

Heart brain axis in health and disease: role of innate and adaptive immunity

Alba Simats¹, Hendrik Sager², Arthur Liesz^{3,4}

¹ Institute of Biomedical Research of Barcelona (IIBB), Spanish National Research Council (CSIC), Barcelona, Spain

² DZHK (German Center for Cardiovascular Research), partner site Munich

³ Institute for Stroke and Dementia Research (ISD), University Medical Center Munich, 81377 Munich, Germany

⁴ Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Correspondence to: alba.simats@iibb.csic.es or arthur.liesz@med.uni-muenchen.de

Abstract

The importance of the brain-heart interaction has been increasingly recognized as a critical physiological axis that is altered in disease. In this review, we explore the intricate relationship between the central nervous system and cardiovascular health, focusing particularly on immunological mechanisms that influence the course of both neurological and cardiovascular diseases. While previous studies have established a key role of the autonomic nervous system in linking brain and the heart, more recent studies have expanded our understanding of the multifaceted inter-organ interactions. As such, circulating mediators include immune cells of the adaptive and innate immune system and their secreted immunogenic factors have come into the focus as mediators along this bidirectional communication. Hence, in this review we briefly discuss the contribution of the autonomic nervous system and then focus on innate and adaptive immune mechanisms along the heart-to-brain and brain-to-heart axes, illustrating how cardiovascular diseases affect cognitive functions and how brain pathologies lead to cardiac complications.

Introduction

The central nervous system (CNS) encompasses a range of hereditary and non-hereditary disorders that have a direct or indirect impact on cardiac function, collectively referred to as brain–heart disorders. Among the most recognized conditions within this category are epilepsy, stroke, subarachnoid hemorrhage, bacterial meningitis, and traumatic brain injuries.

Over fifty years ago, the first electrophysiological studies highlighted electrocardiogram (ECG) abnormalities in patients experiencing cerebral accidents, a term then used to describe what are now recognized as various forms of strokes and hemorrhagic events. Early research by George Burch and his team on patients with cerebrovascular accidents revealed significant findings, including long QT intervals and inverted T waves across the cohort, pointing to the intricate interplay between cerebral incidents and cardiac function.¹ Subsequent studies, such as those by Cropp and Manning, further dissected the nuances of ECG changes in subarachnoid hemorrhage, emphasizing that such cardiac abnormalities stem from autonomic dysregulation rather than ischemic heart disease itself.² This body of work underscores the pivotal role of the autonomic nervous system in brain-heart interactions, particularly highlighting the consequences of autonomic dysfunction on heart failure progression and the multifaceted clinical manifestations arising from neurodegenerative disorders' impact on autonomic control.

Historically, the investigation into brain-heart interactions predominantly concentrated on the autonomic nervous system's (ANS) contribution. The critical role of autonomic dysfunction in the progression of heart failure has been well-documented, highlighting that the most successful interventions for heart failure are those that address the peripheral manifestations of neurohumoral activation.^{3–6} These manifestations, which arise from the dysregulated communication between the brain and heart, include an array of symptoms and signs that result from the imbalance in the autonomic nervous system's regulation of cardiovascular functions. The mechanisms by which neurodegenerative disorders impact heart health illuminate the complexity of this relationship. These disorders often lead to a progressive decline in autonomic control, particularly affecting the sympathetic nervous system. This decline manifests in various clinical symptoms such as orthostatic hypotension, impaired sweating, neurogenic bladder and erectile dysfunction in men, and gastrointestinal dysmotility.^{7,8} These symptoms, while diverse, share a common origin in the impaired autonomic regulation, and their severity can be modulated by the body's compensatory mechanisms. On the other end of the spectrum, acute manifestations of autonomic dysfunction, triggered by vascular, inflammatory, or traumatic damage to the autonomic nervous system or as adverse effects of medications, present as signs of autonomic hyperactivity. This includes an excessive control over cardiovascular functions, which can also become a chronic condition in association with other long-standing neurological disorders, notably sleep disorders.⁹ Further advancements in our understanding

of the brain-heart axis have been propelled by recent studies that delve into the anatomical and functional connectivity between these two critical organ systems. This "hardwired" connection between the brain and the body, has been further explored and detailed in recent reports that underscores an intricate and provide concrete evidence supporting the existence of direct pathways facilitating the communication between the brain and the cardiovascular system.^{10,11}

Recent research has broadened our understanding of brain-heart connections, exploring beyond the previously already well-established contribution of the autonomic nervous system in the heart-brain connection. Such more recently explored mechanisms of inter-organ bidirectional interactions are, among others, extracellular vesicles and the immune system.³ The discovery of myokines and cardiokines as mediators in this cross-talk illustrates the heart's endocrine function in communicating with the brain and other organs, signifying a paradigm shift in understanding heart-brain interactions. This communication is thought to play a pivotal role in coordinating responses to various physiological and pathological conditions.^{12,13}

The interplay between inflammation, cardiovascular disorders, and brain health has garnered significant attention, particularly with the emergence of data linking systemic inflammation to both the onset and progression of neurodegenerative diseases. The association between chronic inflammation, as evidenced by elevated levels of biomarkers like high-sensitivity C-reactive protein (hsCRP), and cognitive decline or dementia highlights the importance of managing inflammation to preserve both cardiovascular and brain health. Importantly, inflammation has been recognized, and further supported in the wake of the COVID-19 pandemic as both causal and consequential roles in brain health.¹⁴ Longitudinal studies, such as the ARIC study, have been instrumental in establishing the detrimental effects of chronic inflammation on the brain's microcirculation, further emphasizing the interconnectedness of brain health, heart health, and immune system function.¹⁵

The increasing recognition of inflammation as a critical factor in the interplay between the brain and heart underscores the imperative for an interdisciplinary approach in both research and clinical interventions. As our comprehension of this intricate relationship deepens, particularly with respect to the role of inflammation, it becomes evident that this dynamic represents a pivotal element in the pathophysiology of both cardiovascular and neurological disorders. The intricate pathways through which inflammation mediates brain-heart interactions suggest potential therapeutic targets, offering promising prospects for the development of strategies aimed at reducing the impact of inflammation on these critical organ systems. Therefore, this review will focus on elucidating the current understanding of inflammation within the context of brain-heart connections. It will explore the potential mechanisms by which inflammation influences this relationship and examine its viability as

a target for therapeutic intervention, aiming to mitigate the intertwined risks and progression of cardiovascular and neurological diseases.

Insights from clinical evidence: heart-to-brain axis

Cardiovascular disease is definitively linked to brain health, predominantly through clinical events like stroke, which often arises from atrial fibrillation or left ventricular thrombus formation. This connection between cardiovascular disease, particularly atrial fibrillation, and the risk of cerebrovascular incidents has been already covered in detail in previous reviews^{16–18} and will therefore not be in the focus of this discussion. However, beyond the increased risk for cerebrovascular incidents, cardiovascular diseases are also associated with an elevated risk of cognitive deterioration, exemplified by an increase in dementia risk among individuals with coronary heart disease.^{19–21} This correlation suggests that interventions for coronary artery disease, including coronary artery bypass graft surgery and other forms of coronary revascularization, might not inherently raise the risk of cognitive decline post-procedure but rather, this risk is attributed to the pre-existing cardiac condition.^{22,23} Moreover, individuals with heart failure also exhibit a risk for cognitive decline.²⁴ Evidence is accumulating that even subclinical cardiac disease, characterized by abnormalities in cardiac structure or function or underlying atherosclerosis, significantly impacts brain health. For instance, atrial cardiopathy, regardless of atrial fibrillation presence, is linked to stroke incidents, silent brain infarcts, white matter hyperintensities on MRI, and dementia.^{16,25,26} Alterations in left ventricular structure, such as increased mass index and wall thickness, correlate with brain infarctions and white matter hyperintensities detected via MRI.²⁷ Furthermore, impaired left ventricular global longitudinal strain is associated with a higher risk of stroke, particularly types that are cardioembolic or cryptogenic.²⁸ Several mechanisms have been proposed to explain the relationship between cardiac disease and brain health, highlighting the complex interactions between these systems. A key factor in this relationship is the increased vascular risk linked to abnormalities in cardiac structure and function, which is associated with stroke, subclinical cerebrovascular disease, cognitive decline, and dementia. A specific mechanism connecting cardiovascular function to brain health is its impact on microvascular dysfunction in the brain. The Cerebral-Coronary Connection (C3) study has demonstrated an association between coronary microvascular dysfunction and MRI markers of cerebrovascular disease and cognitive function, supporting this connection.²⁹ In addition to shared vascular risks, cardiac disease may directly influence brain health. For example, heart failure has been associated with increased systemic and neuroinflammation³⁰ – a potential key factor which is further elaborated below. Reduced cerebral perfusion, observed in certain cardiac conditions and potentially further exacerbated by inflammatory pathways, can contribute to cognitive decline.³¹ This evidence supports the view that cardiovascular health plays a critical role in maintaining cognitive function and brain health.

Insights from clinical evidence: brain-to-heart axis

Increasing clinical (and experimental) evidence not only supports a causal link from the heart to the brain, but also indicates the presence of a bidirectional relationship, highlighting a tight influence of the brain on the heart. Despite associations between brain diseases and cardiovascular complications have received little attention so far, the growing body of literature over the last decade suggests that various acute brain injuries, including ischemic and hemorrhagic strokes, subarachnoid hemorrhages (SAH), traumatic brain injuries (TBI), and brain tumors, among others, can result in cardiac complications. These complications may include from ECG alterations, such as QTc prolongation and left ventricle (LV) diastolic dysfunction, to acute coronary syndromes, congestive heart failure and cardiac arrest.

Cardiac complications following brain injury have been observed both within the acute phase immediately after the primary injury, and during a more chronic phase as well as in chronic brain diseases. Indeed, the recognition of acute brain injuries not only as an immediate consequence of brain injury, but also as chronic conditions enabled the exploration of aspects beyond neurological health and the identification of chronic cardiovascular complications, which may be linked to or influenced by the long-lasting impacts of acute brain injuries. Cardiac complications associated to brain diseases range from mild and recoverable damage in the heart, which most probably resolves alongside improvement of the neurological condition, to more severe cardiac complications, that persist over time potentially resulting in lifelong cardiac problems and, in some instances, fatality.³²

To date, epidemiological studies have reported that cardiac alterations are highly prevalent in ischemic stroke patients, even in the absence of primary heart diseases. Over 60% of acute ischemic stroke patients exhibit ECG abnormalities within the first 24h, including QT prolongations, ST segment changes and inverted “cerebral” T waves.^{33,34} The prevalence of cardiac autonomic dysfunction, lasting from weeks to months, also ranges from 26% to 77% of ischemic stroke patients.^{35,36} Stroke patients are also at high risk of severe cardiac events. In fact, numbers demonstrate that within the first 3 month after ischemic stroke 10% to 20% of patients suffer at least one serious cardiac adverse event³⁷⁻⁴⁰, 28% have impaired LVEF, 9-29% have systolic dysfunction and 20-25% present diastolic dysfunction.^{40,41} Stroke patients with impaired cardiac function have demonstrated poorer functional outcomes and more severe disabilities upon hospital discharge.^{42,43} In fact, cardiac events stand as the second leading cause of post-stroke mortality.^{44,45} Notably, women exhibit a twofold increased likelihood of developing post-stroke acute myocardial injury, associated with a heightened risk of short-term mortality⁴⁶. Serious cardiovascular complications are also common events after hemorrhagic strokes and subarachnoid hemorrhages (SAH).^{47,48} More than half of SAH patients

(71%) develop left-ventricular diastolic dysfunction⁴⁹, and on-third experience arrhythmias, which are associated with an increased risk of cardiovascular comorbidity, prolonged hospital stay and poor outcome or death after SAH.^{50,51} Similar observations have been made after moderate to severe traumatic brain injury (TBI).⁵² Numerous studies have already shown that individuals without pre-existing comorbidities who experience a traumatic brain injury (TBI) face a significantly elevated risk of developing chronic cardiovascular disease compared to those without a history of TBI.⁵³ In fact, in a 20-50% of the cases patients with TBI exhibit ECG abnormalities, 10-20% of patients develop left ventricular dysfunction, and 25-35% are known to experience myocardial injury.^{54,55}

Beyond acute injuries, cardiovascular events may also occur in **chronic neurological disorders**. Whereas the connection between cardiovascular diseases and the risk of dementia has become evident in the past decades, the reverse relationship has yet to be conclusively established. Few studies have demonstrated that diastolic dysfunction could also be an early anomaly in individuals affected by Alzheimer's Disease (AD), and the presence of intramyocardial A β deposits in the myocardium of these patients could potentially be a contributing factor.⁵⁶ In the context of multiple sclerosis (MS), a significant concern revolves around the elevated mortality risk attributed to cardiovascular disease in MS patients when compared to the general population.⁵⁷ Indeed, in MS, as well as in Parkinson's disease, cardiac autonomic dysfunction has been described in two-thirds of the patients.⁵⁸ Furthermore, individuals with MS have reported an increased risk for myocardial infarction and heart failure.⁵⁹ Acute cardiac events, such as paroxysmal atrial fibrillation⁶⁰, cardiogenic shocks⁶¹, neurogenic pulmonary edema⁶², and Takotsubo syndrome⁶³, have been also observed in these MS patients over the progression of the disease. Remarkably, other mental illnesses, including depressive and anxiety disorders, **mental stress**, post-traumatic stress, schizophrenia or **sleep disturbances** have been also reported to be **associated to and** independent risk factors for cardiovascular complications.^{64–66}

The occurrence of the vast majority of these cardiac complications after brain disorders has been traditionally attributed to the presence of pre-existing comorbidities and converging risk factors, including unmodifiable, such as age and sex, and modifiable, in particular hypertension, diabetes, high cholesterol, smoking and physical inactivity. Within the past years, however, it has been increasingly recognized that the tight interaction between heart and brain go beyond being a mere consequence of these conventional risk factors impacting both organs.³⁸ Indeed, the association between brain and heart diseases has suggested additional potential causal pathways via which the brain and the heart bidirectionally communicates. These signaling routes includes a complex network of autonomic nerves and hormones, as well as immune cells and pro-inflammatory mediators such as cytokines, which will be outlined in the following sections. Whether the heart-to-brain bidirectional communication is exclusively driven by these disease-associated signaling pathways or it is also influenced by pre-existing subclinical comorbidities remains unknown.

Mechanisms of brain-heart interactions

Autonomic Nervous System

The autonomic nervous system (ANS) exhibits a complex anatomical and functional organization within the brain and spinal cord. At its core lies the central autonomic network (CAN), a sophisticated neural network comprising cortical (insula, ventromedial prefrontal cortex, anterior cingulate cortex) and subcortical (amygdala, hypothalamus) brain regions along with the brainstem. This network collaboratively regulates autonomic functions, including those of the sympathetic and parasympathetic divisions, ensuring a finely-tuned response to physiological demands. Autonomic neuronal projections exert tight regulatory control over heart function, influencing cardiac repolarization and heart rate.^{67,68} Additionally, the heart also possesses an intrinsic cardiac nervous system, transmitting afferent feedback to the brain through spinal nerves and vagal afferents, projecting to the same CAN structures.⁶⁹

ANS response to disease. Dysfunction of the ANS is a common trait in many brain and heart diseases, contributing significantly to the subsequent morbidity and mortality.^{70–73} In acute lesions, there's often an increase in sympathetic nervous system (SNS) activity, possibly due to loss of descending inhibition, leading to excitatory spinal circuits development.^{74–76} In chronic pathologies like chronic cardiovascular or neurodegenerative disorders, there is also a progressive failure of autonomic control.⁷ Consequently, blood catecholamine levels rise significantly in peripheral circulation, correlating with injury severity.⁷⁷ ANS activation can also stimulate the hypothalamic-pituitary-adrenal (HPA) axis, triggering a cortisol response proportional to the lesion severity and highly associated with morbidity and mortality.^{78,79} **In brain diseases, such** ANS response is intricately influenced by the specific location of the lesion. Lesions in the insular cortex increase vulnerability to cardiac complications, such as blood pressure fluctuations, cardiac arrhythmias, and myocytolysis.⁸⁰ Hypertension and tachycardia are more likely in patients with damage to the putamen or thalamus, suggesting brain-heart interactions are not limited to the insular cortex.⁸¹ Hemispheric lateralization remain controversial, and bilateral insular territories have been shown to influence cardiac function and autonomic control.^{50,75,82,83} **Following cardiac injury, cardiac vagal afferent signaling appears to be also compromised, although little has been yet described.⁸⁴ For example, previous studies suggested that changes in parasympathetic efferent tone could be in part attributed to reduced vagal afferent signaling following MI.⁸⁵ Similarly, acute and chronic pain episodes in the context of cardiovascular alterations can also activate cardiac vagal afferent signaling and result in sympathetic overactivation both from excess spinal nociceptive input (sensory-sympathetic coupling) and by promoting chronic cognitive or emotional stress, which exacerbates sympathetic responses to other stimuli.⁸⁶**

ANS dysfunction in the brain-heart bidirectional communication. The imbalance of ANS activity in response to both brain and heart injuries may exacerbate secondary cardiovascular complications. Increased exposure to catecholamines stimulates cardiac adrenergic receptors, leading to hyperadrenergic activity.⁷³ In the acute setting, heightened sympathetic tone augments ventricular contractility, heart rate, and cardiac output, while inducing systemic vasoconstriction and enhanced venous tone. However, chronic sympathetic stimulation exacerbates cardiac damage by inducing mitochondrial calcium overload, oxidative stress, osmotic swelling, and loss of ATP synthesis, resulting in cardiomyocyte necrosis, hypertrophy, and fibrosis.^{73,87} Prolonged catecholamine exposure may potentially reduce nerve growth factor expression, leading to sympathetic fiber loss⁸⁸, and over-activate NLRP3 inflammasome signaling, promoting IL-1 β production and cardiac adaptive hypertrophy.⁸⁹ These consequences disrupt the endocardial conduction system, causing severe cardiac alterations, arrhythmias, and LV diastolic dysfunction, contributing to myocardial failure progression.^{50,90} Excessive sympathetic discharge may induce paroxysmal sympathetic hyperactivity⁷⁶, likely due to loss of descending inhibition, leading to symptoms like tachycardia, tachypnea, hypertension, sweating, hyperthermia, and decerebrated motor posturing, associated with diffuse brain injury and poor outcomes.^{91,92}

Mental stress and the cardiovascular system. ~~Recently, several activators of the brain-heart/vessel axis were further identified.^{93,94} Mental stress — a yet underexplored non-traditional risk factor for cardiovascular disease — was found to be strong inducer of brain and heart interorgan communication.⁹³~~ Sympathetic nervous activation during mental stress - a yet underexplored non-traditional risk factor for cardiovascular disease⁹³ - has been also demonstrated to contribute to leukocyte recruitment and subsequent vascular inflammation, potentially leading to cardiovascular events.^{94,95,96} Specific brain regions, such as the motor cortex, **promote stress-induced hematopoiesis and leukocyte release from bone marrow**, while the paraventricular nucleus influences the return of monocytes and lymphocytes to the bone marrow in a corticosterone-dependent manner.^{96,97} This redistribution of immune cells impairs adaptive immunity, particularly contributing to stress-mediated upper respiratory tract infections.^{96,97} Conversely, the afferent (heart/vessel to brain) signaling of the bi-directional brain-heart axis can also affect development and progression of cardiovascular disease.⁹⁸ Diseased vessels see immune cell accumulation not only in the intima but also in the lamina adventitia, forming artery tertiary lymphoid organs that amplify inflammation and establish a neuroimmune cardiovascular interface.¹¹

Recent studies reveal that aging diminishes cardiac nerve density, which senolytic treatments can reverse.⁹⁹ Additionally, chronic cardiac conditions result in sympathetic nerve loss and pineal gland dysfunction, causing sleep issues, with macrophage infiltration in the superior cervical ganglion as a key factor.¹⁰⁰ **Sleep disturbances have recently shown to further impair the proper hypothalamic**

release of hypocretin, thereby favoring myelopoiesis and accelerated atherosclerosis, overall compromising the cardiovascular health.¹⁰¹ In summary, the intricate interplay between the autonomic nervous system and cardiovascular health highlights the significance of understanding and addressing ANS dysfunctions to mitigate secondary cardiovascular complications and improve patient outcomes in brain and heart diseases.

Systemic immunity

Inflammation emerges as a shared key factor across many brain and heart diseases, playing a significant role in the development of secondary complications following an incident of any such disorder.¹⁰² In fact, systemic immunity and inflammation is also a common trait observed in most converging risk factors associated with both acute and chronic diseases in the heart and in the brain, including hypertension, diabetes, atherosclerosis, hypercholesterolemia, obesity and aging. Moreover, robust evidence from epidemiological studies consistently demonstrates a strong positive correlation between the inflammatory immune response and the risk of cardiovascular, cerebrovascular and neurological disorders, emphasizing the importance of inflammation in the heart-brain bidirectional communication (**Figure 1**).¹⁰³

Innate immune cells

Innate immunity in acute injuries. Similar mechanisms have been described for the innate immune activation and the early pro-inflammatory response occurring during brain and cardiac diseases. Acute injuries prompt stressed and dying cells to release damage-associated molecular patterns (DAMPs), which are recognized by resident and circulating innate immune cells. This initiates a potent inflammatory cascade, involving cell activation, rapid upregulation of pro-inflammatory mediators like cytokines, chemokines, and interleukins, and the subsequent recruitment of innate immune cells to the brain. This initial inflammatory response further extends beyond localized effects and also involves a profound immune response in the bloodstream. Sympathetic hyperactivity, common in brain and heart disorders, can further activate innate immune cells via NE-induced stimulation of adrenergic receptors. Indeed, sympathetic nerve blockade, notably via the administration of beta-blockers, has shown efficacy in reducing circulating levels of several proinflammatory cytokines such as tumor necrosis factor alpha (TNF- α), Interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6) after injury.¹⁰⁴ Increased sympathetic tone also promotes hematopoietic stem cell and myeloid progenitor proliferation, differentiation, and mobilization from the spleen and bone marrow.¹⁰⁵ Additionally, soluble pro-inflammatory factors such as IL-1 β boost hematopoiesis in the bone marrow^{106,107}, collectively enhancing innate immunity and acute systemic inflammatory responses to injury.

In fact, elevated numbers of circulating innate immune cells early after brain and cardiac insults have been linked to worse outcomes and poor recovery.¹⁰⁸ For instance, elevated circulating CD14+ monocyte counts and monocyte activation, as measured by toll-like receptor (TLR)-4 expression, 3 days post-myocardial infarction, have been associated with heart failure progression and negatively correlated with left ventricular (LV) ejection fraction recovery 6 months later.^{109,110} Similarly, high circulating monocytes and neutrophil counts at admission have been linked to poorer prognosis and increased infection risk after stroke and subarachnoid hemorrhage, respectively.^{111,112} Circulating pro-inflammatory cytokines such as IL-6 and TNF- α , and DAMPs including the double-stranded deoxyribonucleic acid (dsDNA), have been also associated with the extent of the injury, and correlated with poor outcome and the risk for recurrency.^{113–117} Altogether, these evidences point at the acute systemic inflammatory response as a common detrimental factor compromising recovery from brain and heart lesions.

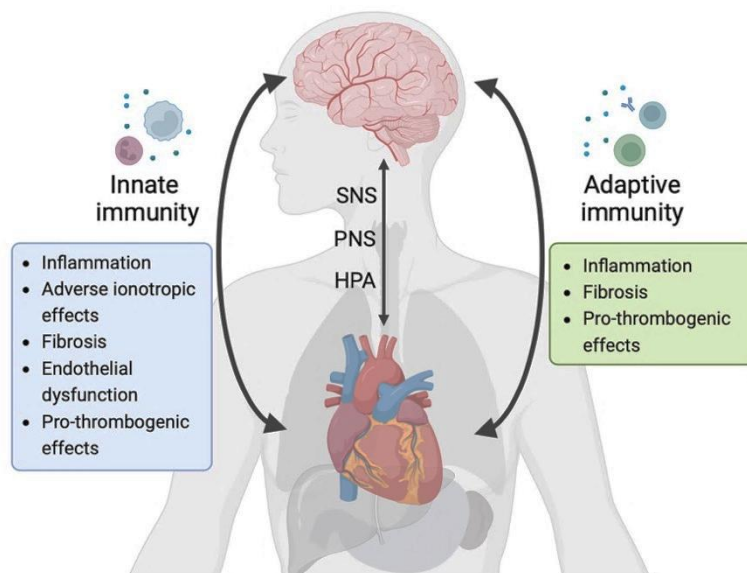


Figure 1. Heart-brain bidirectional communication in disease through innate and adaptive immunity. SNS: sympathetic nervous system; PNS: parasympathetic nervous system; HPA: hypothalamic-pituitary-adrenal

Upon injury, activated innate immune cells quickly migrate to the site of damage, with neutrophils being among the first responders. While traditionally viewed as primarily pathogenic, current understanding stresses the necessity of a delicate balance, ensuring timely neutrophil recruitment and subsequent clearance or apoptosis.¹¹⁸ This balance is crucial in determining whether neutrophils exacerbate inflammation or aid in its resolution, thus facilitating cardiac healing and tissue repair.¹¹⁹ Initially, neutrophils enter the injured heart or brain to clear cellular debris; however, uncontrolled activation can lead to collateral damage through the release of granular content and reactive species.¹²⁰ They also secrete pro-inflammatory mediators like IL-1 β , implicated in adverse cardiac remodeling and dysfunction.¹²¹ Furthermore, neutrophils form extracellular traps (NETs) and release extracellular vesicles that may exacerbate inflammation and injury.¹²² Recent evidence also suggests that neutrophils may play a role in recruiting monocytes to the injured tissue, potentially influencing

macrophage phenotype towards resolution and anti-inflammation.¹¹⁸ Blood monocytes and monocyte-derived macrophages (MDM) are also recruited following acute injuries. In the brain, infiltrating monocytes and MDM demonstrate notable plasticity. Initially, they become potent phagocytes, aiding in necrotic cell clearance while exacerbating neuroinflammation and neuronal injury.¹²³ Later, they are crucial for vascular stability and may influence nearby MDMs and microglia towards an anti-inflammatory state.^{124,125} Similarly, in the injured myocardium, Ly6C-high monocytes early accumulate via CCR2 at the site of injury, and together with cardiac macrophages, they contribute to inflammation, fibrosis, and impaired tissue regeneration by releasing proteolytic enzymes, secrete proinflammatory cytokines, present antigens to T cells, and secrete matrix metalloproteinases (MMPs).^{126,127} Later, Ly6C-low monocytes accumulated via CX3CR1, and may adopt a reparative function, promoting anti-inflammatory cytokine release and tissue repair.^{128,129}

Innate immunity dissemination through the heart-brain axis. Recently, compelling evidences suggest that systemic immune responses to acute injuries further disseminate to areas remote from the primary lesion. Consequently, the infiltration of innate immune cells into “healthy” tissues remote from the initially affected organ could potentially foster the development of peripheral secondary complications. For instance, in experimental models of TBI, ischemic stroke, SAH, and intracerebral hemorrhage (ICH), there is a significant increase in monocyte and neutrophil infiltration into the heart early after acute brain damage.^{130–133} This is associated with severe cardiac complications, including ventricular fibrillation and dysfunction, evidenced by reduced LV fractional shortening, LV ejection fraction and heart rate.^{130–133} Splenectomy in such brain diseases has resulted in the reversal of injury-related cardiac dysfunction, with or without neurological and cognitive functional improvement.^{130,131} Mechanistically, upon infiltration into the “healthy” heart, monocytes and MDM become primary sources of fibrogenic growth factors and cytokines, promoting an inflammatory microenvironment and contributing to fibrosis.^{107,134} For example, systemic monocytes release TGF-beta and MMP-9, increasing myofibroblast activity and collagen synthesis.¹³⁵ Macrophage-derived osteopontin (SPP1) enhances inflammation, fibrosis, and impedes cardiomyocyte conduction.^{134,135} Other pro-inflammatory mediators secreted by these cells within the heart, including TNF- α , IL-1 β , IL-6, and IL-18, can induce negative local inotropic effects.^{133,136–138} Beyond acute inflammation, TBI and ischemic stroke also lead to long-term infiltration of innate immune cells into the heart, worsening cardiac complications over time.^{107,131} A conceivable causal explanation for this chronic accumulation of pro-inflammatory monocytes in “healthy” tissues beyond the acute inflammatory phase has been recently proposed in the context of stroke. Stroke acutely induces innate immune memory, manifested as a long-lasting shift in the transcriptomic signature of bone marrow-derived circulating monocytes towards a pro-inflammatory state, thus enabling the chronic and sustained infiltration of such cells into the healthy the heart.¹⁰⁷ This mechanism could potentially explain the development of

comorbidities in remote organs after acute tissue injury, although further research is needed to explore other peripheral tissues.

The role of innate immune cells in the heart-to-brain bidirectional communication is further supported with clinical data showing that the amount of neutrophils and macrophages is also significantly higher in the myocardium of SAH patients compared to controls.¹³⁹ Similarly, higher counts of CCR2+ infiltrating monocytes have been observed in patients who died due to ischemic stroke, with no previous diagnosed cardiovascular comorbidity.¹⁰⁷ Therefore, strategies that target the recruitment of pro-inflammatory innate immune cells into “healthy” tissues may yield therapeutic benefit for the prevention of secondary complications.¹⁰⁷

In the context of systemic inflammation, circulating pro-inflammatory cytokines can also compromise cardiac function not only locally in the heart but also indirectly from circulation. For instance, these mediators can activate the sympathetic nervous system by upregulating inflammatory and excitatory mediators in the subfornical organ (SFO).¹⁴⁰ Additionally, they can indirectly affect heart function by inducing acute inflammation in remote vital organs like the lung, leading to pulmonary damage and edema.^{141,142} Furthermore, circulating pro-inflammatory cytokines and DAMPs activate vascular endothelial cells, causing changes in vascular structure and permeability, ultimately resulting in vascular leakage, fibrosis, and angiogenesis in the bone marrow.¹⁴³ This leads to enhanced systemic inflammation due to increased production of inflammatory myeloid cells. Endothelial dysfunction can also compromise the integrity of the blood-brain barrier (BBB)¹⁴⁴, contributing to the development of neurovascular and neurodegenerative disorders.¹⁴⁵ These brain complications are exacerbated in cardiovascular diseases with reduced cardiac output, as cerebral hypoperfusion and alterations in cerebral blood flow homeostasis further impact the cerebral endothelium. Moreover, pro-inflammatory factors released from innate immune cells, such as neutrophil extracellular traps (NETs), promote thrombosis and the formation of a scaffold for platelet, erythrocyte, fibrin, and coagulation factor binding, associated with adverse cardiovascular events.¹⁴⁶ These mediators also contribute to the development of comorbidities such as hypertension, diabetes, atherosclerosis, hypercholesterolemia, obesity, and aging, which indirectly influence the incidence of secondary complications following brain and cardiac injuries.^{147–149}

Innate immunity in chronic disorders. Increasing evidence suggests that systemic inflammation following acute brain and heart injuries can persist into chronic phases, leading to sustained long-term systemic inflammation.¹⁵⁰ Indeed, few retrospective clinical studies have already provided evidence that pro-inflammatory mediators mainly secreted by innate immune cells, such as IL-6, IL-1 β and HMGB1 may remain elevated in circulation from 24 h up to 90 days after ischemic stroke or TBI.^{151–155} Chaban and colleagues found that other pro-inflammatory cytokines, including IFN- γ , IL-8, MCP-1 and macrophage inflammatory protein (MIP)-1 β , also remained increased for up to one year

post-TBI.¹⁵⁶ Similarly, prolonged elevation of hsCRP levels has been also associated with major adverse cardiac events and death in coronary artery disease patients.¹⁵⁷ This situation of chronic sustained inflammation long-term after acute injuries could potentially resemble the inflammatory milieu also observed in more chronic and slowly-progressing heart and brain diseases, including chronic heart failure and also neurodegenerative disorders, also characterized by innate immune activation and a sustained low-grade systemic inflammation.¹⁵⁸ For instance, IL-1 β and CRP levels are elevated in chronic heart failure patients^{159,160}, while IL-6 and TNF- α levels are linked to age-related cognitive decline.¹⁶¹ Recent evidence also suggests that other chronic conditions such as atherosclerosis, mental stress or sleeping disorders favor hematopoiesis and the production of innate immune cells, thereby also potentiating systemic inflammation.^{101,162,163} Indeed, mental stress-induced mobilization of circulating progenitor cells has been associated with a higher adjusted risk of adverse cardiovascular events.¹⁶⁴ Despite all these evidences, the origin of such chronic inflammation, whether induced by the primary disease, by pre-existing inflammatory comorbidities, or a combination of both, remains unclear, underscoring the need for further investigations. Nevertheless, chronic inflammation and innate immune activation regardless of its cause represent a risk factor for the development of many diverse diseases with a shared inflammatory component, including cardiovascular, cerebrovascular and other non-vascular brain disorders.¹⁵⁸ For instance, systemic inflammation has been identified as an early pathogenic driver of cognitive decline in older adults and associated with risks for AD dementia.^{165,166} Furthermore, systemic inflammation is suggested to drive secondary vascular events in patients with underlying vascular comorbidities and preceding ischemic events. Therefore, chronic systemic inflammation originating from brain or heart disorders likely plays a significant role in chronic brain-heart bidirectional communication, necessitating further studies to elucidate underlying mechanisms and triggers. Despite limited success during the past decades, recent clinical studies targeting chronic innate immunity and systemic inflammation have highlighted the importance of inflammation-mediated bidirectional communication between the heart and brain. For example, the CANTOS trial testing IL-1 β -specific antibody treatment in patients with previous myocardial infarction and high residual systemic inflammation demonstrated efficacy in preventing cardiovascular and cerebrovascular complications.¹⁶⁷ Similarly, a meta-analysis of randomized controlled trials showed that colchicine treatment significantly reduces the incidence of stroke in patients with high cardiovascular risk.¹⁶⁸ Thus, targeting inflammation within the heart-brain axis holds clinical promise for preventing secondary complications in both vital organs, necessitating further trials to explore alternative anti-inflammatory approaches and drugs.

Adaptive immune cells

Adaptive immunity, **orchestrated by specialized immune cells, primarily lymphocytes**, plays a pivotal role in initiating immunological responses. **These responses encompass the production of cytokines**

and antibodies, facilitated by antigen presentation through Major Histocompatibility Complex (MHC) I and II. These lymphocytes are capable of developing long-lasting memory against previously encountered antigens, enabling them to mount faster and more vigorous responses upon subsequent exposures.^{169,170} This attribute of adaptive immunity has drawn significant attention towards its potential involvement in various heart and brain diseases, acting both as an initiator and a perpetuator of these conditions. Immune-mediated mechanisms have been implicated in a wide range of ischemic and non-ischemic pathologies affecting both the heart and the brain, suggesting their substantial role as mediators along the heart-brain axis. This involvement highlights the complexity of immune responses in disease contexts, necessitating a deeper understanding of their mechanisms and implications.

Adaptive immunity in brain health. Lymphocytes, particularly T cells, play a critical role in maintaining normal brain function, impacting processes such as learning and memory. Studies have demonstrated that mice lacking T cells exhibit cognitive deficits, which can be reversed by reintroducing mature T cells back into the system, showcasing the indispensable role of T cells in cognitive health.^{171–173} This suggests that T cells are vital for sustaining a healthy immune state essential for optimal brain performance. The mechanisms through which T cells influence brain function are thought to involve interactions with resident cells both within the brain parenchyma but also at the brain borders including the meningeal layers and the choroid plexus.^{173–176} Despite the growing body of evidence, the antigenic specificity of these T cells and their precise contributions to brain health remain subjects of ongoing investigation, emphasizing the intricate relationship between the immune system and the central nervous system under normal physiological conditions.

Lymphocytes in brain pathology. While the CNS was traditionally viewed as an immune-privileged site, current understanding recognizes that T lymphocytes regularly surveil the CNS, maintaining neuronal integrity and responding to injury. In conditions such as AD, an imbalance in T cell function can exacerbate neuronal loss. Conversely, in models of CNS injury, T cells have been shown to support neuronal survival and recovery, suggesting a complex, context-dependent role of T lymphocytes in neurodegeneration. Their pathological involvement is evident in neuroinflammatory and neurodegenerative diseases, such as MS and AD, highlighting their dual roles. In MS, immune cells, including subsets of T cells, target the myelin sheath, leading to the disease's debilitating effects^{172,177,178}. Conversely, in AD, lymphocytes, including T cells, have been suggested to modulate disease progression. T cells, particularly clonally expanded CD8+ T cells, infiltrate the brain and cerebrospinal fluid in such neurodegenerative conditions, where they interact with microglia and exacerbate neuroinflammation. These interactions are mediated through signaling pathways like CXCL10–CXCR3 and CXCL16–CXCR6, leading to worsened cognitive decline and associations with tau pathology.^{179–182} Additionally, some evidence is however also pointing towards a protective role

against disease acceleration.¹⁸³ These potentially opposing functions depending on disease state or investigated disease model underscores the broader role of the immune system in tissue maintenance and repair, reflecting the ambivalent nature of lymphocytes in brain pathology. These insights into lymphocytes' roles in both health and pathology of the brain underscore the complex balance between their beneficial and detrimental effects, dependent on the context of their activation and the overall immune response within the CNS.

Acute brain lesions including traumatic brain injury and stroke, induce a systemic immune response that involves significant modulation of lymphocyte populations, including T and B lymphocytes.¹⁸⁴ This response, initiated by the release of DAMPs from necrotic brain tissue, leads to widespread inflammatory signaling and subsequent recruitment of adaptive immune cells to the brain.¹⁰⁷ However, this initial pro-inflammatory response is quickly followed by a phase of systemic immunosuppression, characterized by a decrease in circulating lymphocyte counts.¹⁸⁵ This phase of immunosuppression predisposes patients to infections, highlighting the role of lymphocytes in both the detrimental and potentially reparative processes following acute brain lesions.¹⁸⁶

Neurodegeneration involves progressive neuronal loss within the central nervous system, with the immune system, particularly lymphocytes and their secreted factors, playing a crucial role in the pathogenesis of these conditions. Peripheral T cells and brain-derived cytokines, notably IL-2, have been shown to be significant for neuronal survival and potentially able to even reverse neurodegenerative processes^{187–189}. This understanding opens new avenues for therapeutic interventions, focusing on modulating the immune response to mitigate neurodegenerative processes, underscoring the importance of exploring lymphocyte roles in neurodegeneration for future therapeutic strategies.

Lymphocytes in Cardiac Health and Disease. The role of lymphocytes in cardiovascular health and disease is increasingly recognized, with evidence highlighting their involvement in various aspects of heart pathology, including myocardial injury, repair, and chronic inflammation associated with cardiovascular diseases.^{190,191} T cells, encompassing CD4+ helper T cells and CD8+ cytotoxic T cells, play significant roles in heart disease. For example, CD4+ T cells are implicated in promoting inflammation and fibrosis by secreting pro-inflammatory cytokines including IFN- γ and TNF- α , leading to adverse cardiac remodeling.^{192,193} On the other hand, regulatory T cells (Tregs) mitigate inflammation and fibrosis, showcasing the dichotomous roles of T cell subsets in cardiac pathologies.¹⁹⁴ The contribution of T cells to heart diseases is evident in their involvement in myocardial ischemia-reperfusion injury, where they can exacerbate or ameliorate the damage depending on the specific T cell subsets activated during the immune response.

B cells, through antibody production and antigen presentation, infiltrate the myocardium following injury and contribute to the inflammatory response.^{195,196} These cells are involved in the development of atherosclerotic plaques and the progression of heart failure. However, B cells also exhibit protective roles, particularly in tissue repair processes and attenuation of hypertrophy and fibrosis, reflecting the complex nature of B cell involvement in heart diseases.^{195–197} Research highlights the paradoxical roles of B cells, showing both damaging and healing effects in the cardiac context, underscoring the importance of understanding their specific functions in CVD. The interplay between different lymphocyte subsets and their secreted cytokines significantly influences cardiac inflammation and remodeling. Pro-inflammatory cytokines contribute to cardiac damage and disease progression, while anti-inflammatory cytokines and certain lymphocyte subsets, such as Tregs, promote resolution of inflammation and tissue repair.¹⁹⁸ This balance between pro- and anti-inflammatory responses is crucial for determining the outcome of cardiac diseases. Understanding the complex roles of lymphocytes in cardiovascular diseases opens new avenues for therapeutic interventions. Targeting specific lymphocyte subsets or modulating their activity through immunotherapy holds promise for treating or even preventing CVD.

In conclusion, while only little is known about the direct bi-directional function of adaptive immunity linking heart and brain function, the critical role of lymphocyte subsets with overlapping mechanisms between brain and heart pathologies, suggests a potentially key function of these cells in mediating bi-directional brain-heart communication. For example, the involvement of T cells in both promoting and mitigating inflammatory responses can influence neurological outcomes post-stroke as well as cardiac remodeling post-myocardial infarction. Similarly, the role of B cells in contributing to the inflammatory milieu in both brain and heart diseases indicates a shared mechanism of disease progression and potentially, resolution. This is further supported by the systemic immune response observed in acute brain injuries, such as stroke, which involves significant modulation of lymphocyte populations that could similarly affect cardiac function. Conversely, cardiac events could trigger immune responses that impact brain health, evidenced by the systemic inflammatory response and immunosuppression post-myocardial injury, which may predispose individuals to cognitive deficits or exacerbate neurodegenerative processes. The secretion of cytokines by lymphocytes, such as Interleukin-2 (IL-2), known for its significant role in neuronal survival, further links the adaptive immune response to neurodegeneration and cardiac health. Thus, understanding the intricate interactions and regulatory mechanisms of lymphocytes in both the central nervous system and cardiovascular system could unveil novel therapeutic targets for diseases affecting both organs, emphasizing the need for integrated research approaches to explore the full spectrum of adaptive immunity's role in the heart-brain axis.

Conclusions

The extensive exploration of brain-heart interactions detailed in this review illuminates the intricate and multidimensional relationship between the CNS and cardiovascular health. The initial discovery of ECG abnormalities in patients with cerebral incidents set the stage for a deeper understanding of the complex interplay between brain pathologies and cardiac function. Research advancements have broadened the scope of investigation beyond autonomic contributions to include the previously unrecognized influence of inflammation in mediating bidirectional brain-heart communication. The recognition of inflammation as a critical mediator in this interplay, especially in the context of systemic diseases and the emerging data from the COVID-19 pandemic, underscores the need for an interdisciplinary approach to research and clinical interventions. The heart-to-brain and brain-to-heart axes demonstrate the profound impact of cardiovascular diseases on cognitive functions and the consequential cardiac complications arising from acute and chronic brain injuries and disorders. The detailed mechanisms through which these interactions occur, from ANS imbalances to systemic immune responses, offer a window into potential therapeutic targets aimed at mitigating the intertwined risks and progression of cardiovascular and neurological diseases. As we delve deeper into the understanding of these complex relationships, it becomes clear that addressing the shared pathways of immune responses presents a promising frontier for developing strategies to preserve both cardiovascular and brain health. Therefore, this review not only highlights the current understanding of the brain-heart connection but also calls for further investigation into the underlying mechanisms that link these two critical organ systems, emphasizing the importance of an integrated approach to tackling the shared challenges they present.

Conflict of interest

All authors declare that they have no conflicts of interest.

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