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Heart–brain interactions in cardiac and brain diseases: why sex matters

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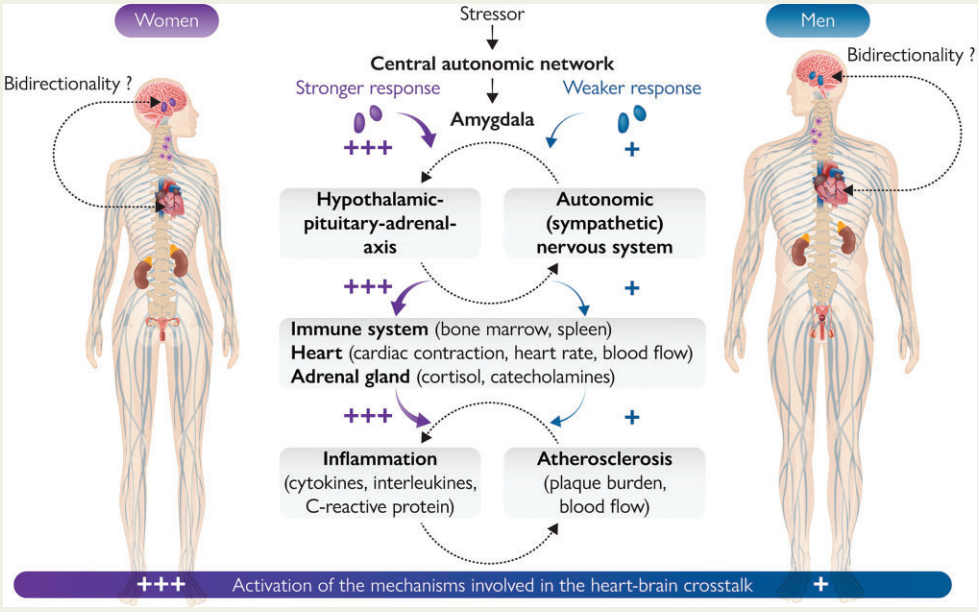

Graphical Abstract Mechanisms involved in the heart–brain crosstalk. Simplified representation of sex differences seen in the main mechanisms and neurohumoral circuits involved in heart–brain interactions. The intensity of activation is represented by a colour code scale, with red indicating the maximal activation. In brief, specific triggers (e.g. stress, acute myocardial infarction) induce the activation of the amygdala via the central autonomic system. Efferent projections increase the activation of the sympathetic nervous system and initiate neurohormonal output through the hypothalamic–pituitary–adrenal axis leading to catecholamine release, myelopoiesis activation, and release of pro-inflammatory cytokines with deleterious effect on the heart. This pro-inflammatory state initiates and promotes atherosclerosis. Current evidence on the pathophysiology of the specific heart and brain disease discussed in this review has shown that the activation of all these mechanisms is more pronounced in women as compared with men. The bidirectionality of heart–brain interactions is still under investigation.

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Cardiovascular disease and brain disorders, such as depression and cognitive dysfunction, are highly prevalent conditions and are among the leading causes limiting patient's quality of life. A growing body of evidence has shown an intimate crosstalk between the heart and the brain, resulting from a complex network of several physiological and neurohumoral circuits. From a pathophysiological perspective, both organs share common risk factors, such as hypertension, diabetes, smoking or dyslipidaemia, and are similarly affected by systemic inflammation, atherosclerosis, and dysfunction of the neuroendocrine system. In addition, there is an increasing awareness that physiological interactions between the two organs play important roles in potentiating disease and that sex- and gender-related differences modify those interactions between the heart and the brain over the entire lifespan. The present review summarizes contemporary evidence of the effect of sex on heart–brain interactions and how these influence pathogenesis, clinical manifestation, and treatment responses of specific heart and brain diseases.

Keywords Heart • Brain • Sex • Gender • Ischaemic heart disease • Heart failure • Takotsubo syndrome • Stroke • Depression • Dementia

Abbreviations

AMI	acute myocardial infarction
BP	blood pressure
CAD	coronary artery disease
CRP	C-reactive protein
^{11}C-mHED	^{11}C-meta-hydroxyephedrine
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry
CT	computed tomography
^{18}F-DOPA	^{18}F-dihydroxyphenylalanine
^{18}F-FDG	^{18}F-fluorodeoxyglucose
fMRI	functional magnetic resonance imaging
FOXO	forkhead box O
$GABA_A$	gamma-aminobutyric acid
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HPA axis	hypothalamic–pituitary–adrenal axis
HRV	hear rate variability
^{123}I-mIBG	^{123}I-metaiodobenzylguanidine
IHD	ischaemic heart disease
IL	interleukin
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MR	magnetic resonance
PET	positron emission tomography
PNS	parasympathetic nervous system
RAAS	renin–angiotensin–aldosterone system
SNA	stress-associated neural activity
SNS	sympathetic nervous system
SPECT	single-photon emission computed tomography
STEMI	ST-elevation myocardial infarction
^{99}Tc-MIBI	^{99}Technetium-methoxyisobutyl isonitrile
TSPO	18kD translocator protein
TTS	Takotsubo syndrome.

> Every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart.
>
> *William Harvey*

Introduction

A growing body of evidence demonstrates an intimate and bidirectional crosstalk between heart and brain, resulting from a complex network of several physiological and neurohumoral circuits.[1] From a pathophysiological perspective, both organs share common risk factors, such as hypertension, diabetes, smoking, and dyslipidaemia, and are similarly affected by systemic inflammation, ischaemia due to atherosclerosis, and dysfunction of the neuroendocrine system. Moreover, an increasing number of reports shows that physiologic interactions between the two organs can drive the development of cardiovascular as well as cardiometabolic conditions.[2–6]

Sex-related differences develop and modify the heart–brain axis during the entire lifespan.[7,8] Therefore, a deeper understanding of how sex affects heart–brain crosstalk is of paramount importance for patient-tailored prevention and treatment of multiorgan dysfunctions resulting from either cardiac or brain damage. In this context, our review article summarizes the state-of-the-art knowledge of the effect of sex on the heart–brain interactions involved in the development and co-occurrence of specific cardiac and brain conditions with a particular focus on ischaemic heart disease (IHD), heart failure (HF), Takotsubo syndrome (TTS), stroke, depression, and dementia (*Table 1*).

(Patho)physiological systems regulating heart–brain interactions

In this section, the (patho)physiological systems and pathways involved in heart–brain crosstalk and the related sex differences are described. In addition, a general overview of the main imaging modalities currently available for the evaluation of the heart–brain axis is provided (*Figure 1*). Indeed, new generation multisystem scanners, such as whole-body positron emission tomography (PET)/computed tomography (CT) and PET/magnetic resonance (MR), offer the unique opportunity to combine molecular with functional and anatomical imaging information, thus allowing a better understanding of the interlinked pathways involved in these complex multisystem interactions.

Vascular system

The vascular system is an obvious connector between heart and brain since atherosclerosis is the systemic process identified as

the culprit for causing both acute myocardial infarction (AMI) and stroke. Atherosclerosis is an inflammatory disease initiated and promoted by endothelial activation and dysfunction, leading to an increased vascular permeability for plasma proteins, upregulation of adhesion molecules, and release of pro-inflammatory cytokines and chemokines.[9,10] The involvement of these local and systemic cascades triggers innate and adaptive immunity[10,11] and induces a state of hypercoagulability,[12] thus increasing the risk of cardiovascular events[13,14] and long-term cognitive impairment.[15]

Thanks to recent technological advances in cardiovascular imaging, it is possible to non-invasively assess atherosclerotic plaques in the coronary arteries, carotids, and aorta[16] as well as their effect on myocardial and brain perfusion. While single and dual-energy coronary CT angiography and MR imaging provide mainly anatomical information on plaque morphology and composition,[17–19] PET radiotracers such as ^{18}F-sodium fluoride, ^{68}Ga-DOTATATE, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) offer additional details on plaque biology and activity,[20,21] thereby allowing a better discrimination between stable and unstable plaques. The current evidence supports a female-specific profile of less obstructive coronary artery disease (CAD) and lower plaque burden, yet with worse clinical outcome.[22]

Regarding the haemodynamic impact of atherosclerosis, single-photon emission computed tomography (SPECT) imaging is the most commonly used non-invasive modality for the evaluation of myocardial perfusion,[23] with a large body of evidence supporting its prognostic role in patients with IHD.[24] Nevertheless, radiation dose associated with SPECT remains an issue,[25] and its performance in perfusion quantification is limited and not standardized.[26] Therefore, PET is considered the reference standard for quantitative measurement of myocardial blood flow by using different radiotracers such as ^{82}Rubidium, ^{13}N-ammonia, ^{18}F-flurpiridaz, or ^{15}O-water.[26] Alternative modalities such as stress echocardiography, MR imaging, and CT are currently available for the evaluation of myocardial perfusion.[27] In the brain, the main techniques currently dedicated to the evaluation of brain haemodynamics are dynamic CT, PET, SPECT, as well as diffusion and perfusion MR.[28,29] Healthy women have been reported to have significantly higher global and regional blood flow than men in both heart and brain.[30–34]

Neurohumoral system

The autonomic nervous system, the limbic network, and the renin–angiotensin–aldosterone system (RAAS) are all important variables affecting the heart–brain axis, hence representing new important therapeutic targets in cardiovascular and neurological diseases.

Through the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), the central autonomic network regulates cardiac contraction, heart rate, and blood flow during basal conditions, as well as in response to different triggers, such as acute and chronic stress.[35] In particular, sympathetic activation has been detected within the prefrontal cortex, anterior cingulate, left amygdala, as well as the right anterior and left posterior insular cortices.[36,37] As such, studies using functional MR imaging (fMRI) techniques to assess connectivity in the brain have demonstrated pathways of heart–brain interactions by identifying the cerebral areas which modulate sympathetic and parasympathetic activity in several conditions, including TSS and hypertension.[38–42] While imaging of adrenergic and cholinergic neurotransmission in the brain is not usually performed, the peripheral autonomic system of the human heart can be interrogated by different approaches.[43] First, heart rate variability (HRV) and heart rate responses to exercise or pharmacological stress are widely used surrogate parameters of the autonomic activity of the heart (*Table 2*). In addition, radiolabelled catecholamine analog-based myocardial imaging by SPECT and PET can provide information regarding the integrity of the cardiac SNS by informing on the status of the pre- and post-synaptic nerve function.[44] At present, ^{123}I-metaiodobenzylguanidine-(^{123}I-mIBG)-SPECT with planar acquisition is considered the reference standard for the evaluation of cardiac sympathetic dysfunction in several cardiac diseases, such as cardiac arrhythmia, IHD, and HF.[45,46] A more sophisticated PET radiotracer is ^{11}C-meta-hydroxyephedrine (^{11}C-mHED), which is characterized by a higher sensitivity and spatial resolution than ^{123}I-mIBG, allowing for the absolute quantification of the regional distribution of cardiac sympathetic neurons.[45,47] Besides ^{123}I-mIBG-SPECT and ^{11}C-mHED-PET, ^{18}F-dihydroxyphenylalanine-(^{18}F-DOPA)-PET, originally used to evaluate the striatal dopaminergic dysfunction in degenerative diseases, has been associated with increased sympathetic activity at cardiac level.[48,49] Sex differences

Table 1 Sex-specific differences identified in the main pathways transmitting along the heart–brain axis for specific cardiac and brain disorders

	IHD	HF	TTS	Stroke	Depression	Dementia
Atherosclerosis	+			+		+
SNS	+	+	+	+	+	
Hyperactivation of amygdala and limbic system	+		+			
HPA axis			+	+		
Inflammation	+			+	+	
RAAS		+				
Impaired cerebral blood flow		+				+

HF: heart failure; HPA: hypothalamic–pituitary–adrenal; IHD: ischaemic heart disease; RAAS: renin–angiotensin–aldosterone system; SNS: sympathetic nervous system; TTS: Takotsubo syndrome.

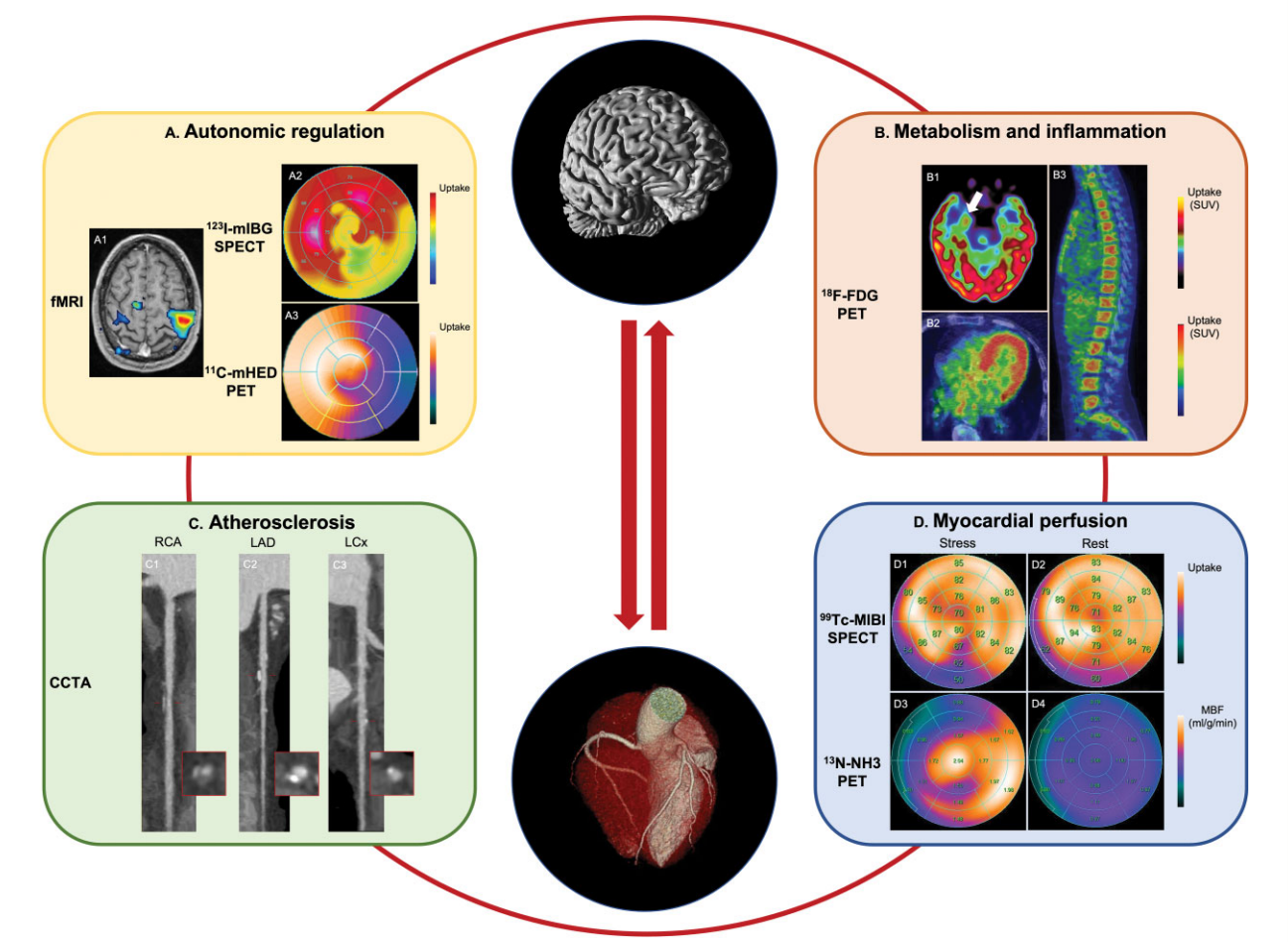

Figure 1 Imaging modalities used to investigate the mechanisms involved in the heart–brain crosstalk. (*A*) Functional MR illustrates activated regions of the brain (A1). ^{123}I-mIBG-SPECT shows a perfusion defect involving the infero-lateral wall of the left ventricle (A2). ^{11}C-mHED-PET demonstrates reduced tracer uptake in the lateral wall of the left ventricle (A3). The findings shown in A2 and A3 are indicative of cardiac sympathetic denervation and, indirectly, of increased sympathetic tone. The uptake scales used for image visualization are reported on the right. (*B*) ^{18}F-FDG-PET images show an increased ^{18}F-FDG uptake at the level of the right amygdala (B1 – white arrow), myocardium (B2), and bone marrow of the spine (B3). The SUV scale used for image visualization is reported on the right. (*C*) Straight multiple curve reconstructions from CCTA show a mixed plaque with positive remodelling of mid RCA (C1), calcified plaque of mid LAD (C2), and spotty calcification of the mid LCx (C3). A cross-section at the level of the corresponding plaque is also shown for each vessel (red box). (*D*) SPECT images acquired during stress (D1) show a reversible myocardial perfusion defect of the left ventricular inferior wall which is not present at rest (D2). Hypoperfusion is detected as a relative decrease of the uptake of the inferior wall (50–62%) as compared to the myocardial territory with the highest tracer uptake. PET images acquired during stress indicate a low MBF (mL/g/min) in the myocardial territory supplied by the LAD (D3). In the LAD territory MBF did not increase during stress (D3) as compared to rest (D4). The uptake and MBF scales used for image visualization and MBF quantification are reported on the right. CCTA: coronary computed tomography angiography; ^{11}C-mHED: ^{11}C-meta-hydroxyephedrine; ^{18}F-FDG: ^{18}F-fluorodeoxyglucose; fMRI: functional magnetic resonance imaging; ^{123}I-mIBG: ^{123}I-metaiodobenzylguanidine; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; MBF: myocardial blood flow; MR: magnetic resonance; ^{13}N-NH3: ^{13}N-ammonia; PET: positron emission tomography; RCA: right coronary artery; SPECT: single-positron emission computed tomography; SUV: standard uptake value; ^{99}Tc-MIBI: ^{99}Technetium-methoxyisobutyl isonitrile.^{123}I-mIBG-SPECT image was provided through the courtesy of Dr Renata Chequer and Prof. François Rouzet from the Nuclear Medicine department of the Bichat Hospital—Assistance Publique Hôpitaux de Paris.

have been detected at several levels of the autonomic nervous system. In fact, animal and human studies have consistently highlighted that, under physiological conditions, men have a higher baseline sympathetic activity, whereas women display a more pronounced parasympathetic tone while maintaining sympatho-vagal balance.[35] Interestingly, this difference attenuates with increasing age,[48,50] possibly resulting from changes in sex hormone concentrations which affect the autonomic system at central and peripheral levels.[51] These findings have been corroborated by using resting-state fMRI which showed that premenopausal women have a stronger negative resting-state functional connectivity with the default mode network (i.e. area responsible for the suppression of the sympathetic outflow in the

central autonomic network) in comparison to age-matched men.[52] The sex-dimorphism related to sympatho-vagal balance disappears after menopause confirming that postmenopausal women have weaker parasympathetic activity and increased sympathetic outflow as compared to younger age.[52] Of note, the distinct balance of autonomic function between women and men translates clinically into sex-divergent effects of beta-blockers.[53,54] Indeed, recent data suggest that women need lower dose of beta-blockers compared to men to reach maximal therapeutic efficacy in HF with reduced ejection fraction (HFrEF).[55] Sex hormones also play an important role in modulating sex differences of the sympatho-vagal balance.[35] Experimental data have shown that receptors for gonadal hormones are present in areas of the central nervous system involved in the regulation of the autonomic nervous system.[35] Accordingly, intravenous or central administration of oestrogens resulted in an enhanced parasympathetic response[35,51,56] whereas testosterone triggered the production and reduced the clearance of noradrenaline.[35] Therefore, menopause represents an important milestone in female health since it indicates a change in cardiac physiology, as well as an increased risk for cardiovascular diseases.[57] Although a disproportionally high sympathetic activity has been associated with unfavourable outcomes in both male and female cardiovascular patients,[58] women seem to be more vulnerable to the detrimental effects of sympathetic hyperactivity.[59] As such, myocardial ^{18}F-DOPA uptake was shown to be higher in elderly women as compared to men, especially at the level of the left ventricular (LV) apex. This distribution pattern of myocardial ^{18}F-DOPA aligns with the area of LV dysfunction involving the cardiac apex in TTS.[48]

The limbic system comprises different cortical areas and subcortical nuclei of the brain, including the amygdala,[60] and mediates most of the vegetative and endocrine functions of the body such as emotions, behaviours, and memory.[60] During stress conditions, the amygdala stimulates the hypothalamus via efferent neurons to increase SNS activity and initiate neurohormonal output through release of adrenocorticotropic hormone by the hypothalamic–pituitary–adrenal (HPA) axis.[61] In this context, the SNS plays a key role in driving systemic inflammation[62] and immune modulation[63] through sympathetic nerve fibres terminating in the bone marrow and stimulating turnover and release of myeloid cells.[6,64] This effect is further mediated by the HPA axis through catecholamine release, myelopoiesis activation, and a further increase in interleukin (IL)-6 and C-reactive protein (CRP) levels.[65,66] The established pro-inflammatory state favours the development of atherosclerosis, thus highlighting the close interdependence between neuroinflammatory circuits and the vascular system.[67–69] By administering the glucose analog ^{18}F-FDG, PET imaging enables the evaluation of regional metabolism of heart and brain.[6] Notably, ^{18}F-FDG-PET demonstrated higher stress-associated neural activity (SNA) in women during physiological aging, which manifests as an increased resting ^{18}F-FDG uptake at the level of the amygdala.[70] This finding may be explained by the greater and prolonged mental stress perceived by women during lifespan compared with men as a reaction to negative emotional episodes.[71] Indeed, while both women and men demonstrated resting-state functional connectivity to sensory and emotion-related regions of the brain on resting-state fMRI, men showed higher connectivity to areas involved in the control of emotions.[72]

Table 2 Heart rate variability and heart rate response: definitions, physiological interpretation, and clinical value

	Definition	Physiological interpretation	Clinical value
HRV	Variations in the beat-to-beat heart intervals evaluated on electrocardiogram[198]	• It reflects the combined activity of sympathetic and parasympathetic tone on cardiac function[198] • Reduced HRV expresses sympatho-vagal imbalance (i.e. increased sympathetic or reduced vagal activity)[198] • At a younger age (<30 years), during resting conditions, men have significantly higher basal sympathetic activity (higher HRV), whereas women have more pronounced parasympathetic tone (lower HRV)[50] • Aging is associated with a greater increase in sympathetic tone in women than in men[50]	• Depressed HRV has been associated with an increased risk of future cardiovascular events in populations without known cardiovascular disease[199] • Depressed HRV has been associated with cardiovascular risk factors such as physical inactivity, hypertension, and diabetes[200–202] • Depressed HRV has been correlated with HF, myocardial ischaemia, and AMI[203–205]
HRR to exercise or pharmacological stress	Maximum percentage change after exercise or pharmacological stress from baseline HR[59]: $[(HR_{maximum} - HR_{baseline})]/HR_{baseline} * 100$	• It reflects the baseline symphatetic activity[59] • HRR to adenosine is influenced by age and sex[206]	• A blunted HRR to stress has been associated with worse outcome in both sex aggregated populations[207,208] and in women[59]

AMI: acute myocardial infarction; HF: heart failure; HR: heart rate; HRR: heart rate response; HRV: heart rate variability.

Finally, the RAAS is well-represented in both heart and brain, where it regulates blood pressure (BP) and tissue blood flow, as well as immune responses and tissue homeostasis in response to ischaemic injury and SNS activation.[73]

Immune system and inflammation

Owing to its ability to alter tissue perfusion and neurohumoral activation, inflammation represents the link between heart and brain in different pathological conditions such as stroke and myocardial infarction.[74] As inflammatory cells are characterized by elevated glucose metabolism, ^{18}F-FDG-PET can be used to quantify spleen[75] and bone marrow activity[6] (i.e. indicative of activation of the haematopoietic system), as well as inflammatory responses within the arterial wall.[6,43] Nevertheless, due to the low specificity of ^{18}F-FDG in inflammation detection, new targets involved in the regulation of the immune system are currently being investigated.[43] Among these, the 18 kD translocator protein (TSPO), expressed on the outer mitochondrial membrane, has shown promising results given that TSPO expression increases in response to immune activation in both microglia and systemic immune system.[76] Preliminary data indicate that TSPO-target imaging in patients with myocardial infarction identifies early post-infarct myocardial inflammation as well as the presence of neuroinflammation.[77] Clinical data point to significant sex differences in inflammatory and innate immune responses, with women showing higher baseline levels of circulating inflammatory markers[78] and more pronounced production of pro-inflammatory cytokines in response to different injuries.[79–82] As such, a significant increase in ^{18}F-FDG bone marrow uptake has been reported in women with impaired myocardial perfusion, but not in men.[80]

The scheme of the **Graphical abstract** integrates the main systems involved in the heart–brain crosstalk, highlighting the sex differences which affect them.

Exploratory concepts for the assessment of heart–brain interaction

Beyond metabolic and perfusion imaging, several brain receptor systems are promising imaging targets to elucidate mechanisms driving heart–brain interactions. Notably, while an enhanced amygdalar metabolic activity was associated with emotional processing, anxiety, and fear, these processes can be attenuated by targeted interventions at the neurotransmitter level, thus suggesting that neuroreceptors are crucial components of the anxiety circuitry.[83,84] Among these neuroreceptors, there is a solid body of evidence implicating fast inhibitory ionotropic gamma-aminobutyric acid ($GABA_A$) receptors in fear and mental stress development.[85–89] As such, the availability of clinically validated $GABA_A$ receptor probes, such as ^{18}F-flumazenil, harbours potential to facilitate heart–brain research and shed light on sex differences in emotional stress processing.[90,91] In addition to $GABA_A$ receptors, serotonergic, adrenergic, and glutamatergic signalling have been linked to critical neurotransmission in anxiety, mental stress, and stress-induced cardiomyopathy.[84,92–94] Notably, advances in translational molecular imaging have channelled the development of suitable radiotracers for the non-invasive assessment of these receptors.[95–97]

Heart diseases

Ischaemic heart disease

Although tremendous improvements in therapeutic strategies have led to a decline in the overall mortality rate for IHD by ~30% during the past decade, this occurred far less in women as compared to men.[98] Furthermore, mortality rates in women presenting with ST-elevation myocardial infarction (STEMI) are higher than in age-matched men[99,100] despite women having less plaque burden and a lower rate of obstructive CAD.[22,101] Therefore, the previous assumption that the pathophysiology of IHD is the same for women and men, but with a later onset in females, is an erroneous and oversimplified concept. Since differences in traditional cardiovascular risk factors cannot totally explain the observed sex disparities, sex-specific genetic risk profiles and non-traditional risk conditions have been proposed as complementary mechanisms.

To begin with, genome-wide association studies have recently identified more than 100 genetic loci across the genome correlated with the development of IHD.[102,103] In this context, sex-specific variants in several genes have been detected by using polygenic risk scores, demonstrating that the genetic effect of IHD is modified by sex.[104] The involvement of the SNS and HPA axis in triggering sex differences in clinical outcomes has also been considered. Clinical results from the large CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) registry showed that LV ejection fraction (LVEF) is significantly higher in women as compared with men.[105] A strong association between LVEF >65% and increased 6-year mortality risk has been documented in women but not in men after adjusting for age, cardiovascular risk factors, and severity of CAD.[106] Interestingly, the prevalence of abnormally low end-systolic volumes was twice as high in older women as compared with younger women or men.[106] These findings support the hypothesis that postmenopausal women live under constant sympathetic hyperactivity to compensate for the disadvantage of small left ventricles, hence predisposing them to cardiac vulnerability in high-stress situations. As such, in women presenting with an acute coronary syndrome, sympathetic activity persisted for approximately nine months after the index event and was associated with an unfavourable prognosis.[107] Accordingly, chronic psychological stress has recently been listed as a risk factor for incident IHD.[108] The Perceived Stress Scale is a validated clinical questionnaire currently used to evaluate individual stress perception.[109] Nevertheless, a more reliable and reproducible stress level assessment can be obtained by measuring SNA by ^{18}F-FDG-PET.[110] Increased metabolic activity of the amygdala (when referenced to counter-regulatory activity from the medial prefrontal cortex or temporal lobe) has been reported as an independent predictor of future major adverse cardiovascular events (MACE) in a population of patients without known IHD or active cancer.[6] Notably, several studies suggested that SNA may represent a key element driving sex differences in IHD pathophysiology through downstream effects on autonomic, immune, and vascular physiology.[111] In fact, endothelial dysfunction in response to cumulative mental stress has previously been described in women but less so in men.[112] In addition, Vaccarino et al. documented that perceived stress after AMI differs

between women and men. In their study, while mental stress-induced myocardial ischaemia was more common in young women with previous myocardial infarction as compared with men, no sex differences were observed after exercise stress testing.[113] Second, our group reported a strong association between increased SNA, myocardial dysfunction, and subclinical inflammation in women, but not in men.[2,81] Similarly, stress-induced IL-6 and monocyte chemoattractant protein-1 have been identified as predictors of future cardiovascular events in women with existing cardiovascular disease, while this association was not observed in men.[114]

Heart failure

Women with HF are usually older than men[115] and have a better prognosis and reduced mortality after treatment.[116] In addition, women are more commonly affected by HF with preserved ejection fraction (HFpEF), which is often associated with diabetes and hypertension. In contrast, HFrEF is more prevalent in men and frequently has an ischaemic aetiology. Overall, the predominance of female sex in HFpEF can be explained by the difference in adaptive ventricular remodelling between women and men in response to increased afterload and aging. As such, postmenopausal women with HFpEF develop more frequently a hypertrophied, stiff, and non-dilated left ventricle as compared to men[117] accounting for the higher prevalence of diastolic dysfunction in this demographic group.[118]

Sex hormones and neurohumoral systems drive the development of HF and related sex differences. Testosterone stimulates RAAS activity and triggers vasoconstriction and cardiac hypertrophy whereas oestrogens attenuate RAAS activity, stimulate vasodilatation, and are associated with a more benign phenotype of cardiac remodelling.[119] The hyperactivation of the SNS has also been recognized as a critical mechanism in the development of HF as it correlates with disease progression and poor prognosis.[120] Indeed, in the acute phase of HF, the activity of the SNS is enhanced to compensate for the reduced myocardial contractility. However, in the long-term, the persistent and excessive stimulation of the SNS promotes maladaptive cardiac hypertrophy and cell death. Of note, SNS hyperactivation is strongly associated with arterial hypertension, obesity, and diabetes, which are the main determinants of HFpEF in women.[121] Enhanced sympathetic outflow as reflected by increased cardiac norepinephrine turnover and pre-synaptic norepinephrine deficits[44] can be detected by ^{123}I-mIBG scintigraphy. A pooled analysis of several multicentre cohort studies demonstrated the independent, long-term prognostic value of ^{123}I-mIBG uptake in patients with HF after adjusting for New York Heart Association functional class, LVEF, and natriuretic peptide values.[122,123] Similarly, cardiac sympathetic denervation evaluated by ^{11}C-mHED-PET imaging has been associated with the severity of diastolic abnormality, contractile dysfunction, and fibrotic burden in patients with HFpEF.[124,125]

Finally, both the heart and the brain have an intrinsic RAAS that is activated in HF, also contributing to sympathetic hyperactivity.[126] In this context, preliminary data from a rat model of ischaemic cardiomyopathy revealed significant sex differences in the central and peripheral manifestations of ischaemia-induced HF, thereby providing a potential explanation for better outcomes seen in women with HF as compared with men.[119] In particular, in the hypothalamic paraventricular nucleus, a key area contributing to neurohumoral excitation in HF, mRNA levels for pro-inflammatory markers, such as tumor necrosis factor-α and IL-1β, increased less in female as compared with male rats. Conversely, plasma norepinephrine levels were lower for female rats suggesting a weaker activation of the SNS.[119] Sex specificity in the involvement of the RAAS and sympathetic hyperactivity has also been observed in patients with both HFpEF[127,128] and HFrEF.[55] In fact, in the PARAGON-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin Receptor Blockers Global Outcomes in HF with Preserved Ejection Fraction) trial,[128,129] among 4796 patients with HFpEF, sex appeared to modify the effect of sacubitril-valsartan versus valsartan, reducing the number of HF hospitalization in women only.[128]

Takotsubo syndrome

Although contemporary evidence strongly suggests an involvement of the limbic system in the pathophysiology of TTS,[40] the exact mechanisms by which a stressful life event translates into the onset of TTS are not fully understood. Notably, recent milestone discoveries have directly linked the amygdala to TSS pathophysiology. As such, enhanced SNA was associated with an increased risk for TTS in a recent study by Radfar and co-workers.[5] Further, among individuals who developed TTS, a heightened SNA was present years before disease onset, indicating that SNA precedes the cardiac manifestation of TTS and may represent a promising prevention target.[5,130] In a cross-sectional study encompassing 20 female TTS patients and 39 age- and sex-matched healthy controls, a reduced thickness of the insular cortex, as well as a reduced amygdalar gray matter volume were observed in TTS patients but not in controls.[38] These anatomical differences were further substantiated by a follow-up study, in which reduced functional connectivity of central brain regions associated with regulation of the limbic system were detected in patients with TTS.[40,131–133] Given these findings, it is tempting to hypothesize that sex differences in emotional stress perception and processing via heart–brain interactions may contribute to the higher prevalence of TTS in women.[48,107,134,135] Although it should be noted that the relatively low prevalence of male TTS patients constitutes a major challenge for the design of appropriate prospective and sex-specific TTS studies, several recent reports concluded that the link between amygdalar metabolic activity and abnormal cardiac function was particularly accentuated in women.[2,81,136,137] Similarly, sympathetic hyperactivity and microvascular dysfunction, both implicated in TSS pathophysiology,[138,139] were found to predict MACE in women but not in men.[59,140] In concert with the high prevalence of TTS in postmenopausal women, oestrogens were found to attenuate sympathetic responses to mental stress in perimenopausal women.[141] Furthermore, through a variety of mechanisms, oestrogens represent a key regulator of endothelial function and vasomotor tone. These mechanisms include, but are not limited to, the attenuation of catecholamine-mediated vasoconstriction[142] and the upregulation of endothelial nitric oxide synthase activity[143]. Consequently, the combination of enhanced baseline sympathetic tone and impaired vasomotor function may render postmenopausal women susceptible to TTS during periods of acute mental or physical stress.[135]

Brain diseases

Stroke

Although the association between genetic risk score and incident stroke has been demonstrated in both women and men, the absolute risk of incident stroke is lower in women.[144] Sex differences in stroke epidemiology have been reported with a specific trend over the lifespan. During youth and early adulthood, stroke incidence is lower in women than men. In the middle-aged, stroke rates start to increase in women[145,146] and progressively grow with aging. The increasing risk of stroke in women above 65 years compared with younger women is partially explained by the loss of neuroprotective effect of sex hormones in the postmenopause period, owing to their ability to maintain vascular endothelial function and attenuate inflammatory responses.[147,148] Similarly, low levels of testosterone in men have been associated with increased systemic inflammation and endothelial dysfunction, thus promoting the development of atherosclerosis as well as increasing the risk for stroke.[149]

Current evidence supports a deep connection between the heart and brain in patients affected by ischaemic stroke. First, stroke and IHD share the same risk factors.[150] Moreover, ischaemic stroke is caused by IHD in about 20% of cases. In this context, stroke due to atrial fibrillation is more common in women as compared with men, particularly at an older age. Stroke is also associated with worse outcomes in women, as shown by the higher all-cause mortality rate in this population.[151] Furthermore, a strong interaction between stroke and HF is well established given that HF induces a state of hypercoagulability thereby leading to decreased blood flow velocity, endothelial dysfunction, enhanced platelet aggregation, as well as reduced fibrinolysis[152] all of which increase stroke risk and, consequently, morbidity and mortality of HF patients.[152] Second, cardiac complications represent the second leading cause of mortality after stroke.[153] Indeed, after the index event, patients may present with a broad range of cardiovascular signs and symptoms (stroke–heart syndrome), including electrocardiogram alterations, elevation of cardiac biomarkers, cardiac dysfunction, arrhythmia, and myocardial infarction.[36] The extent and burden of cardiac complications after stroke correlates with the site of the brain injury and the severity of the index event.[154,155] Notably, several large population-based studies showed a sex-specific risk of MACE after stroke[156,157] with a higher incidence of MACE, cardiovascular mortality, and HF in women as compared to men.[157]

In addition to neurological dysfunction, ischaemic stroke is also associated with an increased risk of acute cardiac events and chronic HF. The hypothesis supporting the pathophysiology of the stroke–heart syndrome is based on the concept that stroke damages specific brain areas of the central autonomic network. As with strong emotions, such as fear, this may lead to an overactivated stress response that triggers the autonomic nervous system and the HPA axis.[36,150,153] As such, the excessive release of cortisol and catecholamines has a detrimental effect on the heart, causing cardiomyocyte necrosis, hypertrophy, and myocardial fibrosis.[150] In a population of 222 consecutive patients admitted due to ischaemic stroke, high troponin I levels were significantly associated with elevation of circulating catecholamines, supporting the concept of an hyperactivation of the sympathoadrenal system.[158] Inflammation represents an additional linking factor since the local inflammatory response induced by stroke extends into the systemic circulation, hence yielding secondary cardiac damage.[150] In an animal model of stroke induced by transient ligation of the middle cerebral artery, PET imaging showed an association between neuroinflammation and cardiac inflammation, as detected by an increased TSPO uptake as well as by a persisting decline in cardiac contractility.[159] At a molecular level, the activation of SNS and HPA axis translates into the activation of forkhead box O (FOXO) genes. FOXO genes have recently been identified as potential molecular target for cardiac dysfunction since they are associated with an increased risk of myocardial infarction.[150] It is likely that the known sex differences in stress response, autonomic function, and the related inflammatory response may disproportionally affect women after stroke.[160,161]

Depression

While depression is evenly distributed between both sexes during childhood, sex and gender imbalance starts at the age of twelve and peaks during puberty, with young women being up to three-fold more often affected than young men.[162,163] Thereafter, the well-known female-male ratio of 2:1 remains stable over the entire adult lifespan. Current evidence supports an association between depression and cardiovascular disease. The prevalence of cardiac comorbidities among adult patients with depression is approximately three-fold greater than in the general population without mood disorders.[164,165] On the other hand, the presence of depressive symptoms is independently associated with higher cardiac and all-cause mortality, re-hospitalization, and quality of life after AMI.[166] Therefore, the European Society of Cardiology recently listed depression as a modifiable cardiovascular risk factor in patients with CAD.[108] Of note, anti-depressant medication, such as escitalopram and sertraline, has been shown to be an effective therapeutic strategy to improve long-term cardiovascular outcomes in both sexes.[167]

The prevalence of depression after AMI is higher in women than men.[166,168] This likely occurs as the result of the combined effect of sex-related differences in several mechanisms involved in heart–brain crosstalk. To begin with, a number of fMRI studies have linked anxiety and depressive disorders to the hyperactivation of the amygdala, insula, and anterior cingulate cortex.[169] In particular, trait anxiety in post-puberal females has been shown to be mediated by elevated perfusion in the left amygdala.[170] Second, depression has been associated with a greater activation of the SNS, as demonstrated by a reduced HRV in patients with depressive disorders.[171,172] Again, this phenomenon is more pronounced in women with depression as compared with men[173] and appears to mediate the detrimental interaction between depression and cardiovascular health.[174] Next, reduced HRV has been linked to peripheral inflammation, another potential mechanism connecting depression and cardiovascular disease.[175] A Mendelian randomization analysis reported that triglycerides, IL-6, and CRP are likely to be causally linked to depression, thus representing promising future targets for pharmacological therapies.[176] Accordingly, incremented levels of inflammatory markers, such as CRP and IL-6, are commonly being measured in patients with depression, and this finding is more pronounced in women.[177,178] Finally, sex hormones, such as progesterone, testosterone, and high oestrogen

levels, are known to be anti-inflammatory and protective in terms of depression.[179] Conversely, lower oestrogen levels have been shown to exert detrimental pro-inflammatory effects during hormonal transition periods such as post-partum and peri-menopause,[180–182] explaining the higher vulnerability of women to the coexistence of depression and cardiovascular disease. In men with depressive disorders, testosterone treatment has been associated with a moderate anti-depressant effect as compared with placebo.[183]

Dementia

Dementia overall affects women twice as often as men.[184] Apolipoprotein E epsilon 4 (ApoE4) is the strongest genetic risk factor for Alzheimer's disease. Although the frequency of ApoE4 genotype is similar between women and men, the risk of Alzheimer's disease in ApoE4 carriers is higher in women than men between 65 and 75 years.[185]

The heart–brain axis has been identified as a potential contributor to the pathogenesis and progression of degenerative diseases. Indeed, cognitive impairment is more common in patients with previous myocardial infarction and chronic HF.[186,187] Similarly, atherosclerosis has been identified as a risk factor for Alzheimer's disease, with endothelial dysfunction and impaired microcirculation being strictly connected to the functional decline.[188,189] In this context, ApoE has been reported to be the link between neuroinflammation and atherosclerosis in Alzheimer patients.[190] In addition, TSPO-target whole-body molecular imaging confirmed the role of inflammation as the critical connector between the heart and the brain after cardiac injury by detecting microglia activation in the early phase of post-myocardial infarction and in the late phase of chronic HF.[77] This is of paramount importance since inflammation represents a potential therapeutic target for decelerating cognitive decline.[77]

Current evidence suggests also that several heart conditions are linked to dementia in a sex-specific manner.[191] First, hypertension has been associated with vascular dementia and Alzheimer's disease.[192] Indeed, both elevated BP and high variability in BP compromise the structural integrity of the cerebral microvasculature by impairing cerebral blood supply and promoting neuroinflammation through disruption of the blood–brain barrier.[193,194] The LIFE-Adult study demonstrated independent and significant associations between white matter lesions and age as well as high BP, stroke, and HF. HF patients had a 2.5-fold increased likelihood of white matter lesions than those without HF. In addition, white matter lesions increased with the duration of HF.[195] Regional cerebral hypoperfusion has been identified in several brain areas of patients with HF, affecting autonomic, mood, and cognitive regulatory cerebral sites.[152,196] Of note, women suffering from hypertension have shown worse cognitive performance than normotensive women in the postmenopausal period.[197]

Conclusion and outlook

The crosstalk between heart and brain is complex, multifactorial, and still insufficiently defined. An additional layer of complexity is added by sex and gender differences that characterize the heart–brain axis, partially explaining sexual dimorphism in epidemiology, pathogenesis, clinical manifestation, and treatment responses of specific heart and brain diseases. Sex hormones, neurohumoral activity, and systemic inflammation are potential pathways mediating sex differences in heart–brain interactions. As many of these pathways represent pharmacological targets, further investigation of molecular mechanisms that regulate the heart–brain axis offers the possibility to interrupt pathogenetic transmission, thereby leading to novel individualized treatment approaches. However, many knowledge gaps remain (*Table 3*). As such, the effect of socio-cultural gender on heart–brain interactions is largely unknown, although increasing evidence emphasizes the importance of both, biological attributes and gender as major modifiers of health and disease.[8] As the mechanisms contributing to the excess risk in women with myocardial infarction remain largely unclear, gender-specific research identifying novel targets reflecting women's biological systems and behaviour is also urgently needed. As such, the brain's stress network and its downstream consequences is a promising signalling pathway given the predisposition of women to mental stress-induced ischaemia and sympathetic over-activity. Indeed, designing therapies and interventions that can interrupt a vicious cycle between stress and cardiovascular events is an attractive strategy to target cardiovascular health inequalities between women and men linked to modifiable risk factors. Future research will also have to investigate the directionality and causality of heart–brain interactions, thus, the currently evolving field of neurocardiology promises to be very active in the upcoming years.

Table 3 Knowledge gaps in heart–brain interactions

- Directionality (or bidirectionality) of heart–brain interactions
- Effects of socio-cultural gender on heart–brain interactions
- How to tailor medical treatments for specific heart and brain diseases taking into account sex differences in heart–brain interactions
- Role of sex hormones in heart–brain interactions

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