Babol University
Of Medical Sciences

IJMCM, Winter 2026, VOL 15, NO 1

International Journal of Molecular and Cellular Medicine

Journal homepage: www.ijmcmed.org

IJMCM

REVIEW ARTICLE

Beyond the Beating: The Dynamic Interplay between Heart and Brain in Emotion and Cognition

Sahand Ashrafpour [1], Mohammad Mahmoudjanloo[2], Manouchehr Ashrafpour[1*]

1. Mobility Impairment Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
2. Student Research Committee, Babol University of Medical Sciences, Babol, Iran.

ARTICLE INFO

Received: 2025/05/7
Revised: 2025/06/3
Accepted: 2025/07/9

***Corresponding**:
Manouchehr Ashrafpour
Address:
Mobility Impairment Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran
E-mail:
mnrashrafpour@yahoo.com

ABSTRACT

The intricate bidirectional communication between the heart and brain, mediated by autonomic, neural, and hemodynamic pathways, plays a pivotal role in neurovisceral integration (NVI) and the regulation of cognitive and emotional processes in the brain. This review synthesizes key mechanisms underlying this interaction, including cross-frequency coupling (CFC), heart rate variability (HRV), and heartbeat-evoked responses (HERs). CFC facilitates the synchronization of low-frequency cardiac rhythms with higher-frequency brain oscillations, supporting cognitive functions such as memory, decision-making, and emotional regulation. HERs, cortical responses synchronized with heartbeats, reflect the brain's integration of cardiac signals into interoceptive awareness and self-consciousness. HRV emerges as a critical marker of autonomic balance, with higher HRV associated with enhanced emotional resilience and cognitive performance. Additionally, pressure pulsatility from each heartbeat influences brain activity via mechanosensitive channels like Piezo2, linking cardiovascular dynamics to sensory processing and cognition. These mechanisms collectively underscore the heart's active role in shaping brain function and consciousness. Abnormalities in these interactions are implicated in neuropsychiatric and neurodegenerative disorders, including Alzheimer's disease, anxiety, and depression, highlighting their clinical relevance. Therapeutic interventions such as vagus nerve stimulation (VNS), biofeedback, and mindfulness practices show promise in modulating heart-brain coherence to improve mental and cardiovascular health. Despite significant advances, limitations remain, including reliance on animal models, incomplete understanding of precise mechanisms, and challenges in isolating heart-brain dynamics from other influencing factors. Future research should focus on bridging these gaps to unlock the full potential of heart-brain coupling for innovative healthcare solutions.

***Keywords*:** Cognition, Emotion, Cross Frequency Coupling (CFC), Neurovisceral integration, Heart Rate Variability (HRV)

Cite this article: Ashrafpour S, et al. Beyond the Beating: The Dynamic Interplay between Heart and Brain in Emotion and Cognition. International Journal of Molecular and Cellular Medicine. 2026; 15(1):1261-1284. DOI: 10.22088/IJMCM.BUMS.15.1.1261

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

Introduction

Historically, the heart has been regarded as central to emotional and cognitive processes. Ancient thinkers held cardiocentric views, proposing that the heart governs irrational emotions such as fear, love, and anger (1). However, the rise of cephalocentric theory shifted this perspective, establishing the brain as the primary organ for reasoning and higher cognitive functions (2). Modern neuroscience underscores the brain's central role in emotion and decision-making (3), while also highlighting the heart's influence through bidirectional brain-heart interplay (BHI), mediated by the autonomic nervous system (ANS) (4). Although the precise molecular mechanisms underlying the BHI in these pathological states remain to be fully elucidated, the BHI theory provides valuable insights into their complex interactions (5).

The intricate complexity observed in electroencephalogram (EEG) and heart rate variability (HRV) time series has been widely investigated across various conditions, revealing the dynamic physiological interplay between the central and autonomic nervous systems. These interactions are both influenced by and capable of influencing pathophysiological changes (6). However, the complexity of these interactions at the level of BHI remains insufficiently explored, particularly in the context of its role in emotion and cognition. This gap highlights the need for a deeper understanding of how BHI dynamics contribute to these fundamental processes. Despite this scientific understanding, the heart remains a powerful cultural symbol of emotion and intuition, reflecting its enduring significance in human experience (7). Nowadays, interdisciplinary research continues to explore the interplay between the heart and brain, integrating findings from psychology, neuroscience, and cardiology to better understand their combined influence on human health and behavior (8).

The brain-heart axis (BHA) reflects the bidirectional communication and interdependence between the central nervous system (CNS) and the cardiovascular system. Neural and humoral signals from each organ modulate the other's physiological activity, with the ANS acting as a key conduit for this cross-regulation (9, 10). The ANS is a complex neural network responsible for controlling involuntary physiological functions critical for sustaining homeostasis. Its precise regulation relies on a sophisticated interaction among higher cortical areas, brainstem nuclei, and peripheral neural pathways (11). Recently, the pivotal role of BHA interactions has been emphasized in the neurovisceral integration (NVI) (12). NVI refers to how the brain and nervous system work together with internal organs (like the heart) to regulate emotions, cognition, and bodily functions. This model posits that the dynamic interplay between the central and peripheral autonomic nervous systems underpins interoception—the perception of internal bodily states—which is critical for maintaining homeostasis and guiding behavior (13, 14).

Interoception, the perception of internal bodily states, arises from the coordinated activity of neural networks and peripheral receptors. These systems generate real-time afferent signals from organs like the heart, which the brain integrates to produce efferent responses that regulate physiological functions and create the subjective experience of interoception (15).

Proper interoceptive signaling is crucial for emotional functioning, and its dysregulation can lead to emotional imbalances (16). The ANS mediates bidirectional communication between the brain and peripheral organs, regulating afferent signals from the heart and gut and orchestrating efferent responses to maintain homeostasis. Dysregulation in ANS function can impair interoceptive accuracy, contributing to conditions like anxiety, depression, and somatic symptom disorders (17). Proper interoceptive function is essential for cognition, enabling the brain to integrate internal signals for emotional regulation, decision-making, and self-awareness. Disruptions in this process are linked to cognitive impairments and psychiatric disorders, underscoring the importance of interoceptive accuracy for mental and cognitive health (3). The directionality of brain-heart interaction is dynamic and state-dependent. In pathological states, such as post-traumatic stress, top-down regulation from the brain to the heart may be impaired. However, effective treatment can restore the ascending flow of signals from the ANS to the brain, highlighting the plasticity of this interaction (15).

Recent studies indicate that the heart’s activity plays a complex role in emotion regulation, primarily mediated by heart rate variability (HRV) and ANS signaling within the HBA. These mechanisms are critical for modulating cognitive and emotional stability (18, 19). HRV serves as a key biomarker of ANS balance, reflecting the dynamic interplay between

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

sympathetic and parasympathetic activity, and providing insight into physiological resilience and regulatory capacity (20). Perturbations in HRV may arise from pathological involvement affecting both central and peripheral components of the ANS, reflecting disruptions in the intricate balance between sympathetic and parasympathetic activity (11).

These alterations in HRV serve as a sensitive indicator of dysregulated autonomic control, often associated with cardiovascular, neurological, and metabolic disorders (21, 22). The relationship between HRV and interoception is supported by robust evidence showing that both processes rely on the same neural and autonomic pathways, particularly involving the vagus nerve and central brain regions like the insula and cingulate cortex, which play critical functional roles in emotional regulation (23, 24). HRV can be seen as a peripheral reflection of the brain's ability to process and respond to internal bodily signals, making it a valuable tool for studying interoceptive function in health and disease (25). This integrative review is divided into three sections. The first explores the functional communication of the BHI through the ANS. The second examines pathological conditions that disrupt BHI, analyzing their impact on both organs. The third investigates heart-brain connectivity through the lens of functional coherence, emphasizing its role in the NVI model and its practical applications.

Heart and Brain intercommunication in HBA

The heart and brain communicate through a complex network of neural, hormonal, biophysical, and biochemical pathways, enabling bidirectional communication between these two vital organs. This interaction is fundamental in regulating cognitive, emotional, and physiological processes (12, 21). However, it seems that the interaction and interplay through the ANS is the primary and dominant pathway of intercommunication in this axis (13). The brain directly regulates the cardiac function via the sympathetic and parasympathetic branches of the ANS (9). Knowledge about the ANS of the heart is essential for accurately understanding heart function and its changes in physiological conditions, as well as in pathological states, and for identifying therapeutic targets. The cardiac ANS operates via two primary components: the sympathetic and parasympathetic divisions.

Sympathetic input originates from preganglionic neurons in the upper thoracic spinal cord segments, synapsing in the cervical and thoracic ganglia, and then postganglionic fibers innervates the cardiac conduction system and the working myocardial cells through the release of norepinephrine and neuropeptide Y (26, 27).

The ANS is considered a key mediator between the mind and body, acting as a vital link between the CNS and the body's organs to facilitate information transmission (28). Other areas of the body, while also participating in afferent and efferent functions, will not be discussed further here. The SNS boosts heart rate and contractile strength, causing the cardiac cycle duration to shorten almost linearly as the frequency of sympathetic postganglionic discharge rises. Additionally, simply decreasing the cycle duration increases both ventricular contractility and the rate of diastolic relaxation (9).

The SNS plays a critical role in regulating cardiac function, with its fibers originating from the intermedio-lateral cell column of the thoracic spinal cord (T1–T4/T5). These preganglionic fibers synapse in the cervical and upper thoracic sympathetic ganglia (e.g., stellate ganglion), and postganglionic fibers project to the heart, releasing norepinephrine (NE) that primarily acts on β1-adrenergic receptors to exert its effects. The most significant physiological effect of sympathetic activation is the increase in cardiac output, ensuring adequate blood flow during stress or physical activity (9, 10). The sympathetic component, in addition to carrying efferent control signals, also contains afferent signals, although about 20% or less of the fibers are afferent (28).

However, the majority of heart afferent fibers are found in sympathetic nerves (27). Cardiac afferent fibers reaching the nodose ganglia travel via vagal nerve branches and are classified as cardiac parasympathetic afferents, while those reaching the dorsal root ganglia pass through paravertebral sympathetic ganglia (without synapsing) and are termed cardiac sympathetic afferents. These afferent signals also converge onto forebrain and cortical neurons, particularly in the insular cortex, exerting a tonic descending influence on efferent pathways (27, 29). Recent studies have highlighted the role of sympathetic over activities in cardiovascular pathologies such as heart failure (HF) and arrhythmias, with beta-blockers remaining a key therapeutic strategy (30). Emerging research also explores the interplay

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

between sympathetic signaling and immune modulation in cardiac remodeling, offering new treatment possibilities (26). In contrary, the preganglionic fibers of parasympathetic efferent originate primarily in the medulla, specifically within the nucleus ambiguus and, to a lesser extent, the dorsal motor nucleus of the vagus nerve.

These fibers innervate the atrial and ventricular myocardium as well as the cardiac conduction system, exerting their effects primarily through the release of acetylcholine (ACh), nitric oxide (NO), and vasoactive intestinal peptide (VIP) (31). Nearly all neurons traveling through the vagus nerves from the brainstem to the heart terminate in ganglionic networks located on the epicardial surfaces, where they modulate the conductivity of the cardiac conduction system, as well as contractility and heart rate (HR). In the heart regulated by the ANS, parasympathetic control typically predominates over sympathetic control (9).

The vagus nerve, a paired structure that innervates the visceral organs, consists of 80,000 to 100,000 fibers in humans. It serves as the primary sensory pathway for transmitting signals from the organs to the brain, with approximately 80% of its fibers dedicated to conveying afferent signals (32). The vagus nerve is vital for the transduction of visceral sensory information and its subsequent integration in the CNS. It plays a crucial role in interoception, which involves the nervous system’s ability to detect, interpret, and assimilate signals originating from the body (29). Interoceptive information originating from the heart, which plays a role in cardiovascular regulation, transmits information about the body's physiological condition through vagal afferent pathways to the nucleus tractus solitarius (NTS) (33). The NTS acts as the primary central hub for receiving interoceptive signals from internal organs, such as the cardiovascular system, along with mechano-sensitive and chemo-sensitive inputs from baroreceptors and chemoreceptors (29, 34).

Then cardiac interoceptive signals are relayed from the NTS to various brain regions, including the amygdala, insula, cingulate, and somatosensory cortices (35). Although no direct connections or pathways exist between the NTS and the hippocampus, these regions are indirectly linked, and functional interactions between them have been observed (34). From a physiological perspective, the most important afferent information relayed to the brain in a regular, cyclic manner originates from the mechanosensitive receptors of the heart. These receptors are activated by changes in the filling pressure of the atria and ventricles, as well as by increases in pressure during systole (29). Additionally, heart interoception, as a component of the NVI, can occur through multiple pathways. For example, cardiac contractions are translated into neural signals via proprioceptive or mechanosensitive receptors that detect the pulsations of blood vessels (36). While the ANS orchestrates broad cardiovascular modulation, finer control emerges from the heart's intrinsic regulatory network- the intrinsic cardiac nervous system (ICNS).

As illustrated in Figure 1, the heart and brain maintain a dynamic bidirectional communication network, primarily mediated by the ANS. The heart contains the ICNS, often referred to as the "heart's little brain," which is a complex network of neurons and ganglia. The ICNS plays a crucial role in regulating cardiac function independently of the CNS (27). The ICNS comprises over 40,000 neurons, along with neuropeptides and support cells, reflecting a structural complexity akin to the CNS (37). This network includes more than 800 ganglia, strategically positioned on the epicardial surface and surrounding the aorta, pulmonary arteries, and coronary vessels (38). These ganglionated plexi contain a mixture of efferent, afferent, and interneurons, integrating sympathetic and parasympathetic inputs to regulate the heart’s electrical, vascular, and contractile functions. Additionally, the ICNS collaborates with upstream neural centers to regulate the heart's electromechanical activity with each heartbeat (27, 37).

The ICNS also exhibits memory-like adaptability, crucial for both normal heart function and the development of heart-related disorders (39). Moreover, vagal denervation through catheter ablation targeting the ganglionated plexi has been shown to manage arrhythmias and cardioinhibitory syncope, further highlighting the neural regulatory system's influence over heart function (40). However, while the central ANS provides top-down modulation, the ICNS- a sophisticated peripheral ganglionated plexus-operates as the heart’s local integrator, refining autonomic output via intra-cardiac reflexes. This dual-level control ensures precise cardiovascular adaptation to both physiological demands and emotional stressors, maintaining homeostasis while dynamically integrating the heart’s activity with higher-order brain functions.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

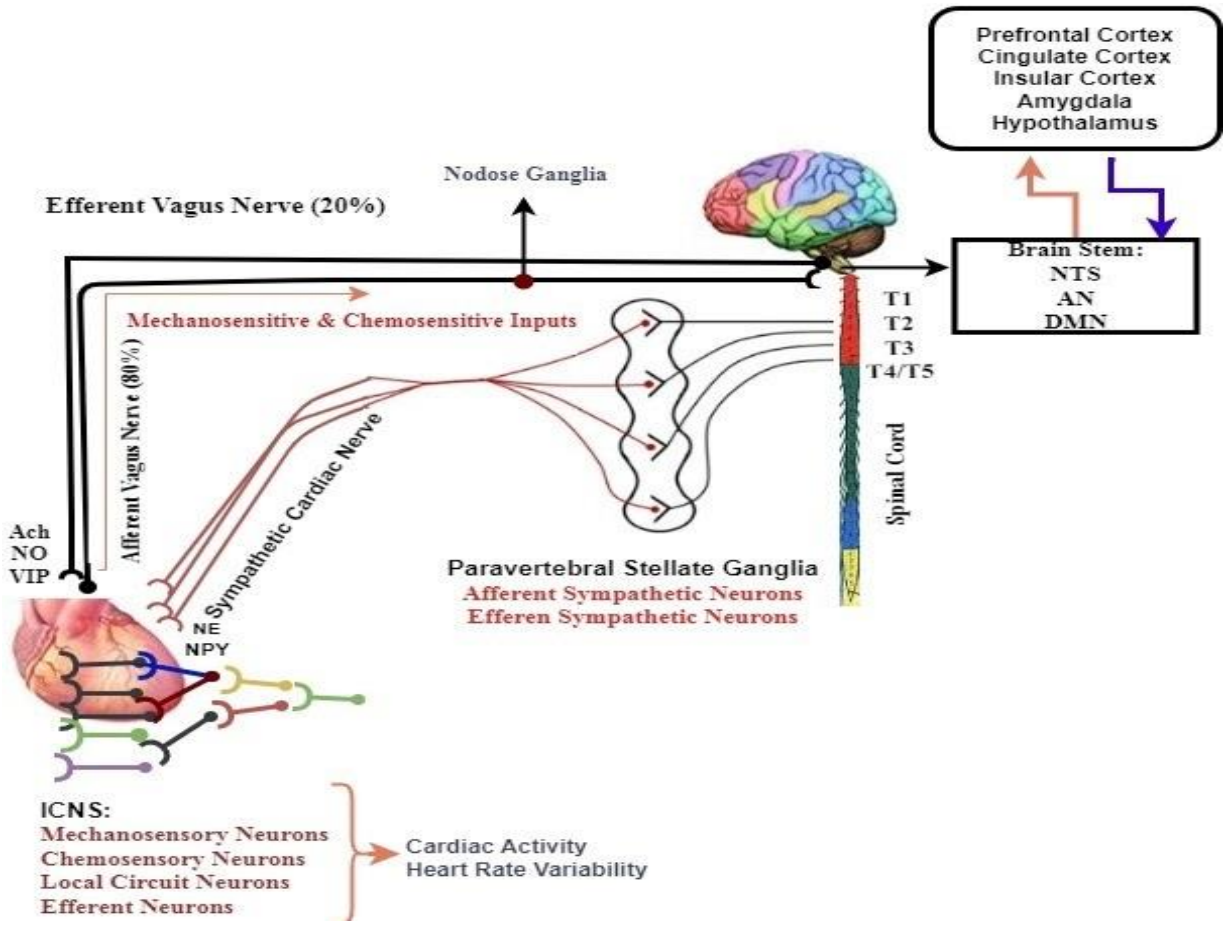

Figure 1. Bidirectional Heart-Brain Communication through the Autonomic Nervous System (ANS). This figure illustrates the dynamic and reciprocal interaction between the heart and brain mediated by the ANS. Efferent Pathways: The brain regulates cardiac function via the sympathetic and parasympathetic branches of the ANS. Parasympathetic signals originate from the ambiguus nucleus (AN) the dorsal motor nucleus (DMN) of the vagus nerve. Sympathetic signals originate from the thoracic spinal cord, increasing heart rate and contractility, while parasympathetic signals via the vagus nerve decrease heart rate and modulate cardiac activity. Afferent signals, including mechanoreceptor and chemo-sensitive inputs, are transmitted to the nucleus tractus solitarius (NTS) in the brainstem through vagal component, influencing neurovisceral integration, emotional, cognitive, and autonomic regulation in regions such as the insula, amygdala, cingulate and prefrontal cortex (PFC). This bidirectional communication supports physiological homeostasis and neurovisceral integration, highlighting the critical role of the ANS in linking cardiovascular health with mental well-being. Additionally, the heart possesses its own intrinsic nervous system, known as the intrinsic cardiac nervous system (ICNS).

It serves as a neural gateway, relaying information from the heart to the brain, and plays a pivotal role in the NVI. This model highlights the importance of BHI in maintaining physiological homeostasis and supporting emotional resilience, with the ICNS acting as a key mediator in this bidirectional communication (12, 41). The ICNS, in conjunction with the ANS, appears to establish mechanisms for localized control of cardiac function, integrating both central and peripheral neural inputs to regulate heart activity dynamically (9, 30). Additionally, it seems that this system can modulate neural activity at various levels of the brain by sending different signals through the vagal and sympathetic afferent pathways, thereby functioning as part of NVI (42). On one hand, vagal activity is involved in relaying afferent signals from the viscera, establishing a fundamental basis for the operational aspects of arousal systems and self-

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

awareness (43). On the other hand, NVI involves the dynamic interplay between the brain's cortical centers (insula, cingulate and prefrontal cortex (PFC)) and subcortical structures (amygdala, hypothalamus, and brainstem) to regulate autonomic, emotional, and cognitive processes (14). This integration ensures that the body's internal states are aligned with external demands, enabling adaptive responses to environmental challenges. Specifically, brain cortical areas such as the anterior cingulate cortex, insula, and PFC, which are integral to NVI, also play a pivotal role in cardiac autonomic regulation. These regions form part of the central autonomic network, modulating HRV and other cardiac functions through parasympathetic and sympathetic pathways (44), suggesting proper autonomic activity is essential for effective NVI in the brain, as it ensures the dynamic balance between the sympathetic and parasympathetic nervous systems. This balance is critical for maintaining homeostasis, regulating emotional and cognitive processes, and facilitating adaptive responses to environmental challenges (42, 44).

Dysregulation of autonomic activity can disrupt neurovisceral integration, leading to impaired interoceptive awareness, emotional dysregulation, and increased vulnerability to stress-related disorders (23, 24). It appears that the ICNS, in addition to playing important roles under normal conditions, is also involved in pathological states that affect the BHA. There is a significantly higher presence of postganglionic sympathetic and parasympathetic nerves at the base of the ventricles compared to the apex, which may play a role in the pathophysiology of brain-heart diseases (45). Interestingly, dysfunctional remodeling of the nervous system, which occurs in conditions such as myocardial infarction, HF, and other cardiac disorders, can disrupt the balance and stability of the ICNS and its dynamic neural functions (46).

Similarly, these maladaptive changes in the ICNS are also observed in neurodegenerative brain diseases, highlighting the ongoing bidirectional interaction between these two organs in both health and disease (31). It is important to note that HRV is regulated by the ANS, with a dominance of parasympathetic division. The effective and dynamic regulation of vagal tone, typically indicated by higher HRV, is believed to underlie the ANS's adaptive capability in response to changing internal and external demands (22). However, this balance is dynamic, and this system exhibits plasticity, allowing it to acquire different phenotype under a range of physiological and pathological conditions. For example, in heart failure, a subgroup of sympathetic fibers can shift to cholinergic fibers, resulting in cholinergic control independent of the parasympathetic vagal pathway. This mechanism can enhance parasympathetic dominance, thereby protecting the failing heart from dangerous dysrhythmias (47). In recent years, numerous studies have specified that lower HRV is generally related to greater levels of psychopathology (22) and worse brain cognitive activity (20, 42).

In addition to the traditional role of the vagus nerve as a key component of the parasympathetic system in regulating cardiac functions, increasing evidence suggests that it also plays a role in modulating pain perception (48). In general, the vagus nerve plays a crucial role in regulating everyday physiological processes. As a result, strategies aimed at modulating its activity could offer a promising and novel avenue for developing therapeutic interventions. Historically, according to both preclinical and clinical evidenc, vagus nerve stimulation (VNS) can alleviate somatic pain by lowering the pain threshold and modulating pain pathways. Today, the positive analgesic effects of VNS, both through invasive and non-invasive methods, have been demonstrated across a range of somatic pain conditions (49). Besides the influence of VNS on pain perception, research has demonstrated that stimulation of the carotid sinus baroreceptors decreases sensitivity to nociceptive stimuli in both hypertensive individuals and those with normal blood pressure (50). This modulatory effect is believed to result from the interaction between the ANS and the brain's descending pain pathways.

The significance of the ANS in pain perception becomes evident when examining the connection between HRV, which serves as a measure of autonomic cardiac regulation, and pain perception. Increased low-frequency HRV is linked to enhanced baroreceptor sensitivity, reduced pain scores, and a higher threshold for pain perception (51). Also, recent studies have demonstrated that VNS improves emotional recognition, predominantly recognition of facial expressions, and enhances selective attention during cognitively demanding tasks. Furthermore, VNS has shown benefits in learning and memory, including associative memory and tasks involving spatial working memory (52). Additionally, the results of a

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

study indicated that while VNS had no significant effect on verbal memory, long-term VNS over a period of more than six weeks improved recall and recognition in patients with cognitive impairments (53). Overall, this evidence suggests that the ANS is not merely a simple regulator of bodily functions or a pathway for bidirectional signal transmission in BHI. Instead, it plays more complex roles and can serve as a potential mechanism for treating a wide range of diseases.

Interconnected Dynamics of Heart and CNS Disorders: Clinical Implications of BHI

The inter-communication in the BHA is crucial not only due to shared mediators influencing both organs but also because they share numerous common pathophysiological mechanisms and are affected by similar risk factors. This reciprocal relationship underscores a cyclical dynamic in which dysfunction in one system amplifies pathological processes in the other, creating a compounding impact on overall health. Understanding this interplay is crucial, especially for exploring how various diseases simultaneously affect both systems. A range of CNS diseases can directly or indirectly affect cardiac function, leading to what are termed brain-heart diseases (BHDs). Secondary heart complications resulting from brain diseases vary widely, ranging from mild and transient issues to more severe and prolonged complications, some of which can be life threatening (26). Conversely, various heart conditions can alter brain function, classified as heart-brain diseases (HBDs). The term 'cardiogenic dementia' was initially introduced to describe a clinical condition marked by cognitive decline resulting from heart disease (54).

This section will explore the clinical implications of these interconnected dynamics, highlighting the importance of recognizing the bidirectional relationship between cardiac health and neurological function. Understanding these complex relationships is crucial for developing effective interventions for patients with both cardiac and neurological disorders. The interaction between these two organs is not only clinically significant but can also contribute to deciphering the complex aspects of their relationship at a basic level. The shared pathological mechanisms underlying BHDs or HBDs and their contributions to emotional and cognitive dysfunction are summarized in Table 1.

Various CNS disorders can lead to autonomic dysregulation, impacting heart function. For example, conditions such as stroke, traumatic brain injury (TBI), and subarachnoid hemorrhage (SAH) can disrupt the normal autonomic balance, leading to cardiac complications like arrhythmias and HF. Among BHDs, traumatic brain injuries (TBI) can be noted, in which patients exhibit cardiac symptoms such as an increased QT interval on ECG. Cardiovascular complications following TBI are prevalent and can manifest in various forms, including stress-induced cardiomyopathy, arrhythmias, alterations in ECG repolarization, and elevated levels of cardiac reactive oxygen species (55).

Table 1. Shared Pathological Mechanisms in the Brain-Heart Axis (BHA) Disorders.

Pathological condition	Heart to Brain Pathway	Brain to Heart pathway	Shared Mechanisms	Clinical Implications	References
traumatic brain injury	N/A	TBI → neurogenic cardiac injury (e.g., arrhythmias, myocardial damage)	autonomic dysregulation, Sympathetic Overactivation, catecholamine surge, Oxidative Stress	increased risk of arrhythmias, Takotsubo cardiomyopathy, and sudden cardiac death post-TBI	(55-57)
Subarachnoid Hemorrhage	N/A	SAH → neurogenic stunned myocardium (e.g., Takotsubo cardiomyopathy, arrhythmias)	catecholamine surge, autonomic dysregulation	increased risk of myocardial injury, arrhythmias, and sudden cardiac death post-SAH	(58-60)

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

Pathological condition	Heart to Brain Pathway	Brain to Heart pathway	Shared Mechanisms	Clinical Implications	References
Stroke	N/A	ischemic stroke → neurogenic cardiac injury and cardiomyopathy	autonomic dysregulation, inflammation, oxidative Stress	increased risk of cardiac arrhythmias and myocardial injury post-stroke	(45, 61)
Takotsubo Cardiomyopathy	N/A	emotional stress → catecholamine surge → transient left ventricular dysfunction	autonomic dysregulation, neuro-hormonal imbalance	reversible heart failure triggered by acute emotional or neurological stress	(9, 62, 63)
Heart Failure	reduced cardiac output → cerebral hypoperfusion → cognitive decline	N/A	autonomic dysregulation, inflammation, neurohormonal imbalance	increased risk of dementia, depression, and stroke in heart failure patients	(64, 65)
Myocardial Infarction	reduced cardiac output → cerebral hypoperfusion → cognitive decline	N/A	autonomic dysregulation, inflammation, thromboembolism	increased risk of stroke, cognitive impairment, and depression post-MI	(66)
Atrial Fibrillation (AF)	AF → thromboembolism → ischemic stroke	Chronic stress → autonomic imbalance → arrhythmia	Thromboembolism, oxidative stress	Higher incidence of stroke and vascular dementia in atrial fibrillation patients	(67)

This table summarizes the shared pathological mechanisms underlying the BHA, highlighting how disruptions in these processes contribute to emotional and cognitive dysfunction. Key mechanisms include reduced cerebral blood flow, neuroinflammation, autonomic dysregulation, neurohormonal activation, and systemic inflammation.

The results of a study conducted on 110 patients with TBI indicated that changes in the ECG, specifically a prolonged QT interval, may serve as a predictive marker for an increased risk of cerebral edema and a higher likelihood of requiring surgery (57). Follow-up studies of patients with mild and moderate TBI have revealed that the incidence of CVDs is higher in individuals with a history of recurrent TBI or even a single TBI event (56).

This may suggest long-term alterations in the signaling pathways and molecular mechanisms associated with HBA. The results of a cohort study indicated that TBI serves as an independent risk factor for an increased likelihood of HF, even when accounting for other variables. Conversely, the use of beta-blockers was associated with a reduction in mortality related to TBI and an improvement in HF outcomes (59).

However, it appears that brain injury caused by TBI generates signals that weaken cardiac function, although the precise nature of these signals remains inadequately understood.

There is a natural neurovascular coupling (NVC) in which cerebral blood flow is automatically influenced by changes in neuronal activity. However, conditions such as stroke or SAH lead to uncoupling, resulting in cerebral blood supply becoming heavily dependent on cardiac function (61). Evidence suggests that heart diseases, including heart failure, lead to the early breakdown of NVC in the brain (63). Clinical studies have shown that ECG changes are observed in 40 to 100 percent of patients with SAH, and 5 percent of these patients experience dangerous dysrhythmias. Additionally, 80 percent of patients exhibit electrocardiographic changes similar to those seen in myocardial ischemia (61). Research has demonstrated

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

that many SAH patients experience cardiac complications ranging from eosinophilia to cross-striations indicative of myocardial injury. In some cases, endocardial hemorrhages may also occur. It is suggested that cardiac lesions result directly from an autonomic storm and intracardiac sympathetic over activities following the activation of reticular formations in the midbrain (62).

On the other hand, stroke is the second most common disease associated with a high risk of cardiovascular complications, increasing the likelihood of cardiovascular issues in patients without previously known heart disease by 25 times following an acute stroke. Additionally, 9% of individuals who experience an acute stroke will suffer from acute myocardial infarction, heart failure, or ischemic diseases within a year (45). Ischemic stroke can profoundly affect the heart, giving rise to a condition known as stroke-heart syndrome. The primary drivers of these effects are ANS dysfunction and widespread inflammation, which impair cardiac cell metabolism, disrupt immune responses, and damage small blood vessels (68). Although researchers have made strides in understanding how stroke and CV health are interconnected, it remains difficult to differentiate between cardiac issues caused by stroke and those stemming from pre-existing heart conditions.

Addressing this challenge requires collaborative efforts across disciplines to uncover new treatment strategies and enhance patient outcomes for those affected by this condition. Similarly, Takotsubo syndrome (TTS), also known as "broken heart syndrome," is a transient cardiac condition often triggered by acute emotional or physical stress, highlighting the intricate interplay between the brain and heart. According to an international study (64), TTS predominantly affects postmenopausal women and mimics acute coronary syndrome with symptoms such as chest pain and transient left ventricular dysfunction, despite the absence of coronary artery disease. The pathophysiology involves exaggerated sympathetic activation due to stress-induced catecholamine surges, leading to myocardial stunning. This syndrome underscores the critical role of the ANS in mediating BHI under pathological conditions, where heightened central stress responses can directly impact cardiac function (9, 69).

In contrary, HBDs represent a complex interplay between various cardiac conditions and their effects on brain function. These conditions can lead to significant neurological consequences, impacting cognition and emotional regulation. Evidence has been presented indicating that dysregulation of autonomic balance in the heart can occur in various cardiac conditions, leading to changes in cerebral blood flow and brain function (13). Conditions such as HF, arrhythmias, and myocardial infarction can lead to reduced cerebral perfusion. This reduction can result in cognitive impairments, including difficulties with memory, attention, and executive function (13, 70).

HF is closely associated with cognitive decline, driven by compromised cerebral blood flow, hypoxia, and systemic inflammation, which adversely affect brain health and contribute to neurodegenerative processes (71, 72). Cognitive impairments, including memory deficits and overall cognitive dysfunction, affect 35% to 65% of HF patients, with prevalence varying based on ejection fraction (EF). Both HF with reduced EF (HFrEF) and HF with preserved EF (HFpEF) are linked to cognitive decline, indicating that this condition is not solely dependent on brain perfusion issues but also involves disturbances in other pathophysiological pathways (65). Preclinical studies on animal models of HF have demonstrated that spatial memory impairment in rats with HF is associated with changes in hippocampal signaling mechanisms, independent of perfusion alterations (65, 73). Furthermore, systemic inflammation and oxidative stress in HF can cross the blood-brain barrier, inducing neuroinflammation and damaging neurons and glial cells, which may contribute to emotional dysregulation (e.g., depression and anxiety) and cognitive impairments (66). On the other hand, heart diseases, such as HF, significantly disrupt neurovisceral integration, impairing the brain's ability to regulate autonomic, emotional, and cognitive processes. The central autonomic network (CAN), which integrates BHIs, becomes dys-regulated in HF, disrupting the balance between the two organs. This dysregulation not only perpetuates cardiovascular instability but also amplifies brain-related pathologies, creating a vicious cycle of shared pathophysiology (66, 73).

In addition to these mechanisms, HF is characterized by a marked attenuation in cardiovascular baroreceptor activity and a simultaneous amplification of the excitatory chemoreceptor reflex, alongside increased inflammatory mediators (70). These changes in brain

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

function arise not only through homeostatic signaling pathways but also via alterations in baroreceptor and chemoreceptor reflexes. While the impact of baroreceptor reflex changes on brain activity, particularly cognitive function, has been relatively well-studied, the effects of arterial chemoreceptor reflexes on the brain remain less explored. Notably, preclinical histopathological studies have revealed that afferent fibers from aortic or carotid chemoreceptors project not only to the NTS but also to extrinsic NTS nuclei, such as the vagal and hypothalamic nuclei, highlighting the complexity of these interactions (67). Collectively, this evidence underscores the multifaceted nature of cognitive and emotional changes in HF patients, which extend beyond EF-related perfusion issues to include systemic inflammation, oxidative stress, and neuro-hormonal dysregulation**.**

Myocardial infarction (MI) is another HBD that underscores the strong bidirectional link between these two organs. This severe condition can lead to significant brain-related changes, primarily driven by diminished cardiac output, widespread inflammation, and thromboembolic events. Following an MI, the ANS often becomes imbalanced, characterized by heightened sympathetic activity and reduced parasympathetic tone, which can exacerbate brain damage. Additionally, post-MI depression is a common occurrence, linked to both autonomic dysfunction and systemic inflammatory processes, further emphasizing the intricate interplay between these two vital organs (58).

In this context, another condition worth mentioning is Atrial Fibrillation (AF), a significant pathological condition strongly linked to brain changes, primarily due to the heightened risk of thromboembolic events like stroke. AF can cause thromboembolism, where blood clots formed in the atria travel to the brain, leading to ischemic stroke.

Additionally, chronic stress and emotional disturbances can trigger autonomic imbalance, potentially exacerbating AF. Furthermore, AF is associated with increased oxidative stress, which can damage both cardiac and brain tissues, underscoring the intricate interplay between the heart and brain in this condition (60).

Lastly, cardiovascular diseases (CVDs), such as hypertension and atherosclerosis, significantly impact brain health by altering cerebral blood flow and vascular integrity. One key mechanism linking CVDs to brain diseases and cognitive impairments is increased arterial stiffness, often measured by pulse wave velocity (PWV). Elevated PWV, a marker of vascular aging and stiffness, reduces the brain's ability to regulate blood flow, leading to chronic hypoperfusion, micro-vascular damage, and neuroinflammation (74).

These changes contribute to the development of cognitive decline, dementia, and neurodegenerative diseases such as Alzheimer's. By impairing the brain's vascular supply, increased PWV exacerbates the risk of white matter lesions, silent brain infarcts, and amyloid deposition, highlighting the critical role of vascular health in maintaining cognitive function (75). Thus, PWV serves as a valuable biomarker for understanding the link between cardiovascular and brain diseases, offering potential targets for early intervention and prevention.

The NVI provides a comprehensive framework for understanding the shared pathological conditions that affect both the heart and the brain, emphasizing their intricate connection through the CAN. This network regulates autonomic, emotional, and cognitive processes, making it a critical mediator of heart-brain interactions.

Dysregulation within this system—whether driven by autonomic imbalance, systemic inflammation, vascular dysfunction, or neurodegenerative changes—can initiate a cascade of interconnected pathologies. For instance, cardiac conditions such as HF or arrhythmias can impair cerebral blood flow and disrupt neurochemical homeostasis, contributing to cognitive decline, mood disorders, or even stroke. Conversely, brain-related pathologies like ischemic stroke, depression, or chronic stress can dysregulate autonomic function, leading to increased risks of cardiovascular events, including myocardial infarction, Takotsubo syndrome, or sudden cardiac death.

The bidirectional nature of heart-brain communication is further underscored by shared mechanisms such as sympathetic overactivation, parasympathetic withdrawal, and inflammatory signaling, which exacerbate both cardiac and neurological dysfunction. By elucidating these pathways, the NVI highlights how pathological states in one organ can propagate to the other, creating a self-perpetuating cycle of dysfunction. This underscores the importance of addressing both systems in clinical

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

practice to break the chain of interconnected pathophysiology and improve patient outcomes.

Neurovisceral Dynamics of BHI in Cognition and Emotional Regulation

NVI provides a robust framework for understanding how the heart and brain communicate to regulate complex processes such as cognition and emotional responses. Central to this interaction is the dynamic interplay between autonomic, neural, and physiological pathways, which ensures adaptability to internal and external demands. This section delves into the mechanisms underlying these interactions, shedding light on their role in maintaining emotional resilience and cognitive health. Figure 2 illustrates the representation of the BHA within the framework of the NVI, highlighting the cortical and subcortical centers involved in processing cardiovascular signals.

NVI not only underscores the dynamic communication between the heart and brain but also highlights how this interaction shapes emotional and cognitive processes (76). Emotion and cognition, traditionally viewed as interconnected phenomena, rely on specific brain regions such as the amygdala for emotional processing and the prefrontal cortex for higher-order cognitive functions like decision-making, attention, and memory (42). Studies reveal interconnected pathways linking these regions with those responsible for cardiovascular regulation (12, 77), emphasizing the role of the ANS in bridging bodily states with mental processes**.**

Vagal pathways serve as critical ascending routes for transmitting interoceptive signals to the brain. These signals are relayed not only to sensory cortices but also to higher brain regions such as the hypothalamus, insula, and anterior cingulate cortex (41). These areas play dual roles: they integrate visceral signals and regulate emotional and cognitive processes. For instance, the insula is crucial for processing cardiovascular signals while also contributing to emotional awareness and decision-making (25). Likewise, baroreceptor afferent data is relayed to the insula, which plays a significant role in representing incoming cardiovascular signals (78)**.**

Interestingly, studies have shown that VNS facilitates body-brain coupling, whereas vagotomy disrupts this mechanism, underscoring the pivotal role of the vagus nerve in maintaining physiological and psychological balance (33, 79). In patients with heart disease, abnormal afferent signals from the damaged myocardium can influence cortical electrical activity, predisposing individuals to arrhythmias and emotional dysregulation. This underscores the reciprocal pathophysiology of the HBA, wherein dysfunction in either organ system can initiate cascading disruptions-compromising homeostatic regulation, emotional processing, and higher-order cognition through shared neural, endocrine, and inflammatory pathways (80). Together, these findings emphasize the intricate relationship between the heart and brain, mediated by neurovisceral pathways. Understanding these dynamics not only deepens our knowledge of emotional and cognitive regulation but also opens new avenues for therapeutic interventions targeting the vagus nerve and autonomic system.

Cardiac interoceptive signals, particularly those mediated by baroreceptors, play a crucial role in shaping emotional and cognitive responses (81). Baroreceptors, activated during systolic contraction, relay information about the strength and timing of heartbeats to the brain.

This process helps coordinate the brain's sympathetic and parasympathetic responses, creating a structured temporal framework for regulating cognition and emotion (82). Studies show that individuals with higher cardiac interoceptive accuracy tend to exhibit enhanced emotional awareness and cognitive flexibility, particularly in decision-making tasks (83, 84). Recent research has deepened our understanding of the neurovisceral dynamics underlying the heart-brain interplay in cognition and emotional regulation.

A notable preclinical study demonstrated that an elevated HR can significantly influence emotional behavior, particularly in high-risk situations. In this study, mice with a normal HR exhibited reduced anxiety-like behaviors, as evidenced by their increased preference for the open arm of a maze. However, when the HR was experimentally increased to 900 beats per minute or higher, the mice displayed heightened anxiety, preferring to remain in the enclosed, safer sections of the maze.

These findings underscore the bidirectional relationship between physical states, such as HR, and emotional responses, highlighting how changes in cardiac activity can directly modulate emotional behavior (85). This aligns with the concept of NVI,

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

where the heart and brain dynamically interact to shape both emotional and cognitive processes.

Regarding the potential role of cardiovascular signals in cognitive and emotional processing, numerous studies suggest that these brain functions are influenced by the timing of external stimuli relative to the phase of the cardiac cycle. For instance, increased baroreceptor activity during the systolic phase of the cardiac cycle has been hypothesized to inhibit cortical neuronal activity. Supporting this hypothesis, a study conducted on healthy volunteers demonstrated that the perception of electrical nociceptive stimuli is significantly reduced when these stimuli coincide with periods of heightened baroreceptor activity (78). Similarly, research on human adults has shown that neurophysiological pain responses are diminished during systole, a phase characterized by high baroreceptor activity, compared to diastole, where such stimulation is minimal (86).

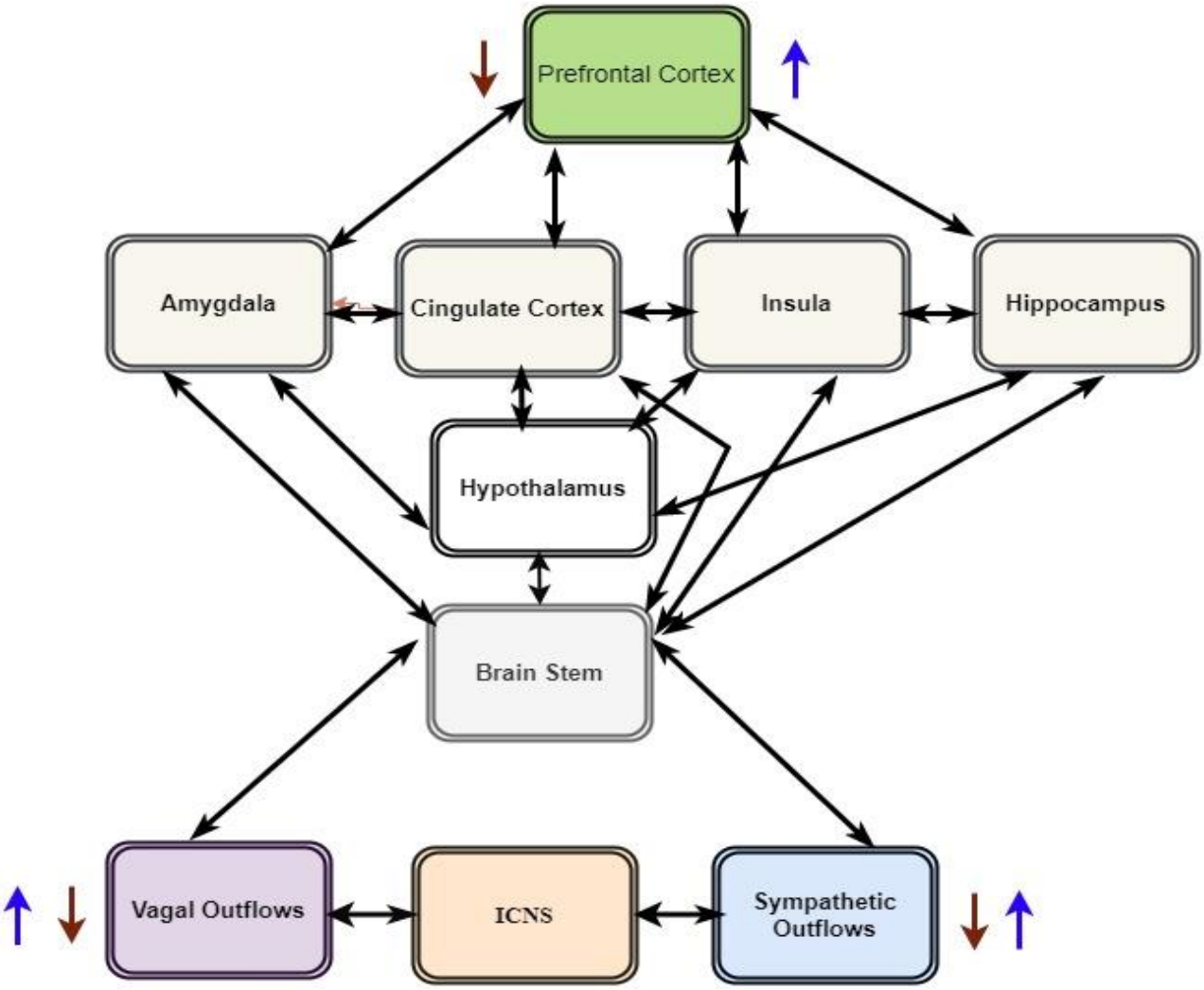

Figure 2. This figure illustrates the bidirectional communication between the peripheral autonomic nervous system (ANS) in the heart and central cortical and subcortical regions involved in processing afferent cardiovascular signals and neurovisceral integration (NVI). These signals are integrated in key brain regions such as the insula, anterior cingulate cortex, and prefrontal cortex, which regulate emotional processing, decision-making, and cognitive functions. The dynamic interplay highlights the brain-heart interactions essential for neurophysiological regulation and NVI. Notably, these same cortical and subcortical regions involved in regulating cardiovascular functions are also critically engaged in modulating emotional resilience, attention, self-awareness, and cognition. ICNS: intrinsic cardiac nervous system.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

Empirical evidence highlights those individuals with higher cardiac interoceptive accuracy—the ability to precisely perceive their own heartbeats-exhibit enhanced emotional awareness and cognitive flexibility, particularly in decision-making tasks (12, 87, 88). These findings emphasize the critical role of cardiac signals in shaping both emotional and cognitive responses, offering further support for the interoceptive theory within the framework of BHI. Notably, baroreceptor signaling has been shown to directly influence the amygdala and related brain regions involved in emotional processing (42, 78), underscoring the active role of the heart in modulating brain function and reinforcing the dynamic interplay central to neurovisceral dynamics. It appears that the performance of cognitive and emotional functions in the brain depends significantly on interoception, which refers to awareness of internal body signals such as heartbeats. Recent research has demonstrated that the perception of external stimuli is influenced by interoceptive signals received from the heart. For instance, when the heart sends stronger systolic signals to the brain, the brain's ability to process external information decreases.

Conversely, when weaker diastolic signals reach the brain, the processing of external stimuli occurs more effectively. These findings indicate that the brain dynamically shifts its focus between internal signals, such as heartbeats, and external inputs, highlighting the integration of cardio-visual signals in shaping human self-awareness and cortical processing (89, 90). This temporal correlation between heart responses and external stimuli underscores the brain's reliance on interoceptive feedback for optimizing cognitive and emotional performance. Recent research has elucidated the precise temporal dynamics through which cardiac interoceptive signals influence social judgments. The findings demonstrate a phase-dependent modulation of trust perception, with faces presented during cardiac systole being both selected less frequently and rated as significantly less trustworthy compared to those displayed during diastole (91).

This selective systolic-phase effect suggests that arterial baroreceptor activation during myocardial contraction may play a privileged role in biasing social cognition through interoceptive-affective integration. These findings shed light on the role of phasic interoceptive information in social perception and decision-making, offering a mechanistic understanding of how visceroception contributes to these processes**.** The interplay between cardiovascular activity and sensory processing is evident in tactile perception, where detection accuracy fluctuates throughout the cardiac cycle. Studies have shown that tactile detection is most accurate during the diastolic phase, and least accurate during systole (87). Interestingly, these cardiac cycle-related variations do not affect the motor component of tactile tasks, suggesting that sensory and motor systems are differentially influenced by cardiovascular dynamics (88). These findings highlight the intricate relationship between the heart and brain in modulating sensory perception, further emphasizing the importance of neurovisceral integration in understanding how physiological states shape cognitive and perceptual processes.

At the core of NVI lies HRV, a dynamic marker of ANS function that reflects the intricate balance between sympathetic and parasympathetic activity. HRV serves as a critical indicator of the body’s adaptive capacity and plays a pivotal role in shaping cognitive and emotional processes. The NVI framework posits that the brain and heart are intricately connected, with the heart actively influencing emotional regulation, behavior, and cognition (12-14). This model highlights the dynamic interaction between the CNS and the ANS, emphasizing the heart's active role in shaping emotional and cognitive states. A study using VNS in adolescents demonstrated increased HRV and PFC oxygenation, alongside decreased heart rate (92). These findings support the NVI, showing that VNS enhances autonomic regulation and PFC activity, underscoring the BHI. This suggests VNS as a potential tool for modulating neurovisceral integration and improving adaptive responses.

A key component of this interaction is HRV, which serves as a marker of effective heart-brain communication. Higher HRV is consistently associated with better emotional regulation, lower anxiety, and improved cognitive performance, especially in tasks requiring attention and decision-making (20-22). Conversely, altered autonomic control can lead to fluctuations in HRV, which have been linked to cognitive performance. Lower HRV is associated with poorer cognitive outcomes and emotional dysregulation (51). Research indicates that individuals with cardiovascular diseases frequently experience neurocognitive disorders. For example, a systematic review found that patients with HF

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

exhibited a higher prevalence of cognitive impairment compared to those without cardiovascular issues (53).

The NVI also underscores the relationship between HRV and executive cognitive functions, mediated by brain regions such as the prefrontal cortex and amygdala (92, 93). For instance, a study involving healthy participants found that higher resting HRV was associated with improved attention maintenance during cognitive tasks (94). Additionally, changes in attention during cognitive or emotional activities can influence autonomic activity (95), further emphasizing the bidirectional nature of BHI. Afferent signals from the heart, transmitted via baroreceptors, play a crucial role in this process by modulating brain regions involved in emotional control, decision-making, and cognitive functions such as memory and attention (12, 26). The schematic representation of the heart's role in the BHA and its impact on NVI, as well as cognitive and emotional performance, is illustrated in Figure 3.

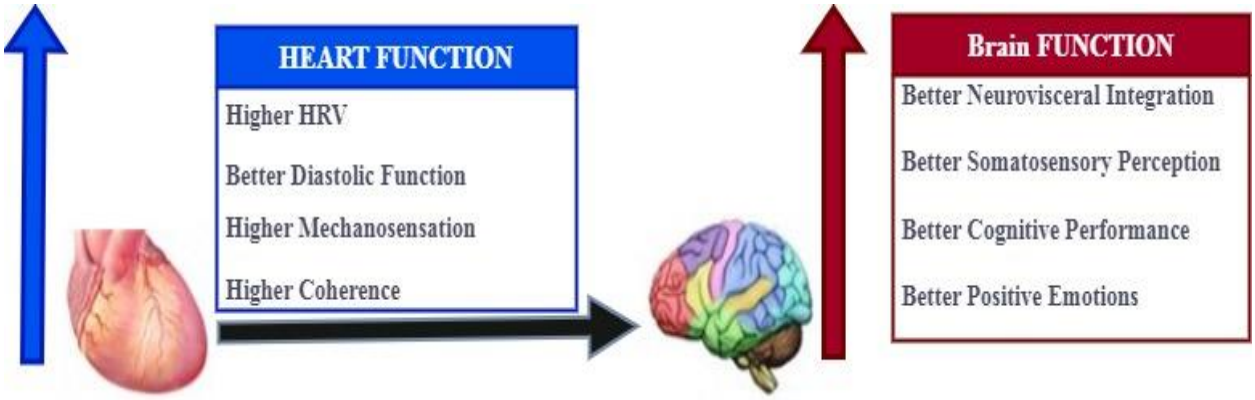

Figure 3. Schematic Representation of the role of heart in Brain- Heart Axis (BHA) and Its Impact on Neurovisceral Integration, Cognitive and Emotional Performance: This figure illustrates the bidirectional communication between the heart and brain, highlighting how improved heart function enhances neurovisceral integration and promotes better cognitive and emotional outcomes. Optimal heart function, characterized by balanced autonomic regulation and higher heart rate variability (HRV), supports efficient transmission of cardiac signals to the brain via afferent pathways, including the vagus nerve and baroreceptors.

Neuromodulatory techniques, including VNS and spinal cord stimulation, offer promising clinical interventions for enhancing cognitive and emotional regulation. These methods may improve cardiac autonomic function and increase cerebral perfusion, benefiting patients with conditions such as HF (52, 96, 97). The vagus nerve serves as a critical link in the HBA, facilitating bidirectional communication and playing a vital role in regulating cognitive and emotional processes. Vagal tone, reflected in HRV, is a key indicator of emotional experience and regulatory capacity. Interventions such as HRV biofeedback and VNS have demonstrated potential to enhance vagal tone, thereby improving emotional well-being and stress resilience (21). As a biomarker of NVI, HRV offers unique insights into the BHI, highlighting its therapeutic potential for addressing emotional and cognitive disorders.

Neurodegenerative diseases, such as Alzheimer's disease (AD), highlight the significance of HRV in NVI under pathological conditions. Reduced HRV is linked to impaired integrity of the central autonomic network, emphasizing its role in both physiological and psychological health (98). HRV is also associated with the adequacy of emotional performance and the accuracy of the related neural network. Findings from a cohort study showed that the tendency toward agitation increases in patients with a definitive clinical diagnosis of AD, and a positive correlation was found in this regard. Changes in HRV were associated with a tenfold increase in the occurrence of agitation and an increase in its score (22). Higher HRV supports self-regulatory efficiency, which is critical for emotional and cognitive functioning, while lower HRV is associated with neuropsychiatric disorders like depression and agitation in dementia (21, 22).

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

Brain structures involved in self-regulation, such as the frontal cortex, also influence autonomic centers in the brainstem, underscoring the interplay between cardiovascular signals and cognitive-emotional performance. On the other hand, the hippocampus, one of the structures affected early in AD, is highly vulnerable to hypoxia and inflammatory factors (99, 100). In their study on hippocampal changes in patients with ischemic heart disease, Niu et al. BHI. Haslacher et al(2022) demonstrated that these patients experience various alterations in brain regions involved in cognitive processing, including the hippocampus. Consequently, the study concluded that the decline in cognitive abilities observed in patients with ischemic heart disease may be related to impairments in cortical neuronal connectivity (101).

Notably, in the reciprocal interaction of pathological changes within the HBA, neurodegenerative diseases such as AD are associated with alterations in the ICNS. Due to the progressive decline in neurotrophins, a severe reduction in myocardial innervation occurs, similar to what is observed in metabolic heart diseases such as HF (31). In summary, HRV serves as a critical measure of autonomic balance and neurovisceral integration, reflecting the dynamic interplay between the heart and brain. Its role in emotional regulation, cognitive function, and overall physiological resilience makes it a valuable target for understanding and improving mental and cardiovascular health.

Coherence and Cross Frequency Coupling: Unveiling the Heart-Brain Synchrony in Emotion and Cognition

The intricate interplay between the heart and brain extends beyond traditional measures like HRV to more sophisticated mechanisms such as cross-frequency coupling (CFC). CFC refers to the synchronization of neural oscillations at different frequencies, enabling efficient communication between brain regions and between the brain and heart. This dynamic process is essential for emotional regulation, cognitive function, and overall NVI (Figure 4). By exploring the role of CFC in BHI, we can gain deeper insights into how these systems work together to support adaptive behavior and resilience.

CFC involves the synchronization of neural oscillations at different frequencies, such as low-frequency heart rhythms interacting with higher-frequency brain waves. This coupling facilitates coordination between the cardiovascular and nervous systems, contributing to cognitive and emotional processes. In the brain, CFC typically involves the synchronization of low-frequency rhythms (e.g., theta or delta waves) with higher-frequency activity (e.g., gamma waves). The most studied form of CFC is phase-amplitude coupling (PAC), where the phase of a low-frequency rhythm modulates the amplitude of a high-frequency oscillation. PAC is believed to facilitate neural communication across distant brain regions (102) and plays a critical role in tasks such as memory encoding and decision-making (103).

In line with the importance of heart-brain coherence, a study conducted on mice demonstrated that modulations in the excitability of neurons in the hippocampus and PFC occur in a cardiac cycle-dependent manner. The study concluded that cardiac pulsations are detected by mechanosensitive neurons in the brain and, through the induction of arousal states, influence interoception, emotional responses, and cognitive processes (104). Therefore, neuronal modulations in the brain during each cardiac cycle, in addition to vagal pathways, are at least partially mediated by pressure pulsation waves.

This synchronization extends beyond brain regions to include interactions between heart rhythms and brain oscillations, particularly in the theta and delta frequency ranges. For example, research has demonstrated coupling between cardiac cycles and theta oscillations during states of general anesthesia, with the heart influencing the brain's theta waves (105). Studies have highlighted the importance of delta oscillations in BHI. Haslacher et al. (2024) demonstrated that heartbeat perception is closely linked to delta phase synchrony in the brain (106). This finding underscore how cardiac signals are transformed into meaningful neural representations, thereby enhancing the accuracy of NVI and optimizing the physiological regulation of emotion and cognition through improved BHI.Another key aspect of BHI is heartbeat-evoked responses (HERs) or heartbeat-evoked potentials (HEPs). HERs are cortical electrical responses synchronized with the R-peaks of the ECG signal and reflect how the brain processes cardiac input (22, 107). Initially attributed solely to baroreceptor activity, HERs are now understood to also arise from other stimuli, such as stroke volume changes (108).

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

These responses influence perception, self-awareness, and emotional processing (109, 110).

HERs have been linked to interoceptive awareness and cognitive functions, such as visual perception and attention during tasks (111). For instance, auditory stimuli presented during diastole elicit stronger HER amplitudes compared to systole, suggesting shared attentional resources for interoceptive and exteroceptive processing (112).

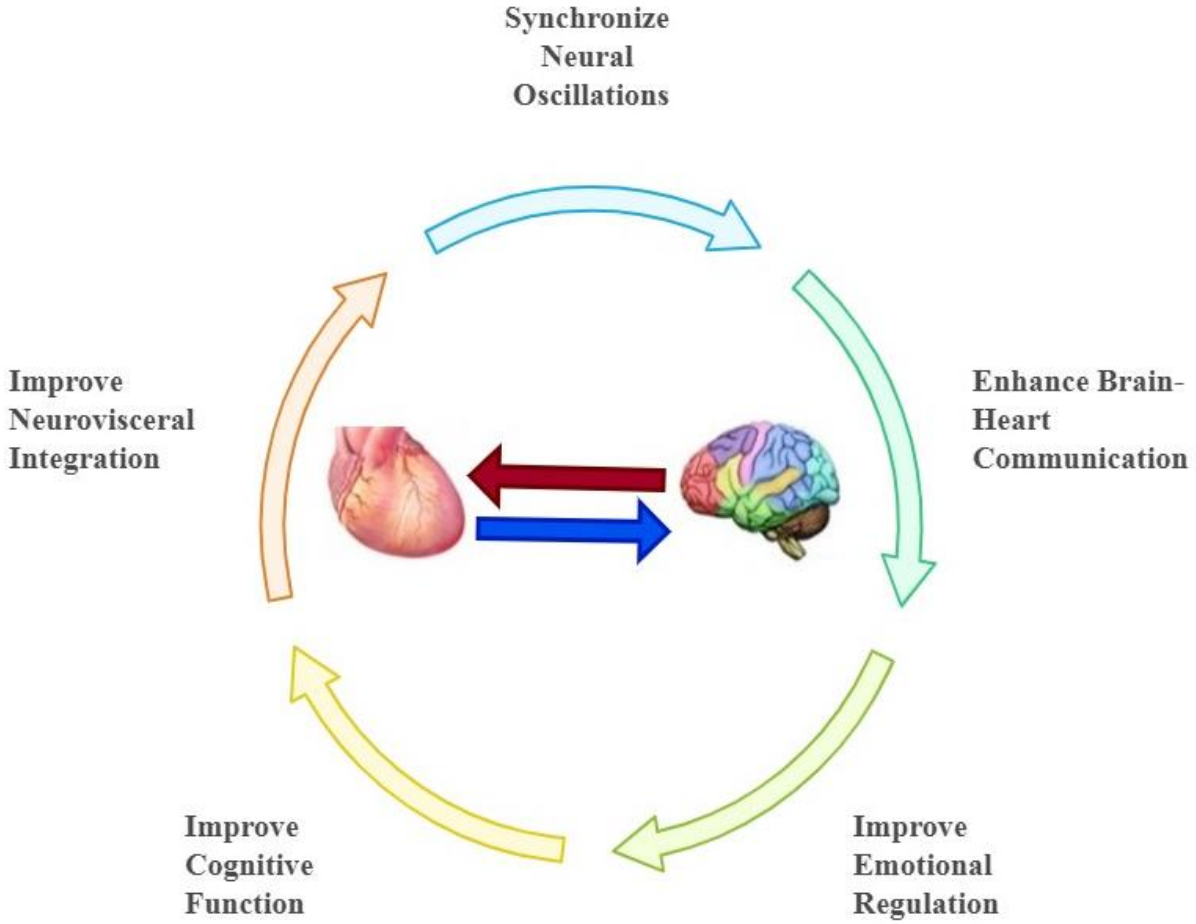

Figure 4. The Role of Cross-Frequency Coupling (CFC) in Neurovisceral Integration (NVI), Cognition, and Emotional Regulation. This figure illustrates the role of CFC in facilitating NVI and its impact on cognitive and emotional processes. CFC involves the synchronization of low-frequency oscillations, such as heart rhythms, with higher-frequency brain waves, enabling dynamic communication between the cardiovascular system and the brain. This mechanism supports neural communication across distant brain regions and enhances cognitive functions such as memory encoding, decision-making, and emotional regulation.

The vagus nerve plays a pivotal role in mediating these interactions. As a complex conduit connecting the viscera to the CNS, it transmits signals to key regions like the insula, which regulates interoception and bodily homeostasis (36).

Studies on VNS show that VNS alters HER amplitudes in brain regions such as the insula, prefrontal cortex, and somatosensory cortex (113), highlighting its potential as a therapeutic target**.** Abnormalities in CFC have been implicated in various neurological and psychiatric conditions (114).

Dysregulation of PAC disrupts the brain's oscillatory dynamics, impairing cognitive and emotional regulation (115). Conversely, practices that enhance heart-brain coherence, such as meditation, have been shown to increase HRV and EEG alpha activity, promoting relaxation and mental clarity (116). Higher HRV is associated with better emotional

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

regulation and cognitive performance, underscoring the importance of autonomic balance in maintaining physiological resilience (22).

Pressure pulsations from the heart also influence brain activity. Each heartbeat generates a pulsatile wave that affects cerebral blood flow and intracranial pressure. . Recent studies have revealed that these pulsations, detected by mechanosensitive ion channels like Piezo2, are not mere noise but actively shape neuronal responses.

For example, pyramidal neurons in the neocortex and hippocampus respond directly to pressure pulsations, linking cardiovascular activity to sensory and cognitive processing (36, 117). This interaction underscores the intricate relationship between heart pulsatility and brain function, particularly in regions like the hippocampus, which are highly sensitive to perfusion changes (118). The detection of pulse pressure in the brain during each cardiac cycle may suggest that, in addition to its well-known hemodynamic roles, this mechanism could also serve new computational function in the brain. However, its significance in humans remains unknown.

In a groundbreaking experiment, Al et al. (2020) demonstrated that cardiac signals significantly modulate cortical and corticospinal excitability. Neuronal excitability peaks during systole and increases with stronger heartbeat pulsations, providing further evidence of the heart's influence on cognitive functions (4). These findings align with the binary hierarchical model of brain-body interactions, which posits that feedback signals from peripheral organs, including the heart, contribute to neural oscillations and consciousness (14, 119).

In summary, CFC provides a framework for understanding the dynamic interplay between heart and brain rhythms. By synchronizing low-frequency heart signals with higher-frequency brain waves, CFC supports NVI accuracy, cognitive performance, emotional stability, and overall physiological resilience. These insights pave the way for innovative approaches to enhancing psychological well-being and addressing cardiovascular and neurological conditions. By optimizing this interplay, CFC contributes to better emotional regulation, and adaptive responses to environmental demands. Thus, the integration of cardiac and neural oscillations through CFC not only supports the accuracy of NVI but also underpins the dynamic interplay between heart and brain in health and disease.

Discussion

To fully appreciate the intricate interplay between the heart and brain, it is essential to consider not only the physiological mechanisms underlying this communication but also their broader implications for emotional regulation, cognitive performance, and clinical applications. Understanding the mechanisms underlying BHDs and HBDs is crucial for developing effective therapeutic strategies that address both neurological and cardiac health. The intricate interplay between the heart and brain, mediated by mechanisms such as CFC, HRV, and HERs, provides a robust framework for understanding their role in cognitive, emotional, and physiological health. By translating these physiological insights into practical applications, we can develop innovative therapeutic interventions and diagnostic tools that address both CV and mental health challenges.

The study by Catrambone et al. (2023) deepens our understanding of the BHI by examining responses to cold stress tests. These tests elicit a range of reactions, including somatic sensations (e.g., pain), emotional responses, and motor control, mediated by both the ANS and CNS. Key brain regions involved in cardiac autonomic control—such as the insula, cingulate cortex, amygdala, and hippocampus—are activated during cold stimulation. The initial response originates in the heart's afferent pathways and propagates to the brain, followed by descending efferent responses (6), resembling high-arousal states like emotional elicitation (76).

By integrating modulations in HERs, delta and gamma frequency bands, and highlighting the CAN as a CNS-ANS link, the study underscores the significance of the brain-heart axis (6). Furthermore, mechanosensitive pyramidal neurons are proposed to act as dynamic receptors for cortical responses to pressure pulsations (104, 119). These findings collectively emphasize the intricate relationship between the heart and brain in regulating emotions and physiology, particularly under stress and arousal conditions.

From a practical standpoint, CFC offers promising avenues for both therapeutic and diagnostic applications. Non-invasive neuromodulation

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

techniques, such as transcranial magnetic stimulation (TMS) or VNS, can target specific frequency bands to enhance CFC. For instance, VNS has been shown to improve cognitive functions like memory and attention by strengthening heart-brain coherence (53, 72, 96). Similarly, mindfulness meditation and biofeedback training increase HRV and enhance CFC, leading to improved emotional regulation and mental clarity (116). Abnormalities in CFC have been linked to neurological and psychiatric disorders, such as Alzheimer's disease (120) and anxiety (114). Measuring CFC using EEG or MEG could serve as a biomarker for early detection of these conditions. Reduced PAC between delta and gamma oscillations, for example, may indicate impaired neural communication in patients with cognitive decline, providing a non-invasive diagnostic tool. Similarly, HERs offer valuable insights for both therapeutic and diagnostic applications. VNS modulates HER amplitudes in brain regions like the insula and prefrontal cortex, improving emotional regulation and cognitive performance (113).

Mindfulness-based interventions enhance interoceptive awareness by increasing HER amplitudes, correlating with better attention and emotional regulation (112). Also, HERs can serve as a neural metric for evaluating interoceptive processing and its role in mental health. Reduced HER amplitudes have been observed in patients with depression and anxiety, suggesting impaired integration of cardiac signals into brain function (110). Advanced EEG or MEG techniques could measure HERs as part of a comprehensive assessment of emotional and cognitive health. Each heartbeat generates pressure pulsations that are detected by mechanosensitive ion channels, such as Piezo2, in neurons of the neocortex and hippocampus (36).

These channels play a crucial role in converting mechanical signals into neuronal activity, thereby influencing brain function. However, repetitive exposure to pulsatile pressure can subtly alter brain activity, with potential implications for sensory processing and cognitive performance. This highlights the importance of understanding how cardiovascular dynamics impact neural function**.**

Building on this insight, managing arterial stiffness and PWV through lifestyle modifications—such as regular exercise, a healthy diet and pharmacological interventions could help mitigate the negative effects of excessive pulsatility on brain function (121). Furthermore, targeted neuroprotection strategies that leverage the role of Piezo2 channels may offer promising avenues for safeguarding against pulsatility-induced brain damage, particularly in conditions like dementia. By addressing the root causes of excessive pressure pulsations and their downstream effects, these approaches hold significant therapeutic potential, paving the way for innovative strategies to preserve both cardiovascular and cognitive health. By leveraging physiological mechanisms like CFC, HRV, and HERs, we can bridge the gap between cardiovascular and mental health, offering innovative solutions for improving patient outcomes. These approaches not only deepen our understanding of BHI but also pave the way for practical applications that enhance cognitive and emotional well-being across a wide range of conditions. As research continues to unravel the complexities of this axis, the potential for transformative interventions in healthcare becomes increasingly evident.

While this article provides valuable insights into BHI, it is important to acknowledge several limitations that highlight areas for future research. First, emotional and cognitive processes are influenced by a wide range of factors beyond BHI, including environmental, psychological, and genetic elements, which complicates the isolation of the BHA in research studies. Additionally, while the role of other organs in these interactions is significant, it was not explored in this study, leaving gaps in our understanding of the broader physiological network. Furthermore, the article does not extensively address how individual differences—such as age, gender, and baseline health status—might influence BHI, which could limit the generalizability of the findings. Moreover, many of the findings discussed are based on correlational studies rather than causal experiments, making it challenging to establish definitive relationships between heart-brain dynamics and their functional outcomes. Finally, some mechanisms, such as the exact physiological pathways underlying HERs and their neural correlates, remain incompletely understood, underscoring the need for further mechanistic investigations. Together, these limitations highlight the complexity of heart-brain interactions and the importance of addressing these gaps in future research**.**

In conclusion, the intricate interplay between the heart and brain, mediated by mechanisms such as CFC,

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

HRV, and HERs, underscores the profound connection between cardiovascular and neural systems in shaping cognitive, emotional, and physiological processes. This bidirectional communication not only facilitates the integration of internal bodily signals with external sensory information but also plays a critical role in maintaining homeostasis, NVI, emotional regulation, and cognitive performance. The findings discussed in this review highlight the potential of leveraging these mechanisms for therapeutic interventions, including biofeedback, VNS, and mindfulness practices, to enhance mental health and treat neuropsychiatric and cardiovascular conditions**.**

Despite these challenges, the growing body of research on BHI offers promising avenues for advancing healthcare. By integrating electrophysiological, neurovisceral, and mechanosensory mechanisms, we can develop personalized interventions that target autonomic regulation, cognitive function, and emotional well-being. Future studies should focus on addressing existing limitations through standardized measurement protocols, and large-scale clinical trials to validate therapeutic applications. Ultimately, bridging the gap between cardiovascular and mental health through a deeper understanding of the heart-brain axis holds transformative potential for improving patient outcomes and fostering holistic well-being**.**

In summary, the heart is far more than a passive organ—it is an active participant in the brain's NVI, regulation of emotion, cognition, and consciousness. As research continues to unravel the complexities of this dynamic relationship, it becomes increasingly clear that interventions targeting heart-brain coherence could revolutionize approaches to psychological and physiological health, paving the way for innovative treatments that address both mind and body.

Acknowledgment

This work was supported by a grant (No. 724137180) from the Deputy of Research and Technology, Babol University of Medical Sciences, Babol, Iran

References

1. Zampieri F, Thiene G, Zanatta A. Cardiocentrism in ancient medicines. Int J Cardiol Heart Vasc. 2023;48:101261.
2. Smith CU. Cardiocentric neurophysiology: the persistence of a delusion. J Hist Neurosci. 2013;22(1):6-13.
3. Barrett LF, Simmons WK. Interoceptive predictions in the brain. Nat Rev Neurosci. 2015;16(7):419-29.
4. Al E, Iliopoulos F, Forschack N, et al. Heart-brain interactions shape somatosensory perception and evoked potentials. Proc Natl Acad Sci U S A. 2020;117(19):10575-84.
5. Abohashem S, Grewal SS, Tawakol A, et al. Radionuclide Imaging of Heart-Brain Connections. Cardiol Clin. 2023;41(2):267-75.
6. Catrambone V, Valenza G. Complex Brain-Heart Mapping in Mental and Physical Stress. IEEE J Transl Eng Health Med. 2023;11:495-504.
7. Fetterman AK, Robinson MD. Do you use your head or follow your heart? Self-location predicts personality, emotion, decision making, and performance. J Pers Soc Psychol. 2013;105(2):316-34.
8. Thayer JF, Ahs F, Fredrikson M, et al. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36(2):747-56.
9. Silvani A, Calandra-Buonaura G, Dampney RA, et al. Brain-heart interactions: physiology and clinical implications. Philos Trans A Math Phys Eng Sci. 2016;374(2067).
10. Catrambone V, Barbieri R, Wendt H, et al. Functional brain-heart interplay extends to the multifractal domain. Philos Trans A Math Phys Eng Sci. 2021;379(2212):20200260.
11. Małkiewicz MA, Malinowski KS, Grzywińska M, et al. Heart Rate Variability and Interoception in Periodic Limb Movements in Sleep: Interference with Psychiatric Disorders? J Clin Med. 2024;13(20).
12. Azzalini D, Rebollo I, Tallon-Baudry C. Visceral Signals Shape Brain Dynamics and Cognition. Trends Cogn Sci. 2019;23(6):488-509.
13. Herman AM, Tsakiris M. The impact of cardiac afferent signaling and interoceptive abilities on passive information sampling. Int J Psychophysiol. 2021;162:104-11.
14. Smith R, Thayer JF, Khalsa SS, et al. The hierarchical basis of neurovisceral integration. Neurosci Biobehav Rev. 2017;75:274-96.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

15. Malandrone F, Catrambone V, Carletto S, et al. Restoring bottom-up communication in brain-heart interplay after trauma-focused psychotherapy in breast cancer patients with post-traumatic stress disorder. J Affect Disord. 2024;351:143-50.
16. Bonaz B, Lane RD, Oshinsky ML, et al. Diseases, Disorders, and Comorbidities of Interoception. Trends Neurosci. 2021;44(1):39-51.
17. Khalsa SS, Adolphs R, Cameron OG, et al. Interoception and Mental Health: A Roadmap. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018;3(6):501-13.
18. Dolphin H, Dukelow T, Finucane C, et al. "The Wandering Nerve Linking Heart and Mind" – The Complementary Role of Transcutaneous Vagus Nerve Stimulation in Modulating Neuro-Cardiovascular and Cognitive Performance. Frontiers in Neuroscience. 2022;Volume 16 - 2022.
19. Garfinkel SN, Critchley HD. Threat and the Body: How the Heart Supports Fear Processing. Trends in Cognitive Sciences. 2016;20(1):34-46.
20. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017;5:258.
21. Reynard A, Gevirtz R, Berlow R, et al. Heart rate variability as a marker of self-regulation. Appl Psychophysiol Biofeedback. 2011;36(3):209-15.
22. Huang Y, Xie M, Liu Y, et al. Brain State Relays Self-Processing and Heartbeat-Evoked Cortical Responses. Brain Sciences. 2023;13:832.
23. Pinna T, Edwards DJ. A Systematic Review of Associations Between Interoception, Vagal Tone, and Emotional Regulation: Potential Applications for Mental Health, Wellbeing, Psychological Flexibility, and Chronic Conditions. Front Psychol. 2020;11:1792.
24. Brewer R, Murphy J, Bird G. Atypical interoception as a common risk factor for psychopathology: A review. Neurosci Biobehav Rev. 2021;130:470-508.
25. Lischke A, Pahnke R, Mau-Moeller A, et al. Heart Rate Variability Modulates Interoceptive Accuracy. Front Neurosci. 2020;14:612445.
26. Simats A, Sager HB, Liesz A. Heart-brain axis in health and disease: role of innate and adaptive immunity. Cardiovasc Res. 2025;120(18):2325-35.
27. Gronda E, Dusi V, D'Elia E, et al. Sympathetic activation in heart failure(). Eur Heart J Suppl. 2022;24(Suppl E):E4-e11.
28. Cameron OG. Visceral brain-body information transfer. Neuroimage. 2009;47(3):787-94.
29. van Weperen VYH, Vaseghi M. Cardiac vagal afferent neurotransmission in health and disease: review and knowledge gaps. Front Neurosci. 2023;17:1192188.
30. Manolis AA, Manolis TA, Manolis AS. Neurohumoral Activation in Heart Failure. Int J Mol Sci. 2023;24(20).
31. Elia A, Fossati S. Autonomic nervous system and cardiac neuro-signaling pathway modulation in cardiovascular disorders and Alzheimer's disease. Front Physiol. 2023;14:1060666.
32. Zanos TP, Silverman HA, Levy T, et al. Identification of cytokine-specific sensory neural signals by decoding murine vagus nerve activity. Proc Natl Acad Sci U S A. 2018;115(21):E4843-e52.
33. Müller SJ, Teckentrup V, Rebollo I, et al. Vagus nerve stimulation increases stomach-brain coupling via a vagal afferent pathway. Brain Stimul. 2022;15(5):1279-89.
34. Forstenpointner J, Maallo AMS, Elman I, et al. The solitary nucleus connectivity to key autonomic regions in humans. Eur J Neurosci. 2022;56(2):3938-66.
35. Zaccaro A, Della Penna F, Mussini E, et al. Attention to cardiac sensations enhances the heartbeat-evoked potential during exhalation. iScience. 2024;27(4):109586.
36. Engelen T, Solcà M, Tallon-Baudry C. Interoceptive rhythms in the brain. Nat Neurosci. 2023;26(10):1670-84.
37. Fedele L, Brand T. The Intrinsic Cardiac Nervous System and Its Role in Cardiac Pacemaking and Conduction. J Cardiovasc Dev Dis. 2020;7(4).
38. Zandstra TE, Notenboom RGE, Wink J, et al. Asymmetry and Heterogeneity: Part and Parcel in Cardiac Autonomic Innervation and Function. Front Physiol. 2021;12:665298.
39. Pius-Sadowska E, Machaliński B. Pleiotropic activity of nerve growth factor in regulating cardiac functions and counteracting pathogenesis. ESC Heart Fail. 2021;8(2):974-87.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

40. Yarkoni M, Rehman WU, Bajwa A, et al. Ganglionated Plexus Ablation Procedures to Treat Vasovagal Syncope. Int J Mol Sci. 2023;24(17).
41. Chen WG, Schloesser D, Arensdorf AM, et al. The Emerging Science of Interoception: Sensing, Integrating, Interpreting, and Regulating Signals within the Self. Trends Neurosci. 2021;44(1):3-16.
42. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev. 2009;33(2):81-8.
43. Koenig J. Neurovisceral regulatory circuits of affective resilience in youth. Psychophysiology. 2020;57(5):e13568.
44. Ma L, Keen LD, 2nd, Steinberg JL, et al. Relationship between central autonomic effective connectivity and heart rate variability: A Resting-state fMRI dynamic causal modeling study. Neuroimage. 2024;300:120869.
45. Sposato LA, Hilz MJ, Aspberg S, et al. Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76(23):2768-85.
46. Hadaya J, Ardell JL. Autonomic Modulation for Cardiovascular Disease. Front Physiol. 2020;11:617459.
47. Fernandez SF, Canty JM, Jr. Adrenergic and cholinergic plasticity in heart failure. Circ Res. 2015;116(10):1639-42.
48. Alshami AM. Pain: Is It All in the Brain or the Heart? Curr Pain Headache Rep. 2019;23(12):88.
49. Frangos E, Richards EA, Bushnell MC. Do the psychological effects of vagus nerve stimulation partially mediate vagal pain modulation? Neurobiol Pain. 2017;1:37-45.
50. Suarez-Roca H, Klinger RY, Podgoreanu MV, et al. Contribution of Baroreceptor Function to Pain Perception and Perioperative Outcomes. Anesthesiology. 2019;130(4):634-50.
51. Forte G, Troisi G, Pazzaglia M, et al. Heart Rate Variability and Pain: A Systematic Review. Brain Sci. 2022;12(2).
52. Wang W, Li R, Li C, et al. Advances in VNS efficiency and mechanisms of action on cognitive functions. Front Physiol. 2024;15:1452490.
53. Mertens A, Gadeyne S, Lescrauwaet E, et al. The potential of invasive and non-invasive vagus nerve stimulation to improve verbal memory performance in epilepsy patients. Sci Rep. 2022;12(1):1984.
54. Liu J, Xiao G, Liang Y, et al. Heart–brain interaction in cardiogenic dementia: pathophysiology and therapeutic potential. Frontiers in Cardiovascular Medicine. 2024;Volume 11 - 2024.
55. Wang J, Su E, Wang H, et al. Traumatic Brain Injury Leads to Accelerated Atherosclerosis in Apolipoprotein E Deficient Mice. Scientific Reports. 2018;8(1):5639.
56. Izzy S, Grashow R, Radmanesh F, et al. Long-term risk of cardiovascular disease after traumatic brain injury: screening and prevention. Lancet Neurol. 2023;22(10):959-70.
57. Yavuz AY, Baskurt O, Kurtulus Y, et al. Prognostic significance of prolonged corrected QT interval in cerebral contusion. Indian J Med Res. 2023;158(2):175-81.
58. Gelosa P, Castiglioni L, Rzemieniec J, et al. Cerebral derailment after myocardial infarct: mechanisms and effects of the signaling from the ischemic heart to brain. J Mol Med (Berl). 2022;100(1):23-41.
59. Huang CH, Yang CT, Chang CC. Traumatic brain injury and risk of heart failure and coronary heart disease: A nationwide population-based cohort study. PLoS One. 2023;18(12):e0295416.
60. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74(1):104-32.
61. Chen Z, Venkat P, Seyfried D, et al. Brain-Heart Interaction: Cardiac Complications After Stroke. Circ Res. 2017;121(4):451-68.
62. Poudel B, Karki P, Panta S, et al. Changes in Electrocardiogram in Patients With Spontaneous Subarachnoid Hemorrhage: A Cross-Sectional Study. Cureus. 2023;15(6):e40045.
63. Staehr C, Giblin JT, Gutiérrez-Jiménez E, et al. Neurovascular Uncoupling Is Linked to Microcirculatory Dysfunction in Regions Outside the Ischemic Core Following Ischemic Stroke. J Am Heart Assoc. 2023;12(11):e029527.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

64. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur Heart J. 2018;39(22):2032-46.
65. Toledo C, Lucero C, Andrade DC, et al. Cognitive impairment in heart failure is associated with altered Wnt signaling in the hippocampus. Aging (Albany NY). 2019;11(16):5924-42.
66. Aimo A, Castiglione V, Borrelli C, et al. Oxidative stress and inflammation in the evolution of heart failure: From pathophysiology to therapeutic strategies. Eur J Prev Cardiol. 2020;27(5):494-510.
67. Zera T, Moraes DJA, da Silva MP, et al. The Logic of Carotid Body Connectivity to the Brain. Physiology (Bethesda). 2019;34(4):264-82.
68. Scheitz JF, Sposato LA, Schulz-Menger J, et al. Stroke-Heart Syndrome: Recent Advances and Challenges. J Am Heart Assoc. 2022;11(17):e026528.
69. Candia-Rivera D, Catrambone V, Thayer JF, et al. Cardiac sympathetic-vagal activity initiates a functional brain-body response to emotional arousal. Proc Natl Acad Sci U S A. 2022;119(21):e2119599119.
70. Triposkiadis F, Karayannis G, Giamouzis G, et al. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol. 2009;54(19):1747-62.
71. Paci M, Cardellicchio P, Di Luzio P, et al. When the heart inhibits the brain: Cardiac phases modulate short-interval intracortical inhibition. iScience. 2024;27(3):109140.
72. Kong Y, Zhao K, Zeng D, et al. Effects of vagus nerve stimulation on cognitive function in patients with epilepsy: a systematic review and meta-analysis. Front Neurol. 2024;15:1332882.
73. Alagiakrishnan K, Mah D, Dyck JR, et al. Comparison of two commonly used clinical cognitive screening tests to diagnose mild cognitive impairment in heart failure with the golden standard European Consortium Criteria. Int J Cardiol. 2017;228:558-62.
74. Alvarez-Bueno C, Cunha PG, Martinez-Vizcaino V, et al. Arterial Stiffness and Cognition Among Adults: A Systematic Review and Meta-Analysis of Observational and Longitudinal Studies. J Am Heart Assoc. 2020;9(5):e014621.
75. Bailey TG, Klein T, Meneses AL, et al. Cerebrovascular function and its association with systemic artery function and stiffness in older adults with and without mild cognitive impairment. Eur J Appl Physiol. 2022;122(8):1843-56.
76. Candia-Rivera D. Brain-heart interactions in the neurobiology of consciousness. Curr Res Neurobiol. 2022;3:100050.
77. Goel M, Mittal A, Jain VR, et al. Integrative Functions of the Hypothalamus: Linking Cognition, Emotion and Physiology for Well-being and Adaptability. Ann Neurosci. 2025;32(2):128-42.
78. Gray MA, Minati L, Paoletti G, et al. Baroreceptor activation attenuates attentional effects on pain-evoked potentials. Pain. 2010;151(3):853-61.
79. Jin H, Li M, Jeong E, et al. A body–brain circuit that regulates body inflammatory responses. Nature. 2024;630(8017):695-703.
80. Gray MA, Taggart P, Sutton PM, et al. A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A. 2007;104(16):6818-23.
81. Schmitt CM, Schoen S. Interoception: A Multi-Sensory Foundation of Participation in Daily Life. Front Neurosci. 2022;16:875200.
82. Kim T, Kim SY, Agarwal V, et al. Cardiac-induced cerebral pulsatility, brain structure, and cognition in middle and older-aged adults. Neuroimage. 2021;233:117956.
83. Stephenson ES, Koltermann K, Zhou G, et al. Cardiac interoception in the museum: A novel measure of experience. Front Psychol. 2024;15:1385746.
84. Tan Y, Wang X, Blain SD, et al. Interoceptive attention facilitates emotion regulation strategy use. Int J Clin Health Psychol. 2023;23(1):100336.
85. Hsueh B, Chen R, Jo Y, et al. Cardiogenic control of affective behavioural state. Nature. 2023;615(7951):292-9.
86. Wilkinson M, McIntyre D, Edwards L. Electrocutaneous pain thresholds are higher during systole than diastole. Biol Psychol. 2013;94(1):71-3.
87. Grund M, Al E, Pabst M, et al. Respiration, Heartbeat, and Conscious Tactile Perception. J Neurosci. 2022;42(4):643-56.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

88. Kunzendorf S, Klotzsche F, Akbal M, et al. Active information sampling varies across the cardiac cycle. Psychophysiology. 2019;56(5):e13322.
89. Sel A, Azevedo RT, Tsakiris M. Heartfelt Self: Cardio-Visual Integration Affects Self-Face Recognition and Interoceptive Cortical Processing. Cereb Cortex. 2017;27(11):5144-55.
90. Ren Q, Marshall AC, Liu J, et al. Listen to your heart: Trade-off between cardiac interoceptive processing and visual exteroceptive processing. Neuroimage. 2024;299:120808.
91. Azevedo RT, von Mohr M, Tsakiris M. From the Viscera to First Impressions: Phase-Dependent Cardio-Visual Signals Bias the Perceived Trustworthiness of Faces. Psychol Sci. 2023;34(1):120-31.
92. Höper S, Kaess M, Koenig J. Prefrontal cortex oxygenation and autonomic nervous system activity under transcutaneous auricular vagus nerve stimulation in adolescents. Auton Neurosci. 2022;241:103008.
93. Quigley KS, Kanoski S, Grill WM, et al. Functions of Interoception: From Energy Regulation to Experience of the Self. Trends Neurosci. 2021;44(1):29-38.
94. Siennicka A, Quintana DS, Fedurek P, et al. Resting heart rate variability, attention and attention maintenance in young adults. Int J Psychophysiol. 2019;143:126-31.
95. Hall KJ, Van Ooteghem K, McIlroy WE. Emotional state as a modulator of autonomic and somatic nervous system activity in postural control: a review. Front Neurol. 2023;14:1188799.
96. De Smet S, Baeken C, Seminck N, et al. Non-invasive vagal nerve stimulation enhances cognitive emotion regulation. Behav Res Ther. 2021;145:103933.
97. Ashrafpour S, Ashrafpour M. Efficacy of spinal cord stimulation as an adjunctive therapy in heart failure: A systematic review. Neurophysiol Clin. 2024;54(3):102945.
98. Schütz J, Koglin U. A systematic review and meta-analysis of associations between self-regulation and morality in preschool and elementary school children. Current Psychology. 2023;42(26):22664-96.
99. Nazifi M, Ashrafpoor M, Oryan S, et al. Neurotoxic effects of high-dose piperine on hippocampal synaptic transmission and synaptic plasticity in a rat model of memory impairment. Neurotoxicology. 2020;79:200-8.
100. Nazifi M, Oryan S, Esfahani DE, et al. The functional effects of piperine and piperine plus donepezil on hippocampal synaptic plasticity impairment in rat model of Alzheimer's disease. Life Sci. 2021;265:118802.
101. Niu J, Zhang J, Yan J, et al. Neural Dysconnectivity in the Hippocampus Correlates With White Matter Lesions and Cognitive Measures in Patients With Coronary Artery Disease. Front Aging Neurosci. 2022;14:786253.
102. Munia TTK, Aviyente S. Time-Frequency Based Phase-Amplitude Coupling Measure For Neuronal Oscillations. Scientific Reports. 2019;9(1):12441.
103. Canolty RT, Knight RT. The functional role of cross-frequency coupling. Trends Cogn Sci. 2010;14(11):506-15.
104. Jammal Salameh L, Bitzenhofer SH, Hanganu-Opatz IL, et al. Blood pressure pulsations modulate central neuronal activity via mechanosensitive ion channels. Science. 2024;383(6682):eadk8511.
105. Stankovski T, Petkoski S, Raeder J, et al. Alterations in the coupling functions between cortical and cardio-respiratory oscillations due to anaesthesia with propofol and sevoflurane. Philos Trans A Math Phys Eng Sci. 2016;374(2067).
106. Haslacher D, Reber P, Cavallo A, et al. Heartbeat perception is causally linked to frontal delta oscillations2024.
107. Liu KY, Whitsel EA, Heiss G, et al. Heart rate variability and risk of agitation in Alzheimer's disease: the Atherosclerosis Risk in Communities Study. Brain Commun. 2023;5(6):fcad269.
108. Buot A, Azzalini D, Chaumon M, et al. Does stroke volume influence heartbeat evoked responses? Biol Psychol. 2021;165:108165.
109. Park HD, Bernasconi F, Salomon R, et al. Neural Sources and Underlying Mechanisms of Neural Responses to Heartbeats, and their Role in Bodily Self-consciousness: An Intracranial EEG Study. Cereb Cortex. 2018;28(7):2351-64.
110. Zhang Y, Zhang J, Xie M, et al. Dual interaction between heartbeat-evoked responses and stimuli. Neuroimage. 2023;266:119817.
111. Park S, Ha J, Kim L. Anti-Heartbeat-Evoked Potentials Performance in Event-Related

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]

Potentials-Based Mental Workload Assessment. Front Physiol. 2021;12:744071.
112. Tanaka Y, Ito Y, Terasawa Y, et al. Modulation of heartbeat-evoked potential and cardiac cycle effect by auditory stimuli. Biol Psychol. 2023;182:108637.
113. Poppa T, Benschop L, Horczak P, et al. Auricular transcutaneous vagus nerve stimulation modulates the heart-evoked potential. Brain Stimul. 2022;15(1):260-9.
114. Yakubov B, Das S, Zomorrodi R, et al. Cross-frequency coupling in psychiatric disorders: A systematic review. Neurosci Biobehav Rev. 2022;138:104690.
115. Abubaker M, Al Qasem W, Kvašňák E. Working Memory and Cross-Frequency Coupling of Neuronal Oscillations. Front Psychol. 2021;12:756661.
116. Kim DK, Lee KM, Kim J, et al. Dynamic correlations between heart and brain rhythm during Autogenic meditation. Front Hum Neurosci. 2013;7:414.
117. Wang J, Hamill OP. Piezo2-peripheral baroreceptor channel expressed in select neurons of the mouse brain: a putative mechanism for synchronizing neural networks by transducing intracranial pressure pulses. J Integr Neurosci. 2021;20(4):825-37.
118. Mueller K, Thiel F, Beutner F, et al. Brain Damage With Heart Failure: Cardiac Biomarker Alterations and Gray Matter Decline. Circ Res. 2020;126(6):750-64.
119. Klimesch W. Heartbeat, Brain Oscillations and Body Awareness: A Commentary. J Integr Neurosci. 2023;22(6):155.
120. Goodman MS, Kumar S, Zomorrodi R, et al. Theta-Gamma Coupling and Working Memory in Alzheimer's Dementia and Mild Cognitive Impairment. Front Aging Neurosci. 2018;10:101.
121. Rajna Z, Mattila H, Huotari N, et al. Cardiovascular brain impulses in Alzheimer's disease. Brain. 2021;144(7):2214-26.

[DOI: 10.22088/IJMCM.BUMS.15.1.1261]