al., 2022)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Decrease in peripheral adrenergic activity, which influences traumatic memories</td>
<td>Decrease traumatic memory and anxiety-like behavior</td>
<td>(Martinho et al., 2021)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Vasodilation, anti-ischemic and antiarrhythmic properties, platelet inhibition, and lowering of catecholamine levels</td>
<td>Interfere with relearning in the recovery from trauma, increasing patients' vulnerability to react with posttraumatic behaviors at times of stress and trauma-related cues</td>
<td>(Guina, Rossetter, De, Nahhas, &amp; Welton, 2015)</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Dilates arteries and veins, reduces cardiac preload and afterload, decreases left ventricular end-diastolic pressure, and improve cardiac function</td>
<td>Postsynaptic adrenergic α2 receptors are involved in the fear response and modulate startle and sleep responses</td>
<td>(Ketenci et al., 2020; Richardson, Yuh, Su, &amp; Forsberg, 2023)</td>
</tr>
<tr>
<td>7,8-DHF</td>
<td>7,9-DHF rescues cardiomyocyte cytotoxicity by inhibiting cardiomyocyte mitochondrial dysfunction and promoting nuclear translocation of p-STAT</td>
<td>7,9-DHF can cross the BBB, effectively simulate the role of BDNF in the brain, and selectively activate the downstream TrkB signaling pathway, thereby exerting neuroprotective effects</td>
<td>(Wang et al., 2022; Yang &amp; Zhu, 2022)</td>
</tr>
</tbody>
</table>
Table 1 The mechanism of drug action on PTSD and Cardiovascular system

6 DISCUSSIONS

The ancient Chinese medical text "Huangdi Neijing" articulates the concept of "heart dominating mind," emphasizing the interplay between the mind and heart. The central tenet is that the human spirit, consciousness, thought, and other mental activities are predominantly governed by the "heart," which in the context of the text, refers to the mind. In the lens of contemporary medical understanding, this can be interpreted as the heart influencing brain function through its role in blood circulation, supplying the brain with essential nutrients, oxygen, and regulatory substances like cardiac hormones. In modern medicine, the heart-brain axis is recognized as a neural pathway connecting the frontal lobes and limbic brain regions to the peripheral autonomic nervous system via the brainstem. This axis facilitates bidirectional communication between the heart and brain, directly influencing various regions and systems implicated in both PTSD and CVD (Fig. 4). Treatments targeting PTSD can have effects across multiple nodes of this heart-brain axis, affecting both psychological well-being and cardiovascular health. This reflects a contemporary understanding that aligns with the "heart-dominating mind" concept, acknowledging the profound connection between emotional states and cardiac function.

PTSD is indeed linked with a heightened risk for the development of cardiac conditions (Seligowski et al., 2022). Discovering pharmacological treatments that can prevent the onset of such cardiac disorders in individuals with PTSD or enduring psychological stress is of considerable clinical importance. Estradiol, a form of estrogen, is known for its cardioprotective effects (Dubey & Jackson, 2001). It aids in shifting the balance towards vasodilation by lowering the production of renin, which in turn reduces sympathetic nervous system activity, and by diminishing the activity of angiotensin II, a peptide hormone that causes vasoconstriction and an increase in blood pressure. Additionally, estradiol has been observed to facilitate fear extinction, which is the process of reducing the conditioned response to a feared stimulus, in female rats during the metestrus phase of their estrous cycle (Graham & Daher, 2016). This evidence suggests a potential dual benefit of estradiol in both cardiovascular and mental health, particularly for conditions like PTSD that affect both the heart and the brain. Further research in this area could illuminate new pathways for treating or preventing the intersection of these health issues. Given that CVD is the foremost cause of mortality among women and that women are more susceptible to PTSD, understanding the impact of estradiol on metabolic and inflammatory markers in women with PTSD is critical, yet currently undefined.

Increased sympathetic nervous system activity is a characteristic feature of PTSD, and sympatholytic agents like propranolol have shown effectiveness in alleviating trauma-related nightmares and fear memories associated with the disorder (Meamar et al., 2023; Meister et al., 2023). Adrenaline is known to facilitate the consolidation of memory, which can play a role in the persistence of PTSD symptoms (Hou et al., 2021). Propranolol, a non-selective beta-adrenergic blocker that can penetrate the BBB, has been linked to a strong positive correlation between cerebrospinal fluid (CSF) norepinephrine levels and the severity of PTSD symptoms. PTSD patients often exhibit increased HR or BP in response to stress cues, indicative of conditioned fear responses (Strawn & Geracioti, 2008). Behavioral studies have shown that the effects of propranolol are centrally mediated, resulting in impaired retrieval of fear memory that is specific to the context in which the fear was learned (Ali Vafaei et al., 2023). Propranolol acts on brain areas critical for learning and memory, including the hippocampus, PFC, and dorsal dentate gyrus (DG) (Szelesczuk & Fraczkowski, 2022). These findings suggest that Propranolol may attenuate PTSD symptoms by interfering with the sympathetic nervous system’s influence on the brain structures involved in fear and memory.

The significance of the heart-brain axis is gaining recognition, as it involves intricate interactions between the heart and brain that can lead to severe complications like arrhythmias, HF, and ACSs. Moreover, the impact of PTSD treatment on various components of the heart-brain axis is well-established. Consequently, future research efforts will concentrate on enhancing CVD risk management in individuals with PTSD through innovative treatment approaches such as "Treatment from the Heart” and "Therapy Together with Heart and Brain" programs.
ARRREVIATIONS:

PTSD: post-traumatic stress disorder; CVD: cardiovascular disease; HPA: hypothalamic pituitary adrenal; BDNF: brain-derived neurotrophic factor; BRS: baroreflex sensitivity; HR: heart rate; BP: blood pressure; ANS: autonomic nervous system; GR: glucocorticoid receptors; HF: heart failure; CHD: coronary heart disease; ROS: reactive oxygen species; ECM: extracellular matrix; BBB: blood-brain barrier; HIF-1α: hypoxia-inducible factor-1α; AMI: acute myocardial infarction; mTBI: mild Traumatic brain injury; NfL: neurofilament light; EVs: extracellular vesicles; MetSyn: metabolic syndrome; HDL-C: high-density lipoprotein cholesterol; TyG: triglyceride-glucose; PFC: prefrontal cortex; SBP: systolic blood pressure; PWV: pulse wave velocity; mPFC: medial prefrontal cortex; vmPFC: ventromedial Prefrontal cortex

CVR: cardiovascular reactivity; InsCtx: insular cortex; CS: conditioned stimulus; US: unconditioned stimulus; PET: positron emission tomography; FDA: food and drug administration; ACS: acute coronary syndromes; 7,8-DHF: 7,8-dihydroxyflavone; eCB: endocannabinoid; LC-MS: liquid chromatography-mass spectrometry

CBD: Cannabidiol; DG: dentate gyrus.

AUTHORS CONTRIBUTION

HPL and ZRZ wrote the manuscript and summarized the literature. KKD, YZ, and FG consulted and created the figures. GQZ offered funds to support and conceive this review. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

This research was supported by the National Natural Science Foundation of China (No. 81673716), Anhui Natural Science Foundation (No.1808085J15), Anhui University Natural Science Research Project (No. KJ2021A0575, 2023AH050825).

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or used during the study appear in the submitted article.

ORCID

Zhengrong Zhang https://orcid.org/0009-0001-0773-888X

REFERENCES


