

Recent Advances in the Etiology and Neural Pathways Underlying Attention-Deficit and Hyperactivity Disorder

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ABSTRACT: The prevalence of mental disorders is increasing across the European Union, with at least one in four individuals expected to experience a psychiatric condition at some point in their lifetime. Notably, men and women often present with distinct symptomatology. Among neuropsychiatric disorders, attention-deficit/hyperactivity disorder (ADHD) is the most common and functionally impairing condition in childhood, affecting approximately 5% of minors. Its persistence into adulthood is substantial, with prevalence estimates reaching up to 3% in adult populations. ADHD is characterized by dysregulated dopaminergic signaling, which disrupts reward processing and motivation. Additionally, disturbances in circadian rhythms contribute to sleep dysregulation and metabolic dysfunction, further exacerbating symptom severity. While both mechanisms have been well-documented, their interaction remains insufficiently explored, particularly regarding its implications for diagnosis and treatment optimization. Future research should systematically examine the interplay between dopaminergic and noradrenergic dysfunction and circadian disruptions in ADHD, particularly in relation to symptom expression and comorbid conditions. Experimental paradigms assessing reward processing may provide valuable insights into dopamine and norepinephrine system alterations, while chronotherapeutic interventions—such as light therapy, sleep regulation, and behavioral adjustments—hold promise as potential therapeutic strategies. By integrating perspectives from neurobiology, chronobiology, and psychopharmacology, a more refined and individualized approach to ADHD management can be developed. Advancing this understanding may not only enhance ADHD treatment strategies but also yield novel therapeutic avenues for addressing its frequently co-occurring conditions.

KEYWORDS: Attention-deficit, hyperactivity disorder, dopamine, norepinephrine, ADHD management.

Introduction

Mental disorders are increasingly prevalent across the European Union, with at least one in four individuals expected to experience a psychiatric condition at some stage in life. The manifestation of mental disorders varies between sexes, with distinct symptomatology observed in men and women. Among neuropsychiatric conditions, Attention-Deficit and Hyperactivity Disorder (ADHD) is the most common and functionally impairing disorder in childhood, affecting approximately 5% of minors. Notably, ADHD frequently persists into adulthood, contributing to an estimated prevalence of up to 3% in the adult population [1,2].

Recent epidemiological data suggest that ADHD may be more widespread than previously reported. In the United States, an estimated 11.4% of children aged 5-17 years have been diagnosed with the disorder, with a higher prevalence among boys (14.5%) compared to girls (8.0%). ADHD diagnosis rates also increase with age, reaching 14.3% in adolescents aged

12-17 years, compared to 8.6% in younger children (5-11 years) [3].

Critically, ADHD represents a gateway to adverse developmental trajectories, as more than 80% of adults with ADHD present with at least one comorbid psychiatric disorder [2].

The burden of ADHD and its comorbid conditions extends beyond individual suffering, profoundly affecting families, communities, and societal structures. It is a leading cause of disability, placing significant strain on healthcare, educational, economic, and social welfare systems. Individuals with ADHD face an increased risk of unemployment, job instability, and financial insecurity [4].

In the EU, over 21 million individuals are estimated to have ADHD, with associated direct medical costs and productivity losses exceeding €70 billion annually [5,6].

Despite its high prevalence and socioeconomic impact, ADHD remains underdiagnosed, particularly in adults, and treatment innovations have been limited. Stimulant medications, introduced decades ago, remain the primary pharmacological

intervention. The persistent stigma surrounding mental disorders may further contribute to inadequate research funding and resource allocation, exacerbating gaps in clinical care and public health responses.

Etiology of ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a complex neurodevelopmental condition arising from a combination of genetic, environmental, and neurobiological factors.

Genetic Factors

ADHD has a strong hereditary component, with studies indicating that genetic factors contribute significantly to its development.

Variations in genes related to dopamine regulation, such as the DRD4 and DRD2 genes, have been associated with ADHD. These genetic differences may affect neurotransmitter pathways, influencing attention and behavior regulation.

Environmental Influences

Environmental factors, particularly those encountered during prenatal development, play a crucial role in ADHD etiology. Recent research has linked prenatal exposure to substances like lead to an increased risk of developing ADHD. A study analyzing blood lead levels from 1940 to 2015 found a significant association between lead exposure and mental health disorders, including ADHD, especially among individuals born between 1966 and 1986, when leaded gasoline usage was at its peak [7].

Neurobiological Factors

Advancements in neuroimaging have provided insights into the brain structures and functions associated with ADHD. A large-scale study by the National Institutes of Health identified atypical interactions between the frontal cortex and deeper brain structures involved in information processing in youth with ADHD. These findings suggest that disruptions in specific neural networks contribute to the symptoms observed in ADHD [8].

Burden of ADHD on Society

ADHD imposes a substantial burden on individuals and society, encompassing economic costs, healthcare utilization, and impacts on quality of life.

Economic Impact

The financial implications of ADHD are considerable. A study estimated that adults with ADHD in the United States incur an annual

societal excess cost of \$122.8 billion, primarily due to unemployment and productivity losses.

Similarly, the economic burden among children and adolescents is significant, with education costs contributing to approximately half of the total excess costs [9].

Healthcare Utilization

Individuals with ADHD often require extensive healthcare services. The disorder is associated with increased medical visits, mental health services, and medication prescriptions. For instance, in England, the first quarter of 2024 saw a record number of 19,400 women aged 25 to 34 prescribed ADHD medication, reflecting heightened awareness and diagnosis rates.

Quality of Life and Social Implications

ADHD affects various aspects of daily living, including academic performance, employment stability, and interpersonal relationships. Unmanaged ADHD can lead to poor health outcomes and a shorter life expectancy. A study published in *The British Journal of Psychiatry* reported that individuals with ADHD have a reduced life expectancy, with men living 4.5 to 9 years less and women 6.5 to 11 years less than their neurotypical peers [10].

In summary, ADHD's etiology is multifaceted, involving genetic predispositions, environmental exposures, and neurobiological abnormalities. The disorder presents a significant societal burden, underscoring the need for comprehensive strategies encompassing early diagnosis, effective treatment, and supportive interventions to mitigate its impact.

Developmental Trajectory and Comorbidities

As a common neurodevelopmental disorder with onset in childhood, ADHD frequently represents the initial manifestation of a trajectory marked by an elevated risk of comorbidities persisting into adulthood, often resulting in adverse health and socioeconomic outcomes [Kooij et al., 2019]. With an estimated prevalence of approximately 5% in children and 3% in adults, ADHD ranks among the most prevalent psychiatric disorders [2,11].

Characterized by persistent symptoms such as hyperactivity, inattention, impulsivity, deficits in executive functioning, and emotional dysregulation, ADHD significantly disrupts daily life. Emotional dysregulation—manifesting as heightened irritability, low frustration tolerance, and emotional lability—is a particularly pervasive feature across all age groups. Evidence suggests

that between 34% and 70% of adults with ADHD exhibit clinically significant difficulties in emotion regulation [12].

ADHD is frequently associated with comorbid mood and anxiety disorders, with studies indicating that up to 80% of adults with ADHD have at least one concurrent psychiatric condition [13].

Additionally, ADHD confers a heightened risk for substance use disorders (SUDs), with impulsivity and emotional instability potentially contributing to maladaptive coping through substance use. Research has consistently demonstrated a greater likelihood of SUD development in individuals with ADHD compared to non-ADHD populations [14,15].

Psychiatric disorders frequently co-occur with other mental and somatic conditions, significantly increasing disease burden and reducing life expectancy. Unlike many other medical fields, psychiatric disorder classification remains largely based on clinical phenomenology rather than underlying pathophysiological mechanisms [16].

This reliance on symptom-based categorization has hindered the development of novel treatments targeting disease-specific biological pathways, with most psychiatric interventions stemming from serendipitous discoveries.

Attention-deficit/hyperactivity disorder (ADHD) often coexists with other prevalent psychiatric conditions, including mood disorders, anxiety disorders, and substance use disorders (SUD), as well as somatic conditions such as obesity. These comorbidities contribute substantially to healthcare burdens, societal challenges, and economic costs [15,17,18].

ADHD serves as a critical focal point in this context, as it emerges in childhood, affecting approximately 5% of children worldwide [1].

Understanding the shared pathophysiological mechanisms underlying ADHD and its common comorbidities may provide essential insights into developing more targeted and effective therapeutic strategies.

Comorbid conditions are present in over 85% of individuals with ADHD], further exacerbating personal distress, family challenges, and societal burden [19,20].

Recent research consistently highlights the high prevalence of psychiatric comorbidities in ADHD. A 2022 study reported that 92% of children and adolescents diagnosed with ADHD had at least one co-occurring psychiatric disorder.

Similarly, a 2020 investigation identified more than 20 distinct comorbid conditions in pediatric ADHD populations, with over 75% of participants presenting at least one additional diagnosis [21].

These findings underscore the necessity of comprehensive clinical evaluation and integrated treatment strategies, given the substantial likelihood of coexisting psychiatric conditions in ADHD.

Emerging evidence suggests that children diagnosed with attention-deficit/hyperactivity disorder (ADHD) exhibit an elevated risk of developing overweight or obesity. A study conducted in the Netherlands on children aged 5 to 17 years with ADHD demonstrated a significantly higher prevalence of excess weight compared to their neurotypical peers.

Furthermore, a meta-analysis indicated that the pooled prevalence of obesity in adults with ADHD reached approximately 28.2%, compared to 16.4% in individuals without ADHD, reflecting a 70% increased risk [22].

Comorbid conditions frequently arise throughout the developmental course of ADHD and are a defining feature of its persistence into adulthood. These associated disorders substantially contribute to disease burden, with evidence suggesting that they more than double mortality risk [23].

Consequently, a significant proportion of children with ADHD continue to experience adverse health outcomes into adulthood due to the emergence of additional comorbidities. Given that ADHD often represents the initial step in a broader trajectory of negative health consequences, it serves as a critical focal point for mechanistic investigations aimed at predicting disease progression and optimizing therapeutic interventions. Addressing these mechanisms holds substantial promise for mitigating public health burdens, reducing disease-related morbidity, and alleviating patient and family distress.

Pathophysiological Mechanisms Underlying ADHD Comorbidity

Recent research has expanded our understanding of mood and anxiety disorders, highlighting the significant role of dopaminergic mechanisms alongside the traditionally emphasized serotonergic system. Dysfunction in dopamine (DA) pathways, particularly within mesolimbic and mesostriatal projections, has been linked to core depressive symptoms such as psychomotor retardation, diminished motivation,

and anhedonia. Anhedonia, characterized by a reduced capacity to experience pleasure, involves blunted processing of incentive salience, motivation, and impaired reinforcement learning.

Studies have identified that reduced activity in the ventral striatum correlates with anhedonic behavior, observable in individuals at increased risk for depression and those experiencing

various stages of the disorder. This ventral striatal blunting aligns with disease severity and shows improvement following effective treatment.

Moreover, alterations in dopaminergic neurotransmission have been associated with heightened trait anxiety, suggesting a broader impact of DA dysfunction across mood and anxiety disorders [24] (Figure 1).

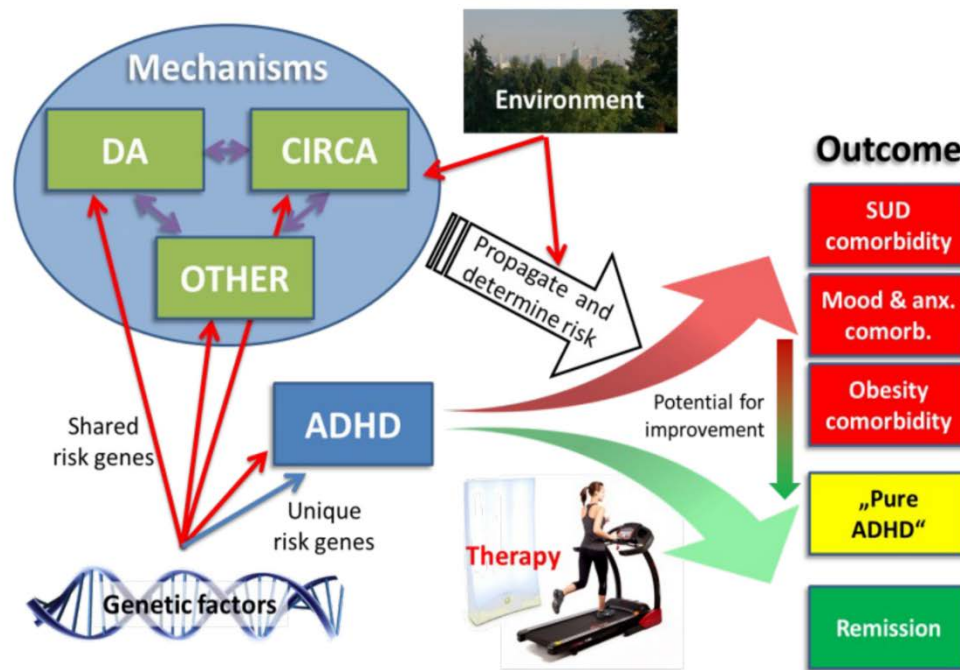


Figure 1. Developmental, genetic and environmental factors contributing to ADHD. While ADHD may have unique risk genes, a substantial proportion of risk variants have a role in the CIRCA and DA systems. Yet unknown pathomechanisms are also influenced by ADHD risk genes and may interact with DA and CIRCA. In interaction with environmental factors, the genetically driven DA and CIRCA pathomechanisms propagate the risk to develop comorbid diseases, i.e. SUD, depression, and obesity in ADHD patients. Therapeutic interventions such as chronobiological modification or exercise - tailored to the patient by stratifying for dysfunctions in DA or CIRCA-bear the potential to prevent comorbidity and thereby improve outcome. Abbreviations: DA, dopaminergic hypothesis; CIRCA, circadian rhythmicity disturbances; SUD, substance abuse disorders.

Circadian Disruptions and ADHD

Recent research has revealed a strong link between Attention-Deficit/Hyperactivity Disorder (ADHD), sleep disturbances, and metabolic dysfunctions, including obesity. Sleep disorders are highly prevalent among individuals with ADHD, with studies estimating that approximately 74.6% of children diagnosed with ADHD also exhibit co-occurring sleep disturbances [25].

Similarly, in adults with ADHD, around 60% screen positive for sleep disorders, with Delayed Sleep Phase Syndrome (36%) and insomnia (29%) being the most frequently reported conditions [26].

Disruptions in circadian rhythms are commonly observed in various psychiatric disorders, including major depressive disorder, bipolar disorder, and schizophrenia [27,28].

These disturbances, which encompass alterations in sleep-wake cycles, core body temperature regulation, and the secretion of hormones such as melatonin and cortisol, appear to be a shared feature across numerous psychiatric conditions.

However, the extent to which circadian dysfunction contributes to the pathophysiology of these disorders remains a subject of debate.

Current evidence suggests that circadian dysregulation may influence psychiatric conditions in multiple ways: (1) as a primary factor, arising from genetic variations in the

circadian system that increase vulnerability to mental illness; (2) as a secondary consequence, resulting from behavioral and environmental influences that lead to misalignment of endogenous rhythms; or (3) as a parallel phenomenon, reflecting common molecular and neurobiological pathways that link circadian function with psychiatric pathogenesis [29,30].

The regulation of circadian rhythms is orchestrated by a complex network of transcriptional regulators that operate in an approximately 24-hour cycle, aligned with environmental light-dark transitions. This evolutionarily conserved system plays a fundamental role in optimizing key physiological functions, including metabolism, feeding patterns, neural activity, endocrine signaling, and sleep-wake regulation [31].

In mammals, circadian rhythms are structured in a hierarchical manner, with the suprachiasmatic nucleus (SCN) of the hypothalamus acting as the central pacemaker that synchronizes peripheral clocks throughout the body [32].

The SCN maintains circadian periodicity independently of external cues, driven by an intricate network of molecular feedback loops that regulate its oscillatory activity [33].

At the molecular level, circadian rhythms are governed by transcriptional-translational feedback loops (TTFLs). The core components of this system include the CLOCK-BMAL1 heterodimer, which activates the transcription of key circadian genes, such as Period (PER) and Cryptochrome (CRY) [34].

The proteins encoded by these genes subsequently inhibit CLOCK-BMAL1 activity, establishing a self-regulating cycle that oscillates over a 24-hour period. This tightly controlled feedback mechanism is essential for maintaining the precise timing of physiological processes, ensuring homeostatic balance across multiple organ systems [35,36].

Circadian Disruptions and Their Broad Implications for Human Health

The disruption of homeostatic mechanisms governing circadian rhythms has far-reaching consequences for human health. Accumulating evidence suggests that circadian misalignment contributes to metabolic dysfunction, including impaired glucose regulation and decreased insulin sensitivity, thereby increasing the risk of disorders such as diabetes [37].

Furthermore, circadian regulation extends beyond metabolism to influence tissue-specific

processes, such as the hair growth cycle and skin homeostasis. Dysregulation of these rhythms has been implicated in conditions such as alopecia and heightened susceptibility to photodamage and other dermatological disorders [38,39].

ADHD is another condition closely linked to circadian disturbances, with approximately 70% of affected individuals exhibiting irregular sleep-wake cycles [40,41].

Beyond its core symptoms, ADHD frequently coexists with sleep-related disturbances, suggesting that circadian dysfunction may exacerbate the disorder. Although the precise mechanisms remain under investigation, emerging evidence indicates a delayed circadian phase in individuals with ADHD, reflecting a shift toward a later biological clock [42,43].

This delay may contribute to difficulties in maintaining regular sleep patterns, further aggravating ADHD symptomatology [40].

Neurobiologically, ADHD has been associated with reduced dopamine levels in the forebrain. Given that light exposure influences dopamine release, bright light therapy (BLT)-which has demonstrated efficacy in treating depression-has been explored as a potential intervention for ADHD. Several studies suggest that morning exposure to BLT not only improves ADHD symptoms but also stabilizes circadian rhythms, with effects persisting for several weeks post-treatment [44].

Additionally, individuals with ADHD often display a preference for late-day activity, aligning with their delayed circadian phase [45-Coogan et al., 2016].

Melatonin supplementation has been shown to effectively regulate sleep-wake cycles and extend sleep duration in children with ADHD experiencing sleep-onset delays [46].

Moreover, exposure to BLT in the morning has been found to suppress melatonin production, reinforcing its potential role in phase-shifting the sleep cycle to an earlier time [47].

Recent research has highlighted the significance of peripheral oscillators and tissue-specific circadian rhythms in maintaining overall circadian homeostasis. These oscillators, located in nearly all organs-including the liver, heart, and lungs-exhibit autonomous rhythmic activity that can be modulated by external factors such as feeding schedules, temperature fluctuations, and hormonal cues. Notably, peripheral clocks can sustain rhythmicity independently of the central pacemaker in the suprachiasmatic nucleus (SCN), underscoring the complexity of circadian regulation [48].

Approximately 50% of genes in various tissues display circadian oscillations, illustrating the extensive role of peripheral clocks in governing gene expression and metabolic processes. These findings challenge the conventional hierarchical model of circadian control, instead supporting a more distributed regulatory framework in which peripheral oscillators significantly contribute to the overall circadian architecture [48,49].

The clinical implications of these insights are substantial, offering new therapeutic strategies for addressing metabolic disorders and other diseases associated with circadian misalignment.

For instance, interventions that manipulate meal timing have demonstrated the ability to reset peripheral clocks, thereby improving metabolic health and reducing obesity risk [50].

These findings highlight the necessity of integrating both central and peripheral circadian dynamics in the development of chronotherapeutic approaches.

Circadian Dysregulation and Sleep Disturbances in ADHD: Implications for Treatment

Emerging evidence continues to highlight the strong association between chronic sleep-onset insomnia and attention-deficit/hyperactivity disorder (ADHD) across the lifespan. In children with ADHD, insomnia symptoms are linked to greater symptom severity and deficits in sustained attention and processing speed [51].

Notably, a substantial proportion of individuals with childhood-onset ADHD-up to 75%-exhibit a delayed circadian rhythm phase, as indicated by a postponed dim-light melatonin onset (DLMO) [52].

This circadian misalignment contributes to difficulties with sleep initiation and maintenance.

Interventions targeting circadian phase shifts have demonstrated potential benefits. For instance, a combination of melatonin administration and bright light therapy has been shown to advance DLMO by approximately two hours in individuals with ADHD, although this phase shift did not correspond with measurable improvements in ADHD symptomatology.

Additionally, low-dose melatonin has been observed to prolong total sleep duration in children and adolescents with ADHD receiving psychostimulant treatment, with a favorable tolerability profile [53].

These findings underscore the necessity of identifying and addressing sleep disturbances in ADHD, as improved sleep regulation may

support broader symptom management strategies.

The link between ADHD and circadian rhythm disruptions is further reinforced by studies examining molecular, endocrine, and behavioral markers. Individuals with ADHD frequently exhibit a phase delay in DLMO, reflecting a shift toward an evening chronotype.

This delay is associated with altered melatonin secretion patterns and contributes to the high prevalence of sleep-onset insomnia in this population [46].

At the molecular level, disruptions in circadian rhythmicity have been observed in adults with ADHD. A study investigating circadian gene expression found that, while *BMAL1* and *PER2* exhibited rhythmic oscillations in control subjects, these patterns were absent in individuals with ADHD.

Furthermore, cortisol secretion rhythms were significantly phase-delayed in the ADHD group, suggesting a broader dysregulation of the circadian system that may contribute to reduced sleep quality and duration [54].

Given these findings, therapeutic approaches aimed at circadian realignment have been explored. Melatonin supplementation has demonstrated efficacy in advancing sleep-wake timing and improving sleep parameters in children with ADHD and persistent sleep-onset insomnia. However, despite improvements in sleep metrics, melatonin treatment did not result in significant changes in behavioral or cognitive outcomes [46].

Overall, these studies highlight the importance of considering circadian mechanisms in the management of ADHD. While circadian-targeted interventions show promise in mitigating sleep disturbances, further research is needed to determine their broader effects on ADHD-related cognitive and behavioral outcomes.

In adults diagnosed with ADHD and delayed sleep phase syndrome, administration of low-dose melatonin has been shown to advance circadian phase and alleviate self-reported ADHD symptoms. However, these beneficial effects were not sustained following treatment cessation [55].

Genetic research has identified associations between ADHD and polymorphisms in circadian clock genes, including *CLOCK*. These genetic variations may not only contribute to ADHD susceptibility but also influence the effectiveness of interventions aimed at circadian dysregulation [56].

Emerging evidence suggests a significant role for melatonin in ADHD pathophysiology. A recent study reported that children with genetic predispositions leading to diminished nocturnal melatonin secretion exhibited more pronounced ADHD symptoms, particularly deficits in attention. This finding supports the hypothesis that circadian rhythm disturbances, mediated by melatonin signaling, may exacerbate ADHD symptom severity [57].

Animal models have provided further insights into the molecular mechanisms underlying ADHD. Zebrafish studies implicate the *per1b* gene in hyperactivity-and impulsivity-like behaviors, linking these phenotypes to dopaminergic regulation and neuronal development. Similarly, murine models with Clock gene mutations reveal interactions between circadian rhythms and dopamine pathways, particularly in relation to dopaminergic activity in the ventral tegmental area. These findings highlight the complex interplay between circadian regulation and dopamine neurotransmission in ADHD pathophysiology [58].

Notably, circadian rhythm disturbances are also implicated in substance use disorders (SUD) and have been linked to genetic variations in CLOCK [59,60].

This suggests that disruptions in the circadian system (CIRCA) may serve as a shared mechanistic pathway underlying the comorbidity between ADHD and SUD.

Genetic and environmental risk factors for ADHD comorbidity

Recent research has identified specific genetic variants associated with neuroanatomical alterations in individuals with Attention-Deficit/Hyperactivity Disorder (ADHD). For instance, studies have demonstrated a link between genetic predispositions and variations in brain imaging phenotypes among individuals diagnosed with ADHD [61,62].

The high heritability of ADHD and its frequent comorbidities, including anxiety disorders, mood disorders, substance use disorders (SUD), and obesity, has been well-documented. Findings from family, twin, and adoption studies consistently indicate that ADHD is a strongly heritable condition, with heritability estimates reaching approximately 74% [63].

Genetic investigations have identified several candidate genes implicated in ADHD,

particularly within the dopaminergic system, including DRD1, DRD2, DRD4, and DAT1 [64].

Additionally, serotonergic pathway genes such as SLC6A4 and glutamatergic system genes including GRIN2B have also been associated with ADHD susceptibility [61].

The frequent co-occurrence of ADHD with other psychiatric disorders suggests a shared genetic etiology. For example, studies report significant genetic correlations between ADHD and major depressive disorder ($r_g=0.31$), indicating overlapping genetic risk factors [65].

Furthermore, genes encoding glutamate and GABA receptors and transporters have been implicated in multiple neuropsychiatric conditions, including ADHD and autism spectrum disorder, further supporting a common genetic basis [66].

Recent genome-wide association studies (GWAS) have provided evidence for shared genetic factors between ADHD and conditions such as major depressive disorder (MDD) and obesity. Large-scale cross-trait analyses have identified significant genetic overlap between obesity-related phenotypes and psychiatric disorders, including ADHD and MDD [67].

Further research has highlighted the role of central nervous system pathways in obesity, with meta-analyses revealing associations between obesity and genes involved in synaptic plasticity and glutamatergic signaling, which are also implicated in ADHD and other psychiatric disorders [68].

Despite growing evidence of a genetic and neurobiological link between these disorders, the specific genetic determinants underlying their comorbidity remain incompletely understood.

Ongoing studies aim to elucidate the shared genetic components to refine our understanding of the complex interplay between ADHD, MDD, and obesity. Similar to genetic influences, individual environmental risk factors exert only modest effects on ADHD susceptibility. Many of these environmental risks are common across multiple psychiatric conditions, including ADHD-related comorbidities such as SUD and mood and anxiety disorders. Additionally, early-life environmental exposures contributing to impaired self-regulation—a phenotype closely linked to ADHD—may elevate long-term risks for adverse mental and physical health outcomes.

This suggests that individuals with ADHD may exhibit increased sensitivity to genetic and environmental factors associated with depression, obesity, and other comorbid conditions.

Expanding research has provided new insights into environmental risk factors for ADHD. Alongside established contributors such as maternal smoking, alcohol consumption, low birth weight, prematurity, and exposure to environmental toxins (e.g., organophosphate pesticides, polychlorinated biphenyls, and lead), novel factors have been identified. For instance, prenatal exposure to certain medications has been implicated. A study conducted at the University of Washington reported that maternal use of paracetamol (acetaminophen) during pregnancy was associated with a threefold increased risk of ADHD in offspring. This study, which measured paracetamol levels in maternal blood during the second trimester and followed children until ages 8-10, provided a more objective assessment than earlier research relying on self-reported medication use. Although the study controlled for variables such as maternal age and body mass index (BMI), the frequency of paracetamol use was not determined. Despite these findings, current medical guidelines continue to classify paracetamol as a safe analgesic during pregnancy, emphasizing the importance of consulting healthcare professionals before use [69].

Exposure to environmental toxins remains a significant public health concern. Recent studies have linked lead exposure, particularly from gasoline emissions, to increased risks of mental health disorders, including ADHD. An analysis of blood lead levels from 1940 to 2015 identified the highest prevalence of lead-associated psychiatric conditions among individuals born between 1966 and 1986, coinciding with peak lead usage in gasoline. Lead exposure, particularly in children under six years of age, has been shown to impair cognitive function, behavior, and neurological development. While leaded gasoline was banned in 1996, residual exposure from older products and materials remains a concern, underscoring the ongoing need for environmental risk mitigation efforts [70].

Additionally, prenatal exposure to neonicotinoid pesticides, the most commonly used insecticides in the United States, has been linked to neurodevelopmental deficits similar to those observed with nicotine exposure. Research suggests that neonicotinoids may contribute to neurodevelopmental impairments such as brain tissue shrinkage, neuronal loss, ADHD symptoms, behavioral dysregulation, and delayed sexual maturation in males. Concerns have been raised regarding the adequacy of current

regulatory measures, as the Environmental Protection Agency has faced criticism for underestimating the potential risks of neonicotinoid exposure, particularly in children.

Given their structural similarity to nicotine, neonicotinoids disrupt insect neural synapses but may also pose neurotoxic risks to humans, with detectable residues found in food, water, and maternal blood samples. These findings highlight the need for stricter regulatory policies and further research into the long-term effects of such environmental exposures [71].

Emerging research has also explored the impact of diet and consumer product exposure on ADHD risk. One study suggested that prolonged contact with plastic toys, particularly through chewing, may pose a risk for ADHD due to bisphenol A (BPA), a known endocrine disruptor [72].

Furthermore, dietary influences on ADHD have been investigated, with research examining associations between ADHD risk and factors such as food additives, maternal smoking, and lead contamination during pregnancy [73].

These findings underscore the complex interplay between genetic predisposition and environmental exposures in shaping ADHD susceptibility.

Conclusions

The interplay between dopaminergic (DA) dysfunction and circadian (CIRCA) disturbances provides a comprehensive framework for understanding the pathophysiology of ADHD and its associated comorbidities, including mood disorders, substance use disorders, and obesity.

Dysregulation of the dopamine system disrupts reward processing and motivation, while alterations in circadian rhythms contribute to sleep disturbances and metabolic dysregulation, exacerbating the challenges faced by individuals with ADHD.

ADHD arises from a complex interplay of multiple neural circuits.

Disruptions in the frontostriatal and frontocerebellar circuits, coupled with dysfunctions in dopaminergic and noradrenergic signaling, play a significant role in the disorder's clinical presentation.

Additionally, imbalances between the default mode network and task-positive networks further contribute to difficulties with attention and impulse control (Figure 2).

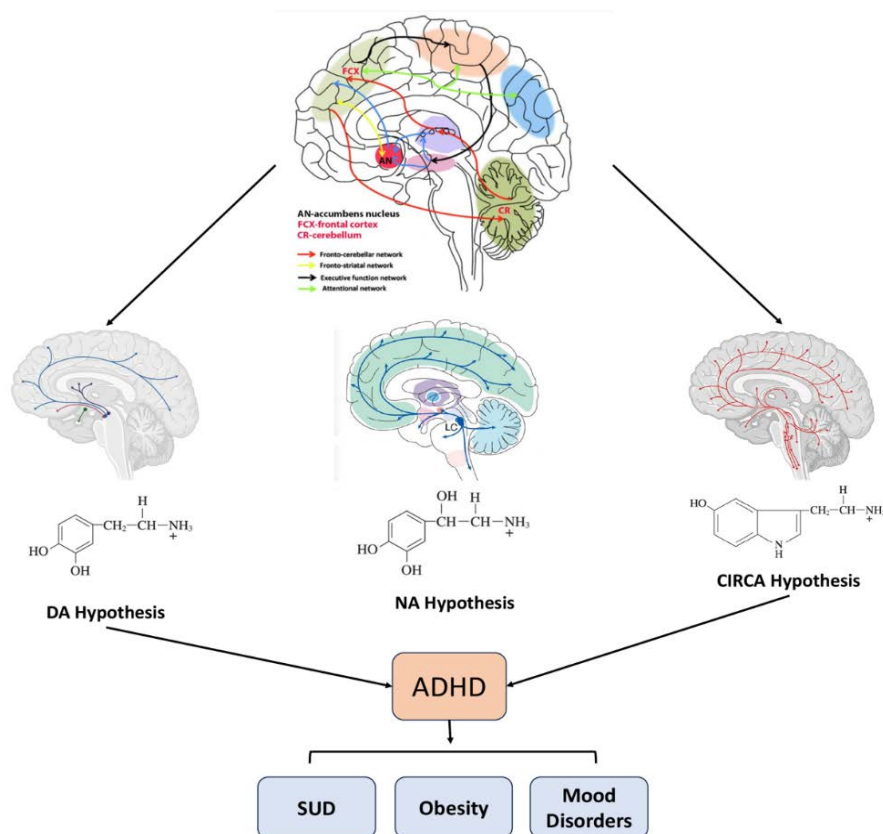


Figure 2. Neural pathways and neurotransmitters contributing to ADHD psychopathology. Abbreviations: DA, dopaminergic hypothesis; NA, noradrenergic hypothesis; CIRCA, circadian rhythmicity disturbances; SUD, substance abuse disorders.

Although converging evidence supports the involvement of DA and CIRCA dysregulation in these comorbid conditions, current knowledge is primarily derived from small-scale studies focusing on individual disorders or specific comorbid pairings.

Notably, non-pharmacological interventions, including structured physical activity and chronobiological strategies, hold promise for modulating both DA and CIRCA pathways. However, further research is needed to elucidate their therapeutic potential and clinical applicability.

Despite substantial evidence implicating these mechanisms in ADHD pathophysiology, their intersection remains underexplored, particularly in relation to diagnostic refinement and targeted treatment strategies.

By integrating findings from neurobiology, chronobiology, and psychopharmacology, a more precise and individualized framework for ADHD management can be established.

Addressing these underlying mechanisms not only advances our understanding of ADHD but also paves the way for innovative treatment strategies with broader implications for its comorbid conditions.

Conflict of interest

None to declare.

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