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Skeletal Muscle – Brain Crosstalk in Cognitive Aging and Dementia: Physiological Roles of Myokines and Lactate Signalling

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ABSTRACT

Aging is accompanied by progressive cognitive decline and an increasing burden of dementia. While physical activity is one of the most effective non-pharmacological strategies for preserving cognitive health, the biological mechanisms underlying its neuroprotective effects remain incompletely understood. In recent years, skeletal muscle has emerged as an active endocrine organ that communicates with the brain through the release of myokines and metabolites during exercise. This muscle–brain crosstalk provides a mechanistic framework linking muscle activity to brain plasticity and cognitive resilience.This clinical and translational narrative review synthesizes experimental and translational evidence on skeletal muscle–brain communication in cognitive aging and dementia, with a specific focus on irisin (FNDC5), brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), and lactate signalling. Exercise-induced irisin enhances hippocampal BDNF expression and synaptic plasticity, while acute muscle-derived IL-6 exerts anti-inflammatory effects that contrast with the chronic inflammatory state of aging. Lactate, once considered a metabolic by-product, is now recognized as a key signalling molecule that supports neuronal metabolism, memory formation, and epigenetic regulation through lactylation.Aging disrupts these beneficial signalling pathways through sarcopenia, metabolic dysfunction, and chronic low-grade inflammation, thereby increasing vulnerability to cognitive decline and dementia. Evidence from animal models, observational studies, and exercise interventions in older adults supports a causal link between skeletal muscle health and cognitive outcomes.By integrating molecular mechanisms with clinical observations, this review highlights skeletal muscle as a modifiable determinant of brain aging. Preserving muscle health through targeted exercise emerges as a physiologically grounded strategy for promoting cognitive resilience and reducing dementia risk.

Keywords : Skeletal muscle–brain axis, Myokines, Irisin, Brain-derived neurotrophic factor, Lactate signalling, Cognitive aging, Dementia, Exercise physiology, Sarcopenia, Neuroplasticity, Aging brain, Physical activity, Alzheimer's disease

INTRODUCTION

Population aging is accelerating worldwide, accompanied by a rapid rise in cognitive decline and dementia. Despite major advances in neuroscience, effective disease-modifying therapies for most neurodegenerative disorders remain elusive. In contrast, lifestyle-based interventions—particularly physical activity—consistently demonstrate protective effects on cognitive health across the lifespan. [1,2]

Regular physical exercise is associated with improved cognitive performance, delayed cognitive aging, and reduced risk of dementia. These benefits are observed across populations and disease states, including mild cognitive impairment and Alzheimer's disease. [1,3] Traditional explanations have emphasized improved cerebral perfusion, cardiovascular fitness, and metabolic health. While important, these mechanisms alone fail to fully account for the magnitude and consistency of exercise-induced neuroprotection.

Over the past decade, skeletal muscle has been redefined as an endocrine organ rather than a passive structure for movement. Contracting muscle fibres secrete a diverse array of bioactive molecules—collectively termed myokines—as well as metabolites that exert systemic effects on distant organs, including the brain. [4,5] This paradigm shift has led to the emergence of the muscle–brain axis as a critical regulatory pathway in brain health and disease.

Among the growing list of exercise-induced myokines, irisin (derived from FNDC5), brain-derived neurotrophic factor (BDNF), and interleukin-6 (IL-6) have received particular attention. Irisin has been shown to enhance synaptic plasticity and memory and to rescue cognitive deficits in experimental models of Alzheimer's disease. [6,7] BDNF is a central mediator of neurogenesis and

synaptic remodelling, with strong evidence linking exercise-induced increases in BDNF to improved cognitive outcomes in older adults and patients with neurodegenerative disorders. [1,3] IL-6, traditionally viewed as a pro-inflammatory cytokine, displays a dual role when released acutely from skeletal muscle during exercise, contributing to anti-inflammatory and neuroprotective signalling cascades. [8]

In parallel, lactate has emerged as a key myo-metabolite linking muscle activity to brain function. Once considered merely a by-product of anaerobic metabolism, lactate is now recognized as an essential energy substrate and signalling molecule in the brain. Experimental studies demonstrate that lactate mediates exercise-induced improvements in learning and memory through BDNF-dependent mechanisms. [9,10] More recently, lactate-driven protein and histone lactylation has been implicated in synaptic plasticity, stress resilience, and neurodegeneration, highlighting a novel epigenetic dimension of muscle–brain communication. [11,12]

Aging profoundly alters both skeletal muscle and brain biology. Sarcopenia, mitochondrial dysfunction, insulin resistance, and chronic low-grade inflammation characterize aging muscle, while the aging brain exhibits reduced neurotrophic support, impaired synaptic plasticity, and heightened vulnerability to neurodegeneration. Growing evidence suggests that sarcopenia is independently associated with cognitive impairment, mild cognitive impairment, and incident dementia, underscoring the clinical relevance of muscle health in brain aging. [2,13]

Despite increasing interest in this field, existing evidence remains fragmented. Studies addressing myokines, lactate signalling, cognitive aging, and dementia are often siloed within exercise physiology, neuroscience, geriatrics, or molecular biology. As a result, integrative frameworks linking molecular mechanisms to translational and clinical outcomes remain limited, particularly in the context of aging and neurodegenerative disease.

The present clinical and translational narrative review aims to address this gap. We synthesize current mechanistic and translational evidence on skeletal muscle–brain crosstalk, with specific emphasis on irisin, BDNF, IL-6, and lactate signalling in cognitive aging and dementia. By integrating findings from experimental models and human studies, we propose a unified physiological framework in which skeletal muscle health emerges as a critical determinant of brain aging and cognitive resilience.

Skeletal Muscle as an Endocrine Organ: Conceptual and Physiological Basis

For much of the twentieth century, skeletal muscle was viewed primarily as a mechanical tissue responsible for posture and movement. This view has changed fundamentally. It is now well established that skeletal muscle functions as a dynamic endocrine organ capable of influencing whole-body physiology, including brain function. [4]

During muscle contraction, skeletal muscle fibres synthesize and release a broad spectrum of signalling molecules into the circulation. These molecules, termed myokines, include cytokines, growth factors, peptides, and enzymes. In addition, contracting muscle releases metabolites such as lactate that act as signalling mediators rather than passive by-products of metabolism. [9] Together, these factors form the muscle secretome and enable bidirectional communication between muscle and distant organs.

Exercise is the principal physiological stimulus for myokine release. Both acute and chronic exercise modulate the quantity, timing, and profile of myokine secretion. Importantly, the pattern of myokine release differs according to exercise modality, intensity, duration, and the metabolic state of the muscle. [4] This allows skeletal muscle to translate mechanical and metabolic stress into systemic biological signals.

The endocrine function of skeletal muscle is tightly linked to its metabolic machinery. Exercise activates intracellular signalling pathways such as AMP-activated protein kinase (AMPK), calcium–calmodulin–dependent kinases, and the transcriptional coactivator PGC-1α. These pathways regulate mitochondrial biogenesis, oxidative metabolism, and the expression of genes encoding myokines and metabolic enzymes. [5] Notably, PGC-1α is a key upstream regulator of FNDC5, the precursor of irisin, linking muscle energy sensing directly to brain-relevant signalling.

Skeletal muscle–derived signals influence the brain through multiple routes. Some myokines and metabolites cross the blood–brain barrier directly, while others act indirectly by modulating systemic inflammation, vascular function, glucose homeostasis, and neuroimmune interactions. [5,10] This multifaceted signalling architecture supports the concept of a muscle–brain axis rather than a single linear pathway.

Aging alters this endocrine function of skeletal muscle. With advancing age, muscle mass and strength decline, a process known as sarcopenia. Aging muscle also exhibits reduced mitochondrial efficiency, impaired oxidative capacity, and altered intracellular

signalling. These changes are accompanied by a shift in the muscle secretome, characterized by reduced release of beneficial myokines and increased basal inflammatory signalling. [2,13]

This age-related dysregulation has important consequences for brain health. Reduced myokine signalling may limit neurotrophic support, impair synaptic plasticity, and weaken adaptive stress responses in the aging brain. At the same time, chronic low-grade inflammation originating partly from dysfunctional muscle may exacerbate neuroinflammation and neurodegeneration. [8] Epidemiological evidence linking sarcopenia with cognitive impairment and dementia further supports this connection. [2,13]

Thus, skeletal muscle should be viewed not merely as a target of aging but as an active regulator of brain aging. The endocrine and metabolic functions of muscle provide a physiological bridge between physical activity and cognitive resilience. Understanding how specific muscle-derived signals influence brain structure and function is essential for unravelling the mechanisms through which exercise protects against cognitive decline. The major muscle-derived mediators implicated in brain aging and cognition are summarized in Table 1.

Irisin (FNDC5): A Key Exercise-Induced Link Between Muscle and Brain

Irisin is one of the most intensively studied myokines linking skeletal muscle activity to brain function. It is generated through proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5), a transmembrane protein whose expression is strongly induced by exercise. [6,7] The discovery of irisin provided early molecular evidence that skeletal muscle communicates directly with the brain in response to physical activity.

Experimental studies provide compelling evidence for the role of irisin in synaptic plasticity and memory. In landmark work, exercise-induced FNDC5/irisin signalling was shown to rescue synaptic dysfunction and memory deficits in mouse models of Alzheimer's disease. [6] Blocking FNDC5 expression abolished the cognitive benefits of exercise, indicating that irisin is not merely associated with, but necessary for, exercise-induced neuroprotection.

Exercise activates the PGC-1α signalling pathway in skeletal muscle, leading to upregulation of FNDC5 expression. Circulating irisin levels increase following both acute and chronic exercise, particularly aerobic and endurance-based activities. [5,14] At the molecular level, irisin enhances brain-derived neurotrophic factor expression in the hippocampus. BDNF is essential for synaptic remodelling, long-term potentiation, and neurogenesis, all of which decline with aging. [3] Irisin-induced upregulation of BDNF thus represents a critical pathway through which skeletal muscle activity promotes cognitive resilience. This irisin–BDNF axis has been repeatedly confirmed in experimental models and is increasingly supported by human data. [7,15]

Irisin also exerts anti-inflammatory and anti-apoptotic effects within the brain. In models of chronic cerebral hypoperfusion and neurodegeneration, exercise-induced irisin reduced microglial activation, suppressed pro-inflammatory cytokine expression, and attenuated neuronal apoptosis in the hippocampus. [16] These findings are particularly relevant to aging and vascular dementia, where neuroinflammation plays a central pathogenic role.

Emerging human studies suggest that circulating irisin levels are positively associated with cognitive performance and inversely associated with cognitive impairment. Lower irisin concentrations have been reported in individuals with mild cognitive impairment and Alzheimer's disease compared with cognitively healthy controls. [7] Although causality cannot yet be established in humans, these observations align closely with mechanistic data from animal models.

Aging appears to disrupt irisin signalling at multiple levels. Sarcopenia, reduced physical activity, and impaired PGC-1α signalling contribute to diminished FNDC5 expression and lower circulating irisin levels in older adults. [2,5] This decline may reduce neurotrophic support and increase vulnerability to synaptic dysfunction, thereby accelerating cognitive aging.

From a translational perspective, irisin represents a promising biomarker and therapeutic target. Exercise interventions that enhance muscle mass and mitochondrial function may restore irisin signalling and, in turn, support cognitive health in aging populations. While pharmacological mimetics of irisin remain experimental, lifestyle-based modulation of this pathway is immediately achievable and clinically relevant. [15]

Brain-Derived Neurotrophic Factor (BDNF): Central Node of Exercise-Induced Neuroplasticity

Brain-derived neurotrophic factor (BDNF) is a critical regulator of brain development, synaptic plasticity, and cognitive function. Declining BDNF signalling is a well-recognized feature of cognitive aging and neurodegenerative disorders. [1,3] Exercise is one of the most potent physiological stimuli for BDNF expression. Both acute and chronic physical activity increase BDNF levels in the brain, particularly in the hippocampus, a region highly vulnerable to aging and dementia. [10] In humans, exercise-induced

increases in circulating BDNF are consistently associated with improvements in cognitive performance, especially executive function and memory. [3] Although BDNF is synthesized within the brain, peripheral sources also contribute to its regulation. Skeletal muscle does not produce large amounts of BDNF for endocrine release, but muscle-derived signals strongly influence central BDNF expression. Exercise-induced myokines, particularly irisin, act upstream to stimulate hippocampal BDNF transcription, creating a functional muscle–brain signalling loop. [6,7]

Lactate provides an additional link between muscle activity and BDNF signalling. During exercise, increased glycolytic flux in skeletal muscle leads to elevated circulating lactate levels. Lactate crosses the blood–brain barrier and acts as both an energy substrate and a signalling molecule. Experimental studies demonstrate that lactate enhances hippocampal BDNF expression through SIRT1-dependent and redox-sensitive pathways, directly coupling muscle metabolism to synaptic plasticity. [9,10]

Aging disrupts BDNF signalling at multiple levels. Basal BDNF expression declines with age, and the responsiveness of the BDNF pathway to physiological stimuli is attenuated. Reduced physical activity, sarcopenia, insulin resistance, and chronic inflammation further suppress BDNF availability in older adults. [2,13] These changes contribute to impaired synaptic plasticity and increased susceptibility to cognitive decline.

Exercise interventions in patients with mild cognitive impairment and Alzheimer's disease have been shown to increase circulating BDNF and improve cognitive outcomes, supporting a causal relationship. [1,3]

Importantly, the effects of exercise on BDNF appear to be dose- and modality-dependent. Aerobic exercise reliably increases BDNF levels, while resistance training may exert complementary effects through improvements in muscle mass, insulin sensitivity, and myokine signalling. [4] This suggests that combined exercise modalities may be particularly effective in restoring BDNF-mediated neuroplasticity in aging populations.

Interleukin-6 (IL-6): A Myokine with Dual Roles in Brain Aging

Interleukin-6 (IL-6) occupies a unique position in the muscle–brain axis. Traditionally classified as a pro-inflammatory cytokine, IL-6 is now recognized as a key myokine released from contracting skeletal muscle during exercise. Its biological effects depend critically on the context, timing, and source of release. [8]

During acute exercise, skeletal muscle produces and releases large amounts of IL-6 into the circulation. This transient increase occurs independently of infection or tissue injury and is proportional to exercise intensity and duration. Importantly, exercise-induced IL-6 acts as a metabolic and anti-inflammatory signal rather than a mediator of chronic inflammation. [4]

As a myokine, IL-6 stimulates the release of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist, while suppressing tumour necrosis factor-α. Through these pathways, IL-6 contributes to the resolution of inflammation and maintenance of immune homeostasis. This anti-inflammatory cascade is highly relevant to brain aging, where chronic neuroinflammation is a key driver of cognitive decline. [8]

IL-6 also influences brain function directly. IL-6 receptors are expressed in neurons, astrocytes, and microglia, particularly within the hippocampus. Acute IL-6 signalling has been shown to support neurogenesis, synaptic plasticity, and neuronal survival under physiological conditions. [10] These effects contrast sharply with the detrimental consequences of sustained IL-6 elevation seen in chronic inflammatory states.

Aging alters IL-6 signalling profoundly. Older adults exhibit chronically elevated basal IL-6 levels, a phenomenon often referred to as "inflammaging." This persistent low-grade inflammation is associated with sarcopenia, insulin resistance, and cognitive impairment. [2,13] In this context, IL-6 contributes to neuroinflammation, synaptic dysfunction, and accelerated neurodegeneration.

Exercise appears to restore the physiological balance of IL-6 signalling in aging. Regular physical activity reduces resting IL-6 concentrations while preserving the beneficial acute IL-6 response to muscle contraction. This shift may attenuate chronic neuroinflammation and enhance brain resilience in older adults. [8] Thus, IL-6 should not be viewed solely as a harmful cytokine but as a context-dependent regulator of brain health.

In neurodegenerative disorders, elevated circulating IL-6 levels are consistently associated with worse cognitive outcomes and faster disease progression. However, exercise interventions have been shown to modulate IL-6 signalling and improve cognitive performance, even in populations with mild cognitive impairment and dementia. [8] These findings underscore the importance of distinguishing pathological IL-6 elevation from physiological myokine signalling.

The dual nature of IL-6 highlights a broader principle in muscle–brain crosstalk. Molecules released from skeletal muscle can exert either protective or harmful effects depending on the physiological environment. In aging, restoring the dynamic, exercise-induced myokine profile may be essential for counteracting chronic inflammation and preserving cognitive function.

Lactate Signalling and Lactylation: From Muscle Metabolism to Memory

Lactate has long been regarded as a metabolic waste product of anaerobic glycolysis. Lactate is now recognized as a central metabolic and signalling molecule that links skeletal muscle activity to brain function. [9,10] During exercise, contracting skeletal muscle produces large amounts of lactate. This lactate is released into the circulation and transported to multiple organs, including the brain. Importantly, lactate readily crosses the blood–brain barrier via monocarboxylate transporters, allowing direct communication between peripheral muscle metabolism and central neural processes. [10]

Within the brain, lactate serves as an efficient energy substrate for neurons, particularly during periods of increased synaptic activity. Experimental studies demonstrate that lactate administration mimics several cognitive benefits of exercise, including enhanced learning and memory. [9]

One of the most compelling discoveries in this field is the link between lactate and BDNF signalling. Lactate has been shown to increase hippocampal BDNF expression through activation of SIRT1-dependent pathways. Blocking lactate transport or metabolism abolishes exercise-induced BDNF upregulation and cognitive improvement, highlighting lactate as a necessary mediator rather than a passive correlate of exercise. [9,10]

More recently, lactate has been implicated in epigenetic regulation through a process known as lactylation. Lactate-derived lactyl groups can modify lysine residues on histone and non-histone proteins, thereby influencing gene transcription. Exercise-induced protein and histone lactylation has been shown to enhance synaptic plasticity, stress resilience, and neuronal survival in experimental models. [11,12]

This epigenetic dimension is particularly relevant to aging and neurodegeneration. Aging is associated with impaired metabolic flexibility, reduced mitochondrial efficiency, and altered redox signalling in both muscle and brain. These changes may blunt lactate production, transport, and signalling, thereby limiting activity-dependent gene regulation essential for synaptic maintenance. [17,18]

Conversely, lactate supplementation or exercise interventions that enhance lactate flux improve synaptic integrity and cognitive performance in experimental models of neurodegeneration. [19,20]

Human data, though still limited, support a role for lactate in cognitive aging. Exercise protocols that generate higher lactate responses are associated with greater improvements in memory and executive function, particularly in older adults. These findings suggest that lactate may act as a dose-dependent signal translating muscle metabolic stress into adaptive brain responses. [4,10]

From a translational perspective, lactate challenges the traditional separation between metabolism and cognition. It illustrates how skeletal muscle metabolism can shape brain function not only acutely but also through longer-term epigenetic mechanisms. In aging populations, preserving the capacity of muscle to generate and signal lactate may be critical for maintaining cognitive resilience. The principal molecular pathways linking skeletal muscle activity to brain plasticity are outlined in Table 2.

Translational Evidence Linking Skeletal Muscle–Brain Crosstalk to Cognitive Aging and Dementia

Translational evidence supporting the muscle–brain axis has expanded rapidly over the past decade. Findings from animal models, observational human studies, and exercise intervention trials collectively indicate that skeletal muscle health is closely linked to cognitive trajectories in aging and dementia.

Animal models provide the strongest mechanistic support. In rodent models of aging and Alzheimer's disease, exercise consistently improves learning, memory, and synaptic plasticity. These cognitive benefits are accompanied by increased expression of FNDC5/irisin, elevated hippocampal BDNF levels, reduced neuroinflammation, and enhanced mitochondrial function. [6,19] Importantly, genetic or pharmacological disruption of these pathways attenuates the cognitive effects of exercise, supporting a causal role for muscle-derived signalling.

Human observational studies further strengthen this link. Reduced muscle mass, strength, and physical performance are independently associated with poorer cognitive function and higher risk of mild cognitive impairment and dementia. Large cohort studies demonstrate that sarcopenia is associated with accelerated cognitive decline and increased incidence of Alzheimer's disease, even after adjustment for age, vascular risk factors, and physical activity levels. [2,13] These findings suggest that muscle health

itself, rather than physical inactivity alone, is a determinant of brain aging. Key translational findings linking muscle health, exercise, and cognitive outcomes are summarized in Table 3.

Circulating biomarkers provide additional translational insight. Lower levels of irisin and BDNF have been reported in individuals with cognitive impairment and neurodegenerative disorders compared with cognitively healthy controls. [3,7] Elevated basal IL-6 levels, reflecting chronic inflammation, are associated with worse cognitive outcomes and faster disease progression, whereas exercise-induced modulation of IL-6 signalling appears beneficial. [8] Although these associations do not establish causality, they align closely with experimental data and support biological plausibility.

Intervention studies offer the most clinically relevant evidence. Randomized controlled trials and meta-analyses demonstrate that structured exercise programs improve cognitive function in older adults, including those with mild cognitive impairment and Alzheimer's disease. [1,3] These cognitive improvements are often accompanied by increases in circulating BDNF and favourable changes in inflammatory markers. While most trials do not directly measure myokines such as irisin or lactate, the consistency of cognitive benefits across studies supports the involvement of shared biological pathways.

Notably, exercise modality appears to matter. Aerobic exercise reliably enhances cardiorespiratory fitness and BDNF signalling, while resistance training improves muscle mass, strength, and insulin sensitivity. Emerging evidence suggests that combined exercise programs may produce greater cognitive benefits by simultaneously targeting multiple components of the muscle–brain axis. [4] This is particularly relevant for older adults, in whom sarcopenia and metabolic dysfunction coexist with cognitive decline.

Evidence from dementia populations, though still limited, is encouraging. Exercise interventions in patients with Alzheimer's disease and vascular cognitive impairment have shown modest but significant improvements in cognition, activities of daily living, and quality of life. [1] These benefits occur even in the absence of major changes in amyloid burden, suggesting that exercise acts through non-amyloid mechanisms such as synaptic preservation, neurotrophic support, and inflammation control.

While animal models provide compelling causal support for muscle-derived signalling in cognitive protection, human evidence remains largely associative, with limited direct confirmation of mechanistic pathways at the molecular level.

Conflicting and Negative Evidence

Despite compelling mechanistic and translational data, not all studies uniformly support a robust muscle–brain signalling effect in humans. Several exercise trials have reported modest or absent changes in circulating BDNF or irisin despite measurable cognitive improvement, raising questions about biomarker sensitivity, assay variability, and timing of measurement relative to exercise exposure. Moreover, inter-individual variability in exercise responsiveness, influenced by age, sex, genetic background, baseline fitness, and metabolic status, complicates interpretation of biomarker–cognition relationships.

Observational studies linking sarcopenia to cognitive decline, while consistent, remain vulnerable to residual confounding by physical inactivity, vascular risk factors, and comorbid illness. In addition, some human intervention trials fail to demonstrate parallel improvements in cognition and circulating myokines, suggesting that peripheral biomarker changes may not always reflect central neurobiological effects.

Finally, most causal mechanistic insights derive from animal models, in which exercise intensity, duration, and metabolic load differ substantially from real-world human interventions. These discrepancies underscore the need for caution when extrapolating molecular findings to clinical populations and reinforce the importance of well-designed human translational studies.

Clinical and Preventive Implications: Exercise as a Molecular Therapy for Brain Aging

The recognition of skeletal muscle as an active regulator of brain function has important clinical implications. It reframes exercise from a general lifestyle recommendation to a targeted, biology-driven intervention for cognitive aging and dementia prevention.

Exercise can be viewed as a form of "molecular therapy." Unlike pharmacological agents that target single pathways, exercise simultaneously activates multiple protective mechanisms. These include enhanced myokine release, increased lactate signalling, improved mitochondrial function, reduced systemic inflammation, and upregulation of neurotrophic support. [4] This multi-target effect is particularly advantageous in complex, multifactorial conditions such as dementia.

From a preventive perspective, maintaining skeletal muscle mass and function across the lifespan may be critical for preserving cognitive resilience. Sarcopenia is increasingly recognized as a modifiable risk factor for cognitive decline and dementia. [2,13]

Early identification and management of muscle loss in midlife and older age could therefore form an integral component of dementia prevention strategies.

Exercise prescription may also benefit from greater physiological precision. Aerobic exercise promotes lactate production, enhances cerebral perfusion, and robustly stimulates BDNF signalling. Resistance training, in contrast, preserves muscle mass, improves insulin sensitivity, and supports myokine secretion, including irisin. Emerging evidence suggests that combined aerobic and resistance training may maximize activation of the muscle–brain axis, particularly in older adults with sarcopenia or metabolic dysfunction. [4]

The intensity and metabolic load of exercise appear to be important determinants of cognitive benefit. Exercise sessions that generate sufficient metabolic stress to elevate lactate levels may produce stronger neuroplastic responses than low-intensity activity. This raises the possibility that individualized exercise prescriptions, tailored to physiological capacity and metabolic responses, could optimize brain outcomes in aging populations. [10]

Biomarkers derived from the muscle–brain axis may further enhance clinical translation. Circulating levels of irisin, BDNF, and inflammatory markers such as IL-6 could potentially serve as indicators of biological response to exercise interventions. While these biomarkers are not yet ready for routine clinical use, they offer promising tools for monitoring intervention efficacy and individual responsiveness. [7,8]

In patients with established cognitive impairment or dementia, exercise should be viewed as an adjunctive therapy rather than a cure. Clinical trials demonstrate modest but meaningful improvements in cognition, functional independence, and quality of life in patients with Alzheimer's disease who engage in structured physical activity. [1] Importantly, exercise remains safe, accessible, and cost-effective, even in advanced age.

Finally, the muscle–brain axis has implications beyond exercise alone. Nutritional status, protein intake, metabolic health, and comorbid conditions such as diabetes influence muscle biology and may modify myokine signalling. Integrated lifestyle interventions that combine exercise with nutritional and metabolic optimization may therefore offer synergistic benefits for brain aging.

Knowledge Gaps and Future Directions

Despite growing evidence, several critical gaps remain. First, most mechanistic data derive from animal models, while human studies linking specific myokines and metabolites to cognitive outcomes are limited. Longitudinal human studies examining changes in irisin, BDNF, IL-6, and lactate alongside cognitive trajectories are needed.

Second, dose–response relationships are poorly defined. The intensity, duration, and type of exercise required to optimally activate muscle–brain signalling in older adults remain unclear. Inter-individual variability, influenced by age, sex, genetics, sarcopenia, and metabolic status, further complicates interpretation.

Third, the interaction between myokines and systemic metabolic disorders such as insulin resistance and type 2 diabetes is underexplored, despite their strong links to both sarcopenia and dementia. Understanding these interactions is essential for translational relevance.

Fourth, lactate signalling and lactylation represent emerging mechanisms with limited human evidence. Whether exercise-induced lactylation meaningfully contributes to long-term cognitive resilience in aging remains to be established.

Finally, the clinical utility of muscle-derived biomarkers is still uncertain. Standardization of assays, timing of measurement, and validation in diverse populations are required before these markers can guide precision exercise interventions.

Limitations

Most mechanistic evidence derives from animal models, and direct causal links in humans remain limited. Biomarker heterogeneity and variability in exercise protocols further constrain translation.

Conclusion

Skeletal muscle plays an active and previously underappreciated role in brain aging. Through the coordinated release of myokines and metabolites such as irisin, IL-6, and lactate, contracting muscle communicates directly with the brain to regulate neuroplasticity,

inflammation, and cognitive resilience. Aging disrupts this muscle–brain dialogue through sarcopenia, metabolic dysfunction, and chronic low-grade inflammation, thereby increasing vulnerability to cognitive decline and dementia.

Exercise restores many of these disrupted pathways not through a single mechanism, but via integrated molecular, metabolic, and neurotrophic effects. This positions physical activity as a biologically targeted, multi-system intervention rather than a generic lifestyle recommendation.

Future clinical translation will require rigorously designed randomized trials that directly interrogate muscle-derived signalling pathways in humans. Priority directions include: (i) longitudinal trials measuring irisin, BDNF, IL-6, and lactate alongside cognitive outcomes; (ii) dose–response studies defining the intensity, modality, and metabolic load of exercise required to optimally activate the muscle–brain axis; and (iii) stratified interventions targeting high-risk groups such as older adults with sarcopenia, insulin resistance, or mild cognitive impairment.

Biomarker validation represents a critical next step. Standardized assays, harmonized sampling protocols, and population-specific reference ranges will be necessary before circulating myokines and metabolites can guide precision exercise prescriptions or serve as surrogate endpoints in dementia prevention trials.

Collectively, these advances will help transform skeletal muscle–brain crosstalk from an emerging physiological concept into a clinically actionable framework for promoting cognitive longevity and reducing dementia risk.

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Table 1. Major myokines and metabolites involved in skeletal muscle–brain crosstalk and their roles in cognitive aging and dementia.

Mediator	Primary source during exercise	Major brain targets	Principal cognitive effects	Key relevance to aging/dementia
Irisin (FNDC5)	Skeletal muscle (PGC-1α–dependent)	Hippocampus, cortex	↑ BDNF, synaptic plasticity, memory	Reduced in aging and cognitive impairment; rescues synaptic dysfunction
BDNF	Brain (activity-dependent), indirectly regulated by muscle signals	Hippocampus	Neurogenesis, LTP, learning and memory	Declines with age; low levels in dementia
IL-6 (myokine)	Contracting skeletal muscle (acute)	Neurons, microglia, astrocytes	Anti-inflammatory signalling, metabolic regulation	Acute exercise IL-6 is protective; chronic elevation contributes to inflammaging
Lactate	Skeletal muscle (glycolysis)	Neurons, astrocytes	Energy supply, ↑ BDNF, synaptic plasticity	Impaired signalling in aging; emerging role in epigenetic regulation

Table 2. Mechanistic pathways through which skeletal muscle–derived signals influence brain plasticity and cognitive aging.

Muscle-derived signal	Key upstream trigger	Major signalling pathway	Downstream brain effect
Irisin	Exercise → PGC-1α activation	FNDC5 cleavage → BDNF induction	Enhanced synaptic plasticity and memory
Lactate	High glycolytic flux during exercise	MCT transport → SIRT1–BDNF signalling	Learning, memory consolidation
Lactylation	Sustained lactate availability	Histone/protein lactylation	Activity-dependent gene expression
IL-6 (acute)	Muscle contraction	IL-6–STAT3 anti-inflammatory cascade	Reduced neuroinflammation
Combined exercise signals	Aerobic + resistance training	Integrated metabolic and neurotrophic pathways	Cognitive resilience in aging

Table 3. Summary of translational evidence linking skeletal muscle health and exercise to cognitive aging and dementia.

Evidence type	Population/model	Key finding	Cognitive implication
Animal models	AD and aging rodents	Exercise ↑ irisin, BDNF, lactate signalling	Improved memory, synaptic preservation
Observational studies	Older adults	Sarcopenia associated with cognitive decline	Muscle health as dementia risk factor
Biomarker studies	MCI and dementia patients	↓ Irisin, ↓ BDNF, ↑ IL-6	Dysregulated muscle–brain signalling
Intervention trials	Older adults, AD patients	Exercise improves cognition and BDNF	Non-pharmacologic cognitive benefit

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