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Review

The Muscle–Microglia Axis in Neurodevelopment: Exercise-Induced Exerkines as a Molecular Landscape with Therapeutic Potential for ASD and ADHD During Pubertal Transition

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Highlights

What are the main findings?

- In this review, we propose a hypothetical muscle–microglia axis conceptual framework, synthesizing predominantly preclinical evidence on how exercise-induced factors may signal across the blood–brain barrier to modulate microglial reactivity and synaptic remodeling relevant to ASD and ADHD.
- Drawing on preclinical neuroendocrine and developmental studies, we hypothesize that the pubertal transition represents a potential high-sensitivity window during which surging sex hormones may interact with exercise-induced signaling and neuroepigenetic regulation, while emphasizing that direct confirmation in pediatric clinical cohorts remains a future research priority.

What are the implications of the main findings?

- This conceptual framework offers a hypothesis-generating basis for exploring candidate exercise parameters under the FITT-VP model in future clinical trials, aiming to align exercise modalities with putative molecular pathways and distinct clinical phenotypes in ASD and ADHD.
- We outline a prospective conceptual proposal integrating candidate biomarkers, wearable sensors, and artificial intelligence as a future translational direction for personalized exercise monitoring in neurodevelopmental disorders.

Abstract

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are prevalent neurodevelopmental disorders in childhood and adolescence in which neuroimmune dysregulation and altered microglial function have been increasingly implicated, albeit with substantially different levels of human versus preclinical evidence. Preclinical (in vitro and rodent) studies indicate that contracting skeletal muscle secretes bioactive exercise-induced factors (exerkines)—including irisin, cathepsin B, lactate, and extracellular vesicles—that can directly cross or indirectly signal across the blood–brain barrier, modulate microglial inflammatory states, and support synaptic plasticity. However, whether this complete peripheral-to-central cascade operates to normalize synaptic pruning in children and adolescents with ASD or ADHD remains unconfirmed. In this review, we propose

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the developmental muscle–microglia axis as a hypothesis-generating conceptual framework and specifically focus on its intersection with pubertal maturation. We critically synthesize in vitro, animal, and human evidence on how key exerkines and multi-pathway brain-derived neurotrophic factor (BDNF) regulation may interact with surging sex hormones during the pubertal transition to influence microglial activity and neuroepigenetic states. Furthermore, we frame modality-specific exercise parameters (FITT-VP model) and multimodal wearable/biomarker closed-loop monitoring as candidate hypotheses and conceptual proposals for future clinical trials in youth with ASD and ADHD, while highlighting methodological limitations, safety considerations, and translational gaps.

Keywords: muscle–microglia axis; exerkines; microglial reactivity; neuroinflammation; ASD; ADHD; pubertal Tanner staging; therapeutic potential

1. Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are two of the most prevalent neurodevelopmental disorders in childhood and adolescence worldwide [1,2]. Epidemiological data have revealed a steady rise in the prevalence of both disorders over recent decades, representing a major challenge for public health systems and affected families [1,3]. Although diagnostic criteria and symptomatic treatments have improved, therapy is largely palliative, with an emphasis on reducing behavioral manifestations and not on the underlying neuropathological substrates [4,5]. Central to the pathophysiology of ASD and ADHD is a disruption of synaptic homeostasis, that is, irregular synaptic pruning and neuroinflammation (NI), with resident immune cells in the central nervous system (CNS) being involved [6]. These crucial pathological features highlight the need for new therapeutic strategies that will target the molecular and cellular mechanisms involved in disease pathogenesis, as opposed to simply managing symptoms [7,8].

Traditional pharmacological therapies (such as stimulants and antipsychotics) have been shown to be effective for symptom control but are limited in their ability to modulate underlying neurobiological abnormalities, including deficits in synaptic remodeling and chronic neuroinflammation [9]. This gap in therapy has spurred research to investigate these endogenous repair mechanisms from a systems biology perspective to integrate knowledge from several fields, including neuroimmunology, endocrinology, and exercise physiology. Recent advances indicate that contracting skeletal muscle functions not merely as a locomotor effector, but as a dynamic secretory organ [10,11]. Terminologically, it is important to distinguish between myokines—which refer specifically to cytokines, peptides, and growth factors synthesized and secreted by skeletal muscle fibers (such as irisin)—and the broader umbrella term exerkines (exercise-induced factors), which encompasses all humoral signaling moieties (including peptides, metabolites such as lactate, nucleic acids, and extracellular vesicles) released into circulation in response to exercise by skeletal muscle as well as other tissues (e.g., liver, adipose tissue, and brain endothelium) [11–14]. These molecules, which are secreted as a response to physical activity, have pleiotropic effects on distant tissues, such as the brain, and affect neuroplasticity, immune regulation, and metabolic homeostasis [13,15]. How peripheral signals can orchestrate central immune responses and synaptic remodeling is a new avenue of understanding, stimulated by the recognition of skeletal muscle as a key modulator of CNS function [16,17].

Recent developments have further clarified the ability of some muscle-derived factors, such as exosomes and protein mediators, to penetrate the blood–brain barrier (BBB), which is traditionally considered a formidable obstacle to peripheral–central communication [18]. The BBB is not fixed and is influenced by developmental stage, hormonal conditions, and

environmental factors such as exercise. This dynamic permeability permits the entry of specific circulating molecules into the CNS microenvironment and their interaction with resident cells of the immune system, including microglia [18–20]. Microglia serve as the brain's innate immune sentinels, playing indispensable roles in maintaining neural circuit integrity through synaptic pruning during critical periods of neurodevelopment [21]. Dysregulation of microglial developmental programs—encompassing both neuroinflammatory reactivity and stage-specific alterations in synaptic engulfment—has been implicated in the pathophysiology of neurodevelopmental disorders, contributing to disrupted neural connectivity and cognitive–behavioral deficits [22,23].

The adolescent transition is a sensitive period of neurodevelopment characterized by extensive cortical synaptic remodeling and surging sex steroid hormones [20]. Preclinical studies suggest that pubertal hormonal fluctuations may influence BBB properties and microglial receptor expression, potentially altering microglial responsiveness to peripheral signals [20,24]. Accordingly, we hypothesize that physical exercise during this developmental transition might interact with neuroendocrine maturation to support homeostatic microglial function and synaptic remodeling, offering potential therapeutic implications for youth with ASD and ADHD [25,26].

In summary, although previous reviews have separately examined broad muscle-to-brain communication [17,27,28], the biology of exerkines and extracellular vesicles (EVs) [12,13,29], and exercise-induced regulation of microglia in general health and neurodegeneration [30–32], the specific intersection integrating exercise-induced peripheral factors, microglial synaptic remodeling, and the neuroendocrine dynamics of pubertal development remains largely unexplored in ASD and ADHD. By examining how muscle-derived signals might interact with hormone-sensitive microglial states during the adolescent transition, this review proposes a developmental muscle–microglia framework for hypothesis-driven neuromodulation. Specifically, we aim to critically synthesize preclinical and clinical evidence at the convergence of exercise physiology, microglial biology, and pubertal maturation, while evaluating the evidence hierarchy, disease-specific differences, and translational challenges of applying these insights to ASD and ADHD.

To ensure a transparent, rigorous, and balanced synthesis in this narrative review, systematic literature searches were conducted across the PubMed, Web of Science, and Scopus databases from database inception through August 2026 (with a primary emphasis on recent advances published between January 2020 and August 2026, supplemented by foundational mechanistic publications prior to 2020 where historically or biologically necessary). Search queries combined keywords and Medical Subject Headings (MeSH) across four core domains: (1) skeletal muscle and exercise factors ("exercise", "physical activity", "exerkines", "myokines", "irisin", "FNDC5", "cathepsin B", "lactate", "extracellular vesicles", "exosomes", "miR-146a"); (2) neuroimmune and synaptic mechanisms ("microglia", "neuroinflammation", "synaptic pruning", "BDNF", "blood–brain barrier"); (3) developmental window ("puberty", "adolescence", "Tanner stage", "sex hormones", "estrogen", "testosterone", "epigenetics"); and (4) target clinical conditions ("autism spectrum disorder", "ASD", "attention-deficit/hyperactivity disorder", "ADHD", "neurodevelopmental disorders"). Eligibility criteria included peer-reviewed original research articles (in vitro cellular assays, preclinical animal models, and human clinical studies), systematic reviews, and meta-analyses published in English, whereas non-peer-reviewed preprints, conference abstracts, and single case reports were excluded. Regarding the study selection process, two authors (X.W. and J.L.) independently screened titles, abstracts, and full texts of retrieved records against the eligibility criteria, with any discrepancies resolved through discussion and consensus with the senior corresponding author (M.Z.). Methodological quality and internal validity were critically appraised according to study type: (1) preclinical animal and

in vitro studies were evaluated based on disease/developmental model validity, sample size adequacy, blinding of outcome assessment, physiological versus supraphysiological dosing regimens, and molecular assay specificity (e.g., distinguishing quantitative mass spectrometry from commercial ELISAs); and (2) human clinical studies were evaluated based on study design hierarchy (prioritizing systematic reviews, network meta-analyses, and randomized controlled trials over observational cohorts), sample size, control group rigor, supervision of exercise protocols, and the use of validated behavioral scales or biomarker endpoints. Both supporting and contradictory findings were purposefully retained to provide a balanced appraisal, and the specific level of evidence is explicitly annotated throughout the text.

2. Conceptual Reconstruction: From Locomotor Organ to Neuroimmune Regulatory Hub—The Theoretical Basis of the Muscle–Microglia Axis

2.1. Historical Evolution of Skeletal Muscle Role Recognition and Contemporary Endocrinological Evidence

Skeletal muscle has long been considered to be predominantly a mechanical effector that is used to produce force and promote movement. Older physiological thinking limited it to the execution of motor commands and focused attention on its contractile function, ignoring interactions with other systems [33]. In the last decade, however, advances in proteomics and secretomics have turned this picture upside down, as it is now known that contracting skeletal muscle actively transcribes and secretes hundreds of bioactive peptides, metabolites, and extracellular vesicles [34]. These secreted factors are collectively known as "myokines" and have been shown to change dynamically according to the type, intensity, and duration of exercise, demonstrating the plasticity of the muscle secretome [35]. This paradigm shift acknowledges that skeletal muscle is an endocrine organ with systemic effects that go beyond locomotion [36].

One of the most striking examples is the myokine irisin, which has been reported to increase in circulating blood following exercise, though systemic response magnitudes exhibit considerable heterogeneity across human trials [37]. Preclinical and human CSF studies suggest that circulating irisin may cross the blood–brain barrier (BBB) via a saturable transendothelial transport mechanism, pointing to a potential humoral link between skeletal muscle activity and central nervous system (CNS) function, although the exact endothelial transporter remains to be fully identified [38,39]. This finding contradicts the existing belief that exercise benefits for the brain are due to a higher firing rate in the neurons or synapses. Rather, it promotes a model in which muscle's molecular signals are conveyed via humoral mechanisms, which affect neuroplasticity and neuroprotection [27,40].

These findings have tremendous endogenous pharmacological implications. They propose that the effect of exercise on the brain may be more mediated by specific factors secreted by the muscles than by the neural activity itself [28]. This perspective may give rise to molecularly targeted therapies that mimic or potentiate the effects of myokines induced by exercise, which may be beneficial to those unable to exercise. Overall, there is solid endocrinological evidence supporting the historical shift from perceiving skeletal muscle as a static "locomotor organ" to viewing it as a dynamic endocrine entity, altering the way that muscle–microglia communication is understood [11].

2.2. The Proposal and Extension of the "Muscle–Microglia Axis" Concept

Previous reviews have extensively characterized broad skeletal-muscle-to-brain communication [17,27,28], the systemic biology of exerkines and exercise-induced extracellular vesicles (EVs) [12,13,29], and the general capacity of physical exercise to modulate microglial reactivity in healthy and aging brains [30–32]. Building upon these foundational concepts, we propose the developmental muscle–microglia axis not as a newly discovered

anatomical pathway, but as an integrative, problem-oriented conceptual framework [41]. Compared with existing muscle–brain models that treat the CNS as a homogeneous target or focus primarily on adult neurodegeneration [16,17,31], the distinct scientific contribution of our framework lies in coupling four specific dimensions: (1) isolating microglia-mediated synaptic pruning and neuroinflammation as a tractable cellular interface for exercise-induced peripheral signals; (2) embedding this peripheral–central signaling within the neuroendocrine dynamics of the pubertal transition [20]; (3) contrasting its mechanistic relevance across the distinct neuroimmune profiles of ASD and ADHD; and (4) using these developmental and molecular hypotheses to inform candidate parameters for phenotype-adapted exercise interventions. Importantly, although broader muscle–brain communication involves bidirectional neuromuscular and autonomic feedback [10], the evidence synthesized in the present framework predominantly reflects unidirectional endocrine and paracrine signaling from contracting skeletal muscle to CNS microglia rather than direct microglia-to-muscle communication.

The basic mechanism of this axis is that the skeletal muscle contraction releases exercise factors (such as myokines, metabolites, and extracellular vesicles) into the bloodstream; these factors then cross the BBB and bind to specific receptors on the surface of microglia [32,42]. This receptor engagement inhibits pro-inflammatory NF-κB signaling and shifts microglia from a pro-inflammatory, cytokine-secreting reactive state toward a homeostatic, anti-inflammatory, and tissue-supportive transcriptional profile [43,44]. In accordance with contemporary microglial nomenclature consensus [43], we avoid treating microglial states as a rigid M1/M2 binary and instead describe specific functional states—such as pro-inflammatory reactive, homeostatic, and phagocytic/synapse-remodeling states—retaining "M1-like" or "M2-like" only when citing original preclinical studies that explicitly measured those specific marker panels [43,45].

By specifying candidate cellular effectors and receptor pathways, this conceptual model provides testable hypotheses for future mechanistic investigation [31]. Within this heuristic framework, exercise-induced peripheral factors can be viewed as candidate endogenous modulators whose potential to attenuate neuroinflammation and support circuit maturation in neurodevelopmental disorders such as ASD and ADHD warrants rigorous clinical evaluation [46].

2.3. Critical Comparison of Microglial Dysfunction, Synaptic Pruning, and Exercise Responses in ASD Versus ADHD

Although ASD and ADHD frequently co-occur and share overlapping executive and behavioral features, they exhibit fundamental differences in neurobiological substrates, the strength and directionality of microglial and synaptic pruning evidence, and clinical exercise response profiles that preclude merging them into a single uniform entity.

In ASD, direct human neuropathological and neuroimaging studies provide relatively robust evidence for central neuroinflammation and microglial alterations. Primary post-mortem histological analyses in individuals with ASD have demonstrated increased microglial density, morphological reactivity, and altered inflammatory profiles across the dorsolateral prefrontal cortex, cerebellum, fronto-insular cortex, and visual cortex [47–49]. However, in vivo translocator protein (TSPO) positron emission tomography (PET) imaging studies in ASD have yielded inconsistent findings [50]: while an early first-generation tracer study reported elevated regional TSPO binding in young adults with ASD [51], subsequent second-generation TSPO PET investigations reported either lower regional TSPO expression [50] or no significant group-level differences compared with neurotypical controls [52]. Moreover, TSPO is not specific to microglia—as it is also expressed by reactive astrocytes and vascular endothelial cells—and TSPO PET does not directly measure

developmental synaptic pruning [50,52,53]. Crucially, however, mechanistic animal models of ASD reveal that developmental synaptic pruning defects are heterogeneous and bidirectional rather than uniform: for instance, mice with autism-associated Scn2a deficiency and human cerebral organoids exhibit excessive microglial phagocytosis (over-pruning) of postsynaptic density-95 (PSD-95)-positive synapses [54], whereas microglial Tmem59 deficiency in mice impairs synaptic engulfment (under-pruning), leading to an excess of excitatory synapses and autism-like behavioral rigidity [22]. Thus, microglial dysfunction in ASD involves complex, region- and genotype-dependent disruptions in developmental synaptic pruning rather than a uniform change in a single direction, ultimately disturbing the excitatory/inhibitory (E/I) synaptic balance [8,22,54,55].

In ADHD, by contrast, direct human post-mortem or in vivo PET evidence of central microglial activation and aberrant synaptic pruning remains scarce. Instead, the hypothesis of neuroimmune involvement in ADHD is supported primarily by indirect clinical observations—such as altered peripheral inflammatory markers and epidemiological associations with prenatal or early-life immune challenges [56]—combined with preclinical rodent models. In rodent models of ADHD-relevant phenotypes (such as striatal/cortical dopamine depletion or route-selection impairment models), increased numbers of Iba-1+ reactive microglia and elevated pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), have been observed in frontostriatal and hippocampal circuits [57,58]. Preclinical evidence suggests that such inflammatory signaling may interfere with dopaminergic neurotransmission, delayed myelination, and the maturation of prefrontal–subcortical networks governing executive function and impulse control [5,56,58,59].

Correspondingly, clinical responses to exercise differ between the two disorders: meta-analyses in pediatric ASD indicate that structured, predictable, skill-based or group movement programs primarily improve social interaction, communication, and stereotypic behaviors [60–62], whereas network meta-analyses in pediatric ADHD demonstrate that moderate-to-vigorous aerobic and cognitively engaging exercises predominantly enhance catecholaminergic-dependent executive functions (inhibitory control, working memory, cognitive flexibility) and reduce core inattention and hyperactivity symptoms [46,63–65]. At the intracellular level, a key molecular node linking neurodevelopmental synaptic pathology to exercise-mediated regulation is the phosphoinositide 3-kinase (PI3K)/AKT/tuberous sclerosis complex (TSC1/2)/mechanistic target of rapamycin (mTOR) signaling cascade (Figure 1): in the CNS, hyperactivation of mTORC1 and consequent suppression of ULK1/ATG13-mediated autophagy in microglia and neurons are well-established drivers of impaired synaptic pruning and excitatory/inhibitory imbalance in ASD and related neurodevelopmental models [4,24,66], whereas in peripheral skeletal muscle, mechanical and metabolic modulation of mTOR and autophagy pathways governs protein synthesis and the release of candidate exerkines and extracellular vesicles during exercise [24,67]. Recognizing both the clinical divergences between ASD and ADHD and these shared intracellular regulatory hubs provides a rigorous foundation for evaluating how exercise-induced peripheral factors might act across neurodevelopmental trajectories [68].

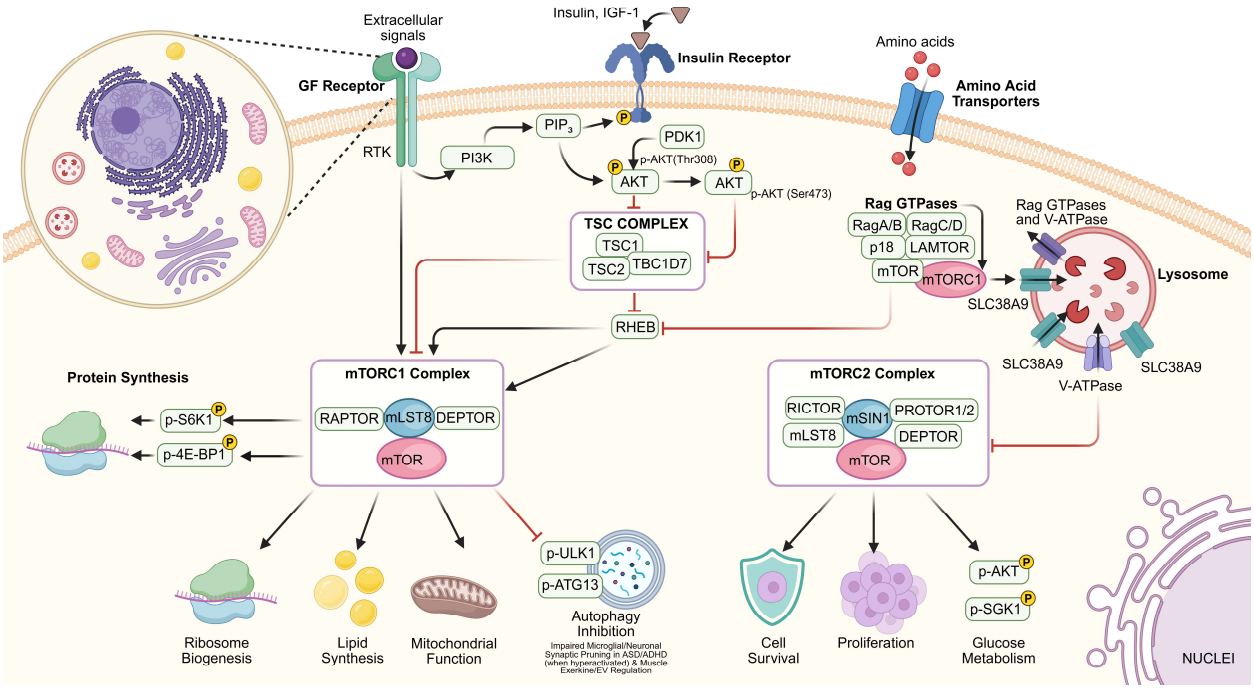


Figure 1. Dual role of the intracellular PI3K/AKT/TSC1-2/mTOR signaling network in neurodevelopmental synaptic pruning pathology and exercise-induced skeletal muscle adaptation. This schematic illustrates the core regulatory architecture of the mTORC1 and mTORC2 pathways, which serve as a critical intracellular nexus in both central neurodevelopmental pathology (Section 2.3) and peripheral exercise physiology (Section 5.1). Upstream signals, such as insulin, IGF-1, and growth factors, activate the RTK/PI3K/PDK1/AKT cascade to inhibit the TSC1/TSC2/TBC1D7 complex, thereby activating mTORC1 via RHEB alongside lysosomal amino acid sensing mediated by SLC38A9, V-ATPase, and Rag GTPases. In the central nervous system (particularly in ASD models such as TSC1/2 or PTEN deficiency), pathological hyperactivation of mTORC1 suppresses ULK1/ATG13-dependent autophagy and dysregulates S6K1/4E-BP1-mediated translation in microglia and neurons, leading to impaired developmental synaptic pruning and neuroinflammation. Conversely, in peripheral skeletal muscle, exercise dynamically modulates mTORC1, mitochondrial biogenesis, and autophagic flux, which is hypothesized to coordinate myofiber remodeling with the synthesis and release of muscle-associated exerkines (e.g., cathepsin B, CTSB) and extracellular vesicles. In parallel, mTORC2 regulates cell survival, proliferation, and glucose metabolism via AKT and SGK1. Abbreviations: AKT (p-AKT), protein kinase B (phosphorylated protein kinase B); CTSB, cathepsin B; DEPTOR, DEP domain-containing mTOR-interacting protein; GF, growth factor; IGF-1, insulin-like growth factor 1; LAMTOR, late endosomal/lysosomal adaptor, MAPK and mTOR activator; mLST8, mammalian lethal with SEC13 protein 8; mSIN1, mammalian stress-activated protein kinase-interacting protein 1; mTOR, mechanistic target of rapamycin; mTORC1/2, mechanistic target of rapamycin complex 1/2; p-4E-BP1, phosphorylated eukaryotic translation initiation factor 4E-binding protein 1; p-ATG13, phosphorylated autophagy-related protein 13; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PROTOR1/2, protein observed with RICTOR 1/2; p-S6K1, phosphorylated ribosomal protein S6 kinase beta-1; p-SGK1, phosphorylated serum and glucocorticoid-regulated kinase 1; p-ULK1, phosphorylated Unc-51-like autophagy-activating kinase 1; p18, late endosomal/lysosomal adaptor, MAPK and mTOR activator 1 (LAMTOR1); RagA/B and RagC/D, Ras-related GTP-binding protein A/B and C/D; RAPTOR, regulatory-associated protein of mTOR; RHEB, Ras homolog enriched in brain; RICTOR, rapamycin-insensitive companion of mTOR; RTK, receptor tyrosine kinase; Ser473, serine 473; SLC38A9, solute carrier family 38 member 9; TBC1D7, TBC1 domain family member 7; Thr308, threonine 308; TSC1/2, tuberous sclerosis complex 1/2; V-ATPase, vacuolar-type H+-ATPase.

3. Molecular Decoding of Cross-Organ Communication: How Exercise Factors Reprogram the Brain Immune Microenvironment

3.1. Biological Characteristics and Putative Blood–Brain Barrier Transport Versus Endothelial Signaling of Representative Exerkines

Physical exercise induces the release of diverse exerkines into the systemic circulation [13,69]. When evaluating how these peripheral factors influence the CNS, it is critical to distinguish between molecules that directly traverse the blood–brain barrier (BBB) into the brain parenchyma and those that act indirectly by binding to receptors on brain microvascular endothelial cells to trigger secondary central signaling cascades [28,38,70].

Irisin, a 12 kDa polypeptide fragment cleaved from the membrane protein fibronectin type III domain-containing protein 5 (FNDC5) [71], is detectable in human cerebrospinal fluid (CSF) [39,72] and has been proposed in preclinical studies to cross the BBB via saturable transendothelial transport, although exercise also directly upregulates endogenous FNDC5 expression within hippocampal neurons [73,74].

Cathepsin B (CTSB) is a lysosomal cysteine protease whose systemic levels increase following aerobic exercise in mice and adult humans [75–77]. Importantly, although running increases Ctsb gene expression in murine gastrocnemius muscle and AMPK activation stimulates CTSB secretion in cultured myotubes [75], CTSB is ubiquitously expressed across many tissues (including immune cells, liver, and brain parenchyma) and has also been identified within circulating extracellular vesicles (EVs) [78,79]. Therefore, exercise-induced elevations in circulating CTSB should be viewed as a muscle-associated exerkine response rather than a strictly muscle-exclusive signal [13,75]. Rather than diffusing passively through intact paracellular tight junctions, circulating EVs and exosomes are thought to interact with or traverse the BBB primarily via transcellular routes across brain microvascular endothelial cells—including receptor-mediated transcytosis, clathrin- or caveolae-dependent endocytosis, macropinocytosis, and adsorptive-mediated transcytosis—or by delivering their cargo directly to endothelial cells to modulate neurovascular signaling [13,29,30,80], whereas free CTSB has been shown in mouse models to cross the BBB and stimulate hippocampal neurogenesis [75].

Lactate, a glycolytic metabolite abundantly released by contracting skeletal muscle, influences the brain via both direct transport and indirect neurovascular receptor signaling. Circulating lactate can directly cross the BBB through proton-linked monocarboxylate transporters (e.g., MCT1) expressed on cerebral endothelial cells to enter neurons and glia, while simultaneously acting as an extracellular signaling ligand for G protein-coupled receptor 81 (GPR81/HCAR1) on brain vascular endothelial and perivascular cells to stimulate cerebral VEGF expression and angiogenesis [81–83].

Crucially, central brain-derived neurotrophic factor (BDNF) is not merely a simple linear downstream product of peripheral lactate or CTSB; rather, central BDNF expression is governed by a complex, multi-source regulatory network [73,84]. During exercise, hippocampal and cortical BDNF transcription is driven primarily by intrinsic neuronal synaptic activity (via calcium/calmodulin-dependent kinases and CREB activation), local neuronal PGC-1α/FNDC5 signaling [73], and epigenetic remodeling of Bdnf promoters [85,86], with peripheral lactate (acting via an endothelial/neuronal SIRT1–PGC-1α–FNDC5 axis [81]) and CTSB [75] serving as complementary systemic modulators rather than sole determinants [84,87]. Moreover, exercise alters the circulating pool of extracellular vesicles containing microRNAs, such as miR-146a [80]. These exosomal miRNAs are hypothesized to participate in peripheral-to-central signaling where they may target neuroinflammatory pathways such as the Toll-like receptor (TLR)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) cascade in microglia [88]. Preserved encapsulation within extracellular vesicles provides molecular stability during systemic transit, representing a

candidate mechanism by which peripheral factors might influence central immune homeostasis [32,89]. Together, these representative exercise factors possess distinct molecular properties and putative BBB transport or endothelial signaling mechanisms that may allow them to influence the central immune microenvironment (Figure 2). Nevertheless, substantial methodological heterogeneity, contradictory findings, and biological uncertainties surround exerkine biology and BBB transport in humans. First, regarding FNDC5/irisin, human translation has been debated because the human FNDC5 gene contains an atypical ATA start codon that may lower translation efficiency compared with the canonical ATG codon in rodents, and commercial enzyme-linked immunosorbent assays (ELISAs) for circulating irisin have historically suffered from nonspecific cross-reactivity and wide inter-assay variability compared with quantitative tandem mass spectrometry [39,72]. Consequently, human exercise studies have reported inconsistent acute and chronic irisin responses depending on assay methodology, sampling timing, fitness status, and age [37]. Second, circulating CTSB is not a strictly muscle-exclusive signal; as a ubiquitously expressed lysosomal protease, systemic CTSB elevations may reflect combined contributions from skeletal muscle, immune cells, and other tissues, and under certain neuropathological conditions (such as neuroinfectious or neurodegenerative states), excessive extracellular CTSB can even exert neurotoxic rather than neuroprotective effects [78,79]. Third, direct in vivo evidence demonstrating intact trans-BBB transport of skeletal-muscle-derived EVs in humans is lacking, as conventional tetraspanin markers (CD63, CD81) cannot reliably distinguish muscle-derived vesicles from the abundant pool of platelet-, leukocyte-, and endothelial-derived EVs in peripheral blood [89,90]. Finally, although endogenous irisin is detectable in human CSF at nanogram-to-picogram per milliliter levels [39,72], many preclinical studies demonstrating robust microglial modulation rely on supraphysiological exogenous recombinant doses or viral overexpression [18,41,70,91]; thus, whether normal physiological exercise in children and adolescents can generate sufficient central concentrations of irisin, CTSB, or muscle-derived EVs in the human brain to replicate experimental effects remains a major unresolved question.

3.2. Receptor Mechanisms Underlying Microglial Functional Modulation: From NF-κB Inhibition to Homeostatic and Anti-Inflammatory Reprogramming

The intracellular signaling cascades linking exerkines to microglial modulation have been characterized primarily in preclinical rodent models of neurological injury and in vitro microglial cultures, rather than in human pediatric neurodevelopmental cohorts [32]. In mouse models of intracerebral hemorrhage, postoperative cognitive dysfunction, and acute glaucoma, as well as in cultured microglia, irisin binds to the integrin αVβ5 receptor on microglial membranes to activate AMP-activated protein kinase (AMPK) or STAT6 signaling, thereby inhibiting NF-κB nuclear translocation and downregulating pro-inflammatory gene expression [41,70,91]. Regarding lactate signaling, in vitro studies in primary microglia demonstrate that L-lactate acts via Gi-coupled GPR81 (HCAR1) receptors to suppress microglial phagocytosis [92]. Although canonical Gi-coupled GPR81 activation inhibits the cyclic AMP (cAMP)/protein kinase A (PKA) pathway in skeletal muscle and cerebral models [82,93] and high-intensity interval training (HIIT) promotes mitochondrial biogenesis via the lactate–GPR81–ERK1/2 and PGC-1α cascade in bulk hippocampal tissue and Neuro-2A neuronal cells [94], whether this complete GPR81–cAMP/PKA–PGC-1α intracellular cascade operates directly within microglia to drive metabolic reprogramming remains a hypothesis extrapolated from non-microglial tissues. This metabolic reprogramming shifts microglia from a glycolysis-dominated pro-inflammatory reactive state toward an oxidative phosphorylation-supported homeostatic and tissue-supportive profile

(characterized in rodent studies by markers such as Arg-1, Ym-1, and IL-10) [32,70,95]. In addition, in rodent models of ischemic stroke and Alzheimer's disease using mesenchymal stem cell-derived exosomes, exosomal miR-146a-5p taken up by microglia post-transcriptionally silences interleukin-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6) in the TLR4/NF-κB pathway [88,96], although direct evidence of skeletal-muscle-derived exosomal miR-146a targeting microglia in adolescents with ASD or ADHD has not yet been established. This silencing effectively reduces inflammatory signaling cascades and promotes the maintenance of the quiescent and anti-inflammatory status of microglia [32,96]. These signaling pathways converge to drive a metabolic and functional switch in microglia: from a glycolysis-dependent pro-inflammatory phenotype to an oxidative phosphorylation-dependent anti-inflammatory phenotype that promote tissue repair and synaptic homeostasis [95]. Crucially, however, contemporary consensus emphasizes that the classical M1/M2 dichotomy is an outdated oversimplification that fails to capture the multidimensional, context-, region-, and stage-dependent transcriptional states of microglia in vivo; throughout this review, we therefore adopt functional state descriptors (e.g., homeostatic, pro-inflammatory reactive, and phagocytic states) and mention "M1/M2-like" only when referring to historical in vitro/rodent marker panels or schematic labels [43]. During neurodevelopment, microglial synaptic pruning is a highly orchestrated physiological event governed by neuronal activity patterns, complement cascades (e.g., C1q/C3), fractalkine (CX3CL1–CX3CR1) signaling, and inhibitory "don't-eat-me" cues (e.g., CD47–SIRPα) [21,43,97]. Therefore, merely reducing neuroinflammation or shifting microglia toward an anti-inflammatory state does not automatically restore normal developmental synaptic pruning or proper neuronal connectivity; indeed, indiscriminate dampening of microglial phagocytic or immune activity during critical windows can itself impair circuit refinement [43,98]. Consequently, the proposed benefit of exercise-induced exerkines is hypothesized to lie not in a simplistic binary "M1-to-M2 switch," but in mitigating pathological neuroinflammation while preserving the metabolic and homeostatic competence required for activity-dependent neuron–microglia communication (Figure 3).

3.3. Restoring Precision in Developmental Synaptic Pruning: The Temporal and Spatial Regulatory Advantages of Exercise Factors

Microglia contribute to neural circuit maturation by pruning synapses in a "use-it-or-lose-it" competitive fashion during neurodevelopment [97]. This process can become bidirectionally dysregulated in neurodevelopmental disorders—manifesting either as aberrant over-pruning when protective "don't-eat-me" signals (such as CD47) are disrupted [54,99], or as impaired microglial engulfment (under-pruning) resulting in a surplus of weak synapses [22,100]. Modulating microglial states through exercise is hypothesized not simply to unidirectionally suppress or elevate phagocytosis, but to help restore activity-dependent fine-tuning of synaptic pruning, allowing for the selective elimination of less active synaptic terminals while preserving functional connectivity [100]. This concept is supported by preclinical evidence in rodent models: in mice exposed to maternal immune activation (MIA, an established environmental risk model for ASD-like phenotypes) that exhibit impaired microglial synaptic engulfment and a consequent surplus of synapses in the hippocampal CA3 region, voluntary wheel running (VWR) in adulthood reversed behavioral abnormalities by stimulating dentate gyrus neuronal activity and promoting microglial engulfment of surplus weaker synapses in CA3, thereby normalizing synaptic density [100]. Separately, in valproic acid (VPA)-induced autistic rats, treadmill exercise was shown to ameliorate motor dysfunction by inhibiting cerebellar Purkinje cell loss [101].

Importantly, the temporal modulation provided by exercise-induced factors differs from pharmacological immunosuppressants, which have been shown to indiscriminately inhibit synaptic elimination and interfere with the integrity of neural networks [98]. By preserving activity-dependent neuronal competition while attenuating excessive inflammation, exercise may support more balanced circuit refinement than indiscriminate pharmacological immunosuppression [98,100]. Key molecular and cellular components of this proposed axis, along with their experimental evidence levels, are summarized in Table 1.

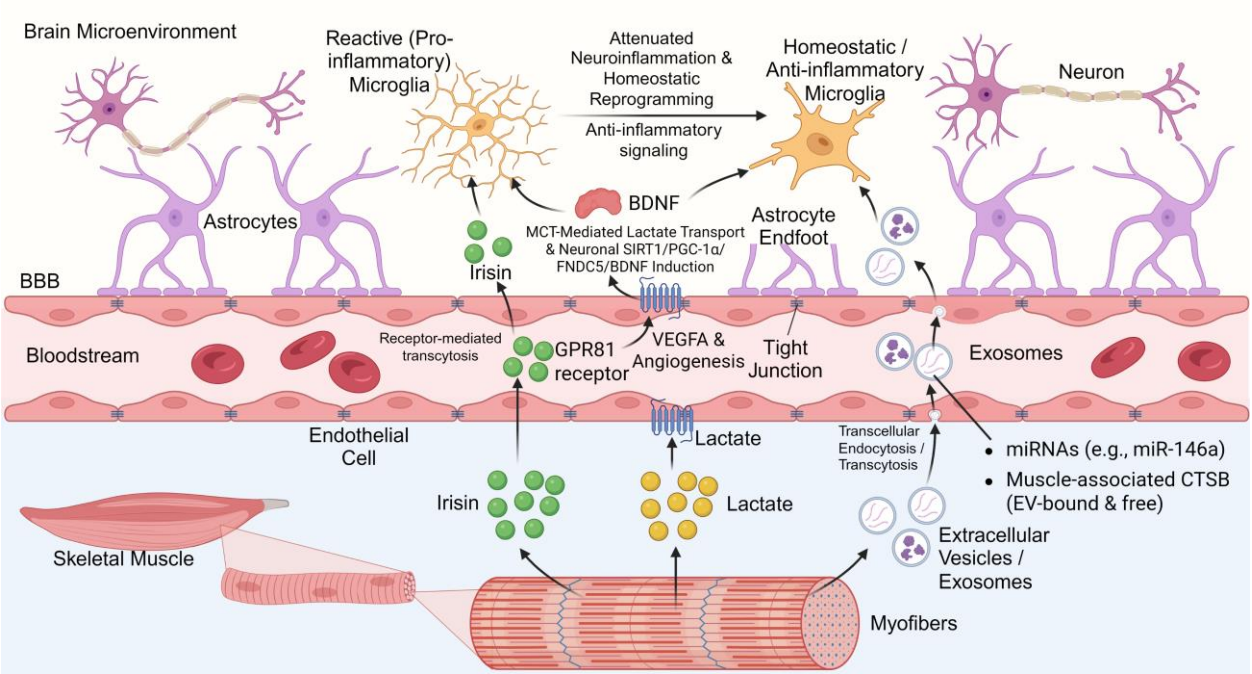


Figure 2. Proposed model of the muscle–microglia axis: hypothetical direct BBB transport and indirect endothelial signaling pathways of exercise-induced factors (based primarily on preclinical evidence). This schematic illustrates the proposed unidirectional communication network linking contracting skeletal myofibers to the central nervous system. Irisin is released into the circulation and is hypothesized to traverse the blood–brain barrier (BBB) via saturable transendothelial transport. Meanwhile, circulating lactate both crosses the BBB via monocarboxylate transporters (MCTs) to stimulate hippocampal BDNF expression via a neuronal SIRT1–PGC-1α–FNDC5 pathway and activates HCAR1 (GPR81) receptors on cerebral perivascular and endothelial cells to promote cerebral VEGFA signaling and angiogenesis; together with intrinsic neuronal activity, these pathways support neurovascular remodeling and central BDNF regulation. Concurrently, circulating extracellular vesicles (exosomes) carrying cargo—such as miRNAs (e.g., miR-146a) and muscle-associated cathepsin B (CTSB)—are proposed to cross or signal across the intact BBB primarily via transcellular endothelial pathways (including receptor-mediated transcytosis, clathrin- or caveolae-dependent endocytosis, and macropinocytosis) rather than paracellular tight junctions, while free CTSB can also cross the BBB directly. Within the brain microenvironment, these signals are hypothesized to interact with astrocytes, neurons, and microglia to attenuate neuroinflammation and support neuroprotection. Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CTSB, cathepsin B; FNDC5, fibronectin type III domain-containing protein 5; GPR81, G protein-coupled receptor 81 (hydroxycarboxylic acid receptor 1, HCAR1); MCTs, monocarboxylate transporters; miRNAs (miR-146a), microRNAs (microRNA-146a); PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

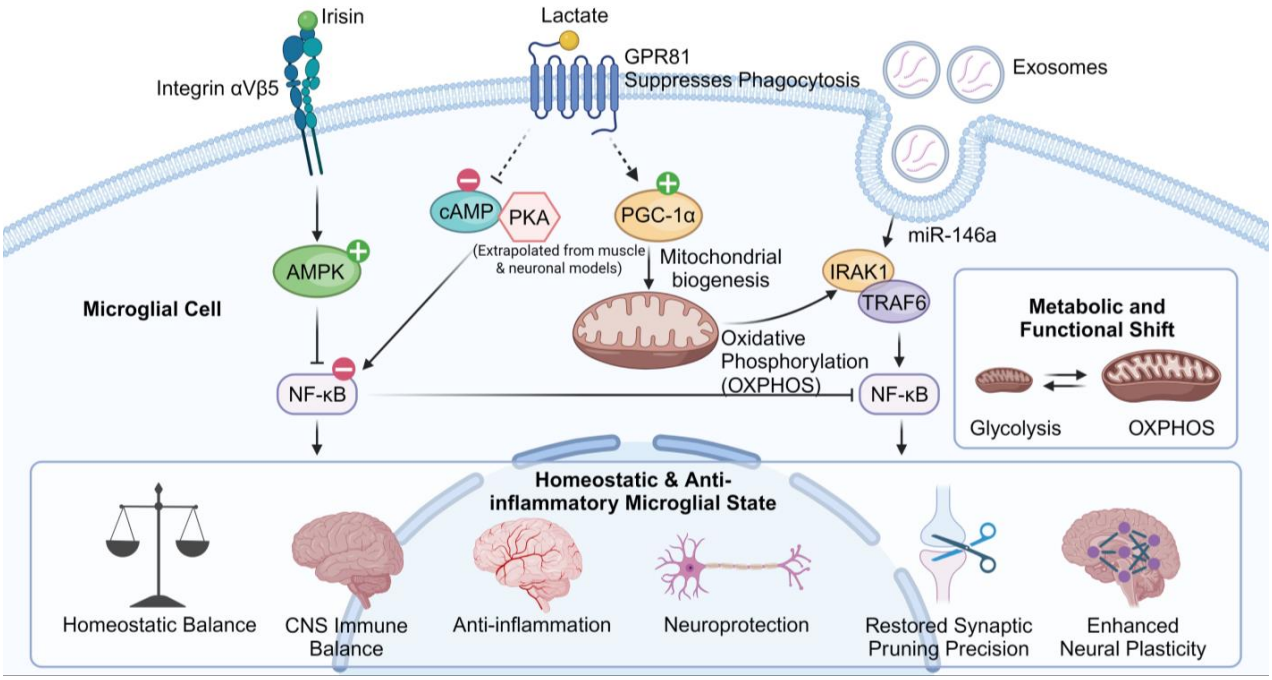


Figure 3. Proposed intracellular signaling pathways mediating exerkine-induced microglial modulation (synthesized from preclinical models). This diagram illustrates putative intracellular signaling cascades within microglial cells triggered by exercise-induced factors based on preclinical studies. Upon binding to the integrin αVβ5 receptor, irisin activates the AMPK pathway, which inhibits pro-inflammatory NF-κB signaling. Concurrently, lactate binds to the GPR81 (HCAR1) receptor, which has been shown to suppress phagocytosis in primary microglia; the downstream cAMP/PKA and PGC-1α mitochondrial biogenesis pathways (indicated by dashed arrows) represent hypothetical cascades extrapolated from skeletal muscle and hippocampal/neuronal models rather than direct measurements in isolated microglia. Additionally, exosome-delivered miR-146a can target IRAK1 and TRAF6 adaptors to attenuate TLR/NF-κB activation. Together, these preclinical pathways are hypothesized to promote an anti-inflammatory, homeostatic microglial state ("M2-like" is shown solely as a schematic shorthand), which may help support synaptic homeostasis and CNS immune balance, although reducing inflammation alone does not automatically guarantee normal developmental synaptic pruning. Abbreviations: AMPK, AMP-activated protein kinase; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; GPR81, G protein-coupled receptor 81; Integrin αVβ5, integrin alpha-V beta-5; IRAK1, interleukin-1 receptor-associated kinase 1; M1/M2, pro-inflammatory (M1-like)/reparative anti-inflammatory (M2-like) microglial signaling state; miR-146a, microRNA-146a; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OXPHOS, oxidative phosphorylation; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA, protein kinase A; TRAF6, tumor necrosis factor receptor-associated factor 6.

Table 1. Key molecular and cellular components of the proposed muscle–microglia axis.

Biological Entity	Category & Source	Target Receptor/Carrier	Primary Neurobiological Role	Experimental Model/Evidence Level	References
Irisin (FNDC5)	Myokine cleaved from skeletal muscle FNDC5	Integrin αVβ5 on microglia	Activates AMPK/STAT6, inhibits NF-κB, attenuates neuroinflammation, and supports synaptic plasticity	Preclinical rodent models (ICH, surgical trauma, glaucoma, AD/tauopathy); human plasma/CSF detection	[26,39,41,70,72,73,91]
Cathepsin B (CTSB)	Lysosomal cysteine protease secreted by muscle	Free protein & extracellular vesicles (EVs)	Crosses BBB, upregulates hippocampal BDNF, and supports neurogenesis and memory	Preclinical models (mice, monkeys); adult human exercise cohorts (young & middle-aged adults)	[75–78]

Table 1. *Cont*.

Biological Entity	Category & Source	Target Receptor/Carrier	Primary Neurobiological Role	Experimental Model/Evidence Level	References
Lactate	Exercise-induced metabolite/signaling molecule	GPR81 (HCAR1) & MCTs on endothelium/glia	Stimulates hippocampal BDNF (via SIRT1/PGC-1α) and cerebral VEGF; modulates microglial phagocytosis/metabolism	Preclinical rodent & in vitro microglial models; adult/adolescent physiological studies	[81,83,84,92,94,102]
miR-146a	Exosomal microRNA	IRAK1 and TRAF6 in microglia	Suppresses TLR4/NF-κB inflammatory cascade in reactive microglia	Preclinical rodent stroke/AD models (MSC-derived EVs); human ASD tissue profiling	[88,96,103,104]
BDNF	Neurotrophic factor (brain parenchyma/endothelium)	TrkB receptor (neurons/synapses)	Promotes neurogenesis, dendritic spine integrity, and cognitive plasticity	Preclinical ASD/exercise rodent models; human peripheral biomarker studies	[68,73,81,105]
Microglia	CNS resident innate immune cells	CX3CR1, TREM2, complement, αVβ5, GPR81	Mediates activity-dependent synaptic pruning, phagocytosis, and neuroimmune homeostasis	Human ASD post-mortem/PET; preclinical ASD/ADHD & adolescent rodent models	[21,43,51,53,54,57,58,97,106]
Estrogen & Testosterone	Gonadal sex steroid hormones	Estrogen/androgen receptors (muscle & CNS)	Modulates muscle satellite cells and tissue FNDC5 in rodents; shapes sex-specific microglial development (pubertal amplification in humans is hypothetical)	Preclinical rodent endocrinology & neurodevelopment models; theoretical hypothesis for human Tanner stages	[20,107–112]

Note: This table summarizes the key molecular and cellular components involved in the proposed muscle–microglia axis across peripheral-to-central communication. It outlines representative exercise-induced factors—including irisin, cathepsin B (CTSB), lactate, and exosomal miR-146a—alongside their putative blood–brain barrier (BBB) transport or endothelial signaling mechanisms and target receptors. Furthermore, the table explicitly distinguishes the experimental level of evidence (predominantly preclinical rodent and in vitro models versus human biomarker detection) supporting each entity's role in modulating neuroinflammation, neurogenesis, and activity-dependent synaptic remodeling. Finally, gonadal sex steroid hormones are included to highlight their hypothesized role in modulating skeletal muscle plasticity and microglial developmental trajectories during the pubertal transition. Abbreviations: AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; AMPK, AMP-activated protein kinase; ASD, autism spectrum disorder; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CSF, cerebrospinal fluid; CTSB, cathepsin B; CX3CR1, C-X3-C motif chemokine receptor 1; EVs, extracellular vesicles; FNDC5, fibronectin type III domain-containing protein 5; GPR81 (HCAR1), G protein-coupled receptor 81 (hydroxycarboxylic acid receptor 1); ICH, intracerebral hemorrhage; IRAK1, interleukin-1 receptor-associated kinase 1; MCTs, monocarboxylate transporters; miR-146a, microRNA-146a; MSC, mesenchymal stem cell; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PET, positron emission tomography; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SIRT1, sirtuin 1; STAT6, signal transducer and activator of transcription 6; TLR4, Toll-like receptor 4; TRAF6, tumor necrosis factor receptor-associated factor 6; TREM2, triggering receptor expressed on myeloid cells 2; TrkB, tropomyosin receptor kinase B; VEGF, vascular endothelial growth factor.

4. Developmental Critical Window: Hypothesized Sensitivity of the Muscle–Microglia Axis During the Pubertal Transition

4.1. Key Biological Events in Pubertal Neurodevelopment and Microglial Functional Switching

Puberty is a critical period in brain maturation, with a second surge of growth and remodeling, especially in the prefrontal cortex, where the maximum number of excitatory

synapses is reached and then rapidly pruned [113]. This synaptic remodeling is vital to the development of effective neural networks responsible for higher cognitive processes. The resident immune cells of the central nervous system, microglia, are important during this time, acting as "architects" in the precise remodeling of synapses [106]. Their synaptic pruning activity is highly correlated with adolescent cognitive flexibility and impulse control, highlighting their functional importance in neurodevelopmental trajectories [106]. In humans, the pubertal transition (clinically categorized across Tanner stages II–IV based on secondary sexual characteristics) is marked by a surge in sex steroid hormones, such as estradiol and testosterone, alongside pronounced cortical restructuring [113]. Crucially, however, clinical Tanner-stage terminology cannot be directly extrapolated from rodent developmental stages (typically defined by postnatal days, vaginal opening, or preputial separation), because rodents lack a prolonged human-like juvenile hiatus and adrenarche and exhibit compressed neurodevelopmental timelines [20,106,113]. Direct mechanistic evidence linking pubertal sex hormone fluctuations to microglial receptor expression—such as CX3CR1 (involved in neuron–microglia signaling) and TREM2 (involved in phagocytosis)—derives primarily from preclinical rodent models rather than human pediatric studies [20,106,108,110]. In adolescent rodents, sex-specific hormonal milieus modulate microglial morphology, immune reactivity, and prefrontal circuit refinement [20,106,108]. While these rodent findings cannot be directly equated to specific human Tanner stages, they support the hypothesis that the pubertal transition may represent a period of heightened neuroimmune plasticity during which microglia could be particularly responsive to systemic signals, including exercise-induced factors [20,106,110,113].

4.2. Hypothesized Interactions Between Pubertal Sex Hormones and Exercise Factors

We hypothesize that the signaling activity of the proposed muscle–microglia axis may be dynamically modulated by the changing endocrine milieu of puberty, although direct clinical evidence comparing exerkine responses across human Tanner stages (e.g., stages II–IV versus prepubertal stage I or adulthood) is currently lacking. This hypothesis is informed by preclinical endocrinological studies demonstrating that sex steroids influence both skeletal muscle plasticity and FNDC5/irisin regulation. In rodent models, hormonal status (such as gonadal steroid manipulation) significantly alters FNDC5 expression and circulating irisin levels across skeletal muscle, adipose tissue, and the hypothalamus [112], and irisin has been shown to interact with neuroendocrine pathways in the primate hypothalamus in vitro [114]. Concurrently, androgens such as testosterone promote myogenesis and activate quiescent satellite cells in rodent skeletal muscle [109,111], while biological sex and sex hormones strongly influence putative myokine signaling networks [107] and microglial developmental trajectories [108]. However, whether rising estradiol or testosterone during human puberty directly enhances exercise-induced FNDC5 transcription, facilitates exerkine transport across the human blood–brain barrier, or amplifies microglial responsiveness remains an untested hypothesis. Given substantial differences in pubertal timing, endocrine profiles, and BBB physiology between rodents and humans, longitudinal pediatric studies stratified by Tanner stage and sex steroid levels are required to test whether human puberty truly constitutes a high-sensitivity window for exercise-induced neuromodulation in ASD and ADHD (Figure 4).

4.3. Long-Term Neuroepigenetic Memory Effects Induced by Pubertal Exercise Interventions

Preclinical studies indicate that physical exercise during juvenile or adolescent developmental windows in rodents (which, as noted above, cannot be directly equated to specific human Tanner stages such as stage III) can induce neuroepigenetic modifications; however, it is essential to specify whether these changes were measured in bulk brain tissue, neurons,

or specifically in microglia, as well as across distinct brain regions. In juvenile mice, early-life voluntary wheel running primes the hippocampal neural epigenome (assessed in hippocampal neuronal and bulk tissue) to facilitate activity-dependent gene expression and memory consolidation [85]. Similarly, forced running exercise in mice mitigates radiation-induced cognitive deficits by regulating DNA hydroxymethylation (5-hydroxymethylcytosine, 5-hmC) and BDNF expression in bulk hippocampal tissue [86], while treadmill exercise in rats exerts age-dependent effects on histone deacetylase (HDAC) enzymatic activity measured in bulk striatal tissue [115]. Regarding glial-specific epigenetic regulation, high-intensity interval training (HIIT) in adolescent rodents exposed to postnatal immune activation was shown to ameliorate mood-related behaviors by modulating histone demethylase KDM6B-regulated glial activation [116]. Separately, the concept that isolated microglia can retain long-lasting epigenetic innate immune memory—characterized specifically by enhancer histone modifications such as monomethylation of lysine 4 on histone H3 (H3K4me1) and acetylation of lysine 27 on histone H3 (H3K27ac)—has been established in adult mouse models of systemic immune challenge [117], whereas promoter H3K4me3 modifications have been examined at the Tnf-α locus in primary rat microglia exposed to lipopolysaccharide and dextromethorphan in vitro [118]. Crucially, neither of these microglial studies [117,118] investigated exercise or demonstrated promoter remodeling at BDNF, TGF-β, or IL-10 loci in microglia. Therefore, because current exercise epigenetics studies examine heterogeneous bulk tissues or neurons across distinct brain regions (e.g., bulk hippocampal 5-hmC at the Bdnf promoter [86] and neuronal H3K27ac [85], or bulk striatal HDAC activity [115]) rather than isolated pubertal microglia, whether adolescent exercise directly establishes persistent H3K4me1, H3K27ac, or 5-hmC marks specifically within microglial chromatin remains an unconfirmed hypothesis that warrants future cell-type-specific epigenomic investigation.

4.4. Comparative Analysis of Dose–Response Relationships Across Developmental Stages

Preclinical studies suggest that the neurobiological and neuroimmune effects of exercise can vary depending on the developmental stage at which the intervention is initiated [119]. For instance, comparative studies in rodents have demonstrated differential effects of wheel running on hypothalamic and hippocampal neuroinflammation and microglial profiles between adolescent and adult cohorts [119]. In mice exposed to chronic unpredictable stress, running exercise alleviates hippocampal neuroinflammation and shifts microglial polarization toward an anti-inflammatory phenotype via adiponectin/AdipoR1 pathway activation [45], while voluntary exercise specifically during the pubertal period in mice promotes spatial memory and enhances hippocampal dentate gyrus (DG)/CA3 synaptic transmission [120]. Furthermore, early-life and adolescent exercise paradigms in rodents have been shown to induce persistent enhancements in hippocampal memory consolidation and glial-mediated behavioral resilience [85,116]. While these preclinical observations suggest that the adolescent neurodevelopmental window may exhibit heightened biological responsiveness to physical activity (note that formal health-economic cost-effectiveness analyses do not exist), direct head-to-head dose–response comparisons across human developmental stages remain limited. Consequently, calibrating exercise intensity and volume to avoid both undertraining and excessive fatigue in youth with ASD or ADHD requires individualized clinical monitoring rather than direct extrapolation from rodent timelines [65,121].

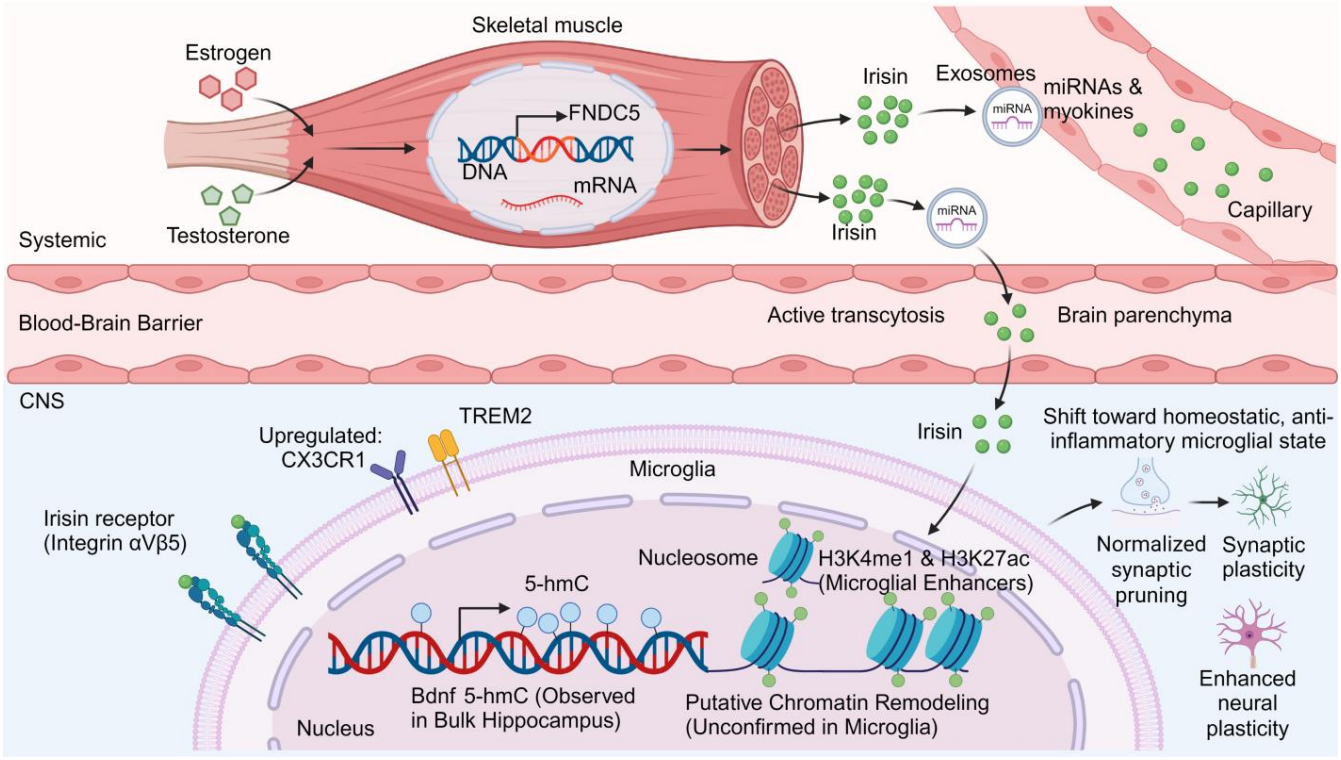


Figure 4. Hypothetical model of the pubertal window: proposed interactions between sex hormones and the muscle–microglia axis. This schematic depicts a theoretical hypothesis extrapolated from preclinical rodent studies regarding how pubertal sex hormones might interact with exercise-induced factors. Based on rodent evidence, systemic estrogen and testosterone are hypothesized to modulate skeletal muscle plasticity, satellite cell activation, and FNDC5/irisin or exosome release. After crossing or signaling across the blood–brain barrier, these factors are proposed to interact with adolescent microglia—which exhibit hormone-sensitive expression of receptors such as CX3CR1 and TREM2 in rodent models—as well as integrin αVβ5. The lower panel illustrates a strictly hypothetical convergence of neuroepigenetic mechanisms—extrapolating from bulk hippocampal DNA hydroxymethylation (5-hmC at the Bdnf promoter in rodent exercise models) and enhancer histone modifications (H3K4me1 and H3K27ac) established in microglial innate immune memory. Note: Direct exercise-induced chromatin remodeling at specific gene promoters within isolated pubertal microglia has not yet been experimentally demonstrated. Abbreviations: 5-hmC, 5-hydroxymethylcytosine; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CX3CR1, C-X3-C motif chemokine receptor 1; DNA, deoxyribonucleic acid; FNDC5, fibronectin type III domain-containing protein 5; H3K4me1, monomethylation of lysine 4 on histone H3; H3K27ac, acetylation of lysine 27 on histone H3; Integrin αVβ5, integrin alpha-V beta-5; miRNA (miRNAs), microRNA (microRNAs); mRNA, messenger ribonucleic acid; TREM2, triggering receptor expressed on myeloid cells 2.

5. Hypothesis-Driven Framework for Candidate Exercise Prescription Parameters (FITT-VP) in Future Clinical Trials

5.1. Exercise Modality Specificity and Molecular Target Matching: Comparison of Aerobic, Resistance, and HIIT

Exploring individualized exercise strategies for adolescents with ASD and ADHD requires examining how different exercise modalities may preferentially engage distinct skeletal muscle signaling pathways while recognizing that current mechanistic evidence derives primarily from preclinical models and healthy adult physiology rather than pediatric clinical trials [65]. In rodent models and adult human studies, sustained endurance (aerobic) exercise stimulates the AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signaling axis [122] and upreg-

ulates skeletal muscle Fndc5 expression and hippocampal BDNF in mice [73], as well as circulating irisin in human endurance cohorts [37]. Notably, however, these exerkine pathways are substantially overlapping rather than exclusive to a single exercise modality: for instance, acute and chronic functional and traditional resistance training also increase circulating AMPK, PGC-1α, and irisin levels in young adult males [123], and HIIT similarly upregulates hippocampal FNDC5/irisin and BDNF in preclinical models [124]. Conversely, while resistance training and HIIT robustly activate the mechanistic target of rapamycin complex 1 (mTORC1) and hypoxia-inducible factor-1 alpha (HIF-1α) pathways in skeletal muscle [67,125], aerobic running also elevates systemic cathepsin B (CTSB) [75,76]. Therefore, endurance training is not proven to be uniquely optimal for ASD via irisin, nor is HIIT uniquely specific for ADHD via lactate; rather, aerobic, resistance, and intermittent modalities engage overlapping candidate exerkine networks that may collectively support neuroimmune homeostasis and executive function across both disorders [62,65,126]. In adult exercise studies and preclinical models, resistance exercise and endurance training have been reported to modulate circulating neuroprotective biomarkers—such as cathepsin B (CTSB)—and extracellular vesicle release [75,127,128]. Given preclinical links between CTSB and hippocampal neurogenesis, resistance exercise could theoretically contribute to neurotrophic support, though whether resistance training reliably elevates central CTSB or alters clinical outcomes in pediatric ASD or ADHD has not yet been established.

During HIIT (such as repeated short bouts of high-intensity sprinting), anaerobic glycolysis generates acute, pulsatile elevations in systemic lactate [102]. Preclinical rodent studies suggest that elevated lactate can activate cerebral G protein-coupled receptor 81 (GPR81/HCAR1) and support mitochondrial and neurotrophic adaptations [83,94]. However, whether intermittent lactate surges are more effective than moderate continuous exercise at modulating microglial function in humans—and specifically in children and adolescents with ASD or ADHD—remains unconfirmed and requires direct clinical investigation.

Implementing HIIT, however, presents a major clinical paradox regarding neurodivergent populations. For teens who are showing signs of sensory hyper-reactivity, the high impact and sympathetic activation of HIIT exercises can cause psychological distress and associated cortisol release, potentially worsening neuroinflammation rather than preventing it [129,130]. Likewise, in ADHD groups, the basic symptoms of poor motor control and impulsivity increase the likelihood of injuries during high-intensity activities. Therefore, the biochemical benefits that can be obtained from lactate-mediated neural adaptations may be negated by physiological stress responses, necessitating caution and phenotype-specific intensity scaling [131].

Taken together, rather than serving as validated clinical prescriptions, these modality-specific molecular associations offer a hypothesis-generating framework for selecting candidate exercise parameters in future pediatric clinical trials. Within this conceptual model, moderate-intensity continuous aerobic exercise is hypothesized to preferentially engage AMPK/PGC-1α/FNDC5 signaling [73,122], resistance exercise to engage mechanotransduction and CTSB/EV release [67,127,128], and carefully scaled intermittent exercise to engage lactate-mediated signaling [83,94], each warranting prospective biomarker-stratified testing in youth with ASD and ADHD (Figure 5).

5.2. Distinguishing Acute Molecular Responses from Chronic Therapeutic Adaptations: Candidate Dose Parameters

When evaluating exercise dose–response relationships, it is essential to clearly distinguish between acute, transient molecular responses to a single bout of exercise and the cumulative, long-term neurobiological adaptations required for sustained clinical therapeutic effects in ASD and ADHD [64,65]. In healthy adults and preclinical models, a

single acute bout of exercise triggers transient elevations in circulating lactate, irisin, and tetraspanin-positive EVs—typically peaking within minutes to 2 h post-exercise before returning to baseline [90,102,132,133]—whereas clinically meaningful improvements in executive function, synaptic remodeling, or core behavioral symptoms require chronic, multi-week training regimens (typically 6–12 weeks or longer) [62,65,75,76,121].

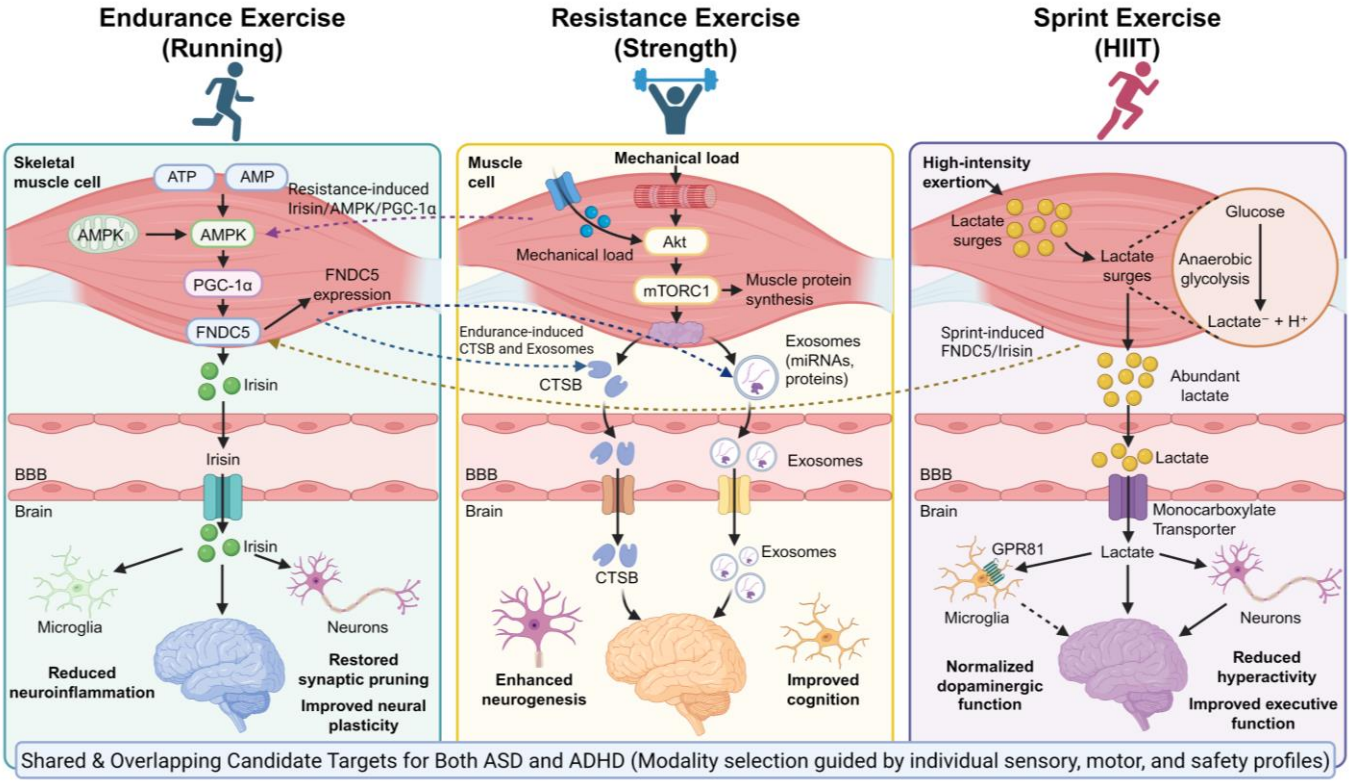


Figure 5. Hypothetical framework illustrating overlapping candidate molecular pathways across endurance, resistance, and high-intensity interval exercise modalities for future clinical exploration in ASD and ADHD. Rather than representing validated, disorder-exclusive treatment choices, endurance (aerobic), resistance, and sprint/high-intensity interval training (HIIT) engage overlapping peripheral signaling cascades (indicated by cross-connecting dashed arrows). Endurance exercise activates the AMPK/PGC-1α/FNDC5 pathway and also elevates systemic CTSB; resistance exercise activates mechanical Akt/mTORC1 signaling and modulates circulating EVs and CTSB while also elevating circulating AMPK, PGC-1α, and irisin; and HIIT generates pulsatile lactate release (acting via monocarboxylate transporters and GPR81) while also upregulating hippocampal FNDC5/irisin and BDNF in preclinical models. Collectively, these overlapping candidate pathways converge on shared neurodevelopmental targets across both ASD and ADHD—attenuating neuroinflammation and supporting neurogenesis, synaptic plasticity, and executive function—while clinical modality selection must be guided by individual sensory tolerance, motor coordination, and safety profiles rather than rigid phenotype-to-exerkine matching. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; Akt, protein kinase B; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ASD, autism spectrum disorder; ATP, adenosine triphosphate; BBB, blood–brain barrier; CTSB, cathepsin B; FNDC5, fibronectin type III domain-containing protein 5; GPR81, G protein-coupled receptor 81; H+, hydrogen ion; HIIT, high-intensity interval training; miRNAs, microRNAs; mTORC1, mechanistic target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

In adult exercise physiology and preclinical studies, acute exerkine kinetics vary with exercise intensity and mechanical load: for example, in healthy young adults, higher-intensity exercise elicits a greater acute circulating irisin response than low-intensity exercise under matched energy expenditure [132], and resistance training near muscular failure

acutely modulates circulating neuroprotective biomarkers and EV subpopulations in healthy men and women [127,128]. Regarding lactate–BDNF coupling, preclinical studies show that exercise-induced lactate contributes to hippocampal BDNF induction via SIRT1/PGC-1α/FNDC5 signaling [73,81,84] and activates cerebral HCAR1 (GPR81) [83,94], while voluntary running in mice rescues metabolic signaling in cerebellar Purkinje cells [66] and short-term high-intensity exercise promotes ceramide-dependent EV secretion in the mouse CNS [133]. In early adolescents, acute resistance and HIIT sessions elicit transient metabolic and blood lactate responses [102].

Crucially, however, no clinical studies have established quantitative biochemical thresholds (such as specific VO2max percentages, resistance set volumes, blood lactate concentrations, or post-exercise feeding intervals) in children or adolescents with ASD or ADHD. Adult or rodent metabolic thresholds cannot be directly extrapolated to neurodivergent youth without rigorous pediatric validation. Instead, recent systematic reviews and meta-analyses in pediatric ADHD and ASD populations indicate that structured moderate-to-vigorous aerobic or multicomponent exercise programs—commonly implemented for approximately 30–60 min per session, 2–5 sessions per week over 6–12 weeks, alongside variable regimen durations and frequencies across trials—are associated with clinically meaningful improvements in executive functions and core behavioral symptoms, although optimal dose–response parameters vary by symptom domain and exercise modality [60–65]. Whether acute post-exercise exerkine surges directly mediate these long-term clinical gains in youth with ASD and ADHD remains a working hypothesis for future longitudinal trials.

5.3. Conceptual Considerations and Candidate Parameters for Adapting Exercise Prescriptions (FITT-VP) in Adolescents with ASD and ADHD

When translating preclinical exerkine hypotheses into clinical trial design for children and adolescents with ASD and ADHD, candidate parameters structured around the FITT-VP (Frequency, Intensity, Time, Type, Volume, Progression) framework must prioritize clinical feasibility, behavioral tolerance, and existing pediatric evidence over unvalidated theoretical cutoffs [62,64,65]. Recent systematic reviews and network meta-analyses performed directly in pediatric ADHD and ASD cohorts indicate that regular, structured physical activity—typically conducted 3 to 5 times per week in sessions of 30 to 60 min over 6 to 12 weeks—significantly improves executive functions, social interaction, and core behavioral symptoms [60,62,64,65].

For children with ASD, predictable routines and structured group or skill-based activities (such as gymnastics or adapted team sports) support both physical activity engagement and social communication [60,61], whereas maintaining moderate intensities helps avoid sensory over-responsivity and psychosocial stress [129,134]. For youth with ADHD, network meta-analytic evidence demonstrates that moderate-to-vigorous aerobic and multicomponent cognitively engaging exercises effectively improve core symptoms and executive function deficits [63–65]. Although we hypothesize that pubertal maturation (across Tanner stages) may influence physiological responsiveness to exercise, specific prescriptions dictating exact heart rate reserve cutoffs by Tanner stage have not yet been empirically tested in pediatric ASD or ADHD cohorts and should be treated purely as candidate variables for future stratified trials.

Regarding exercise timing (chronobiology), scheduling sessions in the late afternoon (approximately 15:00–17:00) versus the morning should likewise be viewed as a candidate parameter governed by both circadian physiology and clinical routines. Physiologically, core body temperature, skeletal muscle contractile performance, and glycolytic capacity typically peak in the late afternoon, and after-school hours provide a practical window for structured group physical activity in school-aged youth [60,135]. In addition, because sleep

disturbances are prevalent in youth with ASD and ADHD—and preclinical evidence in sleep-deprived adolescent mice demonstrates that sleep loss impairs microglial synaptic pruning whereas voluntary exercise during the active phase ameliorates these pruning deficits [136]—completing exercise during daytime or afternoon hours rather than close to bedtime is a practical clinical consideration to avoid pre-sleep sympathetic arousal, although direct pediatric trials evaluating exercise timing on melatonin onset in ASD or ADHD are still needed. Conversely, for adolescents with ADHD receiving morning stimulant pharmacotherapy or experiencing classroom attentional deficits, morning aerobic exercise sessions have also demonstrated clinical efficacy in enhancing daytime executive control and frontal brain activation [137,138]. Because direct head-to-head pediatric trials comparing morning versus afternoon exerkine responses in ASD and ADHD are lacking, exercise timing and volume progression should be individualized to each child's sleep–wake schedule, school routine, motor competence, and standardized symptom assessments [64,65,121,139]. A summary of representative preclinical and clinical exercise studies—explicitly distinguishing animal models from human trials—is provided in Table 2.

Table 2. Representative preclinical and clinical exercise studies relevant to neuroimmune modulation and ASD/ADHD.

Exercise Modality	Protocol/Regimen	Experimental Model/Evidence Level	Molecular/Cellular Findings	Behavioral/Clinical Outcomes	References
Voluntary wheel running (VWR)	Daily running in adulthood (post-weaning MIA offspring)	Preclinical mouse model: Maternal immune activation (MIA)-induced ASD-like mice	Stimulated dentate gyrus neuronal activity; promoted microglial engulfment of surplus synapses in the hippocampal CA3 region	Reversed ASD-like behavioral deficits and normalized CA3 synaptic density	[100]
Treadmill exercise	30 min/day, 5 days/week for 4 weeks	Preclinical rat model: Valproic acid (VPA)-induced autistic rats & adolescent ASD-modeled rats	Inhibited cerebellar Purkinje cell loss; enhanced hippocampal BDNF expression	Ameliorated motor dysfunction and improved spatial cognition	[68,101]
Early-life/Pubertal VWR & Treadmill	1–4 weeks during juvenile/adolescent period	Preclinical rodent models: Juvenile/pubertal mice & developmental rat stages	Primed hippocampal neural epigenome; enhanced DG/CA3 synaptic transmission; modulated striatal HDAC activity	Facilitated memory consolidation and spatial learning	[85,115,120]
Running & HIIT in stress/immune models	Multi-week running or HIIT protocols	Preclinical rodent models: Postnatal immune activation & chronic unpredictable stress mice	Modulated KDM6B-regulated glial activation; shifted hippocampal microglia toward anti-inflammatory state via adiponectin/AdipoR1	Ameliorated mood-related and stress-induced behavioral deficits	[45,116]
Resistance & HIIT protocols (biomarker studies)	Acute resistance training (to/near failure) or HIIT + CoQ10	Healthy human adults & Preclinical AD rat model	Altered circulating neuroprotective biomarkers and EV subpopulations in adults; upregulated hippocampal FNDC5/irisin and BDNF in AD rats	Established peripheral exerkine/EV responsiveness (not yet tested in pediatric ASD/ADHD)	[124,127,128]
Structured aerobic & multicomponent exercise	30–60 min/session, 3–5 sessions/week, 6–12 weeks	Pediatric clinical evidence: RCTs and network meta-analyses in children/adolescents with ASD or ADHD	Direct central molecular/microglial endpoints not measured in pediatric trials	Significantly improved executive function, social interaction, and core ADHD/ASD symptoms	[60–65]

Table 2. *Cont*.

Exercise Modality	Protocol/Regimen	Experimental Model/Evidence Level	Molecular/Cellular Findings	Behavioral/Clinical Outcomes	References
Mobile-health personalized exercise	12-week tailored mHealth exercise rehabilitation program	Pediatric clinical RCT: Children with ADHD	Guided adaptive exercise progression based on clinical response	Significantly improved ADHD hyperactivity and core behavioral scores vs. control	[121]
Chronic aerobic exercise + Methylphenidate	6-week aerobic exercise program (3 sessions/week) combined with methylphenidate	Pediatric clinical trial: Adolescents with ADHD	Increased right frontal and temporal lobe activity measured by fMRI	Improved clinical ADHD symptoms and reduced perseverative errors beyond methylphenidate alone	[137]
Acute aerobic cycling bout	Single 25-min moderate-intensity cycling bout during cognitive testing	Pediatric clinical crossover study: Adolescents with ADHD	Modulated task-related prefrontal and parietal cortical hemodynamics measured by fNIRS during exercise	Enhanced acute executive control and cognitive performance during physical activity	[138]

Note: This table summarizes representative preclinical and clinical exercise regimens relevant to neuroimmune modulation, neuroplasticity, and behavioral outcomes in ASD and ADHD. It correlates different exercise modalities—including voluntary wheel running, treadmill aerobic exercise, resistance training, and high-intensity interval training (HIIT)—with their reported molecular, epigenetic, and cellular effects across specific brain regions. Crucially, the table separates preclinical rodent and adult physiological studies (which provide direct molecular and glial readouts) from pediatric clinical trials and network meta-analyses in youth with ASD and ADHD (which establish behavioral and executive function efficacy without direct central microglial measurements). Together, these stratified findings provide an evidence-graded basis for exploring candidate FITT-VP parameters and combined exercise–pharmacotherapy strategies in future pediatric clinical trials. Abbreviations: AD, Alzheimer's disease; AdipoR1, adiponectin receptor 1; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BDNF, brain-derived neurotrophic factor; CA1/CA3, cornu ammonis 1/3; CoQ10, coenzyme Q10; DG, dentate gyrus; EV, extracellular vesicle; fMRI, functional magnetic resonance imaging; FNDC5, fibronectin type III domain-containing protein 5; HDAC, histone deacetylase; HIIT, high-intensity interval training; KDM6B, lysine demethylase 6B; mHealth, mobile health; MIA, maternal immune activation; RCT, randomized controlled trial; VPA, valproic acid; VWR, voluntary wheel running; fNIRS, functional near-infrared spectroscopy.

6. Candidate Digital and Molecular Biomarkers: A Conceptual Proposal for Closed-Loop Exercise Monitoring in ASD and ADHD

6.1. Circulating Extracellular Vesicles and Exerkines as Candidate Liquid Biopsy Biomarkers

Circulating extracellular vesicles (EVs) and exosomes have been proposed as candidate blood-based biomarkers for exploring systemic exercise responsiveness in preclinical and adult studies [140,141]. In healthy human adults, high-intensity intermittent exercise triggers an acute release of tetraspanin-positive (CD81+/CD63+) EVs into the circulation [90], providing a potential temporal window for sampling acute peripheral exercise responses. Beyond surface markers, preclinical studies indicate that EV cargo—including microRNAs (miRNAs)—may participate in peripheral-to-central signaling [142], and specific miRNAs such as miR-146a and miR-21-5p have been hypothesized as candidate indicators of inflammatory pathway modulation. While mathematical modeling and profiling studies implicate miRNAs such as miR-146a in NF-κB-mediated inflammatory regulation and ASD pathophysiology [103,104,143], and aerobic exercise trials in late middle-aged adults at risk for Alzheimer's disease (26-week intervention) [76] as well as healthy young adults [75,77] have reported correlations between circulating cathepsin B (CTSB) increments and memory performance, these peripheral molecular markers have not yet been validated in pediatric ASD or ADHD exercise trials. These results suggest the potential of circulating extracellular vesicles and exercise-inducible proteins as a blood-based platform

for exploring dynamic molecular responses to exercise in real time [90,141]. Crucially, however, peripheral biomarker changes reflect systemic physiological responsiveness to exercise and should not be assumed to directly mirror central microglial remodeling or automatically predict improvements in complex clinical and behavioral outcomes in ASD or ADHD. Rather, combining exosomal miRNA profiling with candidate proteins such as CTSB represents an exploratory biomarker panel whose clinical predictive utility must be rigorously tested in future longitudinal pediatric trials [77,89,141].

6.2. Wearable Devices and AI-Driven Real-World Exercise Monitoring Systems

With the emergence of sophisticated wearable technologies and artificial intelligence (AI), objective measurements of physical activity in daily life have been transformed beyond the limitations of subjective questionnaires [144]. Tri-axial accelerometers combined with AI algorithms for posture recognition can accurately capture the times spent at moderate-to-vigorous physical activity (MVPA) levels by children in their daily activities, as well as the proportions of physical activities performed [145]. This method reduces recall bias and increases data fidelity in populations of children with neurodevelopmental disorders [146]. The latest smartwatch and patch-based heart rate monitors deliver real-time physiological data, including estimated oxygen consumption (VO2), heart rate recovery times after activity, and blood oxygen saturation levels [147]. These are indirect indicators of lactate production and metabolic stress and provide information on exercise intensity and recovery. Moreover, recent feasibility and case–control studies have begun applying machine learning models to multimodal wearable and physiological data to assist in symptom tracking and activity classification in adolescents with ADHD [144,146,148]. Although wearable sensors cannot directly measure central microglial states, we hypothesize that longitudinal tracking of physical activity, sleep–wake regularity, and autonomic recovery could serve as a non-invasive behavioral and physiological proxy to help clinicians monitor exercise adherence and tolerance in real-world settings [144,146,147]. If validated in future pediatric trials, such digital tools may eventually support timely adjustments to individualized exercise regimens.

6.3. Conceptual Proposal for a Multimodal Closed-Loop Exercise Framework: Feasibility, Ethical, and Algorithmic Challenges

Integrating candidate molecular biomarkers, standardized behavioral evaluations (e.g., SNAP-IV and ADOS), and continuous physiological streams from wearable sensors into an AI-assisted closed-loop framework represents an appealing future direction for personalized neurorehabilitation [149–151]. Crucially, however, such a multimodal closed-loop system currently constitutes a prospective conceptual proposal rather than an established or clinically validated platform in pediatric ASD or ADHD. Within this proposed architecture, longitudinal wearable metrics and periodic clinical ratings could theoretically be analyzed by machine learning models to construct individualized response profiles and guide gradual, clinician-supervised adjustments to FITT-VP parameters [150,151]. Preliminary clinical evidence supporting mobile-health-assisted personalization comes from a recent 12-week randomized controlled trial in children with ADHD, in which a tailored mobile-health exercise rehabilitation program significantly improved hyperactivity and core behavioral scores compared with empirical control routines [121]; nevertheless, that trial did not incorporate exosomal liquid biopsies or automated central neuroimmune tracking. The pathological features and corresponding candidate digital or molecular biomarkers proposed for monitoring the functional status of the muscle–microglia axis are systematically summarized in Table 3.

Before any multimodal closed-loop model can transition from a theoretical concept to clinical practice, substantial barriers regarding clinical feasibility, validation, data quality, algorithmic reliability, ethics, and healthcare accessibility must be addressed: (1) Feasibility

and invasiveness: Repeated venipuncture for profiling circulating exosomes or proteins (such as CTSB) is invasive, costly, and poorly tolerated by children with ASD or ADHD who exhibit severe sensory hypersensitivity and needle phobia [139], underscoring the need for truly non-invasive alternatives (e.g., validated salivary or sweat-based sensors) [152,153]. (2) Data quality and sensor compliance: In naturalistic settings, sensory hypersensitivity and tactile defensiveness frequently lead to wearable device removal or non-compliance [62,139], while motor stereotypies, hyperactivity, and rapid rest–exercise transitions introduce severe motion artifacts that degrade the accuracy of wrist-worn photoplethysmography (PPG) and accelerometry streams [154,155]. (3) Validation and algorithmic limitations: Machine learning models trained on small, homogeneous datasets are prone to overfitting, algorithmic bias, and poor generalizability across heterogeneous neurodevelopmental subtypes, ages, and medication states [144,148,151]. Moreover, peripheral biomarker fluctuations do not necessarily reflect central microglial states or predict clinical behavioral improvements. (4) Ethical, privacy, and regulatory challenges: Continuous digital phenotyping and biological profiling of minors with neurodevelopmental disabilities raise critical ethical concerns regarding pediatric assent, parental informed consent, cybersecurity, data ownership, and the risk of algorithmic stigmatization. (5) Economic cost and accessibility: Multi-omic liquid biopsies, specialized wearables, and AI infrastructure entail high financial and technical burdens that could exacerbate healthcare disparities, limiting real-world accessibility in routine community and school-based rehabilitation settings [135,144].

Table 3. Candidate molecular, neuroimaging, and digital biomarkers for monitoring exercise responses and neuroimmune status.

Candidate Biomarker/Metric	Biological Source & Detection Modality	Physiological/Mechanistic Role	Experimental Model/Current Evidence Level	Key Translational Limitations in Pediatric ASD/ADHD	References
Tetraspanin + EVs (CD81/CD63)	Peripheral blood plasma; single-vesicle analysis/liquid biopsy	Reflects acute exercise-induced extracellular vesicle release into circulation	Healthy human adults (high-intensity intermittent exercise) & preclinical models	Requires venipuncture; muscle-specific origin and CNS uptake kinetics remain unvalidated in children	[89,90,133]
Exosomal miRNAs (e.g., miR-146a)	Circulating EVs or peripheral tissue; small RNA sequencing/RT-qPCR	Modulates TLR4/IRAK1/TRAF6/NF-κB inflammatory signaling pathway	Preclinical stroke/AD models & human ASD stem cell/tissue profiling	Ratio as a real-time exercise biomarker in pediatric ASD/ADHD is hypothetical and requires clinical validation	[88,103,104,141,143]
Circulating Cathepsin B (CTSB)	Peripheral blood plasma/serum; ELISA/proteomic assay	Exercise-inducible protease associated with hippocampal neurogenesis and memory	Preclinical models & human adult exercise trials (young & late middle-aged adults at risk for AD)	Not yet validated in 10-week or longitudinal pediatric ASD/ADHD exercise trials; invasive blood draw	[75–77]
Central TSPO PET binding & post-mortem histology	Brain parenchyma; in vivo TSPO PET imaging & post-mortem tissue analysis	Reflects general neuroimmune/glial state in vivo (TSPO PET); synaptic pruning is assessed only in post-mortem tissue or preclinical models	Human young adults with ASD (post-mortem; inconsistent TSPO PET findings: increased, decreased, or unchanged) & preclinical models	TSPO is not microglia-specific (also expressed by astrocytes and endothelial cells) and cannot directly measure synaptic pruning; human PET findings are inconsistent, and radiation/sedation limit pediatric use	[47–54]

Table 3. *Cont*.

Candidate Biomarker/Metric	Biological Source & Detection Modality	Physiological/Mechanistic Role	Experimental Model/Current Evidence Level	Key Translational Limitations in Pediatric ASD/ADHD	References
Device-measured MVPA & posture	Wrist-/hip-worn tri-axial accelerometers (IMUs) with ML algorithms	Quantifies real-world physical activity volume, intensity distribution, and sedentary behavior	Pediatric cohorts (children and adolescents, including school-based and ADHD feasibility studies)	Tactile defensiveness, sensor removal, and atypical stereotyped movements can introduce signal noise	[62,135,144–146]
Heart rate recovery (HRR) & estimated VO_2	Wearable photoplethysmography (PPG)/chest-strap sensors + ML models	Non-invasive proxies for autonomic recovery, cardiorespiratory fitness, and metabolic load	Human adult and adolescent validation studies	PPG accuracy degrades during rapid rest–exercise transitions and high motion artifact	[147,148,154,155]

Note: This table provides an overview of candidate molecular, neuroimaging, and digital biomarkers proposed for evaluating exercise responsiveness and neuroimmune status in ASD and ADHD. It integrates blood-based liquid biopsy indicators (such as tetraspanin-positive EVs, exosomal miRNAs, and circulating CTSB) and central TSPO PET imaging with non-invasive physiological metrics captured by wearable sensors (including MVPA, heart rate recovery, and estimated VO2). For each metric, the table specifies the current experimental or clinical evidence level alongside key translational limitations in pediatric populations, such as venipuncture invasiveness, sensory-related non-compliance, and motion artifacts. Collectively, these multimodal indicators form the basis of a prospective conceptual proposal for closed-loop exercise monitoring, while emphasizing that peripheral biomarker changes do not automatically predict clinical symptom improvement. Abbreviations: AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CNS, central nervous system; CTSB, cathepsin B; ELISA, enzyme-linked immunosorbent assay; EVs, extracellular vesicles; HRR, heart rate recovery; IMUs, inertial measurement units; IRAK1, interleukin-1 receptor-associated kinase 1; miR-146a, microRNA-146a; ML, machine learning; MVPA, moderate-to-vigorous physical activity; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PET, positron emission tomography; PPG, photoplethysmography; RT-qPCR, reverse transcription quantitative polymerase chain reaction; TLR4, Toll-like receptor 4; TRAF6, tumor necrosis factor receptor-associated factor 6; TSPO, translocator protein; VO_2, oxygen consumption.

7. Translational Medicine Prospects and Key Barriers

7.1. Current Status Assessment and Limitations of Clinical Research Evidence

The field of clinical research on exercise interventions for ASD and ADHD has expanded rapidly, with a growing number of randomized controlled trials (RCTs) investigating behavioral efficacy [61,63]. Despite notable progress, most clinical studies rely on subjective behavioral ratings and symptom checklists, which—while clinically useful—provide limited insight into underlying neurobiological mechanisms [156]. There is a noticeable lack of research that uses biomarkers, such as neuroimaging or molecular assays, to explore the mediating pathways through which exercise affects neurodevelopmental disorders. Moreover, substantial methodological heterogeneity exists across pediatric exercise trials regarding sample sizes, blinding procedures, control group designs, exercise supervision, and self-reported adherence, contributing to variable effect sizes across studies [62,64,65,156].

Crucially, directly extrapolating mechanistic findings from preclinical models (such as microglial remodeling and synaptic pruning rescue) to human neurodevelopment faces major translational barriers [39,156]. First, binary M1/M2 classifications fail to capture the complex, overlapping transcriptional states of human microglia [43]. Second, quantitative proteomic atlases demonstrate substantial interspecies differences in the abundance of BBB transporters, receptors, and tight junction proteins between rodents and primates [157], and preclinical studies frequently employ supraphysiological recombinant exerkine doses that far exceed endogenous post-exercise plasma or CSF increments in humans [39,72]. Because paired plasma-to-CSF pharmacokinetic studies and in vivo microglial imaging (such as

TSPO PET) following exercise interventions are lacking in pediatric cohorts, it remains unknown whether normal, clinically feasible exercise in children and adolescents can produce sufficient central concentrations of irisin and other exerkines to meaningfully modulate microglial activity in the human brain. Therefore, it is now necessary to conduct well-designed mechanistic clinical trials that integrate multiple types of biomarkers—neuroimaging, peripheral molecular signatures, and neurophysiological measures—to verify the biological effects of exercise intervention and establish a rigorous evidence base for personalized therapeutic strategies [36,158].

7.2. Evaluation of Interference from Age Stratification, Sex Differences, and Comorbidities on Intervention Efficacy

Accumulating evidence has highlighted that the heterogeneous nature of ASD and ADHD populations presents major issues in the design and implementation of exercise-based interventions, as age, sex, and comorbid conditions may be modulatory factors in therapeutic outcome [62]. Adolescence is a critical developmental period characterized by dynamic fluctuations in sex steroid hormones—particularly across the female menstrual cycle—that modulate responsiveness to exercise-induced molecular mediators such as myokines and neurotrophic factors. This cyclical hormonal environment may explain why the effectiveness of exercise interventions may vary across the menstrual cycle, and future studies of exercise interventions in female adolescents should consider adding menstrual phase tracking and hormone profiles to guide the optimal timing and dosing of exercise interventions [107,159]. Furthermore, rigorous clinical safety protocols are paramount when prescribing exercise for youth with ASD and ADHD due to the high prevalence of neurological, motor, cognitive, and sensory comorbidities [62,139,160]. First, for children and adolescents with co-occurring epilepsy (which is prevalent in ASD), exercise recommendations should follow established International League Against Epilepsy (ILAE) clinical guidance, which emphasizes that physical activity and sports are generally safe and beneficial for individuals with epilepsy and that unnecessary blanket restrictions should be avoided; following an individualized risk assessment (considering seizure control, seizure type, and supervision needs, particularly for water- or height-related activities), youth with epilepsy can safely participate in physical activities with appropriate medical clearance and a seizure action plan [161]. Second, for individuals with significant intellectual disability or sensory intolerance (e.g., auditory, tactile, or proprioceptive over-responsivity), high-intensity or chaotic group settings can provoke severe distress and behavioral dysregulation [129,134]. These populations require predictable, low-sensory-stimulation environments, visual schedules, simplified step-by-step instructions, and gradual intensity titration; for individuals unable to tolerate active aerobic regimens, low-impact or passive modalities such as supervised whole-body vibration therapy have been explored in preclinical and preliminary studies as potential alternatives [162,163]. Third, in youth with ADHD or ASD who exhibit developmental coordination deficits, postural instability, or high impulsivity, the elevated baseline risk of unintentional musculoskeletal and head injuries [131,160] necessitates structured supervision, simplified motor tasks, protective equipment, and avoidance of high-collision activities.

Equally critical is the management of energy balance at the intersection of stimulant pharmacotherapy and pubertal growth. Physiological calorimetry studies demonstrate that central nervous system stimulants prescribed for ADHD directly alter daily energy balance by modifying basal metabolic rate, total energy expenditure, and spontaneous physical activity levels [164], while clinically, stimulant pharmacotherapy is also well recognized to cause appetite suppression that can reduce daytime caloric intake [5,9]. Importantly, adolescence (particularly during the pubertal growth spurt) is characterized by substantially

increased basal metabolic requirements and heightened energy and protein demands to support rapid somatic growth, bone mineral accrual, and brain maturation. Adding high-volume or high-intensity exercise to a medicated adolescent experiencing stimulant-induced appetite suppression can precipitate a state of relative energy deficiency, potentially impairing linear growth, disrupting pubertal endocrine axes, increasing musculoskeletal injury risk, and blunting skeletal muscle anabolic and myokine responses. Therefore, pediatric exercise interventions must incorporate routine monitoring of body mass index (BMI) percentiles, growth velocity, and dietary intake, alongside practical nutritional strategies—such as scheduling nutrient-dense meals prior to morning stimulant administration and after evening medication wear-off, and moderating exercise volume during periods of inadequate caloric intake—to safeguard adolescent development [139,164].

7.3. Prospective Perspectives on Exercise as a Fundamental Adjuvant in Combination with Pharmacological and Non-Pharmacological Therapies

Emerging clinical and preclinical evidence suggests that structured physical exercise may serve as a valuable non-pharmacological adjuvant alongside standard pharmacological and behavioral therapies in ASD and ADHD [137,138,156]. Pharmacologically, first-line stimulants for ADHD such as methylphenidate act primarily presynaptically by blocking dopamine and norepinephrine transporters (DAT and NET) to increase synaptic monoamine availability, whereas exercise modulates overlapping frontostriatal and catecholaminergic networks, neurotrophic support [105], and neuroimmune homeostasis. Clinically, a randomized trial in adolescents with ADHD demonstrated that adding a 6-week aerobic exercise program to methylphenidate pharmacotherapy yielded greater improvements in clinical symptoms, perseverative errors, and right frontotemporal brain activity (on fMRI) than methylphenidate alone [137], while an acute 25-min cycling bout independently enhanced executive control and task-related cortical activation (on fNIRS) in youth with ADHD [138]. Although these clinical trials do not demonstrate direct exercise-induced modifications of postsynaptic drug-receptor binding, they support the clinical rationale for investigating complementary multimodal interventions combining exercise with standard pharmacotherapy. Preclinical evidence further suggests that exercise can attenuate systemic and central inflammation and promote a homeostatic, anti-inflammatory microglial state, which may help alleviate common comorbidities such as anxiety and gastrointestinal dysfunction frequently associated with these conditions [15]. Upstream modification of the neuroimmune and synaptic environment by exercise provides favorable conditions for downstream targeted intervention, and a stratified treatment approach that aims for pathological repair rather than mere symptom relief has been proposed [15]. Framing exercise as a foundational adjunctive strategy aligns with the goals of personalized medicine, offering a conceptual basis for future trials investigating combined exercise, pharmacological, and behavioral interventions in ASD and ADHD [15,36,158,162].

8. Conclusions and Perspectives

In this review, we have proposed the developmental muscle–microglia axis as a hypothesis-generating conceptual framework linking unidirectional humoral signaling from contracting skeletal muscle to central neuroimmune modulation in ASD and ADHD. Synthesizing predominantly preclinical evidence, we highlight how exercise-induced factors—including irisin, CTSB, lactate, and exosomal miRNAs—may cross or signal across the blood–brain barrier to attenuate pro-inflammatory microglial reactivity and support activity-dependent synaptic remodeling. Rather than operating as a simplistic binary M1-to-M2 switch, these peripheral signals are hypothesized to interact with intrinsic neuronal activity and complex developmental pruning programs across the distinct neuroimmune

landscapes of ASD and ADHD. A central hypothesis of this framework is that the pubertal transition represents a period of heightened neuroimmune and endocrine plasticity during which surging sex steroids may interact with exercise-induced pathways and neuroepigenetic regulation. While these developmental insights offer a theoretical rationale for exploring phenotype-adapted exercise strategies (under the FITT-VP model) and candidate digital/molecular monitoring tools, specific biochemical thresholds, Tanner-stage adjustments, and multimodal AI closed-loop systems currently remain conceptual proposals and candidate parameters rather than validated clinical protocols. The review acknowledges current knowledge gaps and clearly outlines future research needs. It proposes mechanistic human studies with molecular endpoints, including synaptic proteins and neuroinflammatory markers, alongside standardized behavioral scales to validate the proposed pathway. Future pediatric trials must establish age- and sex-specific dose–response relationships, account for stimulant medication–energy balance interactions during adolescent growth, and enforce rigorous clinical safety adaptations for comorbid epilepsy, sensory intolerance, and motor coordination deficits. Through such multidisciplinary validation, exercise-based interventions can be progressively refined to support neurodevelopmental health in youth with ASD and ADHD.

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Abbreviations

The following abbreviations are used in this manuscript:

ASD	Autism spectrum disorder
ADHD	Attention deficit hyperactivity disorder
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
FITT-VP	Frequency, Intensity, Time, Type, Volume, Progression
HIIT	High-intensity interval training
AMPK/NF-κB	AMP-activated protein kinase/nuclear factor kappa-light-chain-enhancer of activated B cells
PGC-1α/FNDC5	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha/Fibronectin type III domain-containing protein 5
CTSB/GPR81	Cathepsin B/G protein-coupled receptor 81
AI	Artificial intelligence
mTORC1/mTORC2	Mechanistic target of rapamycin complex 1/2
PI3K/AKT	Phosphoinositide 3-kinase/protein kinase B
IGF-1	Insulin-like growth factor 1
TSC1/2	Tuberous sclerosis complex 1/2
RHEB	Ras homolog enriched in brain

LTP	Long-term potentiation
PSD-95	Postsynaptic density protein 95
VPA	Valproic acid
MVPA	Moderate-to-vigorous physical activity
ADOS/SNAP-IV	Autism Diagnostic Observation Schedule/Swanson, Nolan, and Pelham-IV Rating Scale
TSPO PET	Translocator protein positron emission tomography
EV	Extracellular vesicle

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