Integrative Neurophysiological Mechanisms Linking Vitamin D, Exercise-Induced Plasticity, and Brain-Derived Neurotrophic Factor in Autism Spectrum Disorder

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Abstract

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent impairments in social communication and the presence of restricted and repetitive behaviors, with a complex etiology involving genetic susceptibility, environmental influences, and disrupted neurophysiological processes. Despite extensive research, the underlying biological mechanisms of ASD remain incompletely understood, and no definitive biomarkers or curative therapies are currently available. Increasing evidence suggests that alterations in brain development, synaptic plasticity, neurotransmitter balance, oxidative stress, and neuroimmune regulation play central roles in ASD pathophysiology. Within this context, vitamin D signaling, brain-derived neurotrophic factor (BDNF), and physical exercise have emerged as key modulators of neurodevelopmental and neurophysiological homeostasis.

Vitamin D, traditionally recognized for its role in calcium and bone metabolism, is now known to exert pleiotropic effects in the central nervous system through widespread expression of the vitamin D receptor and local activation of vitamin D metabolites in brain tissue. These actions include regulation of gene transcription, modulation of oxidative stress and neuroinflammation, influence on neurotransmitter systems, and support of neuronal survival and differentiation. BDNF is a critical neurotrophin involved in neuronal growth, synaptic formation, dendritic spine remodeling, and activity-dependent plasticity, processes that are frequently altered in ASD. Abnormal BDNF signaling has been implicated in disrupted synaptic connectivity and impaired learning and memory in individuals with ASD. Physical exercise represents a non-pharmacological intervention capable of inducing robust neurophysiological adaptations, including enhanced synaptic plasticity, improved neurotransmitter regulation, reduced oxidative stress, and upregulation of BDNF expression through both central and peripheral mechanisms.

The aim of this review is to integrate current evidence on the neurophysiological mechanisms linking vitamin D biology, exercise-induced neural plasticity, and BDNF signaling in ASD. By synthesizing findings from molecular, cellular, animal, and clinical studies, this review highlights convergent pathways through which these factors may interact to influence brain development and function in ASD. Understanding these interconnected mechanisms may help explain the variability in clinical outcomes observed with vitamin D supplementation and exercise interventions, and underscores the need for individualized, mechanism-based approaches. Ultimately, clarifying the integrative roles of vitamin D, exercise, and BDNF may contribute to the development of more targeted preventive and adjunctive strategies aimed at improving neurodevelopmental outcomes and quality of life in individuals with ASD.

Keywords: *Vitamin D, Exercise-Induced Plasticity, Brain-Derived Neurotrophic Factor, Autism Spectrum Disorder*

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by early-onset deficits in social communication and interaction, accompanied by restricted and repetitive patterns of behavior, interests, or activities. The clinical presentation of ASD is highly heterogeneous, encompassing a wide range of cognitive abilities, behavioral profiles, and comorbid medical conditions. Epidemiological data indicate a rising global prevalence, emphasizing ASD as a major public health concern with substantial individual, familial, and societal impact. Despite advances in diagnostic criteria and early screening strategies, the biological basis of ASD remains incompletely defined, and current diagnostic approaches rely primarily on behavioral phenotyping rather than objective biological markers [1].

From a medical physiology perspective, ASD is increasingly understood as a disorder of altered neurodevelopmental and neurophysiological processes rather than a condition attributable to a single causal factor. Converging evidence highlights disruptions in synaptic development, excitation–inhibition balance, neuronal connectivity, and activity-dependent plasticity during critical periods of brain maturation. Genetic susceptibility interacts with environmental and epigenetic influences to shape these physiological processes, leading to long-lasting alterations in neural circuit function. This integrative view aligns with findings that diverse genetic mutations and environmental risk factors often converge on shared molecular pathways regulating synaptic function, transcriptional control, and neuroplasticity in ASD [2].

Vitamin D has emerged as a biologically plausible modulator of neurodevelopment and brain homeostasis due to the widespread distribution of vitamin D receptors and vitamin D–metabolizing enzymes within the central nervous system. Beyond its classical endocrine role, vitamin D participates in gene regulation, antioxidant defense, immune modulation, and neurotransmitter synthesis, all of which are processes implicated in ASD pathophysiology. Epidemiological and experimental studies have suggested associations between prenatal or early-life vitamin D insufficiency and increased ASD risk, although causality remains debated. These observations position vitamin D as a potential contributor to neurophysiological vulnerability during brain development [3].

Brain-derived neurotrophic factor (BDNF) represents a key molecular mediator of neuronal survival, synaptic formation, and activity-dependent plasticity, functions that are fundamental to learning, memory, and adaptive behavior. Alterations in BDNF signaling have been reported in ASD and are thought to contribute to atypical synaptic connectivity and impaired neural network refinement. Importantly, BDNF is highly responsive to environmental and behavioral stimuli, including physical activity, making it a central link between external interventions and intrinsic neurophysiological adaptations. Its role as a convergence point for genetic, metabolic, and activity-dependent signals underscores its relevance in ASD research [4].

Physical exercise has gained increasing attention as a safe, low-cost, and accessible intervention capable of inducing widespread neurophysiological benefits. Exercise modulates neurotransmitter systems, enhances synaptic and structural plasticity, reduces oxidative stress and neuroinflammation, and robustly upregulates BDNF expression. In individuals with ASD, exercise interventions have been associated with improvements in core symptoms, motor skills, behavior regulation, and quality of life, although outcomes vary considerably. From a physiological standpoint, exercise represents a potent activity-dependent stimulus that may partially compensate for disrupted plasticity mechanisms in ASD [5].

Despite growing interest in vitamin D supplementation and exercise-based interventions for ASD, the existing literature is fragmented, and findings are often inconsistent. Many studies examine these factors in isolation, without integrating their shared molecular targets or considering developmental timing,

individual variability, and underlying neurophysiological states. The central research gap lies in the lack of a unifying framework that explains how vitamin D signaling, exercise-induced plasticity, and BDNF pathways interact within the context of ASD neurobiology. Therefore, the aim of this review is to synthesize current evidence from a neurophysiological perspective, integrating molecular, cellular, and systems-level findings to clarify how these interconnected mechanisms may collectively influence brain development and function in autism spectrum disorder [6].

Autism Spectrum Disorder as a Neurophysiological Disorder

Autism spectrum disorder is increasingly recognized as a disorder of altered neurophysiological development rather than a condition defined solely by behavioral manifestations. Normal brain maturation requires precise temporal coordination of neuronal proliferation, migration, differentiation, synaptogenesis, and synaptic pruning, processes that are highly sensitive to genetic and environmental influences. In ASD, disturbances in these tightly regulated mechanisms lead to atypical neural circuit formation, particularly within networks governing social cognition, communication, and executive control. These early physiological deviations establish a foundation for the persistent functional and behavioral characteristics observed throughout development and into adulthood [7].

Building on these developmental disturbances, abnormal synaptic organization and plasticity have emerged as central neurophysiological features of ASD. Numerous ASD-associated genes encode synaptic proteins involved in neurotransmitter release, receptor trafficking, and postsynaptic scaffolding, suggesting that synaptic dysfunction represents a point of convergence for diverse etiological factors. Disruption of synapse formation, stabilization, or elimination interferes with experience-dependent circuit refinement, limiting the brain's ability to adapt to environmental and social stimuli. Consequently, impaired synaptic plasticity may underlie deficits in learning, memory, and adaptive behavior commonly seen in ASD [8].

As synaptic dysfunction progresses, imbalance between excitatory and inhibitory neurotransmission becomes increasingly apparent. The maintenance of excitation–inhibition balance is essential for information processing, network stability, and cognitive flexibility. In ASD, reduced inhibitory GABAergic signaling and/or excessive glutamatergic activity can shift this balance toward hyperexcitability. Such physiological alterations may amplify neural noise, disrupt signal integration, and contribute to core symptoms as well as frequent comorbidities, including epilepsy, anxiety, and sensory processing abnormalities [9].

These functional alterations are further supported by evidence of atypical brain growth patterns in ASD. Neuroimaging studies have identified early brain overgrowth during critical developmental periods, particularly affecting frontal and prefrontal cortical regions. This phenomenon is thought to result from dysregulated cell cycle control, excessive neuronal proliferation, reduced programmed cell death, or impaired synaptic pruning. From a neurophysiological perspective, abnormal regulation of these developmental processes may compromise cortical organization and network efficiency, reinforcing long-term functional impairments [10].

At the molecular level, the observed neurophysiological abnormalities reflect convergence on disrupted gene regulatory mechanisms. Although ASD is genetically heterogeneous, many risk genes converge on pathways controlling transcription, chromatin remodeling, epigenetic regulation, and activity-dependent protein synthesis. These mechanisms are essential for synaptic maintenance and plasticity, allowing neural circuits to respond dynamically to developmental and environmental demands. When these regulatory systems are impaired, the capacity for adaptive neuroplasticity is reduced, increasing vulnerability to persistent circuit dysfunction [11].

Taken together, these interconnected developmental, synaptic, and molecular alterations support a unified view of ASD as a disorder of impaired neurophysiological regulation. Genetic susceptibility and environmental influences interact to disrupt core physiological processes that govern neural connectivity, plasticity, and homeostasis. This integrative framework provides a critical bridge to the subsequent sections of this review, which examine how vitamin D signaling, brain-derived neurotrophic factor, and exercise-induced plasticity intersect with these shared neurophysiological pathways and may

collectively influence brain function in autism spectrum disorder [12].

Vitamin D Neurobiology and Brain Homeostasis

Following the characterization of ASD as a disorder of impaired neurophysiological regulation, increasing attention has focused on biological modulators capable of influencing brain development and functional plasticity. Vitamin D has emerged as one such modulator due to its ability to act as a neuroactive steroid hormone rather than merely a nutrient involved in skeletal metabolism. Vitamin D is synthesized endogenously in the skin following ultraviolet B exposure and undergoes sequential hydroxylation in the liver and kidneys to form its active metabolite, 1,25-dihydroxyvitamin D_3, which exerts biological effects through binding to the vitamin D receptor (VDR). This endocrine–paracrine system provides a physiological basis for vitamin D action beyond classical calcium homeostasis [13].

The relevance of vitamin D to brain physiology is supported by the widespread expression of VDR and vitamin D–metabolizing enzymes within the central nervous system. VDRs are present in neurons, glial cells, and neural progenitor cells across multiple brain regions, including the cortex, hippocampus, and cerebellum—areas critically involved in cognition, learning, and social behavior. This distribution suggests that vitamin D signaling participates directly in neurodevelopmental processes rather than acting indirectly through systemic mechanisms alone. Such localization provides a mechanistic foundation for linking vitamin D insufficiency to altered brain maturation and vulnerability to neurodevelopmental disorders [14].

During brain development, vitamin D contributes to neuronal differentiation, axonal growth, and synaptic formation, processes that are tightly regulated to ensure proper circuit assembly. Experimental studies have demonstrated that vitamin D influences calcium signaling, neurotransmitter synthesis, and cytoskeletal dynamics, all of which are essential for neuronal connectivity and plasticity. Disruption of these processes during sensitive developmental periods may result in long-lasting alterations in neural network organization, aligning with the early-onset and persistent nature of ASD-related neurophysiological abnormalities [15].

Beyond development, vitamin D plays a critical role in maintaining brain homeostasis throughout life. It modulates oxidative stress responses by enhancing antioxidant defenses, regulates immune activity within the central nervous system, and influences mitochondrial function. These actions are particularly relevant to ASD, where increased oxidative stress, neuroinflammation, and mitochondrial dysfunction have been repeatedly reported. From a physiological standpoint, vitamin D deficiency may lower the brain's resilience to metabolic and inflammatory stressors, thereby exacerbating underlying neurodevelopmental vulnerabilities [16].

Vitamin D also exerts significant effects on gene regulation through its function as a transcriptional regulator. Upon activation, the VDR forms a heterodimer with the retinoid X receptor and binds to vitamin D response elements in the promoter regions of target genes. This mechanism allows vitamin D to influence the expression of hundreds of genes involved in cell cycle regulation, apoptosis, synaptic signaling, and immune modulation. Such broad genomic influence provides a plausible link between vitamin D status and the convergent molecular pathways implicated in ASD neurobiology [17].

Collectively, these neurobiological actions position vitamin D as a key physiological factor capable of modulating multiple processes disrupted in ASD, including neurodevelopment, synaptic plasticity, redox balance, and immune regulation. Understanding vitamin D within this integrative neurophysiological framework sets the stage for examining its interactions with ASD-relevant gene networks and signaling pathways, which will be explored in the following section [18].

Vitamin D, Gene Regulation, and ASD-Relevant Molecular Pathways

Building on the neurobiological role of vitamin D in maintaining brain homeostasis, its function as a regulator of gene expression has gained particular relevance in the context of autism spectrum disorder. Vitamin D acts as a transcriptional modulator through activation of the vitamin D receptor, which directly influences gene networks involved in neurodevelopmental timing, synaptic organization, and cellular stress responses. This genomic role is especially important in ASD, where heterogeneous genetic alterations often converge on shared molecular pathways rather than single gene defects [19].

Large-scale genomic and transcriptomic analyses have demonstrated that a substantial proportion of ASD-associated genes are sensitive to vitamin D signaling. Many of these genes are involved in synaptic function, neuronal differentiation, immune regulation, and redox balance, suggesting that vitamin D may act as an upstream modulator of multiple ASD-relevant pathways. From a physiological perspective, insufficient vitamin D signaling during critical developmental windows may alter the expression of these genes, thereby amplifying the functional impact of underlying genetic susceptibility [20].

Epigenetic regulation represents another key interface between vitamin D biology and ASD pathophysiology. Vitamin D signaling has been shown to influence DNA methylation, histone modification, and chromatin accessibility, processes that govern long-term patterns of gene expression without altering the underlying DNA sequence. Epigenetic dysregulation is increasingly recognized in ASD, particularly in genes involved in synaptic plasticity and neuronal connectivity. Altered vitamin D availability may therefore contribute to persistent transcriptional changes that affect brain development and functional maturation [21].

In addition to transcriptional and epigenetic regulation, vitamin D has been implicated in the maintenance of genomic stability. Several vitamin D–dependent genes encode proteins involved in DNA repair and cell cycle control, mechanisms that are essential for protecting neural progenitor cells from excessive mutation burden during rapid brain growth. Impaired regulation of these pathways may increase vulnerability to neurodevelopmental abnormalities, providing a physiological link between vitamin D insufficiency and altered neurodevelopmental trajectories observed in ASD [22].

Apoptotic signaling pathways further illustrate the complexity of vitamin D–gene interactions in the developing brain. Vitamin D influences the expression of pro- and anti-apoptotic proteins that regulate programmed cell death, a process necessary for proper neuronal pruning and circuit refinement. Dysregulation of apoptosis has been reported in experimental models of ASD, where excessive neuronal survival or inappropriate cell loss can disrupt network organization. Vitamin D imbalance may therefore contribute to abnormal neuronal density and connectivity through altered apoptotic control [23].

Taken together, these findings support a model in which vitamin D functions as a broad genomic and epigenomic regulator capable of shaping ASD-relevant molecular pathways. Rather than acting as a singular causal factor, vitamin D appears to modulate the expression and stability of gene networks that govern neurodevelopment, synaptic plasticity, and cellular resilience. This integrative role provides a mechanistic bridge to the next section, which examines how vitamin D–mediated regulation intersects with oxidative stress and neuroinflammatory processes commonly observed in autism spectrum disorder [24].

Vitamin D, Oxidative Stress, Neuroinflammation, and Mitochondrial Physiology in ASD

Extending from vitamin D's genomic influence on neurodevelopmental pathways, a major mechanistic bridge to ASD pathophysiology is its role in controlling redox balance and inflammatory tone within the brain. Oxidative stress is repeatedly reported in ASD and is physiologically important because reactive oxygen species can impair neuronal maturation, synaptic signaling, and membrane integrity—especially during early life when antioxidant defenses may be relatively limited. When oxidative burden exceeds buffering capacity, the developing brain becomes more vulnerable to maladaptive circuit formation and long-term functional dysregulation consistent with ASD phenotypes [25].

Neuroinflammation frequently coexists with oxidative stress in ASD, forming a self-reinforcing cycle that can amplify neural injury and disrupt plasticity. Microglia and astrocytes, which normally support synaptic pruning and homeostasis, can adopt pro-inflammatory states that alter synaptic remodeling and neurotransmission. This is highly relevant physiologically because abnormal inflammatory signaling during sensitive developmental windows can shift the balance of synapse formation and elimination, contributing to atypical connectivity and altered excitation–inhibition dynamics described in ASD [26].

At the biochemical level, disturbances in glutathione (GSH) metabolism are a recurring feature across oxidative stress models of ASD, and this is a central point where vitamin D may exert protective effects. GSH is critical for detoxification and maintenance of cellular redox potential, particularly in neurons with high metabolic demands. Vitamin D has been reported to increase cellular antioxidant capacity,

including mechanisms that support glutathione availability, thereby potentially improving neural resilience against oxidative damage that might otherwise interfere with synaptic development and circuit stability [27].

Mitochondrial physiology provides an additional integrative layer, because mitochondria regulate both energy production and redox signaling—two functions central to synaptic activity and neurodevelopment. In ASD, mitochondrial dysfunction is often discussed alongside oxidative stress because impaired electron transport can increase reactive oxygen species generation and reduce ATP availability needed for synaptic transmission, axonal transport, and activity-dependent plasticity. Physiologically, this combination can limit the brain's capacity to sustain adaptive remodeling, especially under additional stressors such as inflammation or nutrient insufficiency [28].

Vitamin D also intersects with immune regulation in ways that may be neuroprotective when inflammatory signaling becomes excessive. VDR-mediated pathways can influence cytokine production profiles, suppressing pro-inflammatory mediators while supporting anti-inflammatory signaling, which is important for preventing persistent immune activation that can disrupt neurodevelopment and synaptic function. This immunomodulatory dimension is particularly relevant in ASD where sustained inflammatory bias may contribute to behavioral symptoms and comorbidities through effects on neural circuit excitability and plasticity [29].

Overall, oxidative stress, neuroinflammation, and mitochondrial dysfunction represent tightly connected physiological domains that can shape ASD neurobiology, and vitamin D signaling plausibly modulates all three through gene regulation, antioxidant support, and immune control. This convergence helps explain why vitamin D has remained of interest despite mixed clinical outcomes, since effects may depend on baseline redox-inflammatory status, developmental timing, and individual biology. With this redox-immune framework established, the next section will extend the model toward vitamin D effects on neurotransmitter systems and circuit-level excitation–inhibition regulation in ASD [30].

Vitamin D and Neurotransmitter Systems in Autism Spectrum Disorder

Following the discussion of oxidative stress and neuroinflammation, regulation of neurotransmitter systems represents a critical downstream neurophysiological domain through which vitamin D may influence brain function in autism spectrum disorder. Neurotransmitters govern synaptic communication, network synchronization, and plasticity, all of which are essential for social behavior, cognition, and emotional regulation. Disruptions in these systems are consistently reported in ASD and are closely linked to the excitation–inhibition imbalance and circuit-level dysfunction described earlier [31].

Gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain, plays a central role in shaping cortical excitability and developmental circuit refinement. Deficient GABAergic signaling has been implicated in ASD and is thought to contribute to sensory hypersensitivity, seizures, and impaired information processing. Vitamin D is involved in regulating enzymes responsible for neurotransmitter synthesis and may influence GABAergic tone, suggesting that insufficient vitamin D signaling could exacerbate inhibitory deficits and promote cortical hyperexcitability during development [32].

Glutamatergic neurotransmission, which provides the primary excitatory drive in the central nervous system, is also affected in ASD. Alterations in glutamate receptor expression, synaptic localization, and signaling strength can impair synaptic plasticity and learning mechanisms. Vitamin D has been shown to modulate calcium homeostasis and NMDA receptor–related signaling pathways, processes that are fundamental for glutamate-mediated synaptic transmission. Dysregulation of these pathways may therefore contribute to impaired experience-dependent plasticity and altered cognitive function in ASD [33].

Monoaminergic systems, including serotonergic and dopaminergic pathways, further illustrate the breadth of neurotransmitter involvement in ASD. These systems regulate mood, motivation, reward processing, and social behavior, and abnormalities in monoamine signaling have been associated with repetitive behaviors and emotional dysregulation in ASD. Vitamin D-associated mechanisms have been

linked to the regulation of monoamine synthesis and turnover, providing a physiological basis for its potential influence on behavioral and affective domains relevant to autism [34].

Oxytocinergic signaling, which plays a key role in social bonding and affiliative behaviors, has also been implicated in ASD. Although the relationship between vitamin D and oxytocin pathways is less well defined, indirect modulation through gene regulation, inflammatory control, and synaptic plasticity may influence oxytocin-mediated social circuits. This highlights the interconnected nature of neurotransmitter systems and the importance of considering vitamin D effects within a broader neurophysiological network rather than in isolation [35].

In summary, vitamin D intersects with multiple neurotransmitter systems that are central to ASD neurobiology, including inhibitory, excitatory, and modulatory pathways. By influencing neurotransmitter synthesis, receptor function, and synaptic signaling, vitamin D may shape excitation–inhibition balance and circuit stability during critical developmental periods. This neurotransmitter-focused perspective provides a natural transition to the next section, which examines brain-derived neurotrophic factor as a central integrator of synaptic plasticity and activity-dependent signaling in autism spectrum disorder [36].

Brain-Derived Neurotrophic Factor as a Central Integrator in ASD Neurophysiology

Transitioning from neurotransmitter regulation to activity-dependent plasticity, brain-derived neurotrophic factor (BDNF) occupies a central position in the neurophysiological framework of autism spectrum disorder. BDNF is a key neurotrophin that supports neuronal survival, differentiation, and synaptic maturation throughout development and adulthood. Its actions are mediated primarily through tropomyosin receptor kinase B (TrkB), activation of which initiates intracellular signaling casc essential for synaptic strength and circuit refinement. Given that ASD is characterized by disrupted connectivity and plasticity, BDNF has emerged as a critical molecular node linking genetic vulnerability to functional neural outcomes [37].

During neurodevelopment, BDNF regulates axonal growth, dendritic arborization, and synapse formation, processes that determine the architecture and efficiency of neural networks. Precise temporal and spatial control of BDNF expression is required to ensure appropriate synaptic stabilization and elimination during critical periods. Dysregulation of BDNF signaling during these stages may result in aberrant circuit wiring, contributing to the early-emerging behavioral and cognitive features of ASD. From a physiological standpoint, altered BDNF availability can shift developmental trajectories toward persistent network inefficiency [38].

At the synaptic level, BDNF plays a pivotal role in modulating both structural and functional plasticity. It enhances synaptic transmission by regulating neurotransmitter release, receptor trafficking, and postsynaptic density organization, while also promoting dendritic spine formation and maturation. These effects are essential for long-term potentiation and learning-related plasticity. In ASD, where synaptic abnormalities and impaired learning mechanisms are common, altered BDNF signaling may contribute directly to deficits in experience-dependent neural adaptation [39].

Evidence from clinical and experimental studies further supports the involvement of BDNF in ASD. Elevated peripheral BDNF levels have been reported in some individuals with ASD, although interpretation of these findings remains complex due to differences between central and peripheral sources. Physiologically, such alterations may reflect compensatory responses to synaptic dysfunction or disrupted feedback mechanisms within neurotrophic signaling pathways. These observations underscore the importance of understanding BDNF dynamics rather than relying solely on static measurements [40].

BDNF also interacts closely with neurotransmitter systems previously discussed, particularly glutamatergic and GABAergic pathways. By modulating NMDA receptor function and inhibitory interneuron development, BDNF contributes to the maintenance of excitation–inhibition balance within neural circuits. Disruption of this interaction may exacerbate cortical hyperexcitability and impair network synchronization, reinforcing core neurophysiological abnormalities associated with ASD [41].

Importantly, BDNF serves as a convergence point for environmental and behavioral influences on brain

plasticity. Factors such as sensory experience, cognitive engagement, and physical activity robustly regulate BDNF expression, linking external stimuli to internal neurophysiological adaptation. This property positions BDNF as a critical mediator through which interventions may influence ASD-related brain dysfunction. The following section will build on this concept by examining how physical exercise acts as a potent stimulus for BDNF upregulation and synaptic remodeling in the context of autism spectrum disorder [42].

Exercise-Induced Neuroplasticity and Structural Remodeling in Autism Spectrum Disorder

Following the central role of brain-derived neurotrophic factor in activity-dependent plasticity, physical exercise emerges as a powerful physiological stimulus capable of modulating neural structure and function. Exercise is increasingly recognized not only for its systemic health benefits but also for its capacity to induce robust neuroplastic adaptations within the central nervous system. These adaptations include changes in synaptic density, dendritic spine morphology, and neural network efficiency, processes that are particularly relevant in ASD where impaired plasticity and atypical connectivity are core features [43].

At the structural level, exercise has been shown to promote synaptogenesis and dendritic spine formation in multiple brain regions involved in learning, memory, and motor control. Animal studies indicate that sustained physical activity enhances spine density and synaptic stability, contributing to improved circuit integration and behavioral performance. Although direct visualization of such changes in humans remains technically challenging, these findings provide a physiological framework for understanding how exercise may compensate for synaptic deficits observed in ASD models [44].

Molecular signaling pathways activated by exercise further support its role in modulating neuroplasticity. Exercise stimulates intracellular cascades involved in protein synthesis, cytoskeletal remodeling, and synaptic maintenance, including pathways regulated by mechanistic target of rapamycin (mTOR). Dysregulation of mTOR-dependent signaling has been reported in certain ASD models, where reduced protein synthesis impairs synaptic development. Exercise-induced activation of these pathways may therefore help restore synaptic balance and support adaptive remodeling within affected neural circuits [45].

Exercise also influences myelination and axonal integrity, which are essential for efficient neural communication. Enhanced axonal myelination improves signal conduction velocity and synchrony across neural networks, supporting coordinated cognitive and motor function. In ASD, where white matter abnormalities and altered connectivity patterns have been described, exercise-induced improvements in axonal structure may contribute to more efficient information processing and behavioral regulation [46].

Beyond structural remodeling, exercise exerts beneficial effects on behavior and cognition that are particularly relevant to individuals with ASD. Clinical and experimental studies suggest that regular physical activity can reduce stereotypical behaviors, improve attention and executive function, and enhance social engagement. From a physiological perspective, these behavioral improvements likely reflect cumulative effects of enhanced synaptic plasticity, neurotransmitter regulation, and neurotrophic support rather than isolated mechanisms [47].

In summary, exercise-induced neuroplasticity represents a multifaceted physiological process capable of influencing synaptic structure, molecular signaling, and network-level function in ASD. By acting as an activity-dependent stimulus, exercise may partially offset intrinsic plasticity deficits and promote adaptive neural reorganization. This structural and molecular foundation sets the stage for the next section, which focuses on exercise-related neurochemical signaling and metabolic intermediates that further link physical activity to brain function in autism spectrum disorder [48].

Exercise, Neurochemical Signaling, and Metabolic Intermediates in ASD

Extending the structural and molecular adaptations induced by exercise, neurochemical signaling and metabolic regulation provide additional mechanisms through which physical activity influences brain function in autism spectrum disorder. Exercise triggers coordinated changes in neurotransmitter release, neuromodulator availability, and energy substrate utilization, all of which contribute to improved neural

efficiency and plasticity. These effects are especially relevant in ASD, where altered neurotransmission and metabolic dysregulation may compound underlying neurodevelopmental vulnerabilities [49].

One important metabolic intermediary linking exercise to brain function is lactate, a molecule traditionally viewed as a byproduct of anaerobic metabolism but now recognized as an active signaling substrate. During physical activity, lactate is released from skeletal muscle into the circulation and can cross the blood–brain barrier. Within the brain, lactate serves as an alternative energy source to glucose and participates in signaling pathways that support synaptic plasticity and memory formation. This metabolic flexibility is physiologically advantageous for sustaining neuronal activity during periods of increased demand [50].

Lactate also contributes to neurotransmitter metabolism by acting as a precursor for glutamate synthesis, thereby influencing excitatory synaptic transmission. By supporting glutamatergic signaling, exercise-induced lactate availability may enhance synaptic responsiveness and facilitate learning-related plasticity. In ASD, where glutamate signaling can be dysregulated, this mechanism highlights how metabolic intermediates generated during exercise may indirectly modulate excitation–inhibition balance and circuit stability [51].

Beyond metabolic substrates, exercise induces changes in monoaminergic neurotransmission, including serotonin, dopamine, and norepinephrine. These neurotransmitters play critical roles in mood regulation, motivation, attention, and reward processing, domains frequently affected in ASD. Exercise-induced increases in monoamine availability and receptor sensitivity are thought to contribute to improved emotional regulation and cognitive flexibility, providing a neurochemical basis for the behavioral benefits observed following structured physical activity programs [52].

Exercise also influences the release of peripheral factors such as cytokines and growth factors that communicate with the brain to shape neuroplastic responses. For example, exercise-associated modulation of interleukin-6 and other signaling molecules can influence neuroimmune interactions and energy metabolism within the central nervous system. These systemic-to-central signaling pathways further illustrate how exercise acts as an integrative physiological stimulus rather than a purely motor activity [53].

Collectively, exercise-induced neurochemical and metabolic adaptations complement the structural plasticity discussed previously, forming a coordinated physiological response that supports brain function. By enhancing energy availability, modulating neurotransmitter systems, and engaging systemic signaling pathways, exercise provides multiple entry points for influencing ASD-related neurophysiological dysfunction. This integrated neurochemical framework leads naturally to the next section, which focuses on the specific interaction between exercise and brain-derived neurotrophic factor as a key mediator of activity-dependent plasticity in autism spectrum disorder [54].

Exercise-Mediated Modulation of Brain-Derived Neurotrophic Factor in ASD

Building on the neurochemical and metabolic adaptations induced by physical activity, brain-derived neurotrophic factor represents a principal molecular mediator through which exercise exerts sustained effects on brain plasticity. Exercise has been consistently shown to upregulate BDNF expression in key brain regions such as the hippocampus, prefrontal cortex, and motor cortex, areas implicated in learning, memory, executive function, and behavioral regulation. This activity-dependent induction of BDNF provides a direct physiological link between peripheral motor activity and central synaptic remodeling, which is particularly relevant in the context of ASD-related plasticity deficits [55].

The mechanisms by which exercise enhances BDNF signaling involve both central and peripheral pathways. Increased neuronal activity during exercise stimulates calcium-dependent signaling cascades and transcriptional programs that promote BDNF synthesis, while peripheral factors released during physical activity can further influence central BDNF availability. These coordinated mechanisms ensure that BDNF production is tightly coupled to functional demand, reinforcing synapses that are actively engaged during learning and experience. In ASD, where activity-dependent signaling may be blunted, exercise-induced BDNF upregulation may help restore responsiveness within neural circuits [56].

Experimental models of ASD provide compelling evidence for the therapeutic relevance of exercise–

BDNF interactions. In valproic acid–induced models of autism, reductions in BDNF signaling have been associated with decreased synaptic density, impaired neurogenesis, and behavioral abnormalities. Exercise interventions in these models have been shown to reverse aspects of synaptic and behavioral dysfunction, coinciding with normalization of BDNF expression and downstream signaling pathways. These findings support a causal role for BDNF-mediated plasticity in exercise-induced neurophysiological improvements [57].

At the synaptic level, exercise-enhanced BDNF signaling promotes dendritic spine formation, stabilization, and maturation, which are essential for efficient synaptic transmission and learning. BDNF also facilitates long-term potentiation by modulating NMDA receptor function and postsynaptic protein synthesis, processes that are frequently disrupted in ASD. By strengthening synaptic efficacy and network coherence, exercise-driven BDNF signaling may contribute to improved cognitive performance and adaptive behavior in individuals with autism spectrum disorder [58].

Importantly, the timing and intensity of exercise appear to influence the magnitude of BDNF responses. Moderate, sustained physical activity has been associated with more consistent and beneficial increases in BDNF compared with excessive or irregular exercise, highlighting the importance of physiological dosing. This observation aligns with the concept of sensitive developmental and plasticity windows in ASD, during which appropriately timed interventions may yield the greatest neurophysiological benefit [59].

In summary, exercise-induced modulation of BDNF represents a critical intersection between behavioral intervention and molecular neurophysiology in ASD. By enhancing BDNF availability and signaling efficiency, exercise may help compensate for intrinsic deficits in synaptic plasticity and circuit refinement. This interaction forms a central component of the integrative model proposed in this review and sets the foundation for the subsequent section, which synthesizes vitamin D, exercise, and BDNF into a unified neurophysiological framework relevant to autism spectrum disorder [60].

An Integrative Neurophysiological Model Linking Vitamin D, Exercise, and BDNF in ASD

Having examined vitamin D signaling, exercise-induced plasticity, and BDNF biology as individual modulators of brain function, an integrative neurophysiological framework emerges in which these factors converge on shared pathways relevant to autism spectrum disorder. Rather than acting independently, vitamin D, physical exercise, and BDNF appear to interact dynamically to influence neurodevelopment, synaptic remodeling, and circuit stability. This integrative perspective is particularly important for ASD, where multifactorial mechanisms underlie heterogeneous clinical presentations and variable responses to intervention [61].

At the molecular level, vitamin D may function as a permissive regulator that shapes the neurobiological environment in which activity-dependent plasticity occurs. By modulating gene transcription, antioxidant defenses, immune balance, and calcium signaling, vitamin D influences baseline neuronal health and responsiveness. In this context, adequate vitamin D signaling may enhance the capacity of neural circuits to respond adaptively to physiological stimuli such as exercise, thereby facilitating downstream neurotrophic responses including BDNF upregulation [62].

Exercise serves as a potent activity-dependent trigger within this triad, translating environmental and behavioral input into neurophysiological change. Through repeated neuronal activation, exercise engages intracellular signaling cascades that promote synaptic strengthening, metabolic efficiency, and structural remodeling. These processes are strongly dependent on intact neurotrophic support, positioning BDNF as a critical mediator that links physical activity to sustained changes in neural connectivity and function, particularly in ASD-relevant circuits [63].

BDNF occupies a central integrative role by coordinating synaptic, metabolic, and transcriptional responses to both internal and external stimuli. Its signaling interfaces with neurotransmitter systems, mTOR-dependent protein synthesis, and cytoskeletal dynamics, all of which are influenced by vitamin D status and exercise intensity. Disruption at any point within this interconnected network may limit adaptive plasticity, whereas coordinated modulation of multiple components may yield synergistic neurophysiological benefits in ASD [64].

Developmental timing further refines this integrative model, as the effects of vitamin D, exercise, and BDNF are highly sensitive to critical periods of brain maturation. Prenatal and early postnatal vitamin D availability may shape foundational gene expression patterns and redox balance, while childhood and adolescent exercise may harness heightened plasticity windows to strengthen synaptic networks. This temporal dimension helps explain why interventions show variable efficacy and underscores the importance of age-specific physiological contexts in ASD research [65].

In summary, the convergence of vitamin D signaling, exercise-induced neural activity, and BDNF-mediated plasticity represents a unified neurophysiological framework for understanding modulatory influences on ASD brain function. This model does not imply causality but rather highlights interacting pathways that may modify disease expression and functional outcomes. Recognizing these interactions provides a rational basis for interpreting mixed clinical findings and guides the transition to the next section, which critically evaluates clinical evidence, therapeutic implications, and existing controversies surrounding vitamin D and exercise interventions in autism spectrum disorder [66].

Clinical Evidence and Controversies: Vitamin D and Exercise Interventions in ASD

Translating mechanistic plausibility into clinical benefit has been challenging in ASD, largely because clinical trials often enroll heterogeneous populations, use different outcome measures, and vary in intervention timing and dose. Vitamin D and exercise both target broad physiological systems (neuroimmune tone, redox balance, neurotransmission, plasticity), so their measurable effects may depend on baseline biological state (e.g., deficiency vs sufficiency), developmental stage, and ASD subtype. As a result, “no effect” findings in aggregate analyses may obscure clinically meaningful responses in specific subgroups, particularly when trials are not designed around mechanistic stratification or biomarker-guided endpoints [67].

Randomized controlled trials of vitamin D supplementation in ASD have produced mixed results, with several studies showing biochemical correction of vitamin D status but limited improvement in primary clinical endpoints. This pattern suggests that restoring circulating vitamin D levels alone may be insufficient to modify core ASD symptoms within typical trial durations, or that benefits may require targeting earlier developmental windows or specific physiological domains (sleep, irritability, adaptive function) rather than broad autism severity scales. These findings reinforce the need to interpret supplementation trials through a physiology lens that accounts for timing, baseline deficiency, and outcome selection [68].

Systematic reviews and meta-analyses similarly report inconsistent efficacy, often concluding that vitamin D supplementation raises serum levels without consistently improving core ASD outcomes. Importantly, meta-analytic conclusions are sensitive to trial quality, variability in dose regimens, differences in behavioral scales, and small sample sizes. From a neurophysiological viewpoint, it remains plausible that vitamin D modulates intermediary mechanisms (oxidative stress markers, inflammatory profiles, neurotransmitter balance) that are not always captured by primary behavioral endpoints, thereby contributing to mixed clinical signals even when biological effects occur [69].

A further interpretive challenge is the strong placebo-like response and spontaneous improvement that can occur in ASD cohorts even without active treatment, which may dilute detectable intervention effects if trials are underpowered or endpoints are not tightly linked to mechanism. This is particularly relevant in pediatric ASD where developmental gains can occur over time and caregiver expectations can influence reported outcomes. Such trial dynamics underscore why mechanistically anchored biomarkers and objective neurophysiological measures are essential for reducing noise and improving signal detection in intervention studies [70].

In contrast to the vitamin D literature’s inconsistency, exercise interventions show more consistent functional benefit across multiple trials, particularly for behavioral regulation, motor skills, metabolic health, and aspects of social communication. Exercise is physiologically pleiotropic—improving neurochemical signaling, reducing stress reactivity, and supporting plasticity—so benefits may emerge even when core diagnostic features remain. Importantly, the practical advantages of exercise (low cost, low adverse-effect burden, scalability) make it a strong candidate as an adjunctive strategy within

multidisciplinary ASD care [71].

Meta-analytic evidence also suggests that structured physical exercise programs can improve core symptoms and related outcomes in ASD, although heterogeneity in program type, intensity, duration, and participant characteristics remains a major limitation. These findings align with the integrative model proposed earlier: exercise may exert measurable effects through activity-dependent plasticity and neurotrophic signaling, but the magnitude of response likely depends on intervention "dose," adherence, and baseline neurophysiological state. This reinforces the need for optimized, personalized exercise prescriptions and trials that link clinical outcomes to mechanistic markers such as BDNF dynamics, redox status, or excitation–inhibition measures [72].

Conclusion

Autism spectrum disorder is best understood as a complex neurodevelopmental condition arising from disrupted neurophysiological regulation across multiple levels of brain organization, including gene expression, synaptic plasticity, neurotransmission, redox balance, and network connectivity. The evidence synthesized in this review supports a view of ASD not as the consequence of a single pathogenic mechanism, but as the cumulative outcome of interacting biological vulnerabilities that shape brain development and function over time. Within this framework, modulatory factors capable of influencing core physiological processes hold particular relevance for understanding variability in clinical presentation and therapeutic response.

Vitamin D emerges as a broad regulator of neurodevelopmental homeostasis through its actions on gene transcription, oxidative stress control, immune modulation, neurotransmitter systems, and cellular survival pathways. Although current clinical evidence does not support vitamin D as a stand-alone treatment for core ASD symptoms, its physiological roles suggest that deficiency may increase vulnerability to neurodevelopmental dysregulation, particularly during critical periods. Adequate vitamin D signaling may therefore be better conceptualized as a permissive or supportive factor that shapes the neurobiological context in which other adaptive processes occur.

Physical exercise represents a robust, activity-dependent stimulus capable of engaging multiple neurophysiological systems simultaneously. Through its effects on synaptic remodeling, metabolic regulation, neurotransmitter balance, and neurotrophic signaling, exercise offers a practical means of enhancing neural plasticity and functional adaptation in individuals with ASD. Among the molecular mediators of these effects, brain-derived neurotrophic factor occupies a central integrative role, linking environmental and behavioral inputs to lasting changes in neural circuit structure and function.

The convergence of vitamin D signaling, exercise-induced activity, and BDNF-mediated plasticity highlights the importance of integrated, physiology-informed approaches to ASD research and intervention. Rather than evaluating these factors in isolation, future studies should consider developmental timing, baseline biological state, and mechanistic endpoints to better capture meaningful neurophysiological change. Such an approach may help reconcile inconsistent clinical findings and guide more personalized, adjunctive strategies aimed at optimizing neurodevelopmental outcomes and quality of life for individuals with autism spectrum disorder.

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