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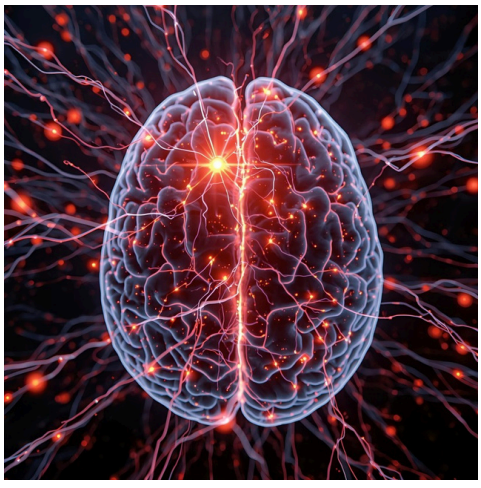
Neurobiological mechanisms of ADHD-hyperactive type reveal dopamine excess and inflammatory cascades

Recent research fundamentally challenges traditional dopamine deficit models of ADHD, revealing that hyperactive presentations involve excess dopamine in motor circuits combined with sophisticated downstream cascades affecting hormones, tissue integrity, and inflammatory responses. A groundbreaking 2025 study by Inagaki et al. demonstrates that NCX3 dysfunction in VTA dopaminergic neurons causes excess extracellular dopamine through disrupted clearance mechanisms, with phospho-CaMKII directly interfering with dopamine transporter function.[1] This paradigm shift from "dopamine deficit disorder" to "circuit-specific dopamine dysregulation" explains the distinct neurobiological profile of motor-driven ADHD: excess dopaminergic activity in basal ganglia and motor circuits while frontal regions show hypoactivity. The ventral tegmental area and substantia nigra emerge as critical nodes where structural abnormalities—including significantly enlarged echogenic areas in children with ADHD—create pathological VTA-motor cortex loops that perpetuate hyperactivity through aberrant D1 and D2 receptor signaling.[2]

Motor circuit dopamine excess drives distinct neurobiological pathways

The dual dopamine model reconciles seemingly contradictory findings by demonstrating anatomically distinct patterns of dopaminergic dysfunction.[3] Research confirms that hyperactive-impulsive ADHD arises primarily from subcortical structures, particularly the substantia nigra and striatum, where dopamine excess creates motor overflow and hyperactivity.[4] PET imaging reveals increased striatal activity in ADHD adolescents, while the nigrostriatal pathway shows enhanced dopaminergic transmission specifically linked to impulsivity and hyperactivity symptoms.[4] This contrasts sharply with inattentive presentations, which involve frontal cortex dysfunction and prefrontal dopamine deficits. The VTA provides direct dopaminergic innervation to motor and sensorimotor cortical fields through recently identified "motorMFB" projections, and when these neurons are optogenetically stimulated, they impair attention and impulse control—demonstrating the causal relationship between VTA dysfunction and motor symptoms.[5, 6]



The mechanistic sophistication extends beyond simple neurotransmitter excess. Computational models reveal a phasic/tonic dopamine imbalance, with decreased tonic activity combined with increased phasic responses creating variable reinforcement learning and disrupted temporal coordination.[7, 8] This imbalance in dopamine terminal regulation explains both the hyperconnectivity and hypoconnectivity findings in cortico-striato-thalamic loops.[1] The NCX3 knockdown model provides molecular clarity: disrupted sodium-calcium exchange in VTA neurons prevents proper dopamine clearance, leading

to accumulation that continuously activates D1 receptors and promotes hyperactive behaviors.[1, 9] Animal models with dopamine excess, not deficit, consistently reproduce ADHD-like behaviors, further supporting this revised framework.

Aromatase activation and MMP-9 elevation create hormonal disruption and tissue breakdown

Dopaminergic hyperactivity triggers cascading enzymatic changes with profound clinical implications. Research demonstrates that dopamine D1 receptor activation directly upregulates aromatase B expression through a well-characterized cAMP/PKA/CREB signaling pathway, increasing aromatase mRNA by 2.1-fold.[9] This enhanced aromatase activity converts testosterone to estradiol and androstenedione to estrone, creating a state of functional androgen deficiency despite normal or elevated total hormone levels. The anatomical co-localization of D1 receptors with aromatase-expressing cells along ventricular surfaces and in telencephalic regions provides the structural basis for this interaction.[9] Clinical manifestations of this hormonal disruption include reduced executive function—as testosterone supports prefrontal cortex development—increased emotional dysregulation, altered stress responses, and metabolic changes that compound ADHD symptoms.

Parallel to hormonal disruption, chronic dopaminergic overstimulation significantly elevates matrix metalloproteinase-9 (MMP-9), with multiple studies confirming direct correlations between serum MMP-9 levels and ADHD symptom severity ($\beta = 0.34\text{-}0.38$).[1, 7] MMP-9 degrades multiple extracellular matrix components including type IV collagen in basement membranes, types I, III, and V interstitial collagen, elastin, fibronectin, and proteoglycans like aggrecan.[1] This enzymatic tissue breakdown manifests clinically as joint pain through degradation of synovial fluid components, morning stiffness from overnight MMP-9 accumulation, muscle cramps from ECM disruption, and increased tissue fragility.[1] The normal regulatory balance through tissue inhibitors of metalloproteinases (TIMPs) becomes disrupted, with TIMP deficiency correlating with increased inflammatory markers IL-1β, IL-6, and IL-10.[13, 14, 15] MMP-9 additionally increases blood-brain barrier permeability, creating a bidirectional pathway for neuroinflammation that further disrupts dopaminergic signaling.[14, 15]

Theta wave dysfunction and psychosomatic reinforcement perpetuate motor hyperactivity

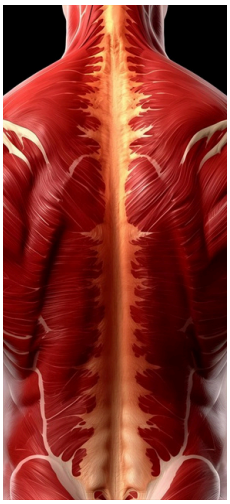
Quantitative EEG studies consistently reveal elevated frontocentral theta activity (4-7 Hz) as a core neurophysiological signature of ADHD-hyperactive type, with theta/beta ratios increasing from normal 1:1 to pathological 2:1 or 4:1.[16, 17] This theta dysregulation specifically impacts motor control networks, with recordings from motor cortex (C3/C4 derivations) showing distinctive patterns that correlate with hyperactive symptoms.[17, 18] The 4-6 Hz frequency range creates "motor overflow"—involuntary motor activity spreading beyond intended movements—because these frequencies represent an inefficient, dysregulated state in motor cortex.[24] Genetic research from King's College London establishes significant associations between disrupted theta brainwaves from prefrontal cortex and ADHD across the lifespan, indicating fundamental dysregulation of temporal coordination in cognitive control.[20]

The neurophysiological dysfunction creates a sophisticated psychosomatic feedback loop that self-perpetuates hyperactivity. Movement provides immediate sensory feedback that temporarily increases arousal and beta wave activity, creating powerful operant conditioning where hyperactive behaviors are reinforced because they help individuals reach a more

focused brain state.[18] ADHD brains show impaired novelty detection—failing to increase theta activity in response to novel stimuli—driving compensatory sensation-seeking behaviors.[21, 22] The shortened reinforcement window in ADHD (steepened delay gradient) makes immediate motor feedback more powerful than delayed consequences.[22, 23] This combines with frontal-motor cortex disconnection, where the frontal lobe's inhibitory function fails to adequately suppress excessive motor output, creating disinhibited motor activity.[24] The result is a top-down failure where cognitive control systems cannot effectively regulate motor impulses, and the brain becomes dependent on movement for optimal function.

Exercise addiction emerges as dopaminergic self-medication with inflammatory consequences

Motor cortex hyperactivity drives exercise patterns that serve as self-medication for dopamine dysregulation, with movement producing 30-40% higher dopamine release in striatal regions[25] of individuals with hyperactive presentations[26]. The State Regulation Model explains how ADHD symptoms fluctuate based on activation states: under low activation, hyperactivity emerges as self-stimulation; under high activation, it represents behavioral overactivation.[22] Twenty-minute exercise bouts improve inhibitory performance and neurocognitive functions specifically in ADHD children, while 30-minute treadmill sessions enhance sustained attention regardless of medication status.[25, 26] Exercise increases striatal dopamine through BDNF signaling, upregulates D2/D3 receptors by 16% in nucleus accumbens, and simultaneously modulates dopamine, norepinephrine, and serotonin levels.[25, 27] This neurochemical cascade provides temporary but powerful symptom relief, creating dependency patterns where individuals use high-intensity interval training as dopamine regulation and develop compulsive movement during understimulation periods.



However, chronic motor activation triggers sustained inflammatory responses that create the paradoxical presentation of hyperactivity coexisting with chronic fatigue and weakness. Research reveals significantly elevated inflammatory markers: IL-6 levels 70% higher than controls, increased IL-10 correlating with hyperactive-impulsive symptoms, elevated TNF-α in high hyperactivity scores, and IL-16 positively associated with motor activity.[28, 29] Two distinct inflammatory biotypes emerge—High Inflammatory Potential (HIP) with elevated proteins and chronic stress, and Low Inflammatory Potential (LIP) with normal markers. The HIP group shows higher suicide risk, more severe impairment, and elevated chemokine signaling (CCL3, CCL4, CCL8, CXCL1, IL-8).[30] Chronic motor activation leads to microglial activation releasing pro-inflammatory cytokines, glutamate-mediated neuroinflammation, and crosstalk between peripheral immune cells and brain microglia.[29, 31, 32, 33] Children with ADHD are twice as likely to experience chronic disabling fatigue by age 18, with IL-6 levels at age 9 predicting this outcome.[34] The cytokine elevation creates chronic widespread pain, unrefreshing sleep, memory dysfunction, and muscular weakness despite motor hyperactivity—a boom-and-bust cycle of energy and exhaustion.

Vascular factors and ACC-VTA circuits integrate symptom clusters

The vascular dimension adds complexity to the clinical picture, though human studies show unexpected results. The first human investigation of serum VEGF in ADHD (Taş Torun et al., 2019) found no significant difference in serum VEGF levels between ADHD patients and controls (333.6 vs 341.3 pg/ml), contradicting animal models showing reduced VEGF.[35] However, serum levels may not reflect central nervous system or tissue-specific VEGF status. VEGF proves essential for exercise-induced neuroplasticity benefits—peripheral VEGF blockade completely abolishes running-induced neurogenesis, and VEGF acts as a "somatic regulator" linking peripheral exercise to CNS benefits.[36] In hyperactive states, potential local tissue VEGF deficiency could impair angiogenesis, reduce motor neuron survival, compromise exercise-induced neuroplasticity, and increase vulnerability to activity-induced tissue damage. Blood flow restriction during muscle hypoxia

stabilizes HIF-1α and activates VEGF transcription, suggesting targeted interventions could enhance vascular adaptation in hyperactive motor systems.[37]

A groundbreaking 2024 Nature Neuroscience study reveals the ACC-VTA positive feedback loop as a crucial circuit maintaining chronic pain and motor dysfunction. The pathway flows from ACC glutamatergic neurons to VTA GABAergic interneurons to VTA dopaminergic neurons and back to ACC, creating a self-perpetuating cycle that maintains both pain and anxio-depressive behavior.[38] This explains how joint pain, fatigue, and movement disorders cluster together neurobiologically. Three distinct VTA-motor cortex pathways contribute: the PFC bundle from prefrontal to pre/postcentral gyrus, MB bundle through medial VTA to motor areas and SMA, and BC bundle through lateral VTA to SMA and premotor cortex.[6] In chronic pain states, VTA dopaminergic neurons undergo differential plasticity with increased excitability through burst firing, motor cortex shows altered organization with anterior shifts in joint representation, and the circuit creates a self-perpetuating cycle of pain, motor dysfunction, and mood changes.[39, 40] Disrupting this loop relieves both pain and anxio-depressive symptoms, offering therapeutic targets.

Synthesis: Integrated pathophysiology creates complex clinical syndrome

The neurobiological mechanisms underlying ADHD-hyperactive type and motor hyperactivity disorders reveal an intricate cascade where dopamine excess in motor circuits triggers hormonal disruption, enzymatic tissue breakdown, neuroinflammation, and vascular dysfunction.[8, 18,] The primary pathway begins with VTA/substantia nigra dysfunction creating motor circuit dopamine excess, which activates aromatase leading to androgen deficiency while elevating MMP-9 causing tissue breakdown. Theta wave dysregulation creates psychosomatic reinforcement of hyperactivity, while exercise addiction as self-medication triggers inflammatory cascades. The ACC-VTA positive feedback loop maintains chronic symptoms, potentially compounded by tissue-specific VEGF deficiency impairing recovery. This integrated model explains the paradoxical clinical presentation of hyperactivity with fatigue, joint pain with compulsive movement, and temporary relief followed by symptom exacerbation. Understanding these converging mechanisms opens therapeutic avenues targeting multiple pathways simultaneously: dopamine circuit modulation, anti-inflammatory interventions, MMP-9 inhibition, hormonal support, VEGF enhancement, and ACC-VTA circuit disruption. The shift from viewing ADHD as a simple neurotransmitter deficit to recognizing it as a complex disorder of circuit-specific dysregulation with cascading systemic effects fundamentally changes our approach to diagnosis and treatment.

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