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Attention-Deficit/Hyperactivity Disorder (ADHD): A Comprehensive Review Integrating Neurobiology, Gender Differences, Cognitive Profiles, Psychosocial Dimensions, and Emerging Therapeutic Approaches

Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental condition characterized by pervasive patterns of inattention, hyperactivity, and impulsivity that impair functioning across academic, occupational, emotional, and social domains. Although traditionally conceptualized as a childhood disorder, longitudinal evidence suggests that symptoms persist into adulthood in approximately 50–65% of cases. Classical research has thoroughly examined ADHD epidemiology, genetics, and neurobiology, but emerging literature reveals additional dimensions that expand the disorder's conceptual framework. These include sex-specific neurobiological patterns, hormonal influences across the female lifespan, emotional dysregulation, rejection sensitivity, sensory processing differences, sleep–wake disturbances, hyper focus, creativity-linked cognitive traits, and the phenomenon of social masking—particularly among females and late-diagnosed adults.

Recent decades have also introduced innovative therapeutic approaches that complement established pharmacological and psychosocial treatments, including neurostimulation, digital therapeutics, microbiome-based hypotheses, and cognitive-enhancement technologies. This integrative review synthesizes classical evidence and recent advances in ADHD research, highlighting the disorder's multifaceted nature and emphasizing the need for individualized, developmentally sensitive, and gender-responsive care

Keywords

ADHD, neurodevelopmental disorder, executive dysfunction, emotional dysregulation, sex differences, hyper focus, sensory processing, neurostimulation, digital therapeutics, microbiome, neuroimaging, multimodal, circadian rhythms, DSM-5, ICD-11.

Review Article

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is among the most extensively studied neurodevelopmental disorders, affecting approximately 5–7% of children and 2.5–4% of adults worldwide [1,2]. Once considered a childhood-restricted condition, ADHD is now recognized as a lifespan disorder associated with academic underachievement, occupational instability, impaired emotional regulation, interpersonal challenges, and elevated psychiatric comorbidity. Global diagnostic rates have increased in recent years—not due to a true rise in incidence, but rather improved awareness, reduced stigma, and expanded access to diagnostic services [3]. Nevertheless, ADHD remains underdiagnosed among females, individuals from lower socioeconomic backgrounds, and older adults, underscoring persisting inequities in clinical recognition.

While traditional conceptualizations emphasized behavioral manifestations of inattention and hyperactivity, contemporary research demonstrates that ADHD encompasses a far more complex interplay of neurobiological, psychological, hormonal, and environmental factors. The purpose of this review is to integrate classical ADHD knowledge

with emerging evidence, including dimensions not traditionally included in standard reviews: neurobiological subtypes, sensory dysregulation, hyper focus, emotional sensitivity, gender-specific presentations, circadian rhythm disturbances, digital therapeutics, neurostimulation, and microbiome research. This integrated perspective offers a broader and more nuanced understanding of ADHD's heterogeneity across the lifespan.

Diagnostic Frameworks and Classification

ADHD is classified in the DSM-5 and DSM-5-TR as a neurodevelopmental disorder marked by persistent symptoms of inattention and/or hyperactivity-impulsivity that interfere with functioning across two or more settings [4]. The DSM-5 introduced onset before age 12 as a criterion, replacing the earlier threshold of seven years. The ICD-11 aligns conceptually with DSM-5, describing ADHD as a persistent pattern of impaired attention and/or hyperactive-impulsive behavior inconsistent with developmental level [5].

Although DSM-5 identifies three presentations—predominantly inattentive, predominantly hyperactive-impulsive, and combined—these categories capture only part of the underlying heterogeneity. Neurobiological research increasingly supports functional subtypes based on patterns of network dysregulation rather than observable behaviors. This conceptual shift highlights limitations in current diagnostic systems and a growing need for precision-based classifications.

Epidemiology and Global Trends

Large meta-analyses demonstrate consistent ADHD prevalence across cultures when standardized diagnostic criteria are applied [1,2]. However, diagnostic rates vary due to cultural stigma, medical access, and differences in healthcare practices. Underdiagnosis remains pervasive in populations where internalizing symptoms predominate, particularly among girls and adult women who may mask or compensate for impairments.

Socioeconomic disparities also affect diagnosis: children from lower-income families face structural barriers such as reduced access to evaluation, fewer educational supports, and greater exposure to adversity, which may exacerbate symptoms. Conversely, overdiagnosis concerns have been raised in certain clinical settings, highlighting the importance of comprehensive assessment.

Etiology and Pathophysiology

Genetic Contributions

Twin and family studies estimate ADHD heritability at 70–80%, placing it among the most heritable psychiatric conditions [6]. Genome-wide association studies support a polygenic risk architecture comprising numerous small-effect variants [7]. Shared genetic vulnerability is well-documented between ADHD and autism spectrum disorder, major depressive disorder, bipolar disorder, and substance use disorders, reflecting overlapping neurodevelopmental pathways.

Neurobiological Mechanisms

Neuroimaging findings consistently indicate structural and functional alterations in the prefrontal cortex, cerebellum, and basal ganglia among individuals with ADHD [8,9]. Functional imaging reveals atypical activation of networks responsible for attention, executive functioning, and emotional regulation. Central to ADHD pathophysiology is dysregulation in dopaminergic and noradrenergic neurotransmission, explaining stimulant medication efficacy.

Environmental Factors

Environmental contributors interact with genetic predispositions throughout development. These include prenatal nicotine or alcohol exposure, low birth weight, prematurity, and early adversity [10]. Although these factors do not independently cause ADHD, they may modulate severity and expression of symptoms.

Beyond Traditional Models: Emerging Neurobiological Subtypes

Traditional diagnostic presentation categories fail to capture underlying neural variability. Emerging neuroscience proposes subtypes reflecting dysfunction in specific brain networks:

Executive Network Dysfunction

Characterized by deficits in planning, organization, working memory, and cognitive flexibility, reflecting impaired fronto-striatal activation.

Default Mode Network (DMN) Intrusion
Abnormal persistence of DMN activity during tasks results in internal distractions and task disengagement.

Reward Deficiency Subtype
Linked to hypoactivation of mesolimbic reward circuits, resulting in low motivation, novelty-seeking, and preference for immediate rewards.

Sluggish Cognitive Tempo (SCT)
A distinct cluster involving daydreaming, mental fogginess, and slowed information processing. Though not included in DSM-5, SCT is increasingly recognized in research.

Gender-Specific Manifestations and Hormonal Influences
Females with ADHD frequently present with inattentive symptoms, internalizing difficulties, and emotional sensitivity, contributing to underdiagnosis [3]. Neuroimaging studies suggest sex-linked differences in brain development, including enhanced limbic-prefrontal reactivity in females and more pronounced hyperactivity-related motor circuitry alterations in males.
Across the female lifespan, hormonal fluctuations significantly influence ADHD symptomatology:

- **Menstrual cycle:** symptoms worsen during low-estrogen phases.
- **Postpartum period:** estrogen drops may intensify ADHD symptoms.
- **Perimenopause/menopause:** increased attentional and emotional difficulties.

These patterns highlight the importance of hormone-informed assessment and treatment.

Clinical Presentation Across the Lifespan

Childhood
Symptoms include hyperactivity, impulsivity, poor sustained attention, and academic difficulties. Disruptive behavior may dominate clinical attention, overshadowing cognitive impairments.

Adolescence
Hyperactivity may diminish, but executive dysfunction and emotional reactivity often intensify. Risk-taking behaviors and academic overwhelm are common.

Adulthood
Symptoms manifest primarily as disorganization, inconsistent productivity, emotional impulsivity, time-management deficits, and occupational instability. Adults may describe chronic internal restlessness and difficulty regulating attention.

Emotional Dysregulation, Hyper focus, and Cognitive Profiles

Emotional Dysregulation
Although not a DSM-5 criterion, emotional lability is highly prevalent. Individuals may experience rapid mood shifts, frustration intolerance, and heightened stress reactivity.

Rejection Sensitivity Dysphoria (RSD)
Many report intense emotional pain in response to perceived criticism, leading to avoidance, social withdrawal, or conflict.

Hyper focus
Despite distractibility, individuals often experience episodes of deep, prolonged concentration on stimulating tasks. Hyper focus can facilitate creativity but impair task-shifting and daily functioning.

Working Memory Impairment
Reduced working memory capacity significantly contributes to academic and functional challenges.

Sensory Processing Differences
Individuals may exhibit hypersensitivity or hyposensitivity to sounds, lights, textures, or movement.

Comorbidity

ADHD frequently co-occurs with:

- Anxiety disorders
- Major depressive disorder
- Substance use disorders
- Sleep disorders
- Learning disabilities

Comorbidity complicates diagnosis and may worsen functional outcomes.

Sleep and Circadian Rhythm Disturbances

ADHD is strongly associated with sleep-wake disruptions,

including delayed circadian phase, insomnia, and poor sleep quality. Sleep deficits exacerbate attentional, emotional, and executive impairments. Treatment of sleep disorders can significantly improve overall functioning.

ADHD in Relationships, Family Dynamics, and Occupational Life

ADHD impacts communication, emotional expression, and household management in romantic relationships. Adults with ADHD are overrepresented among divorced individuals, particularly when untreated. Occupationally, individuals may experience inconsistent performance, time-blindness, and difficulty with routine tasks, yet often excel in dynamic, creative, and fast-paced environments. ADHD traits are disproportionately present in entrepreneurial populations.

Microbiome, Nutrition, and Physiological Factors

Emerging research explores links between gut microbiota and ADHD through immune, metabolic, and neurochemical pathways. Nutritional factors such as omega-3 deficiency may influence symptom severity, and elimination of artificial food dyes may benefit a subgroup of children.

Digital Therapeutics and Technology-Based Interventions

Digital therapeutics, such as the FDA-approved video-game–based treatment EndeavorRx, offer novel cognitive training platforms. Wearable devices enable monitoring and executive-function training. These technologies complement, rather than replace, pharmacotherapy and behavioral interventions.

Neurostimulation Approaches

Non-invasive neurostimulation techniques show promise:

- **Transcranial Direct Current Stimulation (tDCS)** improves working memory.
- **Repetitive Transcranial Magnetic Stimulation (rTMS)** modulates prefrontal networks.
- **Trigeminal nerve stimulation devices** are emerging as pediatric options.

Further research is required to establish efficacy.

Evidence-Based Treatment

Psychostimulant medications remain first-line, with strong efficacy across age groups [11]. Non-stimulant medications—including atomoxetine, guanfacine, clonidine, and viloxazine—provide alternatives for patients who cannot tolerate stimulants [12,13]. Psychosocial treatments such as cognitive-behavioral therapy [14], behavioral parent training, and academic accommodations significantly enhance outcomes. Multimodal treatment consistently outperforms single-modality approaches [15-17].

Prognosis and Public Health Implications

Early diagnosis and continuous support improve academic, occupational, and relational outcomes [18-20]. Untreated ADHD increases risks for substance misuse, accidents, unemployment, economic hardship, and mental-health disorders [21]. Public health systems must address diagnostic inequities and expand access to evidence-based treatments.

Future Directions

Emerging research emphasizes:

- Precision psychiatry
- Biomarker identification
- Artificial-intelligence-assisted diagnostics
- Digital phenotyping
- Hormone-sensitive treatment approaches
- Personalized neuromodulation therapies

These innovations aim to reduce reliance on symptom-based diagnosis and improve individualized care.

Conclusion

ADHD is a multifaceted neurodevelopmental disorder shaped by genetic vulnerabilities, neurobiological alterations, hormonal influences, and environmental factors. Its impact extends far beyond inattention and hyperactivity, encompassing emotional, sensory, cognitive, and social dimensions across the lifespan. Incorporating emerging evidence into clinical practice offers a more comprehensive and humane understanding of ADHD. Multimodal, personalized, and gender-responsive approaches represent the future of effective diagnosis and treatment.

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