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Review article

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The brain–heart axis: integrative cooperation of neural, mechanical and biochemical pathways

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Abstract

The neural and cardiovascular systems are pivotal in regulating human physiological, cognitive and emotional states, constantly interacting through anatomical and functional connections referred to as the brain–heart axis. When this axis is dysfunctional, neurological conditions can lead to cardiovascular disorders and, conversely, cardiovascular dysfunction can substantially affect brain health. However, the mechanisms and fundamental physiological components of the brain–heart axis remain largely unknown. In this Review, we elucidate these components and identify three primary pathways: neural, mechanical and biochemical. The neural pathway involves the interaction between the autonomic nervous system and the central autonomic network in the brain. The mechanical pathway involves mechanoreceptors, particularly those expressing mechanosensitive Piezo protein channels, which relay crucial information about blood pressure through peripheral and cerebrovascular connections. The biochemical pathway comprises many endogenous compounds that are important mediators of neural and cardiovascular function. This multisystem perspective calls for the development of integrative approaches, leading to new clinical specialties in neurocardiology.

Sections

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Key points

- The brain–heart axis is a complex, multidimensional network that is essential for maintaining physiological homeostasis through interconnected neural, mechanical and biochemical pathways.
- The neural pathway features bidirectional communication between the central and autonomic nervous systems, and also integrates signalling from the intrinsic cardiac nervous system and the central autonomic network.
- The mechanical pathway primarily involves mechanoreceptors, particularly Piezo proteins, which detect blood pressure changes and modulate the functioning of both the heart and the brain.
- The biochemical pathway involves endogenous compounds, such as hormones, neuropeptide Y and mediators of both acute and chronic inflammation, that modulate brain, cardiovascular and autonomic functions.
- Insights into the brain–heart axis can guide the development of integrated approaches for comorbid cardiovascular, neurological and neuropsychiatric disorders.

Introduction

In-depth explorations into the physiology of the brain and heart, particularly the interconnected dynamics of the central nervous system (CNS) and autonomic nervous system (ANS), have yielded important insights in the fields of neuroscience, psychiatry, neurology and cardiology. The roots of investigations into the brain–heart axis primarily lie in the concurrent symptomatology of neurological and cardiac pathologies. As early as 1947, Byer and colleagues observed upright T waves and prolonged QT intervals in patients with subarachnoid haemorrhage[1]. Subsequently, in 1975, Vaisrub emphasized the substantial effect of structural brain damage resulting from intracranial haemorrhage on cardiac function[2]. The term 'neurocardiology' emerged in a handful of clinical papers in the 1980s and 1990s[3–5], which conjectured that overlooking the intricate interactions between brain and heart could lead to delayed diagnosis and treatment. Subsequently, neurocardiology emerged as a pivotal field of basic research, bridging the clinical gap between the brain and the heart, and shedding light on how pathologies in one system can have sequelae in the other. However, the interest in neurocardiology was not immediately reflected in the clinical domain and, except for a few papers[6–8], remained largely overlooked until the 2010s[7].

The clinical implications of connected pathologies of the brain and heart are being increasingly recognized. For example, stroke and transient ischaemic attack frequently stem from cardiac arrhythmias[9], and atrial fibrillation can precipitate cognitive disorders[10–13]. Neurological conditions, such as stroke, epilepsy and those presumed to be secondary to environmental stressors (such as panic disorders and emotional dysregulation), can lead to arrhythmias and other cardiovascular disorders[14–16]. Cognitive impairment is frequently reported in patients with chronic heart failure[17]. In addition, variation in heart and brain structure has been associated with both increased vascular risk and reduced cognitive function[18]. Moreover, ANS dysfunction and impairment of brain–heart interaction have been observed in acute and chronic stress[15], neurological injury[19], epilepsy[20,21], parkinsonisms[22–24], Alzheimer disease[25], psychosomatic disorders[26,27], schizophrenia[28,29], anxiety[30] and mood disorders[31–34]. Activation of the reward system in the brain has been proposed to improve outcomes after acute myocardial infarction, suggesting a potential neurocardiac therapeutic target[35]. Additionally, the identification of a vagal–brainstem interoceptive circuit, which mediates cough-like defensive behaviours in mice[36], highlights the complex neural regulation of protective reflexes with broader implications for cardiopulmonary health.

To date, hundreds of important studies on the brain–heart axis have been published, with a substantial increase in the past decade, and several reviews contain insightful generalizations and models of the brain–heart axis[37–44]. However, the specific constituents of this axis, which are essential to our understanding of the interactions between these two organs, remain largely undefined.

In this Review, we integrate research from the fields of cardiology, neurology and neuroscience to identify the anatomical and functional constituents of the brain–heart axis and related interactions. In addition to phenotypic and genetic connections[45], we show that the brain–heart axis primarily operates through three functional pathways — neural, mechanical and biochemical (Fig. 1). The neural pathway (connected through ionic currents) involves the ANS and intrinsic cardiac nervous system (ICNS) that target the central autonomic network (CAN), which controls autonomic functioning. The mechanical pathway (connected through blood pressure waves) involves mechanoreceptors, specifically those with Piezo protein channels, which primarily convey information on peripheral and cerebrovascular blood pressure dynamics. The biochemical pathway is mediated by a complex system of biomolecules, including cardiac steroids and natriuretic and neural peptides, which act independently of neural and cardiovascular tissues. We discuss in detail the mechanisms involved in each of these pathways individually as well as the interactions that occur between pathways, and the specific regulatory processes generated.

The neural pathway

The neural pathway comprises the bidirectional connection between the CNS and the ANS through both sympathetic and parasympathetic branches. The heart is the first organ to develop during embryogenesis, beginning to beat around day 21 or 22 after fertilization, whereas neural regulation does not develop until week 8 after fertilization[46]. Therefore, the original flow of information is likely to be in the heart-to-brain direction.

In the heart, the ICNS mediates interaction with the brain, allowing regulatory cardiovascular feedback through an ICNS–ANS control loop. In the brain, the neural pathway is identified by the CAN. Research suggests that the brain engages different neural networks in the CAN to receive and control various autonomic signals in a time-resolved and task-dependent manner[22,25,33,41,47–50]. A hierarchical model has been proposed, in which the cortical and subcortical hubs[51] of the CAN supplement the intrathoracic ganglia and ICNS[52].

The central autonomic network

The CAN is a complex integratory network in the CNS that regulates autonomic functioning[22,25,40,48,49,53–56] and involves several regions of the brain (Box 1), discussed individually below[56]. Through intricate anatomical and functional interaction, the CAN integrates information from the CNS and peripheral nervous system. Signals are sent

from the CAN to the cardiovascular system via the efferent pathways of the ANS, and input is received through the opposing, afferent nerves[57]. The sympathetic and parasympathetic branches of the ANS then directly influence heartbeat dynamics, cardiac contractility and vascular tone.

Cerebral cortex. Higher brain centres in the cerebral cortex participate in the modulation of autonomic regulation during emotional and cognitive processes, such as those related to stress or anticipation, and in the conscious control of physiological responses[58]. The most important parts of the cerebral cortex in the CAN include:

- The medial prefrontal cortex, which is involved in the processing of emotions and baroreflex function[59].
- The orbitofrontal cortex, which is closely connected with the amygdala and has a primary role in voluntary cognitive control over autonomic functioning, olfactory perception and the reinforcement of affective states through reward processing[41].
- The anterior cingulate cortex, which integrates cognitive and emotional information[60], as well as exteroceptive and interoceptive cues (contributing to self-awareness[61]). The subgenual anterior cingulate cortex is linked to prefrontal cortical regions and the vagal system. Magnetic stimulation of communication between these areas has provided insights into the treatment of depression[62].
- The posterior cingulate cortex is thought to integrate interoceptive, sensory and cognitive information from other brain regions to modulate autonomic regulation[41].

Insular cortex. The insular cortex, also known as the insula, is part of the limbic system and modulates cardiac function in response to interoceptive and emotional sensations[63–65]. Located deep in the lateral sulcus, beneath the frontal, parietal and temporal lobes (Box 1), the insula is divided into bilateral anterior and posterior regions, each associated with distinct functions. The right anterior insula preferentially controls sympathetic activity, which increases arousal, heart rate and blood pressure[63–65]. The left anterior insula is associated with parasympathetic activity, which reduces these cardiovascular functions[40,66–68]. Indeed, the perception of heartbeats, which is related to interoception or self-awareness, is thought to be sustained by the insula, and the level of perception is dependent on the connectivity of inner insula structures[69]. Somatosensory perception involves brain–heart interactions[70], and increased perception of heartbeats might promote empathic sensitivity and regulation of arousal, which are specifically controlled by the right anterior insula[66,68,71,72].

Hypothalamus. The hypothalamus functions as a central command hub for the coordination of autonomic modulatory mechanisms. This region receives sensory information from various sources and integrates these signals to modulate the autonomic adjustment of variables, such as heart rate, blood pressure and body temperature. The hypothalamus also modulates autonomic reactions to stress, emotion and other physiological stimuli[73]. One of the most important parts of the hypothalamus is the paraventricular nucleus, where afferent and efferent signals from the heart and kidneys are integrated. These signals are a vital part of the hypothalamic–pituitary–adrenal (HPA) axis. The role of the paraventricular nucleus is to respond to stress through the release of corticotropin, which induces the release of adrenocorticotropin from the pituitary gland, ultimately activating the adrenal cortex in the kidneys to release cortisol, the main stress hormone[74]. This cascade is often related to catecholamine-induced effects on neuronal firing rate and receptor expression in the brain[75,76], and to a pathological or acute physiological increase in sympathetic activity and blood pressure[77,78].

Thalamus. The thalamus is located below the cerebral cortex and above the midbrain[79] (Box 1) and has strong bidirectional connections with the hypothalamus[80]. The thalamus has a key role in integrating and relaying afferent cardiac sensory and nociceptive signals to higher regions of the CAN, such as the insula and anterior cingulate cortex, where emotional and cognitive processing, visceral sensations and autonomic modulation of heart rate and blood pressure occur[79]. Activity of thalamic neurons is mainly determined by afferent signals that originate from cardiac rhythm and breathing[81].

Amygdala. The amygdala, which is part of the cerebrum and the limbic system, is involved in processing emotions[40], particularly in the regulation of affective states such as fear and anxiety. This region is also involved in memory and sociobehavioural reactivity and self-regulation (in response to both external and internal stimuli), and is highly

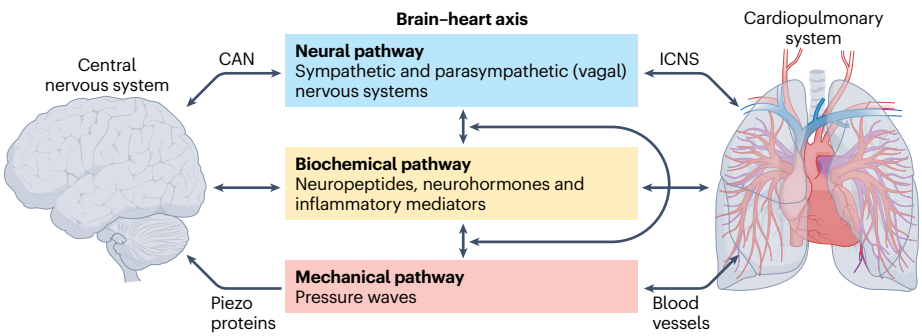


Fig. 1 | Neural, mechanical and biochemical pathways involved in the brain–heart axis. The neural pathway involves the central autonomic network (CAN) and the intracardiac nervous system (ICNS), operating through the sympathetic and parasympathetic (vagal) branches of the autonomic nervous system, connected through ionic currents. The biochemical pathway features neuropeptides and neurohormones that facilitate communication between the brain and the heart, together with other biochemical agents, such as those involved in inflammatory processes. The mechanical pathway is mediated by mechanoreceptors (Piezo proteins) and the blood vessels, in which brain–heart communication is achieved through blood pressure waves. Individually and in combination, these pathways control many physiological functions, such as blood pressure regulation.

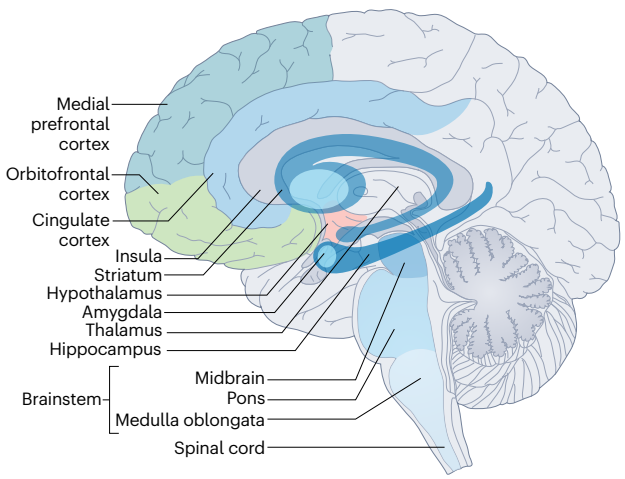
interconnected with the hypothalamus, insula and other autonomic centres[82]. Through the amygdala, emotional and mental stress can strongly influence CAN activity, with consequences for autonomic regulation of the cardiovascular system[83–87].

Brainstem. The three components of the brainstem — the midbrain, medulla oblongata and pons (Box 1) — contain important autonomic nuclei that control cardiovascular functions. The upper brainstem responds to physiological stress and pain, mediated by various areas of the forebrain on the basis of nociceptive information and emotional and cognitive excitations[88], whereas the lower brainstem controls blood circulation and breathing.

In the midbrain, the periaqueductal grey (PAG) matter receives signals from the prefrontal cortex, insula, cingulate cortex and amygdala[41], as well as some afferent inputs from cardiac nociceptors[37].

Box 1 | Main regions of the central autonomic network

- Medial prefrontal cortex
- Orbitofrontal cortex
- Cingulate cortex
- Insula
- Striatum
- Hypothalamus
  - Paraventricular nucleus
- Amygdala
- Thalamus
- Hippocampus
- Brainstem
  - Midbrain (containing the periaqueductal grey matter)
  - Pons (containing the locus coeruleus and parabrachial nucleus)
  - Medulla oblongata (containing the caudal ventrolateral medulla, rostral ventrolateral medulla, paraventricular nucleus, nucleus tractus solitarius, nucleus ambiguus, dorsal motor nucleus and area postrema)
- Spinal cord



The primary purpose of the PAG is to arouse the cardiovascular system in painful or stressful situations. Increased PAG activity, and consequently suppressed baroreflex sensitivity, occur during stressful cognitive tasks[41].

Several areas of the medulla are particularly important in the brain–heart axis[89,90]. In the vasomotor centre, for example, subnuclei such as the rostral ventrolateral medulla control sympathetic drive and are involved in the regulation of vascular tone through the contraction and relaxation of smooth muscles in arterial walls, thereby regulating blood pressure and flow[91,92]. Also in the medulla is the dorsal vagal complex, which comprises the nucleus tractus solitarius (NTS), the nucleus ambiguus (the main nucleus responsible for vagal drive to the heart and lungs), the dorsal motor nucleus and the area postrema[92]. One of the crucial functions of the NTS in the brain–heart axis is control of respiratory and heartbeat dynamics. The NTS receives afferent inputs from peripheral chemoreceptors in the carotid and aortic bodies, which register O_2, CO_2 and pH levels in the blood[93], and from central chemoreceptors in the medulla oblongata, which monitor pH and CO_2 levels in the cerebrospinal fluid[94]. Additionally, the NTS receives and processes signals from mechanoreceptors located in the heart, blood vessels and smooth muscle walls in the lungs[95]. The NTS then relays this information to other autonomic centres, including the pre-Bötzinger complex in the medulla[96] and the locus coeruleus and parabrachial nucleus in the pons, to modulate the rhythm and depth of breathing and synchronize heart rate and blood pressure dynamics[97].

In the pons, the locus coeruleus is primarily involved in the modulation and synchronization of cardiac and respiratory rates[98] via the secretion of noradrenaline into the synapse. Increased secretion of noradrenaline, as part of the arousal response[99], increases both sympathetic activity (and consequently heart and breathing rates) and the activity of somatosensory, olfactory, auditory, visual and cognitive brain processing circuits[100,101], which influences cognition and selective attention[101,102]. The locus coeruleus achieves optimal noradrenaline secretion with the integration of sensory and higher brain inputs, and ageing has been associated with reduced locus coeruleus integrity[103]. Moreover, in the pons, the frequency of neuronal oscillatory activity is consistently around 0.15 Hz[104,105]. This phenomenon is thought to derive from phase locking between heartbeat and cerebrovascular dynamics[106], breathing[107] and the cerebral cortex[108], and acts as a 'pacemaker'. Consequently, the locus coeruleus and parabrachial nucleus in the pons are considered to be important regulatory centres of the brain–heart axis that also mediate interhemispheric communication in the insula[109]. In the spinal cord, a lower level of control facilitates the coordination of sympathetic reflexes.

The CAN in cardiovascular disease. The importance of the CAN in the neural pathway of the brain–heart axis came to the fore after patients with heart disease were observed to have anomalous CAN activity and connectivity compared with healthy individuals[110]. For example, increased activity in the amygdala[111,112] and reduced connectivity with some other parts of the CAN[113–116] have been identified in patients with takotsubo syndrome. However, other studies of individuals with this condition have shown evidence of increased CAN connectivity (between the amygdala, prefrontal cortex, anterior cingulate cortex and insula, which are involved in emotional processing and autonomic regulation)[116,117]. Analysis of effective connectivity in the CAN of healthy individuals has revealed directed communication from the right amygdala to the anterior cingulate cortex and the ventrolateral prefrontal cortex, which could represent a specific neural circuit involved in

regulating cardiovascular dynamics, such as heart rate and heart rate variability (HRV)[118]. Reduced connectivity between subnetworks of the cerebral cortex left hemisphere (involved in the regulation of emotional, cognitive and affective functions) and the thalamus has also been found in patients with coronary heart disease, a condition that is often accompanied by depression[119].

The intrinsic cardiac nervous system

The ICNS is a crucial component of the brain–heart axis, acting as a vital neural network that can process information independently of the CNS[37–39,120]. The human heart contains >40,000 ICNS neurons[121], primarily located on the posterior surfaces of the atria, but also present in the ventricles and coronary arteries, albeit in smaller populations[122]. In mice, high-resolution imaging studies have demonstrated a substantial population of neurons at the base of the heart, approximately at the level of the atria[123,124], which has been identified as the ICNS[125]. Neurons of the ICNS are characterized by high synaptic plasticity and have an important role in maintaining cardiovascular homeostasis, including heartbeat dynamics, contractility and coronary blood flow[121]. Dysregulation of these neurons can lead to the development of cardiac arrhythmias[126–129].

The ICNS is influenced by sympathetic and parasympathetic activity; most ICNS neurons are cholinergic, with a small number of noradrenergic or dual phenotype neurons[130]. The ICNS also contains sensory neurons that detect mechanical and biochemical changes in the heart. These neurons send signals to local intracardiac circuits and to higher centres in the CAN[131]. Therefore, the ICNS receives sensory feedback from within the heart, processes this information locally and integrates regulatory signals that can be dependent on or independent of CNS commands[132]. In this way, complex ICNS neural networks[121] can also modulate neural plasticity and memory[132]. However, some ICNS neurons do not receive or send signals to the ANS, and their function remains unknown[132]. Interestingly, transplanted hearts can still exert autonomic regulation through hormone release despite the ICNS being disconnected from the brain[42].

The sympathetic and parasympathetic ANS

The neural pathway of the brain–heart axis includes the sympathetic and parasympathetic branches of the ANS. The vagus nerve (the tenth cranial nerve) is part of the parasympathetic nervous system and originates from the dorsal vagal nucleus and the nucleus ambiguus in the medulla oblongata[133]. After exiting the medulla, the vagus nerve travels down the preganglionic vagus efferent (descending) nerve, reaching the carotid artery in the neck where it branches into the left and right vagal nerves[134]. These nerves pass through the chest to the cardiac plexus, from which multiple vagal fibres descend and permeate the sinoatrial node, atrioventricular node, atria and, to a lesser extent, the ventricles (bundle of His and Purkinje fibres)[135]. Vagal signalling between the heart and the medulla oblongata, NTS[136] and higher brain regions[137] is an example of a purely neural communication pathway.

The sympathetic pathway involves a series of neural connections, starting from the intermediolateral cell column of the thoracic and upper lumbar spinal cord segments (T1 to L2 in the lateral horn). From there, preganglionic fibres descend to the paravertebral ganglia (sympathetic chain)[138], where some preganglionic neurons synapse with postganglionic neurons. Postganglionic fibres then travel along blood vessels (including the coronary arteries) to the cardiac plexus. Finally, sympathetic fibres penetrate the sinoatrial node, atrioventricular node, ventricular walls and coronary arteries, where adrenergic receptors (predominantly β-type) are activated by noradrenaline released from sympathetic endings[139].

Efferent pathways transmit sympathetic and parasympathetic activity from the ANS to the sinoatrial node, which characterizes heartbeat dynamics. As such, power spectral analysis of HRV series is the main non-invasive method of quantifying sympathovagal activity. In the HRV spectrum, power in the low-frequency range (0.04–0.15 Hz) reflects both sympathetic and parasympathetic (vagal) activity, whereas power in the high-frequency range (0.15–0.40 Hz) can reflect some parasympathetic activity, but only if respiratory frequency is between 0.15 and 0.40 Hz[140]. HRV has been identified as a fundamental ANS biomarker, revealing the dynamic interaction between cardiac and brain activity (for example, in cognition, regulation of mood and emotion, and in disease states)[87,141,142]. Increased HRV, and so higher-frequency power, has been consistently associated with greater efficiency of neural networks involving the prefrontal cortex and subcortical structures, facilitating improved self-regulation and adaptability to stress[143]. In addition to the low-frequency and high-frequency bands, oscillations whose frequency falls in an intermediate range (0.10–0.20 Hz or 0.12–0.18 Hz) of the HRV spectrum seem to be involved in CNS–ANS interactions[63,144]. Alternatively, the low-frequency band can be divided into two sub-bands: 0.04–0.10 Hz, which is assumed to originate from sympathetic control of vascular activity, and 0.10–0.15 Hz, which seems to be linked to central control of vagal efferent pathways[145]. Respiratory sinus arrhythmia is also important for sympathovagal balance, and the question of whether it originates from a central or a baroreflex mechanism is open for discussion[146]. The hypothesis of a central mechanism points to the pacemaker-like activity of an autonomous oscillator located in the CNS operating at a frequency of around 0.15 Hz (closely linked to arterial Mayer waves)[147]. The role of this oscillator is to adjust respiratory sinus arrhythmia to achieve optimum blood pressure[148] (discussed in greater detail below) as well as pulmonary blood and air flow (perfusion–ventilation) for physical and mental functioning, which is achieved by varying the heartbeat within breathing cycles[149,150].

The mechanical pathway

The mechanical pathway of the brain–heart axis involves baroreceptors (mechanoreceptive neurons) and cardiorespiratory dynamics, and is initiated by afferent heart-to-brain communication. The activity of the left ventricle, aorta and brain modulates left ventricular contractility (measured by end-systolic elastance), aortic stiffness, pulse wave velocity and heartbeat dynamics, to regulate carotid pulsatile power and cerebral blood flow[151]. Notably, cerebral blood flow is not the primary signal in heart-to-brain communication, because mechanically induced nerve activation precedes changes in cerebral blood flow[151].

Piezo proteins and cerebrovascular dynamics

The mechanical pathway of the brain–heart axis relies on mechanoreceptive neurons that transduce mechanical stimuli into electrical signals. Piezo proteins, such as Piezo-type mechanosensitive ion channel component 1 (PIEZO1) and PIEZO2, are protein structures around the opening of mechanosensitive transmembrane ion channels[152–154], which detect blood pressure changes and are an integral part of baroreflex afferent pathway in the brain–heart axis[155,156]. Mechanoreceptors expressing Piezo proteins can detect various types of mechanical stress[146] — shear, stretching and tensile stress, hydrostatic pressure, as well as stiffness and elasticity[157] — depending on the direction of action of the mechanical force. Several brain regions respond to Piezo signalling[156,158–160]. The somatosensory and auditory cortices

use signals from Piezo proteins to process tactile and proprioceptive information from the body and from sound stimuli in the inner ear[161]. The brainstem and thalamus also receive and process signals from mechanoreceptors throughout the body[81].

PIEZO1 seems to be present primarily in cardiac[159,162], CNS and vascular cells, including endothelial cells in brain capillaries[163] and astrocytes[164,165], in which shear stress is detected from fluid flow[159,166]. The Human Protein Atlas contains a comprehensive overview of PIEZO1 and PIEZO2 gene and protein expression in various brain regions. PIEZO2 is found predominantly in various somatosensory neurons[159], but also in a very small number of astrocytes and glial cells more generally[167]. PIEZO2 expression increases with greater stiffness in the white matter and viscoelasticity in the pons, and an inverse relationship exists between PIEZO2 expression and deformation in the pons[168]. PIEZO2 has an important role in brain signalling[169], not only in mechanotransduction throughout the brain, but also in the mechanosensation of stimuli in the blood vessels derived from heartbeat dynamics[160,167,170]. Therefore, many brain[168] and cardiac structures, afferent baroreflex pathways[155] and the hair cells of the inner ear[161] contain both PIEZO1 and PIEZO2 (ref. 158), indicating that afferent (interoceptive) nerves and interneurons in the thalamus and cerebral cortex are modulated through interactions with capillary endothelial cells via pericyte PIEZO1 and PIEZO2 channels. In addition, proliferation of brain pericytes is highly dependent on the influence of blood flow (shear stress[166]) through PIEZO1 expressed in endothelial cells[171].

Intrinsic autoregulatory mechanisms are essential for neurocardiac interactions. Cerebral autoregulation is the process by which blood flow in the brain is maintained at an approximately constant level despite changes in systemic arterial blood pressure[172]. This mechanical mechanism is a crucial component of the brain–heart axis and highlights the interaction between cardiovascular function and neural regulation[173]. Impaired cerebral autoregulation is associated with conditions such as hypertension, stroke, heart failure[174,175] and cognitive decline[176]. Similarly, coronary autoregulation supports cardiac stability and indirectly influences cerebral perfusion, notably in patients with heart failure[177]. Endothelial function, which regulates vascular tone via nitric oxide, is crucial to both cerebral and coronary autoregulation. Endothelial dysfunction, often driven by oxidative stress and inflammation, disrupts neurocardiac balance[178]. In the brain, the neurovascular unit (a complex network of cells and extracellular components) ensures that blood flow aligns with brain activity; impairments in this structure are associated with neurodegeneration[179].

Cardiorespiratory dynamics

In the context of the brain–heart axis, the heart is a neural–mechanical–humoral organ located at the crossroads of sympathetic and parasympathetic innervation. Left ventricular ejection fraction (LVEF), a variable of particular interest in the interaction between the heart and the brain, quantifies the ratio between the amount of blood ejected during systole (stroke volume) and the amount of blood ejected at the end of diastole[180]. The estimated LVEF provides insights into the condition of the left ventricle, which performs the crucial task of receiving oxygenated blood and ejecting it through the aorta into the systemic circulation[181]. As blood is delivered to the brain, pulsatile mechanical pressure energy is transferred, substantially affecting brain activity[151,160,182–184]. The latest research suggests that a fundamental relationship exists between LVEF and CAN activity, particularly with the functional and structural integrity of the right insula[185,186]. Moreover, right insula activation during stressful, emotional or physically demanding situations seems to be associated with increased sympathetic activity[48,77,114], which acts on both ventricles and could also reflect nociceptive processing in the brain[187,188]. These findings suggest that increased sympathetic and right insula activity (such as in the context of ischaemic stroke) could be causally involved in cardiovascular disorders characterized by reduced LVEF[185,186]. Importantly, parasympathetic activity can also influence ventricular contraction through cardiac cholinergic neurons, which have a role in modulating heartbeat dynamics and cardiac contractility[189].

Information about pulsatile blood pressure oscillations is received by baroreceptor neurons. High-pressure arterial baroreceptors are located in the aorta and carotid sinus[160], whereas low-pressure baroreceptors are concentrated in the atrial walls, ventricles and intrathoracic vessels[190,191]. As a fundamental part of the mechanical brain–heart axis, afferent signals from baroreceptors in the aortic arch are transmitted by the vagal nerve, and from the carotid sinus by the glossopharyngeal nerve[160], to the NTS and other areas of the medulla where the information is integrated[160]. Compensatory feedback signals are then generated to restore homeostatic blood pressure levels[42]. From the NTS, baroreceptor signals are also transmitted to the thalamic nuclei, insula, amygdala and cingulate cortex. Additional processing and activation in these regions result in heart-evoked potentials in the brain, which typically exhibit latency that reflects the time required for the signal to propagate from the carotid sinus[160]. Disturbance of connectivity between the insula and the amygdala promotes excessive sympathetic activity and impaired baroreflex control[114].

Respiratory activity also has an important role in brain–heart communication. The coupling of heart and breathing rhythms is both mechanical, due to the proximity of the heart and lungs in the chest cavity, and neural, owing to CAN hubs shared by these organs[192]. Networks in the brainstem and cerebellum, with driving oscillations at 0.10 Hz and 0.15 Hz, dictate patterns of cardiorespiratory coupling during physiological conditions, such as rest, sleep, meditation, physical activity and in response to body posture[145,192]. The variable oscillations of breathing cause physical movement of the heart, exerting a mechanical influence on its rhythm through respiratory sinus arrhythmia[145,193,194] and, above all, by inducing changes in aortic pressure[193]. In addition, the NTS is both a neural generator of cardiorespiratory coupling and a neural hub in which local oscillators are connected to peripheral cardiorespiratory oscillators[195]. The main mechanical indices of the cardiorespiratory system with which the brain is linked are preload, blood pressure, heart rate, inspiration, expiration and respiratory rate. Preload provides information on hydrostatic pressure during filling of the heart chambers, detected by stretch receptors (mainly cationic PIEZO1, transient receptor potential channels and large-conductance calcium-activated potassium (BK_{Ca}) channels in the myocytes and fibroblasts of the atria and ventricles)[159,196–200]. As discussed above, blood pressure is sensed by baroreceptors in the aortic arch and carotid sinus[201], whereas inspiration, expiration and respiratory rate are discerned by stretch receptors in the lungs[202–204]. Information on these indices is sent as afferent signals to the CAN[201], particularly the NTS, insula and the locus coeruleus in the pons of the brainstem[98,205].

The biochemical pathway

The biochemical pathway of the brain–heart axis operates through a complex network of biomolecules secreted by the CNS, the neuroendocrine system and the cardiovascular system. These biochemicals are detected by neuroreceptors and chemoreceptors throughout the body, particularly in the CNS and cardiovascular system. Several subsystems, such as

the renin–angiotensin–aldosterone system and the HPA axis, as well as processes related to microRNAs, cytokines and hormones, contribute to the biochemical pathway[206,207]. Important methodological advances, particularly in biochemical imaging and chemical biology, have enabled the sensing and manipulation of biochemicals, such as neuromodulators and neuropeptides, released throughout the brain and the body[208,209].

Natriuretic hormones

Natriuretic hormones, including natriuretic peptides and endogenous cardiac steroids, have a vital role in the biochemical pathway of the brain–heart axis. Natriuretic peptides are classified into three types: atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP and BNP are primarily released from the atria, whereas CNP is produced by vascular endothelial cells. Natriuretic peptides have potent cardiovascular and renal effects, particularly in blood pressure regulation; are involved in bronchodilation and vasorelaxation; and have anti-inflammatory and metabolic effects. Notably, these hormones also influence brain activity, and several natriuretic peptide receptors have been identified in the CNS, where they act as neurotransmitters and neuromodulators involved in higher-order brain functions[210].

Endogenous cardiac steroids are a group of compounds produced in the adrenal gland and hypothalamus[211] that affect sodium and potassium metabolism[210]. For example, the human ouabain-like compound (a cardiac glycoside) modulates both brain and heart activity by inhibiting the Na^+/K^+-ATPase pump, which leads to disruptions in ion homeostasis, particularly sodium and calcium levels. Through this purely biochemical pathway, neural excitability and synaptic plasticity in the brain is increased and, in the heart, elevated intracellular calcium levels lead to enhanced cardiac contractility[212]. Endogenous cardiac steroids also affect other physiological processes, such as blood pressure control[213–216].

Neuropeptide Y

Among the many biochemicals that mediate sympathetic and parasympathetic activity[217], neuropeptide Y (NPY) is a constituent of many neural, cardiovascular and psychophysiological processes[218–220]. NPY is primarily produced in the CNS, particularly in the hypothalamus, amygdala and brainstem[221]. Additionally, NPY is synthesized and released by neurons in peripheral tissues, including the adrenal glands, sympathetic nervous system and enteric nervous system in the gastrointestinal tract[222,223]. NPY is involved in various physiological processes, including appetite regulation, stress response and modulation of cardiovascular function[224].

NPY mediates autonomic regulation by suppressing both noradrenaline and acetylcholine, which are drivers of sympathetic and parasympathetic activity, respectively[225]. However, through independent mechanisms, both adrenaline and NPY can cause vasoconstriction, increased blood pressure and ventricular tachycardia. Although the suppression of noradrenaline release by NPY can, in rare cases, lead to reduced vasoconstriction, its direct vasoconstrictive effect predominates in pathophysiological conditions such as heart failure, hypertension and acute stress[226–228].

In the brain, NPY type 1 receptors (NPY1Rs) have been identified in the cerebral cortex, thalamus, NTS, the dorsal medial subdivision of the hypothalamus, the dorsal medial striatum (in the basal ganglia in the forebrain) and in a small number of neurons in the rostral ventrolateral medulla[225,229]. NPY1Rs are also found in cardiomyocytes, endothelial cells and the vasculature of cardiac structures[230]. NPY1Rs are coactivated by noradrenaline, thereby modulating sympathetic communication between the brain and heart[229,230]. NPY type 2 receptors (NPY2Rs) are expressed in several CAN regions, such as the hippocampus, brainstem and hypothalamus, and in autonomic nerves, endothelial cells, adipocytes and cardiac cells. NPY2Rs inhibit glutamate and noradrenaline, thereby modulating vasoconstriction and blood pressure[225].

In 2023, Lovelace and colleagues demonstrated that the relationship between vagal afferent pathways and the ICNS is the basis of the Bezold–Jarisch reflex, which triggers syncope and is controlled by sensory neurons expressing NPY2Rs[151]. These NPY2R vagal sensory fibres are primarily located in the ventricular walls but are also present in the atrium and aortic arch[151]. Although the ventricles contain fewer intracardiac neurons than the atria, the presence of NPY in intracardiac neurons[231,232] close to afferent sensory fibres[121] is an important finding. The connection between intracardiac neurons and ANS sensory fibres is, therefore, likely to be dependent on NPY. Indeed, a vagal afferent pathway mediated by NPY receptors runs through the nodose ganglia and leads to a small region of the postrema in the brainstem, ending with a population of NPY2R neurons expressing the same receptor subtype (Y2R) as the cardiac vagal afferent neurons. This commonality implies a parallel role for these neurons in the reflex loop and underscores the functional unity of the vagal afferent pathway from the heart to the brainstem mediated by NPY2Rs. Cardiac NPY2R neurons sense a physical lack of blood in the ventricle and send a signal to the postrema via the vagus nerve. Subsequently, the afferent signal travels from the postrema to the parabrachial nucleus and then to the hypothalamus and other CAN nuclei. Therefore, the postrema, parabrachial nucleus and paraventricular nucleus, which all have <100 ms of neural activation latency after photostimulation[151,233], are central hubs for rapid vagal amplification and, when necessary, for transient loss of consciousness as syncope. Whether this specific afferent brain–heart axis signalling pathway is activated only in syncope or is also part of normal crosstalk between these two organs is not yet fully understood. From a pathological viewpoint, deficient vagal activity in patients with depression[33] might be related to the activity of NPY2R neurons, and reduced expression of NPY is known to be associated with depression and suicidal behaviour[234].

Inflammatory mediators

Inflammatory mediators form part of the biochemical pathway in the brain–heart axis[78,235]. Both acute and chronic inflammatory states modulate cardiac and cerebral functions by releasing mediators, such as cytokines and chemokines, which maintain physiological homeostasis, but can also contribute to various pathologies. For example, acute myocardial infarction triggers a strong inflammatory response, leading to the release of pro-inflammatory cytokines, such as IL-1β, IL-6 and tumour necrosis factor. These cytokines can cross the blood–brain barrier, activating microglial cells in the brain and initiating neuroinflammation, which can be associated with cognitive impairment and symptoms of depression[236]. Similarly, acute cerebral ischaemia can lead to myocardial damage due to excessive sympathetic stimulation and inflammatory mediator release[237,238]. Moreover, chronic inflammation is a hallmark of numerous cardiovascular and neurological diseases, such as atherosclerosis, hypertension and heart failure, and can impair cerebral vessels, leading to cognitive impairment and an elevated risk of dementia[239,240].

Interactions between pathways

As well as operating independently, the three pathways of the brain–heart axis interact through specific directional connections (Fig. 2), improving regulatory dynamics[217]. For example, the baroreceptor reflex in the mechanical pathway initiates neural signalling, which can then

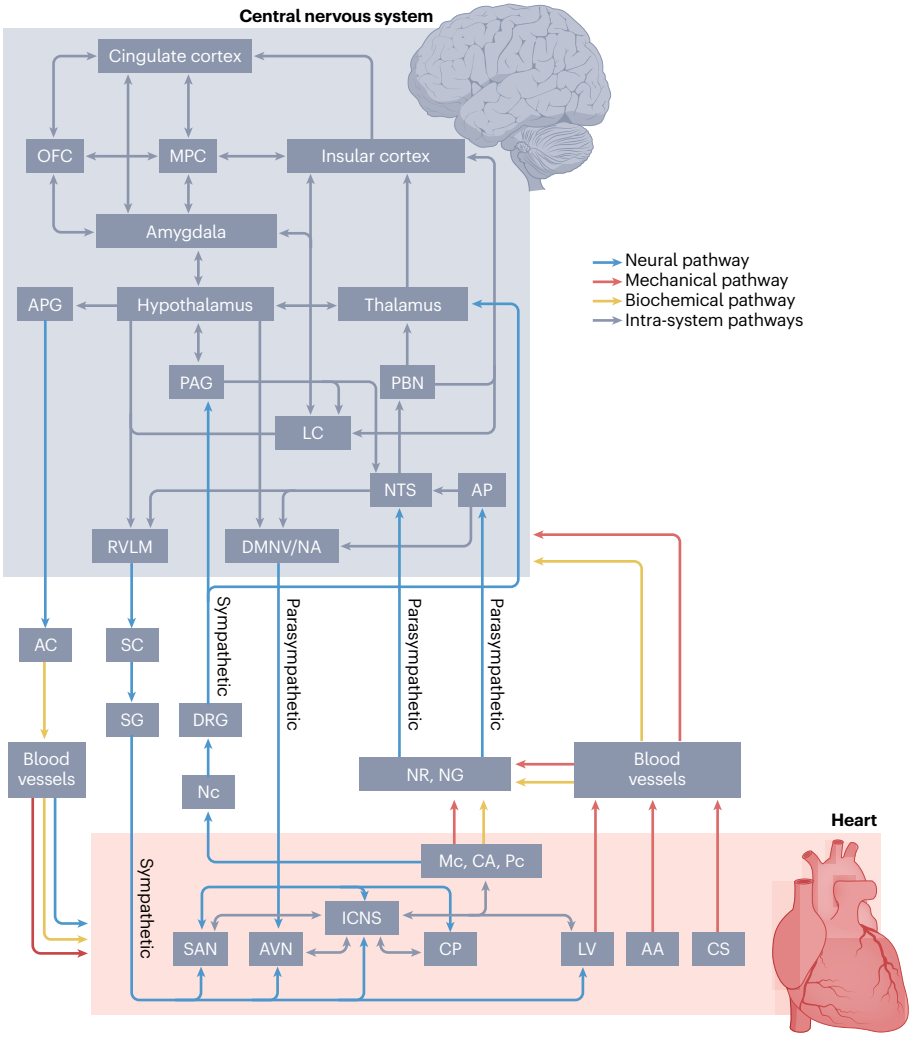


Fig. 2 | Functional communication in the brain–heart axis. The direction of functional communication is indicated by the direction of the arrows. AA, aortic arch; AC, adrenal cortex; AP, area postrema; APG, anterior pituitary gland; AVN, atrioventricular node; CA, coronary arteries; CP, cardiac plexus; CS, carotid sinus; DMNV, dorsal motor nucleus of vagus; DRG, dorsal root ganglia; ICNS, intrinsic cardiac nervous system; LC, locus coeruleus; LV, left ventricle; Mc, myocardium; MPC, medial prefrontal cortex; NA, nucleus ambiguus; Nc, nociceptors; NG, nodose ganglia; NR, neuroreceptors; NTS, nucleus tractus solitarius; OFC, orbitofrontal cortex; PAG, periaqueductal grey matter; PBN, parabrachial nucleus; Pc, pericardium; RVLM, rostral ventrolateral medulla; SAN, sinoatrial node; SC, spinal cord; SG, sympathetic ganglia.

trigger biochemical reactions related to brain oxygenation as well as the release of neurotransmitters. Therefore, mechanical, neural and biochemical signalling is integrated via sympathovagal activity and the CAN. Similarly, mechanical blood pressure signals detected by intracerebral Piezo receptors are processed by neurons, exemplifying neuromechanical interaction through neurovascular coupling. In addition, the NTS receives afferent input from peripheral chemoreceptors in the carotid and aortic bodies connected to the vagus nerve, demonstrating interaction between the biochemical and neural pathways.

Blood pressure control

Blood pressure regulation is a paradigmatic example of neural, mechanical and biochemical interaction. The heart chambers, aorta, brain capillary pericytes and Piezo receptors promote and detect changes in pressure. This afferent information seems to be processed primarily in the NTS, insula and locus coeruleus, enabling the brain to operate several concurrent regulatory mechanisms. Through the action of a pacemaker-like oscillator, operating at approximately 0.15 Hz, the brain homeostatically adjusts various physiological indices, such as respiratory sinus arrhythmia, to maintain optimal blood pressure. The primary systemic drivers are the parasympathetic (cholinergic) and sympathetic (adrenergic) activities that synchronize central, cardiac and respiratory functions. The locus coeruleus has a crucial role in these processes by secreting noradrenaline, which amplifies sympathetic and cortical activity, thereby increasing arousal and attention while also modulating heart rate and respiratory rate. Integrated signalling of the paraventricular nucleus, HPA axis and rostral ventrolateral medulla regulates blood pressure, whereas the NTS and locus coeruleus regulate cardiorespiratory coupling and slow breathing resonance effects. The ventromedial prefrontal cortex modulates the baroreceptor reflex and, eventually, the anterior cingulate cortex mediates self-awareness and initiates voluntary slow breathing[241]. The synergy between integrated neural signalling in the CAN and mechanical sensing via Piezo receptors, enables allostatic fast responses (such as freezing, syncope and the diving reflex), as well as slower interoceptive responses (such as meditative states and a sense of self). However, the degree to which mechanical stimuli (such as gravity and blood pressure oscillations) shape neural plasticity and CAN connectivity, and how relevant these stimuli are for maintaining interoceptive performance[161] and in pathogenesis[242], is not yet clear.

PIEZO1 and PIEZO2 modulate the activity of autonomic neurons in the brainstem nuclei involved in heart rate, blood pressure and breathing control[155], as well as the activity of hypothalamic nuclei involved in regulating stress responses. Therefore, connectivity between ICNS clusters can be hypothesized, akin to the known analogous connectivity among CAN regions. Moreover, computational modelling has enabled researchers to demonstrate the role of ICNS and CAN connectivity in maintaining respiratory sinus arrhythmia, blood pressure and heart rate[243]. This mechanical coupling induces energy exchange, which is most effective when phase matching of oscillations is achieved[192]. In that sense, coupling and modulation of physiological oscillations (such as breathing and heart rate) maintain optimum blood pressure. Resonant breathing of 0.1 Hz has been shown to facilitate entry into a meditative state[244]. It can be argued that resonance is achieved through the functional interaction between blood pressure and respiratory dynamics[245], reinforcing baroreflex sensitivity and characteristic 0.1 Hz oscillations resulting from Mayer waves[246]. Baroreceptors become more responsive, sending afferent signals via the NTS to the nucleus ambiguus, thereby increasing vagal tone and shifting autonomic balance towards parasympathetic predominance[246], leading to steadier blood pressure control. Pulmonary stretch receptor input also projects to the locus coeruleus, potentially reducing sympathetic outflow via inhibition of noradrenergic activity, further contributing to vagal predominance[147]. NPY also seems to effectively link the ICNS and CAN, by altering PIEZO1 and PIEZO2 calcium signalling involved in sensing blood pressure changes in the heart and vessels[151]. These communicative pathways are established owing to the presence of both Piezo receptors and NPY in the ICNS of the heart and in brain structures[151].

Regional activation

In the past few years, research on the brain–heart axis has highlighted the importance of specific regional activation in modulating the three pathways. In this section, we provide illustrative descriptions focusing on the insula, as well as the olfactory and hippocampal regions, which are part of the CAN.

Insula. As described above, the insula is a vital hub for integrating autonomic and visceral stimuli, regulating neurocardiovascular homeostasis, as well as emotional processing and regulation[84–86]. The anterior insula connects extensively with limbic structures, such as the amygdala and anterior cingulate cortex[68], contributing to emotional processing, interoceptive awareness (the perception of internal bodily states) and cognitive functions, such as decision-making[247]. All these processes could be dependent on the timing of the cardiac cycle[248]. The posterior insula receives input from thalamic nuclei[249] and is involved in sensory processing, particularly visceral and somatosensory information, such as pain, temperature and touch[84–86]. The posterior insula is also involved in the cardiogenic control of emotional states[250], through which heartbeat dynamics sustain (and might initiate) emotional processing[87].

The insula modulates ANS activity by influencing both sympathetic and parasympathetic branches and interacting with autonomic centres, such as the hypothalamus and brainstem nuclei[85,86,251]. Autonomic control is lateralized in the insula, with the right side predominantly associated with sympathetic activation, and the left side linked to parasympathetic activity[85,86,252], indicating specialized roles for each hemisphere in maintaining autonomic balance and driving symptomatology[253]. Given the role of the insula in emotional processing, this region is important in the context of psychiatric disorders, particularly anxiety and depression, which are linked to emotional dysregulation[254].

Olfactory regions. Brain dynamics mediated by the brain–heart axis occur in the olfactory regions, which include the olfactory epithelium, olfactory bulb and associated cortical areas (predominantly the orbitofrontal cortex). These regions are highly vascularized and depend on precise haemodynamic regulation to meet metabolic demands. Blood supply to the olfactory regions primarily comes from branches of the anterior cerebral artery. Neurovascular coupling ensures that neuronal activity aligns with changes in blood flow, mediated through complex interactions between neurons, astrocytes and vascular endothelial cells[255]. Any disruptions in blood flow can affect olfactory function. Normal odour stimulation increases blood flow to olfactory areas, whereas physical exercise and stress can cause transient changes in cerebral perfusion, affecting olfactory sensitivity. In addition, cardiovascular disorders, such as congestive heart failure, can affect blood flow and neurovascular coupling, potentially reducing olfactory sensitivity[256]. Neurodegenerative diseases, including Alzheimer and Parkinson diseases, also lead to olfactory dysfunction[257]. Together, these findings demonstrate the link between cardiovascular health and olfactory and cognitive functions.

Hippocampus. Brain dynamics mediated by the brain–heart axis also occur in the hippocampal regions. Hippocampal neurons can synchronize with heart rhythms[258], mediated by signals from the vagus nerve and baroreceptors, indicating coordination between the ANS and CNS. Abnormal activity in hypothalamic nuclei, such as the paraventricular nucleus, contributes to the development of hypertension[259]. Cardiac pulsations drive cerebrospinal fluid dynamics, promoting metabolic waste clearance that supports hippocampal health[259]. Additionally, increased HRV is associated with improved prefrontal and, indirectly, hippocampal function[143]. Inflammation from cardiac conditions such as myocarditis[260] and myocardial infarction[261] can induce neuroinflammation, damaging hippocampal plasticity[262]. Additionally, cardiovascular stress can also lead to epigenetic changes, affecting hippocampal gene expression and cognition[263].

The brain–body network

On a broader scale, the brain–heart axis functions as an integral part of a wider network, in which all organs contribute to maintaining bodily functions[264]. Emerging evidence supports the existence of other physiological axes — defined as intricate functional and structural interactions between two or more organs or systems — such as the gut–brain axis, HPA and heart–brain–lung axis[265], and even broader networks, including metabolic–cognitive and temperature regulation systems (Fig. 3). These insights suggest that a multi-axis perspective should be adopted when considering brain–body interactions.

Phenotypic and environmental variation

Various genetic, ethnic and sex-based differences, as well as environmental and socioeconomic factors, exert an effect on the brain–heart axis. For example, Black individuals are disproportionately affected by hypertension and left ventricular hypertrophy, which increases susceptibility to neurogenic myocardial injury and adverse cardiac events[266]. People with post-traumatic stress disorder and early-life adversity, who are at increased risk of myocardial ischaemia due to heightened sympathetic activity and inflammation affecting the coronary microvasculature, often develop ischaemia in subcritical lesions owing to microvascular dysfunction[267]. Indeed, in 2024, the pathogenesis of post-traumatic stress disorder was shown to be associated with dysfunction of the brain–heart axis[268]. Women have greater parasympathetic activity at rest but heightened sympathetic responses under stress compared with men,

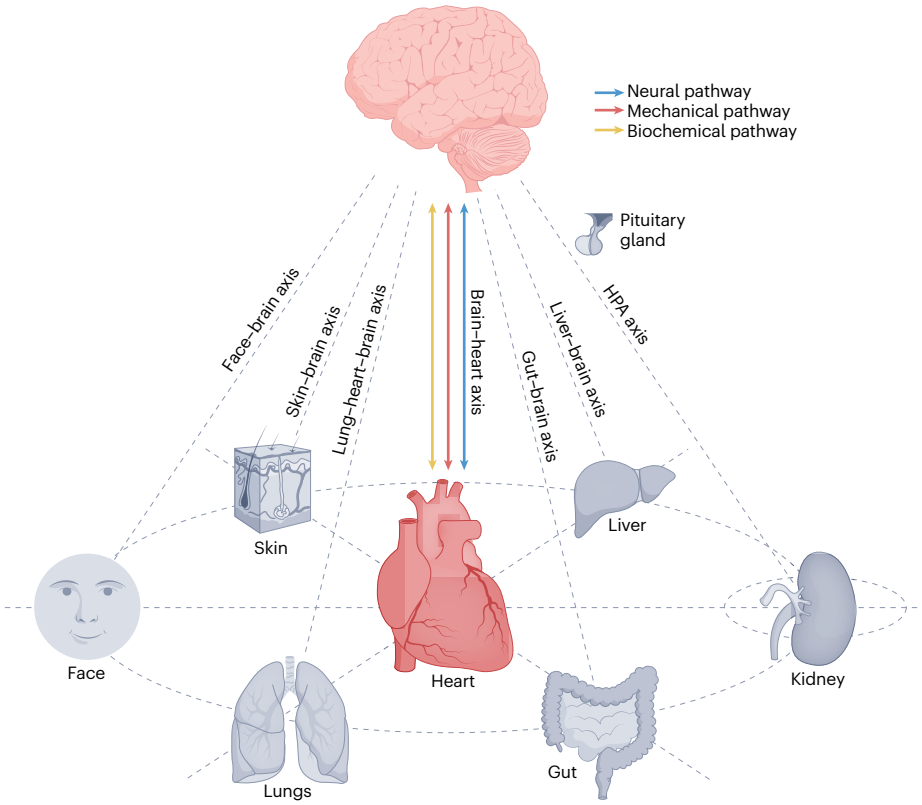


Fig. 3 | Brain–body interactions. Axes between the brain and the body involve interactions between various organs and systems, highlighting the integrative and interconnected nature of physiological functioning. HPA, hypothalamic–pituitary–adrenal.

influencing HRV and stress reactivity[269]. Altered catecholamine responses also contribute to the increased susceptibility of women to pathologies such as takotsubo syndrome[270]. This form of cardiomyopathy is characterized by transient left ventricular dysfunction after intense emotional or physical stress. Additionally, altered catecholamine responses might underly the higher prevalence of ischaemia with non-obstructive coronary arteries in women than in men[271]. In addition, in the past 2 years, genetic colocalizations and correlations between structure and function of both the heart and the brain have been discovered[45].

Conclusions

The brain–heart axis is a multiple-loop, multidimensional network that is crucial for maintaining physiological homeostasis and responding to various stressors. In this Review, we elucidate the primary components of the brain–heart axis, namely the neural, mechanical and biochemical pathways. What was previously considered 'noise' (that is, heartbeat-induced pressure pulsations in cerebral arterial vessels) is now recognized to be a fundamental component of the brain–heart axis, comprising mechanosensitive ion channels in specific subsets of neurons[272]. This paradigm shift should lead to the re-evaluation and reinterpretation of extensive data in the field of neurocardiology, presenting both substantial challenges and exciting opportunities for the research community. At the forefront of this movement is the importance of a multisystem perspective on cardiovascular and neural dynamics, promoting the emergence of specialized clinical disciplines in neurocardiology.

Future research should focus on further delineating specific interactions in the brain–heart axis, particularly the hierarchical recruitment of cortical and subcortical hubs and the mechanistic links between the neural and mechanical pathways. Indeed, despite decades of anatomical and functional research, technological advances continue to reveal novel autonomic pathways, particularly in vagal communication[189,217,273]. Understanding these intricate relationships will be pivotal for advancing therapeutic strategies for conditions arising from dysfunction in the brain–heart axis, such as heart failure and hypertension, as well as neurological and neuropsychiatric disorders. Future studies should also account for phenotypic variations affecting the brain–heart axis, including genetic, ethnic and sex-based differences, which can affect pathogenesis through distinct environmental and socioeconomic factors[45,266,274]. Research efforts should also be directed towards understanding the mutual disturbance of NPY2R neurons and vagal regulation, as well as hybrid therapy comprising vagal nerve stimulation and antidepressants that increase NPY expression[234]. Patterns of CAN connectivity, and correlations with LVEF, in the context of health and disease should also be elucidated. Moreover, novel techniques, such as invasive monitoring with intracranial electroencephalography, and the use of animal models should be leveraged to deepen our understanding of the brain–heart axis. All the aforementioned avenues for research should include standardized protocols, particularly in data-processing methods, because even minor differences in the processing pipeline can result in substantial variation in the resulting inferences[275].

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