

REVIEW ARTICLE

Pain at the brain–heart interface: A narrative review

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Abstract

Pain is a frequent and clinically meaningful feature of both neurological and cardiovascular diseases, yet it is rarely examined from an integrated brain–heart perspective. Growing evidence indicates that pain perception, autonomic regulation, and cardiovascular vulnerability are closely interconnected through shared central networks, particularly the insula, cingulate cortex, and brainstem, as well as peripheral neuroimmune and neuroendocrine pathways. Despite this progress, current knowledge remains fragmented across neurology, cardiology, and pain medicine, limiting mechanistic insight and translational application. This narrative review synthesizes literature published from January 2020 to December 2025 on pain within brain–heart interactions. The synthesis highlights mechanistic pathways, clinical pain phenotypes, prognostic relevance, and emerging therapeutic strategies bridging neurological and cardiovascular domains. Key thematic areas include stroke–heart syndrome and central autonomic dysfunction, central post-stroke pain and maladaptive nociceptive processing, the role of chronic pain as a modifier of cardiovascular risk, the burden and impact of pain in heart failure and cardiac surgery survivorship, advances in neuroimaging of central autonomic networks, and the translational potential of neuromodulatory interventions such as vagal nerve and spinal cord stimulation. The reviewed evidence supports the concept of pain as a mechanistic “connector” between brain and heart diseases, influencing symptoms, disease progression, and outcomes. However, heterogeneity in pain definitions, study designs, and outcome measures continues to limit causal interpretation. A unified pain–brain–heart framework, incorporating harmonized phenotyping and mechanism-informed research, is warranted to advance precision assessment and management in this complex clinical domain.

Keywords: Pain; Brain; Central post-stroke pain; Neurogenic cardiac injury; Cardiac pain; Neurocardiology

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1. Introduction

Pain is increasingly recognized not merely as a symptom accompanying disease, but as a systems-level stressor capable of exerting profound and sustained effects on human physiology.¹ Beyond its sensory and affective dimensions, pain influences autonomic balance, neuroendocrine activity, immune and inflammatory pathways, sleep architecture, physical mobility, and mental health.² Through these interconnected domains, pain can actively shape both neurological and cardiovascular outcomes, contributing to disease progression, disability, and reduced quality of life.³ Advances in neurocardiology have provided a unifying framework for understanding these interactions, emphasizing the role of the central autonomic network (CAN) as a key integrative system.⁴ The CAN comprises interconnected cortical and subcortical structures (including the insula, midcingulate and anterior cingulate cortices, amygdala, hypothalamus, and brainstem nuclei) that integrate interoceptive, emotional, cognitive, and nociceptive signals while regulating sympathetic and parasympathetic outflow to the heart.⁵ Importantly, these same regions are central to pain perception, salience detection, and affective-motivational processing, suggesting a shared neurobiological substrate for pain modulation and cardiovascular control. Meta-analytic neuroimaging studies have consolidated the CAN as a reproducible functional circuit anchored in the dorsal anterior insula and midcingulate cortex, providing robust anatomical and functional evidence for brain–heart coupling that is directly relevant to pain processing.⁶ In parallel, cerebrovascular research has formalized the concept of stroke–heart syndrome, describing a spectrum of acute and delayed cardiovascular complications following ischemic stroke.⁷ These complications (including arrhythmias, myocardial injury, heart failure exacerbation, and sudden cardiac death) are largely mediated by autonomic dysregulation, excessive catecholaminergic activation, systemic inflammation, and disruption of central regulatory networks.^{8,9} Notably, many of these mechanisms overlap with those implicated in chronic pain persistence and central sensitization, including impaired descending inhibition, sustained sympathetic activation, and neuroimmune crosstalk.^{10,11} This convergence has prompted growing interest in an integrative pain–brain–heart research agenda, in which pain is considered both a consequence and a potential amplifier of neurocardiac dysfunction.^{12,13}

Experimental and clinical neuroimaging studies further reinforce this integrative view. Functional connectivity within pain-related cortical and brainstem networks, such as interactions between the dorsal anterior cingulate

cortex and periaqueductal gray, has been shown to covary with autonomic indices, including heart rate variability, supporting direct coupling between pain processing and autonomic regulation.^{14,15} These findings challenge traditional models that treat pain and cardiovascular control as parallel but independent processes, instead suggesting partially shared regulatory circuitry.

From a clinical standpoint, pain is highly prevalent across cardiovascular disease states, including heart failure and post-cardiac surgery survivorship.^{16–18} However, it is often under-recognized, inconsistently assessed, and rarely addressed within a mechanistic brain–heart framework. Large population-based studies in heart failure populations demonstrate a substantial burden of chronic pain, including chronic widespread pain, with significant implications for physical function, psychological well-being, and overall quality of life.¹⁹ Despite this, pain remains largely peripheral in cardiovascular guidelines and care pathways.

Against this background, a narrative synthesis of recent evidence is warranted. This review discusses literature published between 2020 and 2025 that explores pain within the context of brain–heart interactions, with the aim of clarifying key mechanisms, highlighting emerging clinical phenotypes, and identifying conceptual and methodological gaps. By integrating perspectives from neuroscience, cardiology, and pain medicine, this review seeks to advance a more unified and mechanism-informed understanding of pain in brain and heart diseases, thereby informing future research directions and translational strategies.

1.1. Terminology and core definitions

Given the cross-disciplinary scope of this review, spanning neurology, cardiology, and pain medicine, the following definitions are provided upfront to harmonize nomenclature and ensure conceptual clarity across readerships. [Table 1](#) presents the key terminology and conceptual constructs adopted in this review. Definitions were aligned with the terminology proposed by the International Association for the Study of Pain (IASP)²⁰ whenever available. For concepts not formally defined within IASP terminology, landmark references describing the original conceptual framework are reported, accompanied where possible by recent supporting publications to reflect contemporary use of these constructs ([Table 1](#)).

2. Methods

This narrative review was conducted in accordance with the principles of the Scale for the Assessment of Narrative Review Articles (SANRA), which provides a structured

Table 1. Glossary of core constructs used in this review

Term	Definition	Key references
Central autonomic network	An interconnected network of cortical and subcortical structures, including the insula, anterior and midcingulate cortices, amygdala, hypothalamus, and brainstem nuclei, that integrates interoceptive, emotional, cognitive, and nociceptive signals while regulating sympathetic and parasympathetic outflow to the heart and other viscera.	Ferraro <i>et al.</i> ⁶
Nociceptive pain	Pain arising from actual or threatened damage to non-neural tissue, caused by activation of peripheral nociceptors. The somatosensory nervous system itself is functionally intact. Serves a protective biological role and is the predominant pain type in inflammatory and musculoskeletal conditions.	IASP ^{20,21}
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system (peripheral or central). Characterized by spontaneous pain, allodynia, hyperalgesia, and sensory abnormalities in a neuroanatomically plausible distribution. Central post-stroke pain is a prototypical central neuropathic pain syndrome addressed in this review.	Treede <i>et al.</i> ^{22,23}
Nociplastic pain	Pain arising from altered nociception despite no clear evidence of tissue damage or somatosensory nerve lesion. Reflects central sensitization and dysfunctional endogenous pain modulation. Encompasses conditions such as fibromyalgia and chronic widespread pain. Formally introduced by the International Association for the Study of Pain in 2016 to complement the nociceptive/neuropathic classification.	Kosek <i>et al.</i> ^{24,25}
Pain phenotype	A clinically and mechanistically characterized pain profile encompassing pain type (nociceptive, neuropathic, nociplastic, or mixed), distribution, intensity, temporal pattern, and associated sensory or autonomic features. Phenotyping enables mechanism-informed stratification and is essential for comparing findings across neurological, cardiovascular, and pain medicine research.	Fillingim <i>et al.</i> ^{26,27}
Central sensitization	Amplification of nociceptive signaling within the central nervous system resulting in pain hypersensitivity, including allodynia, temporal summation, and spread of sensitivity beyond the primary site of injury. A key mechanism underlying nociplastic pain and chronic pain persistence; mechanistically linked to autonomic dysregulation through shared central autonomic network circuitry.	IASP ^{20,28}

framework to enhance transparency, methodological rigor, and scientific credibility in narrative evidence synthesis.²⁹ In accordance with the SANRA methodology, we structured our paper around its six evaluative components:

- (i) Justification of importance: pain at the brain–heart interface represents a clinically under-addressed and mechanistically complex domain with direct implications for neurological and cardiovascular practice, as detailed in Section 1.
- (ii) Statement of aims: the review aims to synthesize contemporary evidence on shared pain-autonomic-cardiovascular mechanisms, identify clinical phenotypes, and map translational gaps, as specified in Section 2.1.
- (iii) Literature search: a systematic, reproducible search strategy was applied across four major databases with predefined Boolean terms, date filters, and eligibility criteria, as described in Sections 2.2 and 2.3.
- (iv) Referencing standards: only peer-reviewed

publications in English were included; primary sources were prioritized over secondary citations where available.

- (v) Scientific reasoning: evidence was appraised and synthesized thematically with explicit narrative judgment of methodological quality, as described in Section 2.4.
- (vi) Presentation of data: findings are organized into seven thematic domains reflecting mechanistic, clinical, and translational dimensions, with consistent structure across subsections to facilitate cross-disciplinary reading.

2.1. Review aim and scope

The primary aim of this narrative review was to synthesize contemporary evidence on the role of pain within brain–heart interactions, with particular attention to shared neuroanatomical, autonomic, neuroimmune, and clinical pathways linking neurological and cardiovascular diseases. The scope was intentionally interdisciplinary,

encompassing neuroscience, cardiology, pain medicine, and related translational fields. To ensure clinical and conceptual relevance, the review focused on adult human studies and emphasized mechanistic insight, clinical phenotypes, and therapeutic implications rather than exhaustive quantitative comparison.

2.2. Literature search strategy

A comprehensive literature search was performed across four major electronic databases: MEDLINE/PubMed, Embase, Scopus, and Web of Science Core Collection. The search was limited to peer-reviewed publications published between January 1, 2020, and December 31, 2025, to capture contemporary concepts, methodologies, and classifications relevant to brain–heart–pain interactions. Search terms were developed iteratively and combined controlled vocabulary (where applicable) with free-text keywords related to pain (e.g., “pain,” “chronic pain,” “central sensitization,” “nociceptive pain,” “mixed pain”), brain–heart interactions (e.g., “brain–heart axis,” “neurocardiology,” “central autonomic network,” “autonomic dysfunction”), and clinical conditions of interest (e.g., “stroke,” “heart failure,” “cardiovascular disease,” “cardiac surgery”). Boolean operators and database-specific filters were applied to optimize sensitivity while maintaining relevance. When referring to the development and validation of assessment instruments, questionnaires, or methodological frameworks, the original methodological publications were intentionally cited, even when published prior to 2020, as these represent the primary sources describing the conceptual design and validation of the instruments.

The database-specific search strategies are summarized in [Table 2](#).

2.3. Study selection and eligibility

In keeping with SANRA guidance, inclusion criteria were predefined but applied flexibly to allow conceptual breadth. Eligible publications included original clinical or translational research, systematic and narrative reviews, and meta-analyses involving adult human populations that explicitly addressed pain in the context of neurological and/or cardiovascular disease, with reference to autonomic, neurocardiac, neuroimmune, or central pain-processing mechanisms. Animal-only studies, conference abstracts without full text, editorials, and commentaries lacking original data or substantive synthesis were excluded. To enhance reproducibility, eligibility decisions were made by two reviewers (A.P., D.M.) independently, with discrepancies resolved through discussion and consensus. A pilot screening phase was conducted on a random

sample of 20 records prior to full screening to calibrate the application of inclusion criteria and minimize subjective variability inherent to the flexible eligibility approach required by this review’s interdisciplinary scope.

2.4. Evidence synthesis and narrative integration

Rather than formal data extraction or quantitative pooling, the included literature was critically appraised and thematically synthesized. Studies were grouped into conceptual domains, such as stroke–heart interactions and autonomic dysfunction; central post-stroke pain (CPSP) and central nervous system (CNS) reorganization; overlap between CAN architecture and pain circuitry; pain burden in heart failure and cardiovascular populations; chronic pain as a cardiovascular risk modifier and outcome driver; post-cardiac surgery pain and survivorship; and neuromodulation at the intersection of pain relief and cardiac autonomic control, based on mechanistic and clinical relevance. Emphasis was placed on consistency of findings, biological plausibility, translational value, and identification of knowledge gaps.

In accordance with SANRA methodology, the review does not aim to provide exhaustive coverage or formal risk-of-bias assessment, but instead offers a reasoned, evidence-informed narrative that integrates current knowledge, highlights methodological limitations, and proposes directions for future research at the intersection of pain, brain, and heart diseases.

3. Results

The narrative synthesis of the literature published between 2020 and 2025 revealed a rapidly expanding and conceptually convergent body of evidence supporting the relevance of pain within brain–heart interactions. For clarity, the results are presented across seven thematic domains, reflecting mechanistic, clinical, and translational dimensions of the field.

3.1. Stroke–heart interactions and autonomic dysfunction as a mechanistic substrate

A substantial portion of the contemporary literature has focused on the bidirectional relationship between acute brain injury and cardiovascular dysfunction, formalized under the concept of stroke–heart syndrome. High-impact reviews and consensus statements describe how ischemic stroke can precipitate a spectrum of cardiac complications, including arrhythmias, myocardial injury, stress cardiomyopathy, and heart failure exacerbation, through mechanisms such as central autonomic dysregulation, excessive catecholamine release, systemic inflammation, and disruption of regulatory brain networks.^{8,30} These

Table 2. Database-specific search strategies

Database	Search string	Date range/filters	Initial returns (approx.)	Number of included studies
MEDLINE (via PubMed)	("pain"[MeSH] OR "chronic pain"[MeSH] OR "nociception"[MeSH]) AND ("heart"[MeSH] OR "cardiovascular system"[MeSH] OR "autonomic nervous system"[MeSH]) AND ("brain"[MeSH] OR "central nervous system"[MeSH] OR "neurocardiology")	2020–2025; English; humans	1,392	28
Embase	(pain OR chronic pain OR nociception) AND (heart OR cardiovascular OR autonomic nervous system) AND (brain OR neurocardiology OR central autonomic network)	2020–2025; English; humans	1,010	18
Scopus	TITLE-ABS-KEY(pain AND (brain OR neurocardiology) AND (heart OR cardiovascular OR autonomic)) AND PUBYEAR > 2019 AND PUBYEAR < 2026	2020–2025; English	1,160	14
Web of Science Core Collection	TS = (pain AND (brain-heart OR neurocardiology OR central autonomic network) AND (cardiovascular OR autonomic))	2020–2025; English	980	9
Total and included			4,542	47

Note: Counts of included records by database are not additive because the same study could be retrieved from more than one database; after de-duplication and screening, 47 unique studies were included.

processes underscore the vulnerability of the cardiovascular system to CNS injury and highlight the CAN as a critical mediator of brain-driven cardiac pathology.

More recent studies have refined this model by emphasizing the role of insular cortex involvement, demonstrating that insular lesions are associated with autonomic asymmetry, altered sympathetic-parasympathetic balance, and worse cardiovascular outcomes.³¹ This finding is particularly relevant to the present review, as the insula is also a core hub for pain perception and interoception. Lesions affecting this region therefore represent a plausible anatomical bridge linking dysregulated pain processing with altered cardiovascular control. Complementing this perspective, a 2025 narrative review focusing on autonomic dysfunction after stroke highlights its high prevalence, prognostic significance, and emerging diagnostic and therapeutic strategies, including autonomic testing and targeted modulation.³²

Although pain outcomes are rarely primary endpoints in stroke-heart studies, this body of work provides a robust neurobiological framework within which pain could influence cardiac risk and, conversely, cardiac dysfunction

could shape central pain processing. The characterization of CAN injury and dysregulation constitutes a foundational substrate for integrating pain into stroke-heart models. The consensus statements and narrative reviews underpinning this section are methodologically robust in synthesis scope, but most primary studies are observational and single-center, with limited sample sizes and inconsistent autonomic measurement protocols, which constrain causal inference regarding CAN-mediated pain-cardiac interactions.

3.2. Central post-stroke pain and central nervous system reorganization

Central post-stroke pain remains one of the most studied examples of brain-driven chronic pain and serves as a prototypical model of maladaptive central reorganization following focal brain injury.³³ Comprehensive integrative systematic reviews synthesized evidence on lesion localization, somatotopic patterns, clinical manifestations, and neurophysiological alterations associated with CPSP, emphasizing the role of disrupted sensory integration, impaired descending inhibitory control, and maladaptive plasticity.^{33,34}

Although CPSP research has traditionally focused on sensory and functional outcomes rather than cardiovascular consequences, its mechanistic underpinnings are highly relevant to brain–heart interactions. In particular, CPSP frequently involves lesions affecting the thalamus, insula, brainstem, and spinothalamic pathways, regions that also participate in autonomic regulation.³⁵ Experimental and clinical studies suggest that such lesions may simultaneously predispose patients to chronic pain and autonomic instability, potentially coupling pain syndromes with dysautonomia and cardiovascular vulnerability.³⁶ Thus, CPSP provides an important conceptual parallel to stroke–heart syndrome, illustrating how localized brain injury can result in persistent, system-wide consequences that extend beyond the primary neurological deficit. The absence of integrated cardiovascular assessments in CPSP studies represents a notable gap identified through this review. The 2021 systematic review on CPSP applied explicit inclusion criteria and neurophysiological outcome mapping, representing the strongest methodological contribution in this section; however, the small number of eligible primary studies ($n = 4$ with quantitative neurophysiological data) and their heterogeneous TMS parameters limit the generalizability of conclusions.

3.3. Overlap between central autonomic network architecture and pain circuitry

From a systems–neuroscience perspective, convergent lines of evidence indicate considerable overlap between neural circuits involved in autonomic control and those subserving pain processing. A landmark meta-analysis published in 2022 consolidated data from multiple neuroimaging studies to define the CAN as a reproducible functional network centered on the dorsal anterior insula and midcingulate cortex.⁶ These regions emerged as key integrative nodes coordinating viscerosensory input, emotional salience, cognitive control, and autonomic output. This overlap is highly relevant for understanding the pain–brain–heart interface, as the same regions are consistently implicated in pain chronification, threat appraisal, and interoceptive awareness. Experimental pain neuroimaging studies provide robust mechanistic evidence for this integration. Resting-state functional connectivity analyses have demonstrated that baseline low-frequency heart rate variability (LF-HRV) predicts functional connectivity changes in both the dorsal anterior cingulate cortex and periaqueductal gray during pain stimulation.¹⁴ Specifically, a three-way relationship exists between cardiac autonomic indices, cortical brain networks underpinning pain processing, and subjectively reported pain experiences.¹⁴ During experimental pain, functional connectivity between these seed regions and other cortical

areas, including the right dorsolateral prefrontal cortex, left anterior insula, and precuneus, correlates significantly with both LF-HRV measurements and pain ratings.^{2,14} This convergent evidence establishes that cardiovascular autonomic parameters are directly linked to brain activity changes involved in nociceptive information processing, providing a neurobiological substrate for the reciprocal relationship between autonomic and pain-related systems. All these findings challenge reductionist models that treat pain and cardiovascular control as independent processes. Instead, they support a framework in which both are partially co-governed by shared central networks, providing a neurobiological rationale for the observed clinical associations between pain, dysautonomia, and cardiovascular outcomes.³⁷ The 2022 neuroimaging meta-analysis consolidating CAN architecture used pre-registered coordinates and GingerALE software across multiple datasets, representing high methodological rigor. The experimental pain–heart rate variability (HRV) connectivity study, while mechanistically compelling, was conducted in healthy volunteers with a modest sample size, limiting direct clinical translation to cardiovascular or neurological patient populations.

3.4. Pain burden in heart failure and cardiovascular populations

Epidemiological and clinical studies published during the review period consistently demonstrate that pain is highly prevalent and clinically significant in cardiovascular disease, particularly in heart failure populations. Data from the HUNT study indicate that individuals with heart failure experience high rates of chronic pain and chronic widespread pain, often with moderate to severe intensity and substantial impact on daily functioning.¹⁹ These findings support the conceptualization of pain as a core comorbidity rather than a secondary or incidental symptom. Additional cohort and cross-sectional studies reinforce these observations, reporting associations between pain severity and reduced quality of life, increased psychological distress, and impaired physical capacity in heart failure patients.³⁸ Despite this, pain assessment remains inconsistent in cardiovascular practice, and mechanistic explanations linking pain to disease progression are rarely explored. The reviewed literature highlights a disconnect between the recognized burden of pain and its limited integration into cardiovascular care pathways. The HUNT study provides relatively strong epidemiological evidence because of its large population base and use of validated pain measures. Other cross-sectional studies are further limited by self-reported pain measures, lack of detailed pain phenotyping, and inadequate control for cardiac disease severity and analgesic use.

3.5. Chronic pain as a cardiovascular risk modifier and outcome driver

Beyond simple coexistence, an emerging body of longitudinal evidence suggests that chronic pain may act as a modifier of cardiovascular risk and outcomes. Recent cohort studies published between 2024 and 2025 have examined pain trajectories, multisite pain, and chronic pain burden in relation to incident cardiovascular events and surrogate risk markers.³⁹ These studies provide empirical support for mechanistic hypotheses involving sustained sympathetic activation, hypothalamic-pituitary-adrenal axis dysregulation, chronic inflammation, physical inactivity, and adverse health behaviors. A comprehensive 2025 review in preventive cardiology synthesizes these findings and emphasizes that chronic pain shares multiple risk factors with cardiovascular disease, including obesity, depression, sleep disturbance, and socioeconomic stressors.⁴⁰ While this domain is characterized by methodological heterogeneity (particularly in pain definitions, exposure measurement, and confounding control), it has reached sufficient maturity to warrant structured mapping and targeted hypothesis testing. A 2024 United Kingdom (UK) Biobank study analyzing nearly 422,654 individuals provided compelling evidence for a dose-response relationship between chronic pain burden and cardiovascular dysfunction.⁴¹ Participants with chronic pain in multiple sites demonstrated significantly greater cardiovascular risk compared to those with single-site or no pain, with arterial stiffness indices increasing proportionally with the number of pain sites. This finding was corroborated by data from the China Health and Retirement Longitudinal Study (CHARLS), which demonstrated that dynamic changes in pain status, particularly worsening or persistent pain, were independently associated with incident cardiovascular disease in middle-aged and elderly populations.³⁹ Moreover, recent work has established chronic pain as a modifiable perioperative cardiovascular risk factor: preoperative chronic pain affects up to 30% of surgical patients and is associated with increased perioperative cardiovascular morbidity, with attributable risk comparable to traditional cardiovascular risk factors.⁴² These converging lines of evidence position chronic pain assessment as an essential component of cardiovascular risk stratification.

Recent mechanistic research has elucidated specific pathways through which chronic pain influences cardiovascular health. Chronic pain is associated with sustained sympathetic nervous system activation, contributing to elevated blood pressure, increased heart rate, and reduced heart rate variability, all established cardiovascular risk factors.³⁷ Beyond autonomic

dysregulation, chronic pain promotes systemic low-grade inflammation characterized by elevated C-reactive protein, interleukin-6, and tumor necrosis factor- α , which accelerate atherosclerosis and endothelial dysfunction.^{23,43} The neuroimmune interface is particularly relevant: central sensitization processes that maintain chronic pain share molecular pathways with cardiovascular pathology, including microglial activation and neuroinflammatory cascades.^{43,44} Depression and social isolation, both highly prevalent in chronic pain populations and associated with worse cardiovascular outcomes, further amplify cardiovascular risk through combined behavioral and biological mechanisms.⁴³ Importantly, these mechanistic insights suggest that interventions targeting chronic pain may confer cardiovascular protective effects, representing a dual therapeutic opportunity warranting systematic investigation.⁴³ The UK Biobank analysis provides the highest level of epidemiological evidence in this section, with nearly 500,000 participants and objective arterial stiffness measures, though the cross-sectional design precludes causal inference. The CHARLS longitudinal data strengthen temporality, but rely on self-reported pain without mechanistic phenotyping. The perioperative cardiovascular risk estimate is derived from a narrative review and requires prospective validation with standardized pain assessment tools.

3.6. Post-cardiac surgery pain and survivorship

Persistent pain following cardiac surgery has gained increasing attention as a survivorship issue rather than a purely perioperative complication. Contemporary reviews highlight that chronic postsurgical pain intersects with psychological vulnerability, autonomic dysregulation, and impaired participation in cardiac rehabilitation.⁴⁵ A 2025 review synthesizes evidence on incidence, risk factors, and clinical trajectories of chronic pain after cardiac surgery, situating it within broader recovery and long-term outcome frameworks.⁴⁶

While earlier meta-analyses established baseline incidence estimates, recent studies expand on pain phenotyping, the role of anxiety and central sensitization, and the need for integrated perioperative care models. These developments underscore the relevance of brain–heart mechanisms in shaping long-term pain outcomes after cardiac interventions. Evidence in this section is predominantly derived from narrative and scoping reviews with variable primary study quality. Incidence estimates for chronic postsurgical pain vary widely across studies due to inconsistent pain duration thresholds, assessment timepoints, and case definitions, reflecting the absence of a universally adopted diagnostic framework for this population.

3.7. Neuromodulation at the intersection of pain relief and cardiac autonomic control

Neuromodulation represents a key translational domain linking mechanistic insights to therapeutic application. In refractory angina, spinal cord stimulation (SCS) has been extensively reviewed as an intervention capable of reducing pain while modulating sympathetic activity.⁴⁷ A 2025 review provides an updated synthesis of SCS mechanisms, clinical efficacy, and safety in refractory angina populations⁴⁸, with emerging prospective studies continuing to evaluate its role.⁴⁹ Similarly, transcutaneous vagus nerve stimulation (t-VNS) has been investigated in heart failure and related conditions. A 2025 review summarizes evidence suggesting improvements in functional capacity, inflammatory markers, and autonomic balance.⁵⁰ Although pain outcomes are rarely primary endpoints in these trials, vagal modulation plausibly influences pain through anti-inflammatory reflexes and central autonomic pathways. This domain highlights both the promise and the current limitations of neuromodulation research, particularly the tendency to silo cardiac and pain outcomes rather than integrating them within a unified pain–brain–heart framework. Together, these domains delineate a coherent yet fragmented evidence base, underscoring both the maturity of the field and the need for integrative, mechanism-informed approaches in future research. The SCS evidence base consists largely of small uncontrolled or single-arm studies, with the 2025 review⁴⁸ acknowledging limited randomized trial data in refractory angina. The t-VNS meta-analysis included 10 RCTs with a pooled sample of 374 patients, providing moderate-quality evidence for cardiac functional outcomes, but pain was not assessed as a primary endpoint in any included trial, substantially limiting conclusions about analgesic efficacy in this population.

From a translational standpoint, the following assessment protocol is proposed for clinical and research settings evaluating patients at the pain–brain–heart interface. At first contact, a minimum screening battery should include: a validated pain questionnaire capturing type, distribution, intensity, and temporal pattern (e.g., PainDETECT for neuropathic screening⁵¹, the Brief Pain Inventory for functional impact⁵²); a short autonomic assessment comprising resting heart rate variability and orthostatic blood pressure response; and a cardiovascular risk summary score (e.g., SCORE2⁵³ or equivalent). In patients with confirmed chronic pain and cardiovascular comorbidity, a second-tier assessment should add quantitative sensory testing for central sensitization profiling, 24-h ambulatory blood pressure monitoring, and echocardiographic evaluation of diastolic function

where clinically indicated. This stratified approach allows risk categorization into three operationally distinct profiles: predominant nociceptive pain with preserved autonomic function (lower cardiovascular interaction risk); neuropathic or nociplastic pain with autonomic dysregulation (intermediate risk, requiring integrated neurocardiology input); and mixed pain phenotype with established cardiovascular disease (high risk, warranting coordinated pain-cardiology care). These profiles are not diagnostic categories but pragmatic stratification anchors to guide research design and inform multidisciplinary clinical triage.

To illustrate the bidirectional interactions between the cardiovascular system and CNS, [Figure 1](#) summarizes the major clinical and mechanistic pathways linking brain and pain-related brain dysfunction with cardiac outcomes, and conversely cardiac pathology with pain, neuroinflammation, and central reorganization.

[Table 3](#) summarizes the reviewed literature into the thematic domains, detailing study characteristics, methodological approaches, and key contributions to understanding pain within brain–heart interactions.

4. Discussion

The body of evidence published between 2020 and 2025 collectively supports the existence of a biologically plausible and clinically relevant pain–brain–heart continuum, in which pain emerges not as a passive epiphenomenon but as an active systems-level modifier of both neurological and cardiovascular function. While pain, brain disorders, and heart disease have traditionally been investigated within distinct disciplinary silos, recent advances in neuroimaging, autonomic physiology, and large-scale cardiovascular epidemiology now allow these domains to be integrated into a coherent conceptual framework. This narrative review highlights how convergent mechanistic, clinical, and translational findings increasingly support such integration. Several narrative reviews addressing aspects of the brain–heart axis have been published since 2022, and it is important to situate the present work within this landscape. Scheitz *et al.*⁹ provided an authoritative synthesis of stroke–heart syndrome mechanisms and clinical management, while Hu *et al.*¹² reviewed neuroinflammatory interactions along the brain–heart axis with a focus on cardiovascular disease pathogenesis. More recently, Valenza *et al.*⁵⁴ published a comprehensive mechanistic review of the brain–heart axis, delineating neural, mechanical, and biochemical pathways with rigorous systems-level integration. Ziegler *et al.*⁵⁵ further characterized neural mechanisms in cardiovascular health and disease from a molecular and translational

Table 3. Practical summary of the analyzed literature

Thematic domain	Study (Year)	Methods	Key findings
Central autonomic network and pain processing	Ferraro <i>et al.</i> , 2022 ⁶	Meta-analytic neuroimaging synthesis	Identifies dorsal anterior insula and midcingulate cortex as reproducible hubs regulating both autonomic outflow and pain processing
	Hohenschurz-Schmidt <i>et al.</i> , 2020 ¹⁴	Resting-state fMRI with HRV during experimental pain	Establishes three-way coupling between dACC/PAG connectivity, low-frequency HRV, and subjective pain ratings
	Reynolds <i>et al.</i> , 2023 ³⁷	Mechanistic review (molecular/autonomic focus)	Elucidates sustained sympathetic nervous system activation linking chronic pain to cardiovascular dysfunction
Stroke–heart syndrome and neurogenic cardiac injury	Sposato <i>et al.</i> , 2020 ⁸	State-of-the-art review with mechanistic synthesis	Defines post-stroke cardiovascular complications via central autonomic dysregulation and catecholamine excess
	Fontes <i>et al.</i> , 2024 ³¹	Clinical autonomic research review	Highlights right insular lesions as determinants of autonomic asymmetry and cardiovascular vulnerability
	Barkhudaryan <i>et al.</i> , 2025 ³²	Clinical review with therapeutic management perspectives	Summarizes post-stroke autonomic dysfunction prevalence, prognosis, and therapeutic strategies
	Fan <i>et al.</i> , 2024 ³⁶	Mechanistic review of brain–heart crosstalk	Synthesizes pathophysiology and clinical implications of stroke-related brain–heart interactions
Central post-stroke pain and CNS reorganization	Yuan <i>et al.</i> , 2025 ³³	Comprehensive clinical and preclinical review	Advances understanding of central post-stroke pain mechanisms and clinical manifestations
	Betancur <i>et al.</i> , 2021 ³⁴	Integrative systematic review with neurophysiology	Maps somatotopic damage, sensory integration failure, and descending inhibitory dysfunction in CPSP
	Mohanan <i>et al.</i> , 2023 ³⁵	Overview of mechanisms and management	Provides a comprehensive overview of stroke-induced central pain mechanisms and emerging therapeutic targets
Pain prevalence and impact in heart failure	Vikan <i>et al.</i> , 2024 ¹⁹	Population-based cross-sectional study (HUNT)	Establishes a high prevalence of chronic and widespread pain in HF with substantial functional impact
	Mhesin <i>et al.</i> , 2022 ³⁸	Multicenter cross-sectional study	Demonstrates pain-psychological distress-QoL associations in HF requiring integrated assessment
	Ärnlöv, 2025 ⁴⁰	Expert preventive cardiology review	Positions chronic pain as a cardiometabolic risk factor, emphasizing routine cardiovascular assessment
	Qin <i>et al.</i> , 2025 ⁴¹	Large-scale cohort study (UK Biobank)	Demonstrates the association between pain and incident arrhythmias in over 422,000 individuals
	Yang <i>et al.</i> , 2025 ³⁹	Longitudinal analysis of pain trajectories	Provides evidence for the temporal relationship between pain changes and cardiovascular outcomes
	Sikandar <i>et al.</i> , 2025 ⁴²	Systematic review with mechanistic analysis	Identifies preoperative chronic pain as a modifiable perioperative cardiovascular risk factor

(Cont'd...)

Table 3. (Continued)

Thematic domain	Study (Year)	Methods	Key findings
Pathophysiological mechanisms linking pain and CVD	Reynolds <i>et al.</i> , 2023 ³⁷	Mechanistic review (sympathetic nervous system focus)	Details of the sustained sympathetic activation pathway from chronic pain to cardiovascular dysfunction
	Zhang <i>et al.</i> , 2025 ⁴³	Systematic review with translational emphasis	Identifies neuroimmune crosstalk and inflammation as shared pathways for dual-benefit interventions
Post-cardiac surgery pain and recovery	Xiao <i>et al.</i> , 2023 ⁴⁵	Prospective cohort study	Establishes chronic postsurgical pain prevalence and risk factors in cardiac surgery populations
	Dost <i>et al.</i> , 2025 ⁴⁶	Narrative review	Frames cardiac surgery pain as a survivorship issue affecting rehabilitation and long-term outcomes
Neuromodulation for pain and autonomic control	Paradiso <i>et al.</i> , 2024 ⁴⁷	Historical and conceptual review	Traces the origins of modern cardiac neuromodulation from historical perspectives to current applications
	Gazzeri <i>et al.</i> , 2025 ⁴⁸	Narrative review of SCS for refractory angina	Updates evidence for spinal cord stimulation reducing cardiac pain while modulating sympathetic activity
	Gasimova <i>et al.</i> , 2025 ⁴⁹	Prospective single-center SCS cohort	Provides contemporary clinical evidence for SCS efficacy in refractory angina management
	Sun <i>et al.</i> , 2025 ⁵⁰	Systematic review and meta-analysis of t-VNS	Demonstrates that vagal stimulation improves HF functional capacity and autonomic balance with pain implications

Abbreviations: CHARLS: China Health and Retirement Longitudinal Study; CNS: Central nervous system; CPSP: Central post-stroke pain; CVD: Cardiovascular disease; dACC: Dorsal anterior cingulate cortex; HF: Heart failure; HRV: Heart rate variability; HUNT: Trøndelag Health Study; PAG: Periaqueductal gray; QoL: Quality of life; SCS: Spinal cord stimulation; t-VNS: Transcutaneous vagus nerve stimulation.

standpoint. While these reviews have substantially advanced understanding of brain–heart coupling, none have explicitly adopted pain as a primary organizing construct bridging the neurological and cardiovascular domains. Existing reviews either address pain incidentally within broader neurocardiology frameworks or focus on single pain conditions (such as CPSP or refractory angina) in isolation. The present review is, to our knowledge, the first to synthesize the contemporary evidence base with pain explicitly positioned as a mechanistic connector between brain and heart diseases, integrating nociceptive, neuropathic, and nociplastic phenotypes alongside autonomic and cardiovascular endpoints within a unified framework.

A central and unifying observation across the reviewed literature is the identification of a shared neuroanatomical and functional substrate linking pain perception and cardiovascular regulation.^{38,55} Meta-analytic neuroimaging studies have robustly demonstrated that the CAN constitutes a reproducible functional system, with core hubs in the dorsal anterior insula and the midcingulate/anterior cingulate cortices.⁶ These regions are critically

involved in interoception, salience attribution, emotional appraisal, and pain modulation, while simultaneously exerting descending control over sympathetic and parasympathetic outflow through brainstem nuclei.⁵⁶ This dual role provides a compelling mechanistic “meeting point” at which nociceptive processing and cardiovascular regulation converge. Importantly, experimental pain neuroimaging studies reinforce this integration by showing that functional connectivity within pain-related cortical-brainstem circuits covaries with autonomic indices such as HRV, suggesting shared regulatory control rather than parallel, independent processes.¹⁴ This neurobiological integration extends beyond cortical hubs to include brainstem and spinal cord structures, as demonstrated by recent corticospinal imaging studies.⁵⁷ The periaqueductal gray, a critical brainstem nucleus involved in descending pain modulation, simultaneously coordinates autonomic responses, including cardiovascular adjustments during stress and pain states.¹⁴ Functional connectivity between the periaqueductal gray and ventromedial prefrontal cortex has been shown to correlate with both LF-HRV variability during pain and subjective pain ratings, establishing a triadic relationship between pain experience,

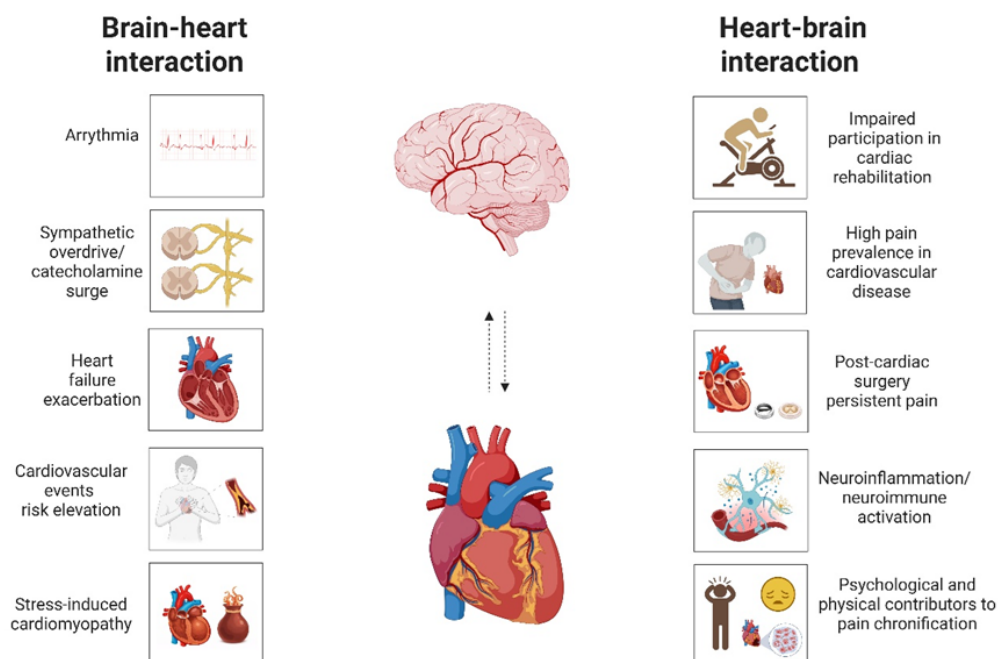


Figure 1. Bidirectional brain-heart interactions involving pain and cardiovascular dysfunction. This schematic highlights how neurological injury, autonomic imbalance, neuroimmune activation, and stress responses may adversely influence cardiac physiology (left panel), contributing to arrhythmias, sympathetic overdrive, heart failure exacerbation, elevated cardiovascular event risk, and stress-induced cardiomyopathy. Conversely, cardiac disease processes (right panel), including high prevalence of pain in cardiovascular populations, post-cardiac surgery persistent pain, and psychological and physical contributors to pain chronification, may promote maladaptive neuroplasticity and sustained CNS dysfunction. Created in BioRender. TRAN VAN, Y. (2026) <https://BioRender.com/78priha>.

autonomic regulation, and cortical network dynamics.¹⁴ These findings fundamentally challenge traditional pain models that conceptualize central processing as purely sensory-discriminative, instead supporting an integrative framework in which pain, emotion, interoception, and autonomic homeostasis are co-regulated through shared neural circuitry.

Within clinical neurology, stroke–heart syndrome represents a paradigmatic model of brain-driven cardiac vulnerability.⁹ High-impact reviews and consensus statements have established that acute ischemic stroke (particularly when involving insular, cingulate, or brainstem structures) can precipitate a wide range of cardiovascular complications, including arrhythmias, myocardial injury, stress cardiomyopathy, heart failure exacerbation, and sudden cardiac death.⁹ These complications are mediated by autonomic imbalance, excessive catecholaminergic activation, neuroinflammatory cascades, and disruption of central regulatory networks. Notably, these same mechanisms are also implicated in the development and persistence of chronic pain, including sustained sympathetic activation, impaired parasympathetic tone,

and central sensitization. Recent clinical autonomic reviews emphasize that post-stroke autonomic dysfunction often persists beyond the acute phase, reinforcing its relevance for long-term symptom burden, rehabilitation, and recovery trajectories.³² Although pain outcomes are rarely systematically assessed in stroke–heart studies, the mechanistic overlap strongly suggests that pain may interact bidirectionally with neurocardiac dysfunction in this population.

From a cardiovascular perspective, the reviewed literature clearly demonstrates that pain is common, under-recognized, and clinically consequential in heart disease, particularly in heart failure. Large population-based studies, including analyses from the HUNT cohort, consistently show a high prevalence of chronic pain and chronic widespread pain among individuals with heart failure, with clinically meaningful associations with disability, symptom burden, and reduced quality of life.¹⁹ These findings challenge the traditional marginalization of pain within cardiology and underscore its relevance as a core comorbidity rather than a secondary or incidental symptom. Mechanistically, pain may contribute to adverse

cardiovascular outcomes through multiple pathways, including reduced physical activity, impaired adherence to treatment and rehabilitation, neuroendocrine stress responses, and sustained autonomic imbalance. Despite this, pain assessment remains inconsistent in cardiovascular care pathways, and mechanistic brain–heart perspectives are rarely incorporated into routine management. Considering these factors, a recent expert consensus highlighted the importance of routine pain assessment in cardiovascular populations, arguing that chronic pain, irrespective of its underlying mechanism (neuropathic, inflammatory, or musculoskeletal), should be regarded as a cardiometabolic risk modifier warranting structured evaluation and management.⁴⁰ This perspective shift is particularly important, given emerging evidence that chronic pain and cardiovascular disease share fundamental modifiable risk factors including obesity, physical inactivity, sleep disturbance, depression, and adverse health behaviors.⁴⁰ The integration of cardiology, pain management, and behavioral medicine into collaborative care models has been proposed as a patient-centered approach to address this intersection, although implementation remains limited by fragmented specialty care and reimbursement constraints.

Beyond comorbidity, an emerging and particularly important theme is the role of chronic pain as a modifier of cardiovascular risk and outcomes. Advances in longitudinal cohort design and data linkage have enabled investigators to examine pain trajectories, multisite pain, and pain chronicity as predictors of incident cardiovascular events. Recent studies provide empirical support for long-hypothesized associations mediated by sustained sympathetic activation, hypothalamic-pituitary-adrenal axis dysregulation, low-grade inflammation, sleep disturbance, and adverse health behaviors.³⁹ A comprehensive preventive cardiology review synthesizes this growing body of evidence and positions chronic pain as a potential, modifiable cardiovascular risk factor, while also emphasizing the substantial methodological challenges inherent to this research area, including confounding, reverse causality, and shared psychosocial determinants.⁴⁰ These challenges highlight the need for carefully designed longitudinal and interventional studies to clarify causal relationships, better characterize bidirectional effects and evaluate whether targeted pain modulation can meaningfully influence cardiovascular outcomes.

At the translational level, neuromodulation strategies emerge as a clinically actionable point of convergence between pain relief and cardiovascular regulation. SCS, traditionally employed for refractory angina and chronic pain syndromes, has been shown to modulate sympathetic

activity while improving both ischemic symptoms and pain perception.⁴⁸ However, most studies continue to prioritize either cardiac or pain endpoints in isolation, limiting mechanistic insight. Similarly, t-VNS has demonstrated promise in heart failure populations, with reported improvements in functional capacity, autonomic balance, and inflammatory markers.⁵⁰ From a mechanistic standpoint, vagal modulation is particularly relevant to pain through the cholinergic anti-inflammatory reflex and central autonomic circuits.⁵⁸ The absence of integrated outcome frameworks that simultaneously assess pain, autonomic function, and cardiovascular endpoints remains a major limitation, constraining causal inference and translational impact.

Despite these advances, the reviewed literature reveals substantial and persistent gaps that justify the present narrative synthesis. Pain phenotyping remains highly heterogeneous, with wide variation in definitions, instruments, and thresholds, and limited alignment with contemporary mechanistic classifications such as nociceptive, neuropathic, nociplastic, and mixed pain.⁵⁹ This heterogeneity hampers comparability across studies and obscures mechanistic interpretation. Furthermore, the predominance of cross-sectional designs limits the ability to disentangle directionality between pain, autonomic dysfunction, and cardiovascular outcomes. Only a minority of studies integrate multimodal measures spanning brain network function, autonomic physiology, and detailed pain phenotyping, resulting in persistent “measurement silos” that undermine systems-level understanding.

Nonetheless, this review has several limitations. As a narrative synthesis, this review aims to map and critically interpret the available evidence rather than quantify effect sizes or establish causality. The included literature is heterogeneous with respect to study design, populations, pain definitions, and autonomic measures, limiting direct comparability.⁶⁰ Additionally, the predominant use of single-time-point assessments limits understanding of temporal dynamics: chronic pain is inherently fluctuating, and cardiovascular risk may be differentially influenced by pain persistence, severity trajectories, and multisite involvement over time.^{39,61} The reviewed literature would benefit from longitudinal designs with repeated pain phenotyping, serial autonomic assessments, and cardiovascular imaging to better characterize temporal sequences and dose-response relationships.⁶² Furthermore, mechanistic studies rarely integrate comprehensive multimodal assessments spanning subjective pain reports, quantitative sensory testing, brain network function, peripheral and central autonomic measures, inflammatory biomarkers, and cardiovascular structure and function within the same

cohort, limiting systems-level interpretation. Many cardiovascular studies assess pain without mechanistic brain measures, while neuroscience studies often lack clinically meaningful cardiovascular endpoints.⁵⁵ In addition, restriction to English-language publications may underrepresent global evidence.⁶³ Formal risk-of-bias assessment was not undertaken, consistent with SANRA guidance and the narrative scope of this work. To translate these limitations into actionable guidance, future research in this field should consider adopting the following harmonization strategies. First, pain phenotyping should be standardized using the IASP-endorsed multiaxial classification system, incorporating quantitative sensory testing profiles alongside self-reported measures to enable mechanistic subtyping across nociceptive, neuropathic, nociplastic, and mixed pain categories. Autonomic assessment should follow a minimum battery approach inclusive of time- and frequency-domain HRV, baroreflex sensitivity, and validated orthostatic testing, aligned with European Heart Rhythm Association and Autonomic Neuroscience Society recommendations. Multimodal study designs should integrate, at a minimum, standardized pain phenotyping, a core autonomic measure, and at least one structural or functional cardiac endpoint within the same cohort to overcome the measurement silos identified here. Collaborative cross-disciplinary consortia, analogous to models established in stroke–heart syndrome research, should be prioritized to enable the sample sizes and outcome breadth required for causal inference. Adoption of these strategies would substantially improve comparability across studies and accelerate mechanistic understanding of the pain–brain–heart continuum.

5. Conclusion

The evidence reviewed supports a paradigm in which pain, brain function, and cardiovascular regulation are deeply interconnected. Recognizing pain as a systems-level contributor, rather than a peripheral symptom, has important implications for research design, clinical assessment, and therapeutic innovation. Future progress will depend on harmonized pain phenotyping, longitudinal and interventional designs, and integrated multimodal approaches capable of capturing the full complexity of the pain–brain–heart continuum.

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References

- Varrassi G, Leoni MLG, Fari G, Al-Alwany AA, Al-Sharie S, Fornasari D. Neuromodulatory Signaling in Chronic Pain Patients: A Narrative Review. *Cells*. 2025;14(17). doi: 10.3390/cells14171320
- Cao B, Xu Q, Shi Y, *et al.* Pathology of pain and its implications for therapeutic interventions. *Signal Transduct Target Ther*. 2024;9(1):155. doi: 10.1038/s41392-024-01845-w
- Armstrong M, Castellanos J, Christie D. Chronic pain as an emergent property of a complex system and the potential roles of psychedelic therapies. *Front Pain Res*. 2024;5:1346053. doi: 10.3389/fpain.2024.1346053
- Herring N, Ajjola OA, Foreman RD, *et al.* Neurocardiology: translational advancements and potential. *J Physiol*. 2025;603(7):1729–1779. doi: 10.1113/JP284740
- Hafez OA, Chang RB. Regulation of Cardiac Function by the Autonomic Nervous System. *Physiology*. 2025;40(3):258–270. doi: 10.1152/physiol.00018.2024
- Ferraro S, Klugah-Brown B, Tench CR, *et al.* The central autonomic system revisited - Convergent evidence for

- a regulatory role of the insular and midcingulate cortex from neuroimaging meta-analyses. *Neurosci Biobehav Rev*. 2022;142:104915.
doi: 10.1016/j.neubiorev.2022.104915
7. Buckley BJR, Harrison SL, Hill A, Underhill P, Lane DA, Lip GYH. Stroke-Heart Syndrome: Incidence and Clinical Outcomes of Cardiac Complications Following Stroke. *Stroke*. 2022;53(5):1759–1763.
doi: 10.1161/STROKEAHA.121.037316
 8. Sposato LA, Hilz MJ, Aspberg S, *et al*. Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;76(23):2768–2785.
doi: 10.1016/j.jacc.2020.10.009
 9. Scheitz JF, Sposato LA, Schulz-Menger J, Nolte CH, Backs J, Endres M. Stroke-Heart Syndrome: Recent Advances and Challenges. *J Am Heart Assoc*. 2022;11(17):e026528.
doi: 10.1161/JAHA.122.026528
 10. Duan YW, Chen SX, Li QY, Zang Y. Neuroimmune Mechanisms Underlying Neuropathic Pain: The Potential Role of TNF-alpha-Necroptosis Pathway. *Int J Mol Sci*. 2022;23(13).
doi: 10.3390/ijms23137191
 11. Zhang S, Ning Y, Yang Y, *et al*. Decoding pain chronification: mechanisms of the acute-to-chronic transition. *Front Mol Neurosci*. 2025;18:1596367.
doi: 10.3389/fnmol.2025.1596367
 12. Hu JR, Abdullah A, Nanna MG, Soufer R. The Brain-Heart Axis: Neuroinflammatory Interactions in Cardiovascular Disease. *Curr Cardiol Rep*. 2023;25(12):1745–1758.
doi: 10.1007/s11886-023-01990-8
 13. van der Wall EE, van Gilst WH. Neurocardiology: close interaction between heart and brain. *Neth Heart J*. 2013;21(2):51–2.
doi: 10.1007/s12471-012-0369-4
 14. Hohenschurz-Schmidt DJ, Calcagnini G, Dipasquale O, *et al*. Linking Pain Sensation to the Autonomic Nervous System: The Role of the Anterior Cingulate and Periaqueductal Gray Resting-State Networks. *Front Neurosci*. 2020;14:147.
doi: 10.3389/fnins.2020.00147
 15. Matusik PS, Zhong C, Matusik PT, Alomar O, Stein PK. Neuroimaging Studies of the Neural Correlates of Heart Rate Variability: A Systematic Review. *J Clin Med*. 2023;12(3):1016.
doi: 10.3390/jcm12031016
 16. Alemzadeh-Ansari MJ, Ansari-Ramandi MM, Naderi N. Chronic Pain in Chronic Heart Failure: A Review Article. *J Tehran Heart Cent*. 2017;12(2):49–56.
 17. Walton LL, Duff E, Arora RC, McMillan DE. The Role of the Cardiac Surgery Patient in Pain Management: The Patient Perspective. *Clin Nurs Res*. 2024;33(7):538–544.
doi: 10.1177/10547738241273232
 18. Krakowski JC, Hallman MJ, Smeltz AM. Persistent Pain After Cardiac Surgery: Prevention and Management. *Semin Cardiothorac Vasc Anesth*. 2021;25(4):289–300.
doi: 10.1177/10892532211041320
 19. Vikan KK, Landmark T, Gjeilo KH. Prevalence of chronic pain and chronic widespread pain among subjects with heart failure in the general population: The HUNT study. *Eur J Pain*. 2024;28(2):273–284.
doi: 10.1002/ejp.2176
 20. Raja SN, Carr DB, Cohen M, *et al*. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;161(9):1976–1982.
doi: 10.1097/j.pain.0000000000001939
 21. Karcz M, Abd-Elsayed A, Chakravarthy K, *et al*. Pathophysiology of Pain and Mechanisms of Neuromodulation: A Narrative Review (A Neuron Project). *J Pain Res*. 2024;17:3757–3790.
doi: 10.2147/JPR.S475351
 22. Treede RD, Jensen TS, Campbell JN, *et al*. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630–1635.
doi: 10.1212/01.wnl.00000282763.29778.59
 23. Leoni MLG, Mercieri M, Viswanath O, *et al*. Neuropathic Pain: A Comprehensive Bibliometric Analysis of Research Trends, Contributions, and Future Directions. *Curr Pain Headache Rep*. 2025;29(1):73.
doi: 10.1007/s11916-025-01384-1
 24. Kosek E. The concept of nociplastic pain-where to from here? *Pain*. 2024;165(11S):S50–S57.
doi: 10.1097/j.pain.0000000000003305
 25. Kaplan CM, Kelleher E, Irani A, Schrepf A, Clauw DJ, Harte SE. Deciphering nociplastic pain: clinical features, risk factors and potential mechanisms. *Nat Rev Neurol*. 2024;20(6):347–363.
doi: 10.1038/s41582-024-00966-8
 26. Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of Chronic Pain: Domains, Methods, and Mechanisms. *J Pain*. 2016;17(9 Suppl):T10–20.
doi: 10.1016/j.jpain.2015.08.010
 27. Nijs J, De Baets L, Hodges P. Phenotyping nociceptive, neuropathic, and nociplastic pain: who, how, & why? *Braz J Phys Ther*. 2023;27(4):100537.
doi: 10.1016/j.bjpt.2023.100537

28. Nijs J, Malfliet A, Nishigami T. Nociceptive pain and central sensitization in patients with chronic pain conditions: a terminology update for clinicians. *Braz J Phys Ther.* 2023;27(3):100518.
doi: 10.1016/j.bjpt.2023.100518
29. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev.* 2019;4:5.
doi: 10.1186/s41073-019-0064-8
30. Mitrica M, Lorusso L, Badea AA, *et al.* The Hidden Heart: Exploring Cardiac Damage Post-Stroke: A Narrative Review. *Medicina.* 2024;60(10).
doi: 10.3390/medicina60101699
31. Fontes MAP, Dos Santos Machado LR, Viana ACR, *et al.* The insular cortex, autonomic asymmetry and cardiovascular control: looking at the right side of stroke. *Clin Auton Res.* 2024;34(6):549–560.
doi: 10.1007/s10286-024-01066-9
32. Barkhudaryan A, Doehner W, Jauert N. Autonomic dysfunction after stroke: an overview of recent clinical evidence and perspectives on therapeutic management. *Clin Auton Res.* 2025;35(4):553–563.
doi: 10.1007/s10286-025-01120-0
33. Yuan X, Hu S, Fan X, *et al.* Central post-stroke pain: advances in clinical and preclinical research. *Stroke Vasc Neurol.* 2025;10(3):391–406.
doi: 10.1136/svn-2024-003418
34. Betancur DFA, Tarrago M, Torres I, Fregni F, Caumo W. Central Post-Stroke Pain: An Integrative Review of Somatotopic Damage, Clinical Symptoms, and Neurophysiological Measures. *Front Neurol.* 2021;12:678198.
doi: 10.3389/fneur.2021.678198
35. Mohanan AT, Nithya S, Nomier Y, *et al.* Stroke-Induced Central Pain: Overview of the Mechanisms, Management, and Emerging Targets of Central Post-Stroke Pain. *Pharmaceuticals.* 2023;16(8).
doi: 10.3390/ph16081103
36. Fan X, Cao J, Li M, *et al.* Stroke Related Brain-Heart Crosstalk: Pathophysiology, Clinical Implications, and Underlying Mechanisms. *Adv Sci.* 2024;11(14):e2307698.
doi: 10.1002/advs.202307698
37. Reynolds CA, Minic Z. Chronic Pain-Associated Cardiovascular Disease: The Role of Sympathetic Nerve Activity. *Int J Mol Sci.* 2023;24(6).
doi: 10.3390/ijms24065378
38. Mhesin D, Nazzal H, Amerah J, *et al.* Prevalence of pain and its association with quality of life of patients with heart failure in a developing country: findings from a multicenter cross-sectional study. *BMC Cardiovasc Disord.* 2022;22(1):426.
doi: 10.1186/s12872-022-02864-7
39. Yang Z, Zheng L, Zhao H, *et al.* Impact of dynamic changes in pain on cardiovascular disease in Chinese middle and elderly people: results from China Health and Retirement Longitudinal Study (CHARLS). *BMC Public Health.* 2025;25(1):3489.
doi: 10.1186/s12889-025-24552-9
40. Arnlov J. The cardiovascular consequences of chronic pain. *Eur J Prev Cardiol.* 2025.
doi: 10.1093/eurjpc/zwaf404
41. Qin P, Nicholl BI, Ho FK, Hanlon P, Celis-Morales CA, Pell JP. Association between pain and incident arrhythmias in 422,654 individuals: evidence from the UK Biobank cohort. *Eur J Prev Cardiol.* 2025.
doi: 10.1093/eurjpc/zwaf153
42. Sikandar S, Ackland GL. Chronic pain: a modifiable target to reduce perioperative cardiovascular morbidity. *Br J Anaesth.* 2025;134(3):627–631.
doi: 10.1016/j.bja.2024.11.019
43. Zhang Y, Wu X, Gao F, Wang J. Pain in the body, harm to the heart: advances in research on the impact of chronic pain on cardiovascular diseases. *Front Cardiovasc Med.* 2025;12:1629145.
doi: 10.3389/fcvm.2025.1629145
44. Boccella S, De Filippis L, Giorgio C, *et al.* Combination Drug Therapy for the Management of Chronic Neuropathic Pain. *Biomolecules.* 2023;13(12).
doi: 10.3390/biom13121802
45. Xiao MZX, Khan JS, Dana E, *et al.* Prevalence and Risk Factors for Chronic Postsurgical Pain after Cardiac Surgery: A Single-center Prospective Cohort Study. *Anesthesiology.* 2023;139(3):309–320.
doi: 10.1097/ALN.0000000000004621
46. Dost B, Karapinar YE, Karakaya D, *et al.* Chronic postsurgical pain after cardiac surgery: A narrative review. *Saudi J Anaesth.* 2025;19(2):181–189.
doi: 10.4103/sja.sja_829_24
47. Paradiso B, Pauza DH, Limback C, Ottaviani G, Thiene G. From Psychostasis to the Discovery of Cardiac Nerves: The Origins of the Modern Cardiac Neuromodulation Concept. *Biology.* 2024;13(4).
doi: 10.3390/biology13040266
48. Gazzeri R, Mosca J, Occhigrossi F, Mercieri M, Galarza M, Leoni MLG. Spinal Cord Stimulation for Refractory Angina Pectoris: Current Status and Future Perspectives, a Narrative Review. *J Cardiovasc Dev Dis.* 2025;12(1).
doi: 10.3390/jcdd12010033

49. Gasimova NZ, Paltsev AA, Zayachkovskiy NA, *et al.* Prospective evaluation of spinal cord stimulation in refractory angina: insights from a single-center cohort. *Front Cardiovasc Med.* 2025;12:1681623.
doi: 10.3389/fcvm.2025.1681623
50. Sun Z, Liu L, Peng H, Zhang R. The efficacy of transcutaneous vagus nerve stimulation in heart failure management - a systematic review and meta-analysis. *BMC Cardiovasc Disord.* 2025;25(1):481.
doi: 10.1186/s12872-025-04919-x
51. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin.* 2006;22(10):1911–1920.
doi: 10.1185/030079906X132488
52. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain.* 1983;17(2):197–210.
doi: 10.1016/0304-3959(83)90143-4
53. Hageman S, Pennells L, Ojeda F, *et al.* SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J.* 2021;42(25):2439–2454.
doi: 10.1093/eurheartj/ehab309
54. Valenza G, Matic Z, Catrambone V. The brain-heart axis: integrative cooperation of neural, mechanical and biochemical pathways. *Nat Rev Cardiol.* 2025;22(8):537–550.
doi: 10.1038/s41569-025-01140-3
55. Ziegler KA, Engelhardt S, Carnevale D, *et al.* Neural Mechanisms in Cardiovascular Health and Disease. *Circ Res.* 2025;136(11):1233–1261.
doi: 10.1161/CIRCRESAHA.125.325580
56. Valenza G, Cio FD, Toschi N, Barbieri R. Sympathetic and parasympathetic central autonomic networks. *Imaging Neurosci.* 2024;2.
doi: 10.1162/imag_a_00094
57. Kaptan M, Pfyffer D, Konstantopoulos CG, *et al.* Recent developments and future avenues for human corticospinal neuroimaging. *Front Hum Neurosci.* 2024;18:1339881.
doi: 10.3389/fnhum.2024.1339881
58. de Melo PS, Gianlorenco AC, Marduy A, *et al.* A Mechanistic Analysis of the Neural Modulation of the Inflammatory System Through Vagus Nerve Stimulation: A Systematic Review and Meta-analysis. *Neuromodulation.* 2025;28(1):43–53.
doi: 10.1016/j.neurom.2024.03.002
59. Varrassi G, Fari G, Narvaez Tamayo MA, *et al.* Mixed pain: clinical practice recommendations. *Front Med.* 2025;12:1659490.
doi: 10.3389/fmed.2025.1659490
60. Barker TH, Stone JC, Sears K, *et al.* The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. *JBI Evid Synth.* 2023;21(3):494–506.
doi: 10.11124/JBIES-22-00430
61. Frumkin MR, Carpenter RW, Rodebaugh TL. Heterogeneity in Temporal Dynamics of Pain and Affect Among Individuals With Chronic Back Pain and Associations With Risk for Future Opioid-Related Problems. *Clin Psychol Sci.* 2024;12(4):706–720.
doi: 10.1177/21677026231196121
62. Yang W, Cai S, Chen X, *et al.* Patterns of Comorbidity Between Chronic Pain and Chronic Diseases in US Adults: A Cross-Sectional Analysis of NHANES Data. *J Pain Res.* 2026;19:555970.
doi: 10.2147/JPR.S555970
63. Bahji A, Acion L, Laslett AM, Adinoff B. Exclusion of the non-English-speaking world from the scientific literature: Recommendations for change for addiction journals and publishers. *Nord Alkohol Nark.* 2023;40(1):6–13.
doi: 10.1177/14550725221102227