



## When the Heart Talks to the Brain: Rethinking Cardiovascular-Neurodegenerative Interfaces

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### Abstract

Emerging research reveals a bidirectional interface between cardiovascular diseases—such as atrial fibrillation (AF) and heart failure (HF)—and neurodegenerative disorders, including Alzheimer’s disease (AD) and Parkinson’s disease (PD). While traditional models have emphasized shared risk factors such as aging, chronic inflammation, and metabolic dysfunction, newer evidence points to a more dynamic and causative framework: a reciprocal interactome composed of signaling molecules, extracellular vehicles, and neurohormonal circuits linking cardiac and cerebral systems. Cardiokines (e.g., natriuretic peptides, FGF21), neurokinins (e.g., BDNF, NGF), exosomes carrying noncoding RNAs, and systemic axes such as the renin–angiotensin–aldosterone system (RAAS) and hypothalamic–pituitary–adrenal (HPA) axis act as molecular bridges that mediate cross-organ communication. This review shifts focus from risk association to causative molecular dialogue, demonstrating how these interactomes drive remodeling, dysfunction, and progressive degeneration in both systems and repositions the heart–brain axis as a site of active disease–disease interaction, where reciprocal complications emerge from disrupted signaling rather than isolated end-organ pathology. Three clinical vignettes are presented to illustrate the translational relevance of this model. We propose that therapeutic strategies targeting these inter-organs signaling networks—rather than treating individual organ dysfunction in isolation—may offer a more effective and systems-level approach to managing age-related syndromes.

**Keywords:** Cardiovascular diseases; Neurodegenerative disorders; Atrial fibrillation; Heart failure; Alzheimer’s disease; Parkinson’s disease; Interactomes; Cardiokines; Neurokinins; Exosomes

### Introduction: Beyond Shared Risk Factors

Cardiovascular diseases like atrial fibrillation (AF) and heart failure (HF), and neurodegenerative diseases such as Alzheimer’s (AD) and Parkinson’s (PD), are traditionally treated as isolated aging-related conditions. While traditionally managed in silos by distinct medical specialties, emerging research uncovering high rates of co-occurrence and overlapping pathophysiology challenges this dichotomy and highlights their interdependence [1-8]. Conditions such as AF and HF are now recognized not only as contributors to vascular dementia and cognitive decline but also as active players in the progression of neurodegenerative diseases like AD and PD. Likewise, neurodegeneration may influence cardiac health through autonomic dysregulation, altered circadian rhythms, and systemic inflammation. These new observations suggest the presence of a new type of disease-disease interactions (DDIs): reciprocal complications [8].

The recognition of overlapping molecular drivers—such as mitochondrial dysfunction, chronic inflammation, oxidative stress, and impaired proteostasis—suggests that these disorders should not be viewed in isolation. Rather, they represent interconnected nodes within a broader aging-related network. Increasing evidence suggests that molecular signals originating in one organ actively influence pathology in the other. The concept of *interactomes*—complex networks of tissue-to-tissue molecular communication—offers a more accurate model for understanding these bidirectional interfaces or reciprocal complications [8]. Instead of attributing comorbidity to coincidence, interactomes point to causative reciprocity. Understanding and intervening in these cross-talk mechanisms may redefine prevention and treatment of both cardiovascular and neurodegenerative diseases. This systems-level perspective opens new avenues for early diagnosis, shared biomarkers, and therapeutics that transcend traditional boundaries.

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## Clinical Vignette 1: AF and Hippocampal Degeneration

Mr. A, a 76-year-old retired accountant, presents with paroxysmal AF and mild memory complaints. He denies prior stroke. Brain MRI reveals bilateral hippocampal atrophy without infarcts. Plasma levels of GDF15 and NT-proBNP are elevated. Cognitive testing shows reduced verbal recall and executive slowing.

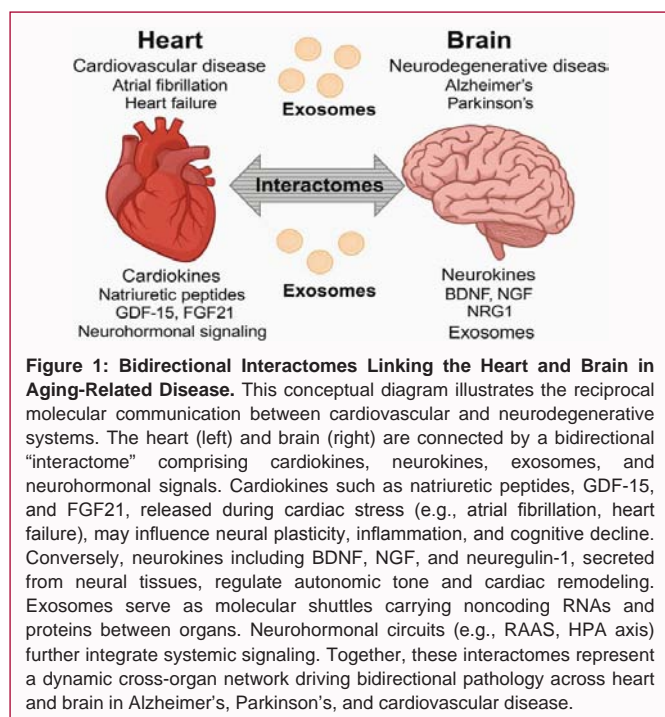
This case exemplifies a common clinical observation: the co-occurrence of AF and cognitive decline without a clear ischemic event. Traditional explanations focus on hypoperfusion and microemboli. However, recent studies reveal that cardiokines such as growth differentiation factor-15 (GDF15) and natriuretic peptides, released during cardiac stress, can cross the blood-brain barrier (BBB), where they may influence neuroinflammation and synaptic plasticity [9-12]. GDF15, in particular, has been linked to hippocampal dysfunction, microglial activation, and accelerated brain atrophy [13,14]. Rather than simple vascular consequences, the cardiocerebral dialogue itself may be pathogenic.

Epidemiological studies show that even short episodes of subclinical AF increase the risk of cognitive decline. Furthermore, oral anticoagulation—while effective for stroke prevention—does not fully abrogate the risk of dementia, suggesting non-embolic mechanisms at play. Monitoring and managing AF in patients with early cognitive symptoms may represent a key opportunity for neuroprotection.

## Interactomes: Defining the Molecular Messengers

An *interactome* is not a single molecule but a system of cross-organ messengers [15-19] (Figure 1). These include:

- Cardiokines: Proteins secreted by stressed myocardium (e.g., ANP, BNP, GDF15, FGF21) with systemic effects [20-25].
- Neurokines: Brain-derived factors (e.g., brain-derived



neurotrophic factor BDNF, nerve growth factor NGF) affecting cardiac autonomic function and myocardial plasticity [26,27].

- Exosomes and extracellular vehicles (EVs): Lipid-bound vehicles carrying noncoding RNAs, proteins, and metabolites from one organ to another.
- Neurohormonal signals: Feedback circuits involving the renin-angiotensin-aldosterone system (RAAS), hypothalamic-pituitary-adrenal (HPA) axis, and autonomic networks.

These interactomes operate in a dynamic, adaptive feedback loop, leading to reciprocal complications [8] (Figure 1). Cardiac injury alters central neuroimmune tone; neurodegeneration shifts cardiac electrophysiology and vascular tone. The interactome is, in essence, the *molecular bloodstream* of systems medicine.

## Cardiokines in Neurodegeneration

Cardiac tissue under stress secretes a range of proteins that can impact the central nervous system:

- Natriuretic peptides (ANP, BNP): Traditionally known for volume regulation, BNP receptors are expressed in the hippocampus and cortex. Chronic BNP elevation is associated with cognitive impairment and reduced hippocampal volume [20-22].
- GDF15: A marker of cardiovascular strain and inflammation, GDF15 has been implicated in appetite suppression, mitochondrial dysfunction, and cognitive frailty [23,24].
- FGF21: A metabolic hormone with cardioprotective effects that also influences neurovascular coupling and neurogenesis [25].

These cardiokines can traverse the BBB, modulate astrocyte function, and influence neural plasticity. In chronic cardiovascular stress, this becomes maladaptive, contributing to cognitive decline and neurodegeneration.

## Neurokines in Cardiac Remodeling

Just as the heart can speak to the brain, the brain signals back:

- BDNF: While essential for synaptic health, BDNF also regulates heart rate variability and baroreflex sensitivity. Low circulating BDNF predicts both dementia and incident heart failure [26,27].
- NGF: Crucial for sympathetic nervous system development, NGF also modulates cardiac remodeling and ischemic tolerance [28,29].
- Neuregulin-1 (NRG1): Released by neurons and glial cells, NRG1 has protective effects on cardiomyocytes, promoting survival and attenuating hypertrophy [30,31].

In neurodegenerative diseases, these neurokines are often deficient or dysfunctional. This not only exacerbates neural loss but may compromise cardiac homeostasis—especially under stress.

## Exosomes and Microvehicles: The Molecular Mail Carriers

- Extracellular vehicles (EVs), particularly exosomes, are increasingly recognized as mediators of heart-brain communication [32,33]. Originating from endosomal compartments, exosomes carry microRNAs (miRNAs), proteins, and lipids. Key features: Cardiac-derived exosomes in HF carry inflammatory miRNAs (e.g., miR-

21, miR-146a) that influence microglial activation and blood-brain barrier permeability [34].

- Brain-derived exosomes in AD contain tau and amyloid fragments, but also regulatory RNAs that modulate endothelial function and cardiac remodeling [35].

- Cross-organ EVs have been detected in both CSF and peripheral blood, suggesting systemic dissemination of pathology [36,37].

Intervening in exosome release or uptake may offer disease-modifying potential.

## Clinical Vignette 2: HFpEF and Parkinsonism

Ms. B, a 79-year-old woman with HFpEF and long-standing type 2 diabetes, presents with a new diagnosis of Parkinson's disease. She reports fatigue, exertional dyspnea, and slow gait. Plasma BDNF and FGF21 levels are low; exosomal miR-124 is elevated. Echo shows preserved LVEF with diastolic dysfunction.

This case illustrates reciprocal interactome collapse. Neurodegeneration reduces neurokinine output (BDNF), impairing autonomic regulation and cardiac adaptation. Simultaneously, cardiac dysfunction reduces FGF21 and raises exosomal miRNAs that may worsen dopaminergic neuron vulnerability. Therapeutic targeting of either organ in isolation may be insufficient without modulating the molecular cross-talk.

## Hormonal Interfaces: RAAS, HPA, and Autonomic Feedback

Major neurohormonal systems orchestrate adaptive responses to stress:

- RAAS activation, common in HF, promotes BBB disruption, cerebral inflammation, and impaired clearance of amyloid proteins.
- Corticosteroids released via HPA activation influence hippocampal neurogenesis and cardiovascular remodeling, particularly under chronic stress.
- Sympathetic overdrive, frequently seen in PD and HF, exacerbates oxidative stress and arrhythmogenic potential.

These hormonal circuits form a low-frequency but high-impact feedback system. Therapeutic modulation (e.g., ARBs, beta-blockers, mineralocorticoid antagonists) may confer dual benefits by restoring balance across systems.

## Diagnostic and Therapeutic Targeting of Interactomes

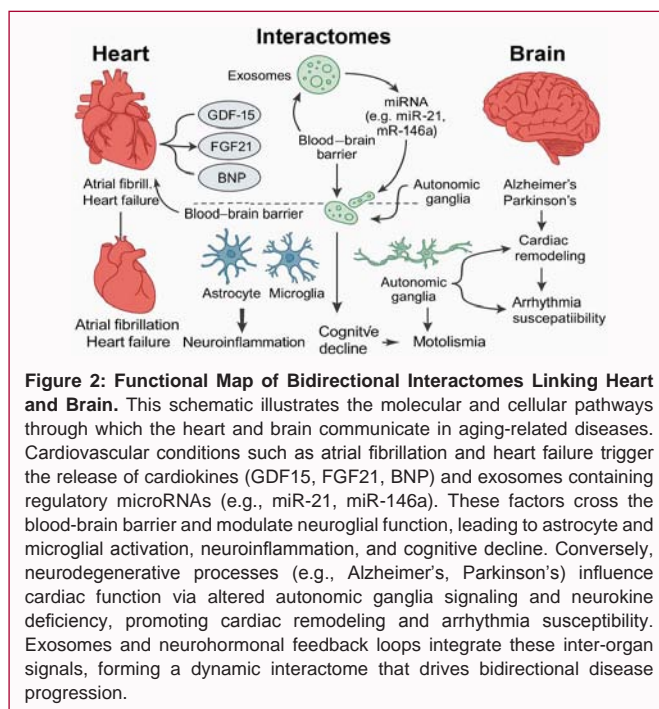
Moving from correlation to causality demands new diagnostic and therapeutic paradigms:

### Biomarkers of Interactome Dysfunction

- Circulating GDF15 and NT-proBNP (cardiac distress)
- Serum BDNF and NRG1 (neural signaling capacity)
- Exosomal miRNA panels (inter-organ communication)

### Therapeutic Opportunities

- Recombinant neurokinines (e.g., BDNF mimetics)
- Exosome blockers or designer EVs
- Interactome-informed polypharmacy, targeting signaling



overlap (e.g., SGLT2 inhibitors, GLP-1 agonists)

This approach reframes pharmacology as modulation of molecular relationships—not just symptom control.

## Clinical Vignette 3: Silent AF in Alzheimer's Disease

Mr. C, an 82-year-old man with early Alzheimer's, presents with a syncopal episode. Holter monitoring reveals paroxysmal AF. Plasma NT-proBNP and GDF-15 are elevated. CSF shows mild tau pathology. Despite anticoagulation, his memory continues to decline.

This case challenges the stroke-centric view of AF in dementia. AF-related cardiokines may accelerate neurodegeneration through non-thrombotic mechanisms. Monitoring these interactome markers may guide therapy even when ischemic burden is absent.

## Conclusion: A New Era of Systems Integration

The traditional dichotomy between cardiovascular and neurodegenerative disease is dissolving. Interactomes—dynamic signaling networks involving cardiokines, neurokinines, EVs, and hormonal feedback—drive pathology across organs leading to reciprocal complications [8]. These organ cross-talk or DDI mechanisms not only explain comorbidity but offer new diagnostic windows and therapeutic strategies. Rather than managing disease at its end stages, we must intervene at the molecular conversations between organs or between diseases. This shift—from fragmentation to integration—is the future of translational aging medicine.

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## Author Contributions

Wang Z conceptualized the work and drafted the manuscript. Ju J refined the concept and performed editing, polishing, and

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