REVIEW ARTICLE

Exercise-induced neuroplasticity: Molecular mechanisms and implications for cognitive health and disease intervention

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ABSTRACT

This review synthesizes recent advances in elucidating the molecular basis underlying the effects of exercise on neuroplasticity. Specifically, we will focus on how exercise induces changes in neural connectivity at different levels of organization through conserved signalling pathways mediated by brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and dopamine, which differentially modulate region-specific synaptic plasticity, neurogenesis, and large-scale brain network reorganization. Recent technological breakthroughs have enabled the exploration of cellular heterogeneity and circuit-level plasticity in the hippocampus and prefrontal cortex through single-cell sequencing and optogenetics following chronic and acute exercise interventions. Additionally, recent evidence suggests that the gut microbiota-brain axis plays a regulatory role in mediating the effects of exercise on neuroplasticity. Clinically, exercise interventions can mitigate the pathophysiology of neurodegenerative diseases (NDs), psychiatric disorders, and aid recovery after brain injury. In the future, we envision personalized exercise prescriptions based on individual molecular and phenotypic profiles as an emerging concept in the field of precision medicine. From an evolutionary perspective, the co-adaptation of physical activity and cognitive capacity highlights the adaptive significance of exercise-induced neuroplasticity. Through the integration of basic and clinical science, we hope this review will propel the field forward to new, more targeted, efficacious interventions.

Keywords: Exercise-induced neuroplasticity, Molecular mechanisms, Cognitive health, Neurodegenerative diseases, Interdisciplinary research, Gut microbiota-brain axis, Personalized exercise prescription.

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INTRODUCTION

Physical exercise has attracted considerable attention as a powerful non-pharmacological intervention to enhance cognitive function and brain health across populations ranging from healthy individuals to clinical populations with specific neurological or psychiatric conditions. The accumulating evidence base supports exercise's benefits for brain health, including promoting neuroplasticity, enhancing cerebral metabolism, reducing neuroinflammation, and maintaining neurovascular integrity. It has therefore become an essential topic of interest across the fields of public health, neuroscience, and clinical rehabilitation given the increasing burden of cognitive decline and neurodegenerative diseases in modern aging populations.

The mechanisms by which exercise modulates brain health are through exercise's ability to enhance neuroplasticity – the brain's ability to reorganize both structurally and functionally in response to environmental stimuli and experiences. Learning, memory consolidation, and recovery from injury are all dependent on neuroplasticity and the existing evidence supports the idea that exercise exerts its effects on brain health through the modulation of neuroplasticity via a complex set of molecular, cellular, and systemic mechanisms, including upregulation of neurotrophic factors (for example: brain-derived neurotrophic factor, BDNF), modulating neurotransmitter systems, increasing cerebral blood flow and vascular function, and enhancing neurogenesis and synaptogenesis (Barnes et al., 2021; Hashimoto et al., 2021; Oyovwi et al., 2025). Recent studies have demonstrated that exercise-induced neuroplasticity is heterogeneous and region-specific within targeted brain regions involved in cognition, including the hippocampus, prefrontal cortex, and medial temporal lobe.

For example, aerobic exercise has been shown to be associated with greater hippocampal volume and greater functional activation (or connectivity) within memory-related circuits, and these changes were associated with better executive function and memory performance in older adults (Sinha et al., 2021; Szabo-Reed et al., 2022). Critically, both the intensity and modality of exercise can modify both the nature and amount of neuroplastic changes following exercise (Dhahbi et al., 2025; Jiang et al., 2025). Methodological developments—such as multimodal neuroimaging and electrophysiological phenotyping—have allowed us to characterize the induced brain changes in greater detail following exercise. Functional MRI (fMRI) studies have demonstrated that the types and amounts of exercise modify activity and connectivity within multiple brain networks, including the default mode, salience, and central executive networks, which are involved in cognitive control and attention (Bray et al., 2021; Rosso et al., 2025). Electroencephalography and transcranial magnetic stimulation have additionally supported exercise-induced changes in cortical excitability and synaptic plasticity mechanisms by which exercise may influence cognitive speed and inhibitory control (Turco & Nelson, 2021; Wu et al., 2022). Finally, exercise results in the release of signalling molecules called exerkines—such as lactate, myokines, and microRNAs—that give rise to both systemic and central adaptations. Lactate, a metabolic waste product, serves as a signalling molecule that supports neuroplasticity and cerebral metabolism, thus integrating peripheral muscle activity with brain function (Hashimoto et al. 2021; Zhu et al. 2025). Exercise results in increases in BDNF and other neurotrophic factors that induce changes in synaptic remodelling, neurogenesis, and neuronal survival, which are essential for cognitive resilience and recovery after neurodegenerative disease (Abuleil et al. 2022; Oyovwi et al. 2025).

The clinical application of exercise-induced neuroplasticity has value for individuals with or at risk for cognitive impairment and neurodegenerative disease, including mild cognitive impairment, Alzheimer's disease, Parkinson's disease, and stroke. Randomized controlled trials have shown that different forms of structured exercise improve global cognition, executive function, and memory, along with beneficial changes in brain structure and function (Da Silva-Grigoletto et al. 2024; Karamacoska et al. 2023; Klein et al. 2023; Li et al.

2021). Exercise also reduces neuroinflammation and vascular dysfunction, both of which are critical mediators of cognitive decline and the pathophysiology of dementia (Barnes et al. 2021; Ribarič, 2022). The exciting new frontier in exercise science and clinical practice is the combination of cognitive and physical training modalities that induce neuroplastic and cognitive changes.

Multimodal exercises, including aerobic and resistance exercise combined with cognitive tasks, hold potential for greater brain functional enhancements beyond exercise (Dhahbi et al., 2025; Mantovani et al., 2024). Novel approaches targeting potentiation of exercise-induced plasticity through virtual reality, neurofeedback, and non-invasive brain stimulation are also being developed (Calabrò et al., 2025; Szabo-Reed et al., 2022). However, no clear guidelines exist yet for the exercise components (type, intensity, frequency, and duration) for targeted interventions in clinical use for a broad spectrum of patients. Longitudinal studies with good designs and high quality, including multimodal biomarkers to decode the exercise–neuroplasticity–cognition loop are urgently needed, particularly in vulnerable populations (Dhahbi et al., 2025; Karamacoska et al., 2023; Sinha et al., 2021). In conclusion, physical exercise represents a powerful, accessible, multifactorial modulator of neuroplasticity with clear implications for cognitive health and intervention in neurodegenerative diseases. It triggers a cascade of molecular, cellular, and network changes that add up to provide better brain function and resilience (Figure 1). The new findings open questions for future interdisciplinary studies connecting neuroscience and exercise physiology with clinical practice to harness exercise-induced neuroplasticity for the sake of cognitive health..

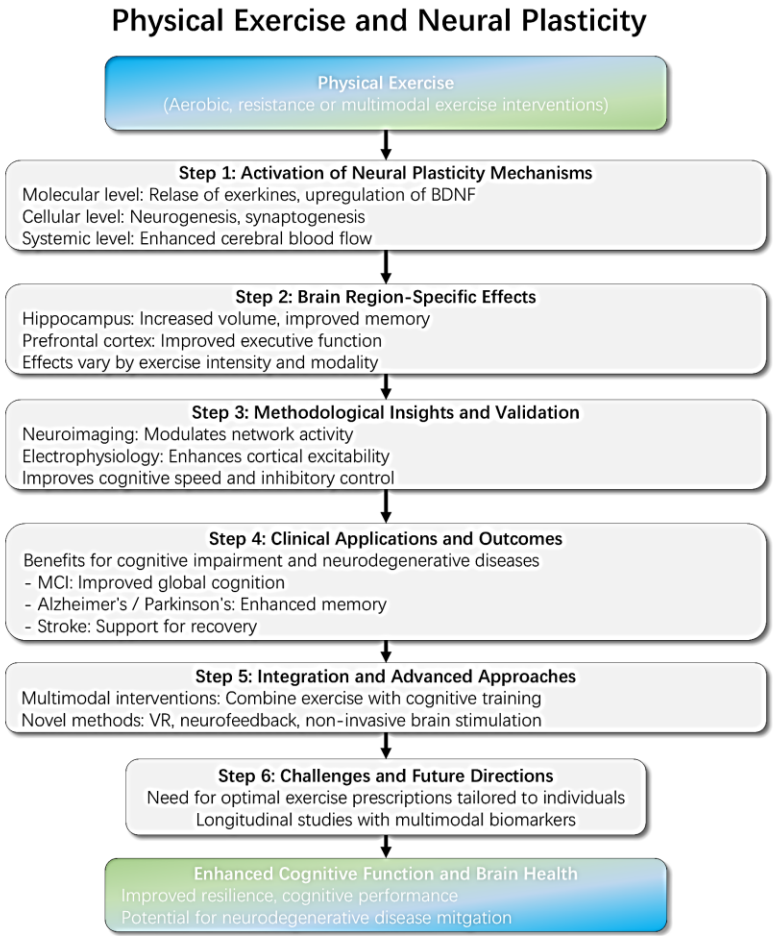

Figure 1. The exercise-neuroplasticity-cognition axis: mechanisms and clinical implications.

MAJOR MECHANISMS OF EXERCISE-INDUCED NEURAL PLASTICITY

Molecular and cellular mechanisms

Key neurotransmitters and growth factor signalling pathways

Physical exercise strongly promotes neuroplasticity at multiple stages by modulating some prototypical neurotransmitters and growth factors that regulate synaptic remodelling, neurogenesis, and cognition. Among them, brain-derived neurotrophic factor (BDNF) is a well-known regulator. Exercise upregulates BDNF expression both peripherally and centrally. Metabolic mediators such as lactate, generated during high-intensity aerobic exercise, promote exercise-induced upregulation of peripheral and brain BDNF expression. This, in turn, provides positive feedback for synaptogenesis, long-term potentiation, and neurogenesis (Müller et al., 2020; Oyovwi et al., 2025; Vints et al., 2022). BDNF exerts its actions through the TrkB receptor and its downstream signalling cascades that promote synaptic plasticity and neuronal survival. Recently, two different BDNF transcript variants, Bdnf I and Bdnf IV, were reported to have different roles in the regulation of dendritic growth and synaptic spine formation, and protein catabolism and fear memory, respectively, suggesting the complexity of BDNF plasticity (Bach et al., 2023, 2024).

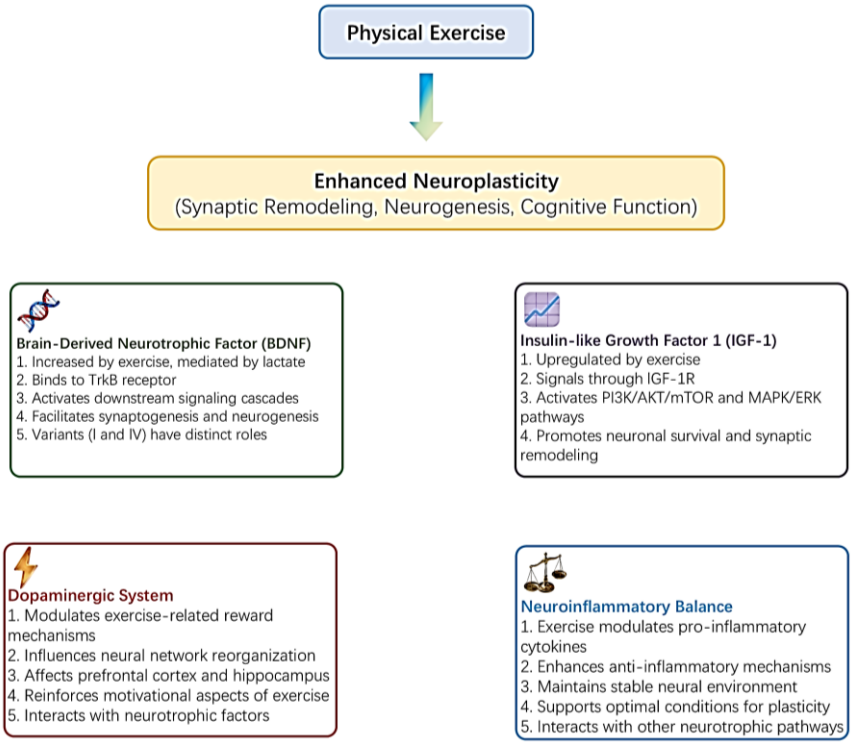

Figure 2. Molecular pathways mediating exercise-induced neuroplasticity.

Insulin-like growth factor 1 (IGF-1) is another important growth factor that is upregulated by exercise. IGF-1 is involved in neuronal survival and synaptic remodelling. IGF-1 signalling through its receptor (IGF-1R) activates downstream intracellular signalling pathways such as PI3K/AKT/mTOR and MAPK/ERK (Hochmuth & Hirrlinger, 2024; Oyovwi et al., 2025; Pike et al., 2020). Exercise also induces upregulation of IGF-1, and IGF-1 signalling pathway interacts with BDNF signalling pathway to mediate exercise-induced enhancements in cognition and neuroprotection (Oyovwi et al., 2025). The dopaminergic system regulates the reward mechanisms elicited by exercise and modulates neural network reorganization in the prefrontal cortex and hippocampus. The dopamine release during exercise not only enhances motivational properties of exercise

but also interacts with neurotrophic factors to promote plasticity (Turco & Nelson, 2021). In addition, exercise modulates neuroinflammation by regulating the balance between pro- and anti-inflammatory cytokines to maintain a stable neural environment for plasticity (Chen et al., 2025; Zou & Hao, 2024). As illustrated in Figure 2, interacting neurotransmitter and growth-factor pathways collectively mediate exercise-induced changes in brain structure and function.

Epigenetic regulatory mechanisms

Exercise-induced neuroplasticity is also controlled by dynamic epigenetic modifications that affect gene expression without changing the DNA sequence. These modifications include DNA methylation and histone modifications, which affect the accessibility of chromatin and the transcriptional state of genes involved in neuroplasticity (Chen et al., 2020; Shalabi et al., 2024). Exercise can change the methylation state of DNA in promoter and enhancer regions of genes, activating or repressing genes involved in synaptic plasticity and neuronal growth. For example, Pérez et al. showed that the methylation state of blood tissue-specific enhancer elements is associated with functional states in blood during early life, and thus exercise may induce epigenetic remodelling of the methylome in neural tissues (Pérez et al., 2019).

MicroRNAs (miRNAs) are small noncoding RNAs that regulate the expression of target genes at the post-transcriptional level. Many miRNAs are involved in exercise-induced neural adaptations by modulating genes involved in neuroinflammatory pathways, synaptic plasticity, and neuronal survival, which in turn affect cognitive functions ("*MicroRNAs*", 2025; X. Xu, R. Liu, et al., 2024). Exercise can change the expression of several miRNAs, such as miR-21, miR-146a, and miR-155, which are involved in the anti-inflammatory response and neuroprotection. In addition, several miRNAs are involved in feedback regulation of the microRNA machinery itself, which helps to fine-tune the expression of other genes during neuroplastic changes (Liu et al., 2021; Min et al., 2024). RNA methylation may also exert feedback regulation on DNA methylation or vice versa (Xu & Shen, 2022).

In total, epigenetic modifications provide a quick and easily reversible mechanism by which exercise modulates the expression of neural genes to induce long-lasting neuroplasticity. Epigenetic modifications induced by exercise provide potential biomarkers and therapeutic targets for cognitive health and neurological diseases.

Intercellular signal transduction and neural network remodelling

Astrocytes and microglia, the two major glial populations in the central nervous system, contribute to exercise-induced neuroplasticity by supporting neurons and regulating immune responses. Exercise induces region-specific remodelling of astrocyte morphology and reactive gene expression, which is favourable for the enhancement of synaptic support and neurorehabilitation (Li et al., 2021; Lundquist et al., 2019). Astrocytes, microglia, and neurons exhibit crosstalk to promote synapse formation and neurogenesis as well as cerebrovascular remodelling, which leads to the reorganization of neural circuits (Chen et al., 2025; Li et al., 2021). Exercise modulates activation phenotypes of microglia to regulate different states of microglial activation to facilitate neural circuit homeostasis (Cornelison & Fadel, 2022; Sarkar et al., 2020).

Intercellular communication mediated by neurotransmitters, neuropeptides, and growth factors facilitates the dynamic remodelling of neural networks during exercise. For instance, dopamine released during exercise modulates synaptic plasticity and neural circuit function, whereas astrocyte-neuron signalling modulates activity of the mesolimbic dopamine circuit (Corkrum & Araque, 2021). Exercise also induces adjustments in functional connectivity within and between brain regions, which facilitate integration of cognitive networks (Müller et al., 2020; Turco & Nelson, 2021). The interaction between neurons and oligodendroglia facilitates

myelination and neural circuit maturation and repair through regulation of activity-dependent calcium signalling (Thornton & Hughes, 2020). In this way, the intercellular signalling pathways and glial-neuronal interactions generate a plastic and adaptive neural environment. Modulation of these cellular networks by exercise may underlie the improvement in cognitive function and recovery after neurological insults. The involvement of glial cells and the importance of signal transduction in modulating neural networks facilitate our understanding of exercise-induced neuroplasticity.

Advanced technologies and emerging pathways in exercise-induced neuroplasticity

Single-cell sequencing technology to decipher cell type-specific responses

Single-cell RNA sequencing (scRNA-seq) has enabled transcriptomic profiling at the level of single cells and has empowered the investigation of cellular heterogeneity in brain regions involved in cognition and motor skills, such as the hippocampus and prefrontal cortex, by identifying the cell type-specific gene expression changes induced by exercise. For instance, by resolving diverse neuronal subpopulations within these brain regions, scRNA-seq may reveal transcriptional responses to physical activity that are difficult to distinguish in bulk tissue transcriptomes. In other words, the dynamic expression profiles of genes across neuronal and glial populations will be informative of the underlying transcriptional responses driving the modulation of neuronal plasticity, neurogenesis, and metabolic adaptation by exercise. Alternatively, the analysis of cellular heterogeneity in the transcriptomic profiling of neuronal and non-neuronal cells will be informative of how exercise may affect cell fate decisions and functional differentiation, for example promoting neurogenic lineages, or altering the balance between inhibitory versus excitatory neuron development. This will be critical for understanding the cellular mechanisms underlying exercise-induced neuroplasticity, and putative molecular targets that may contribute to cognitive enhancement and neuroprotection. This is possible because we can profile non-neuronal cell types, like astrocytes, microglia, and oligodendrocyte precursor cells, and gain insights into the modulatory and, perhaps, supportive effects these cells may undergo during exercise-induced brain remodelling.

All in all, we suggest that single-cell sequencing provides a means to decode the type-specific molecular adaptations induced by physical exercise on the central nervous system (Crow & Gillis, 2019; Marciante et al., 2024; Thornton & Hughes, 2020).

Optogenetics and neural circuit functional analysis

Optogenetics is an approach that uses light-sensitive opsins to enable spatiotemporal control of specific neuronal populations in targeted brain regions. Here we provide a schematic overview of these applications and mechanisms in Table 1. To understand the plasticity of neural activity induced by exercise, optogenetics has been used to dissect motor-related neural circuits by selectively activating or inhibiting excitatory neurons that participate in motor planning, execution, and learning. It has also been used to dissect discrete neuronal subtypes within motor cortex, basal ganglia, and spinal cord circuits to understand their respective contributions to exercise-induced behavioural improvements and synaptic plasticity. For example, optogenetic activation of motor cortex neurons after stroke enhances motor recovery by promoting synaptic plasticity and circuit reorganization (Berglund et al., 2021; Chowdhury & Yamanaka, 2021; Lu et al., 2019; Vogt, 2020).

By combining optogenetics with approaches such as calcium imaging or functional MRI, researchers can dynamically observe changes in neural network activity induced by exercise or other specific manipulations. This integrated approach characterizes how exercise modulates functional connectivity and neural ensemble dynamics underlying improved motor and cognitive functions. Finally, recent advances in fibreless optogenetics and bioluminescence-driven optogenetics have eliminated many limitations of invasive light

delivery and enabled chronic and minimally invasive modulation of neural circuits during natural behaviours. These methodological advances open new opportunities to study exercise-induced plasticity in freely moving animals and for translational applications in neurorehabilitation and brain–machine interfaces.

Table 1. Key applications and mechanisms of optogenetics in studying exercise-induced.

Aspect	Description	Key findings/Applications
Core Technology	Enables precise spatiotemporal control of specific neuronal populations using light-sensitive opsins.	Selective activation/inhibition of neurons in motor planning, execution, and learning circuits.
Application in Research	Dissects motor-related neural circuits involved in exercise-induced plasticity.	Identifies neuronal subtypes in motor cortex, basal ganglia, and spinal cord; links their activity to synaptic remodelling.
Therapeutic Example	Optogenetic stimulation post-stroke enhances motor recovery.	Promotes synaptic plasticity and circuit reorganization in motor cortex.
Integrated Methods	Combined with calcium imaging or functional MRI for dynamic monitoring of neural activity.	Elucidates changes in functional connectivity and neural ensemble dynamics induced by exercise.
Recent Advances	Fibreless and bioluminescence-driven optogenetics enable less invasive and chronic modulation during natural behaviours.	Facilitates study of plasticity in freely moving animals and supports translational neurorehabilitation applications.
Overall Significance	Provides causal insights into relationships between neural circuit activity and exercise-driven functional outcomes.	Critical for advancing neurorehabilitation and brain-machine interface technologies.

Note. Optogenetics enables the dissection of motor-related neural circuits by selectively activating or inhibiting the excitatory neurons that participate in motor planning, execution, and learning.

Regulatory role of the gut microbiota-brain axis

Rising reports suggest the presence of a gut microbiota-brain axis that is capable of significantly modulating neuroplasticity, with physical exercise being a powerful influencer of gut microbial composition and function. Changes in the gut microbiome induced by exercise result in the modulation of microbial metabolites such as short-chain fatty acids and precursors of neurotransmitters that are capable of crossing the gut barrier and influencing brain function. These metabolites modulate neuroinflammatory responses, neurogenesis, and synaptic plasticity to confer cognitive and motor improvements following physical exercise. The gut microbiota also communicates with the enteric nervous system and central nervous system through neural, immune, and endocrine pathways to form a bidirectional communication network that influences brain health. It is worth noting that exercise can modulate populations of microbial life in the body to bestow enhancements in the production of neuroactive steroids and other classes of signalling molecules that modulate neuronal excitability and plasticity. This microbiota-gut-brain axis represents a previously unknown means by which exercise imparts neuroprotectant and neuroplastic effects and provides new opportunities to treat neurological disease. Modulation of the gut microbiota through probiotics or other dietary manipulations in combination with exercise may confer additive effects that enhance plasticity and cognitive resilience. Modulation of the gut microbiota alters multiple gut microbiota–brain interactions, which must be carefully considered when designing exercise-based interventions (Blair et al., 2025; Cryan et al., 2019; Lee et al., 2023).

Clinical applications and future directions

Applications in neurodegenerative diseases

Exercise has exhibited promising potential as a non-pharmacological intervention to preserve and improve cognitive and motor functions in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Meta-analyses and systematic reviews have demonstrated that exercise interventions can improve cognitive function, activities of daily living, and neuropsychiatric symptoms in individuals with AD. For instance, aerobic, resistance, and multicomponent exercises can improve the Mini-Mental State Examination (MMSE) scores and decrease the Neuropsychiatric Inventory (NPI) scores. Longer exercise interventions (>16 weeks) showed greater improvements (López-Ortiz et al., 2021; Roy et al., 2023; Z. Xu et al., 2024). In PD, exercise can induce neuroplastic changes that may delay disease progression and improve motor symptoms, such as gait, balance, and motor scores after aerobic, resistance, dance, and task-oriented training (Lorenzo-García et al., 2024; Sandroff et al., 2020; Yang et al., 2025). The molecular basis underlying the protective effects of exercise on neurodegenerative diseases includes exercise-induced upregulation of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) (Müller et al., 2020), insulin-like growth factor-1 (IGF-1) (Oyovwi et al., 2025), and exerkines, which can promote synaptogenesis, neurogenesis, and long-term potentiation, and further enhance neuroplasticity (Vints et al., 2022). Exercise can also modulate neuroinflammation and oxidative stress, two hallmarks of neurodegenerative pathology (Ribarič 2022). Furthermore, exercise can improve cerebrovascular function and brain metabolism to facilitate neural repair and functional recovery (Huang et al. 2022; Hwang et al. 2023). Sex differences in exercise effects were also found in AD, with women showing larger cognitive improvements and neurotrophic support after exercise, highlighting the importance of sex-specific exercise prescriptions. New technologies, including virtual reality and neuroimaging, were applied to improve exercise interventions and neuroplastic changes (Huang et al. 2022; Yi et al. 2022). In summary, exercise provides comprehensive neuroprotective effects on NDs by modulating neuroplasticity, neuroinflammation, and vascular and metabolic brain health to preserve cognitive and motor functions.

Application in mental disorders and brain injury rehabilitation

Exercise interventions improve neurofunctional outcomes and emotional regulation in rehabilitation of mental disorders and brain injury. Exercise interventions also contribute to neural function in mood disorders (depression and anxiety) via modulation of neuroplasticity-related pathways and neurotrophic factors, which subsequently alleviate mood disorders and improve cognitive function (Bendau et al., 2024; Deng et al., 2024; Pascoe et al., 2020). Exercise reduces symptoms of anxiety and depression by acting on the endocannabinoid system, enhancing endorphin release, and improving self-esteem and body image (Pujari, 2024). Moreover, exercise also improves cognitive impairment and executive function in psychiatric populations (Ashdown-Franks et al., 2020).

Brain injury includes TBI and stroke. Exercise improves neuroplasticity via modulation of neurotrophic factors, facilitating synaptic remodelling, neural regeneration, and interhemispheric connectivity, which subsequently improve motor and cognitive recovery (Singaravelu Jaganathan & Sullivan, 2022; Snowden et al., 2023; Xing & Bai, 2020). Early mobilization and individualized exercise programs including aerobic, resistance, and task-specific training after brain injury could improve physical function, cognition, and quality of life (Nakamura, 2021; Romanov et al., 2021). In addition, exercise intensity and timing critically affect the outcomes of rehabilitation programs. Moderate intensity programs could induce maximal neuroplasticity with minimal adverse effects (Taguchi et al., 2019; White et al., 2023). Moreover, both cognitive training and motor training in virtual reality and exercise could further enhance brain health and functional outcomes (Sakhare et al., 2021). Exercise could alleviate anxiety, depression and fatigue in end-stage renal disease patients and other

chronic patients (Zhao et al., 2019) and improve cognitive impairment and executive function (Deng et al., 2024).

Challenges and prospects of personalized exercise prescription

Personalized exercise prescriptions, based on individual genetic, epigenetic and neurofunctional profiles, present opportunities and challenges. Variability in response to exercise has been demonstrated within and between individuals and is influenced by intrinsic factors (sex, age, hormonal status, genetics) and extrinsic factors (exercise dose, time of day, circadian rhythms, diet, medication) (Noone et al., 2024).

Evidence is emerging for the use of biomarkers such as neurotrophic factors (BDNF, IGF-1), myokines and neuroimaging features to guide personalized interventions (Gao et al., 2024; Savettiere et al., 2025). Figure 3 shows an integration of multi-dimensional data and technology. We outline a personalized exercise-prescription framework that includes core concepts (genetic, epigenetic and neurofunctional profiles), individual modifiers (intrinsic and extrinsic), actionable biomarkers (for example: BDNF, IGF-1, myokines) and enabling technologies (computational tools, wearables, AI, telehealth) and challenges and future opportunities.

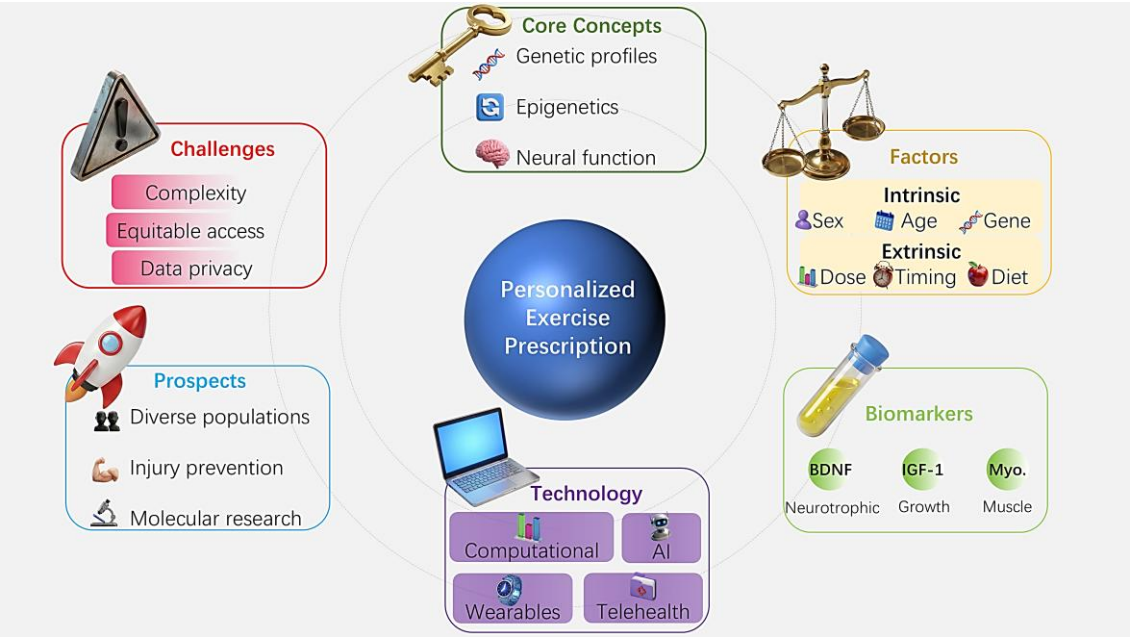

Figure 3. Challenges and prospects of personalized exercise prescription.

Given the complexity of interactions between these modifiers, computational models will be required to optimize the intensity, time and modality of exercise for individuals (Yuan et al., 2025; Zou & Hao, 2024). The adoption of personalized exercise prescriptions will raise ethical and social challenges around access, data privacy and consent, and adherence monitoring that will require multidisciplinary input to address (Xu et al., 2024). The feasibility and acceptability of digital interventions have been demonstrated across different populations, including individuals with Long COVID and Parkinson's disease, enabling remote monitoring and personalized intervention modifications (Ha et al., 2024; Xu et al., 2024).

Personalized prescriptions based on tendon strain and muscle-tendon balance have shown promise in injury prevention and rehabilitation, with potential for use throughout the rehabilitation process from acute injury

through to return to sport and prevention of re-injury (Mersmann et al., 2025; Weidlich et al., 2024). Standardized protocols and core outcome sets will be required to improve reproducibility and clinical translation (Peng et al., 2025; Playle et al., 2019). Future research should focus on understanding the underlying molecular mechanisms and refining predictive biomarkers and adaptive, user-centred exercise programs that take motivational and behavioural factors into account to improve long-term adherence and therapeutic outcomes (Wackerhage & Schoenfeld, 2021; Yang et al., 2021).

CONCLUSION

Investigation of exercise-induced neuroplasticity is an emerging interdisciplinary area that bridges neuroscience, exercise science and epigenetics. The review delineates the basic principles of complicated molecular signalling pathways and cell type-specific regulatory mechanisms underlying the beneficial effects of physical activity on brain function. The complexity of these biological processes requires an integrated multidisciplinary approach to comprehensively understand the mechanisms by which exercise modulates neuroplasticity. Figure 4 is a conceptual integration of multiple disciplines, crucial basic mechanisms (i.e., gut-microbiota-brain axis, advanced technology, and clinical application), an evolutionary perspective, and the potential of exercise-induced neuroplasticity. The combination of powerful techniques, such as single-cell sequencing and optogenetics, has enabled us to understand how exercise influences brain circuit function with previously hard-to-attain resolution. These tools allow us to dissect neural heterogeneity and circuit dynamics with great care, revealing previously inaccessible insights into activity input-induced neural remodelling. As the cumulative knowledge of the gut microbiota-brain axis gradually widens our conceptual space, we suggest that the influence of exercise on cognition and mental health may be through systemic, bidirectional processes that go beyond the central nervous system. Integration of multiple research perspectives, ranging from molecular to cellular to systemic levels, is required for an integrated understanding of the multifaceted effects of exercise on brain health.

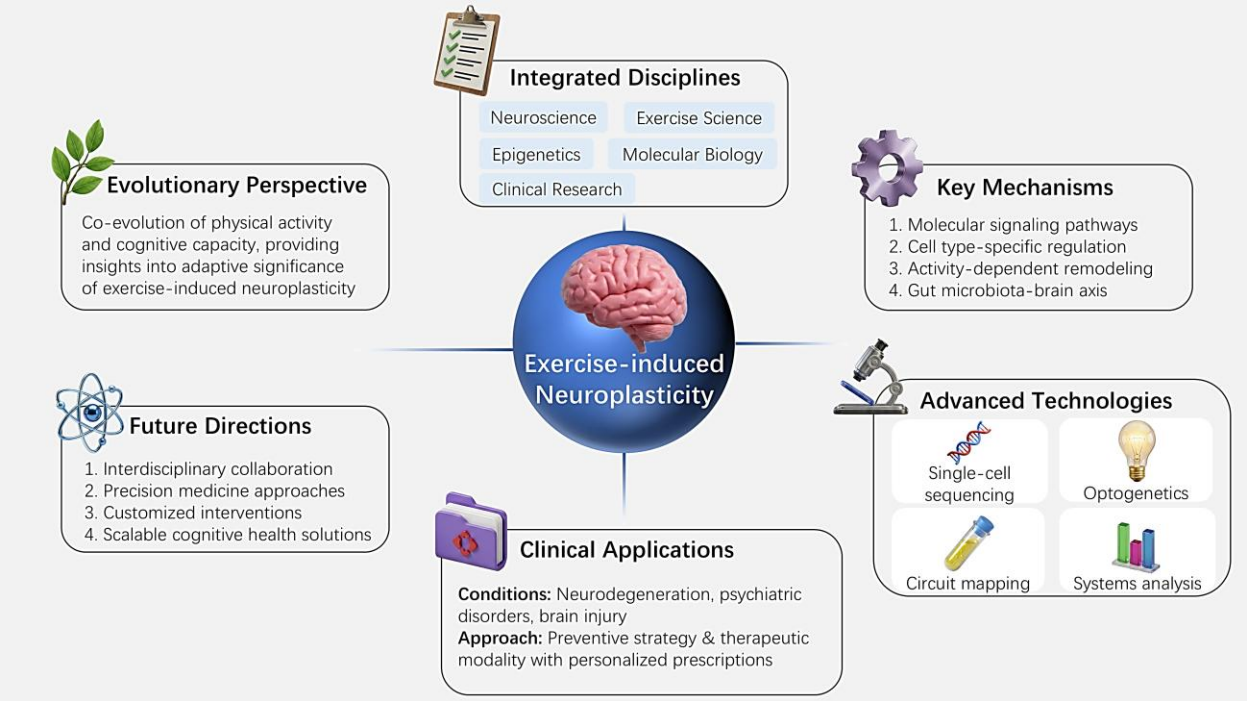

Figure 4. Exercise-induced neuroplasticity: integration and future directions.

The evidence supports the effectiveness of exercise as both a preventive and a therapeutic modality that promotes neuroplasticity and functional recovery, which has considerably facilitated the development of highly personalized exercise programs tailored to individual patient profiles with the potential for enhanced treatment effects. The presence of patient population heterogeneity and exercise protocol variability suggests the need for highly standardized methodologies to resolve conflicting findings and improve clinical guidelines.

From an evolutionary biological perspective, the coevolution of physical activity and cognitive capacity highlights the adaptive role of exercise-induced neuroplasticity. The understanding of this interaction facilitates researchers' and clinicians' ability to confront modern public health issues caused by sedentary behaviour and cognitive degeneration. Contemporary research models emphasize the relevance of an evolutionary perspective. Future progress in this domain hinges on robust interdisciplinary engagement between molecular biologists, clinical researchers, modelers, and behavioural scientists. Enhanced mechanistic comprehension is poised to expedite the evolution of exercise neuroscience into personalized medicine, enabling customized exercise interventions aligned with genetic, epigenetic, and environmental variables. The progression would unveil prospects for paradigm-shifting, scalable methods aimed at improving cognitive health on a global scale, alongside diminishing the impact of neurological and psychiatric ailments.

The integration underscores the dynamic and rapidly evolving landscape of exercise-induced neuroplasticity research. The convergence of varied research perspectives and the employment of cutting-edge technologies positions the scientific community to uncover new therapeutic avenues and to foster a shift towards personalized, mechanism-based exercise interventions. The integrative approach is crucial for promoting lifelong brain health and cognitive resilience amidst global complexities and aging demographics.

AUTHOR CONTRIBUTIONS

Conceptualization: MZ; Writing - original draft preparation: HC, JL, LY, SZ, ZJ, YX and WZ; Writing - review & editing: YL, YS and JL; Visualization: YS,JL and ZM; Supervision: MZ; Project administration: MZ; Funding acquisition: MZ. HC and JL have made equal contributions to this paper.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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