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What do we know about ADHD?

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ABSTRACT
Attention deficit hyperactivity disorder (ADHD), classified in ICD-10 as hyperkinetic disorder (HD), is one of the most common neurodevelopmental conditions, affecting approx. 5–7% of children and 2.5–4% of adults. Despite decades of research, its clinical presentation remains heterogeneous and debated, with diagnostic differences between ICD-10 and DSM-5. Core symptoms – inattention, hyperactivity, and impulsivity – significantly impair social, academic, and emotional functioning and frequently co-occur with oppositional defiant disorder, conduct disorder, anxiety, depression, and substance use disorders. Historically, the concept of ADHD evolved from early descriptions of "moral control defects" to contemporary evidence of neurobiological underpinnings. Neuroimaging studies demonstrate reduced volumes of frontal lobes, basal ganglia, cerebellum, and abnormalities within fronto-striatal and limbic networks. Neuropsychological models highlight impaired response inhibition, executive dysfunction, and difficulties with delayed reward processing.
Attention deficit hyperactivity disorder is highly heritable (70–80%), with numerous candidate genes implicated in dopaminergic, noradrenergic, serotonergic, and glutamatergic pathways. However, its etiology is multifactorial, involving complex gene–environment interactions. Environmental risk factors include prenatal exposure to nicotine and alcohol, toxic pollutants, maternal stress, and broader psychosocial influences. Given its strong links with emotional difficulties, behavioural disorders, and addiction risk in adolescence, ADHD represents a major public-health challenge. A comprehensive understanding of its neurobiology, developmental trajectory, and etiological complexity is essential for accurate diagnosis and effective individualized treatment.
Keywords: attention deficit hyperactivity disorder; ADHD; hyperactivity disorder; heredity; neurodevelopmental conditions.

INTRODUCTION

Psychiatry continues to struggle with the diagnosis of hyperkinetic disorder (HD), whose clinical presentation consistently surprises with its diversity. Despite a vast body of accumulated data, research into its etiological factors remains ongoing, and scientists persist in seeking solutions that would benefit patients – particularly given the significant social and economic costs associated with HD. It is estimated that symptoms of attention deficit hyperactivity disorder (ADHD) occur in 6.8% of the general population [1]. Considering this relatively high prevalence, the disorder constitutes an important area of interest in both medical practice and psychological research. Attention deficit, hyperactivity and impulsivity of variable severity, manifesting in various life circumstances, present before the age of 7 and leading to difficulties in social functioning are classified as HD according to the International Statistical Classification of Diseases and Health Related Problems, Tenth Revision (ICD-10) [2], or ADHD as classified by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision (DSM-5) [3]. In clinical practice, the acronym ADHD is commonly used to denote HD or ADHD. These terms, however, are not synonymous, as the diagnostic scoring thresholds differ between available classification systems [4, 5]. Despite decades of observing symptoms and publishing clinical descriptions of ADHD, the nature of the disorder remains subject to debate and controversy among psychiatrists, neurologists, psychologists, educators, and sociologists [6]. This stems from the fluctuating symptom severity, which are also found in healthy child populations without impairing their social functioning.

In turn, attempts to link the symptoms to various environmental factors affecting development of the central nervous system (CNS) – e.g., perinatal complications, illnesses, socioeconomic conditions, and cultural models of child-rearing – for years hindered recognition of ADHD as a distinct diagnostic entity. In the 1960s, researchers started to acknowledge that some of the symptoms of childhood ADHD persisted into adulthood. The 1990s yielded numerous studies confirming the presence of ADHD in adults and establishing it as a clinically relevant condition requiring intervention [7, 8]. In 2003, the European Network Adult ADHD was established, which led to the publication of the *2010 European Consensus Statement on the Diagnosis and Treatment of Adult ADHD* [9], based on analyses of available randomized studies. Since then, HD/ADHD is no longer considered a disorder that individuals simply "grow out of". Neurobiological, neuroanatomical, psychopharmacological, neuropsychological, and genetic data have refined hypotheses regarding the biological origins of ADHD [10]. One hypothesis emphasizes difficulties in delaying gratification. Combined with frequent negative social feedback

and attempts at self-medicating distress, this may contribute to increased experimentation with psychoactive substances among adolescents with HD/ADHD [11, 12]. As the most readily accessible intoxicant, alcohol tends to be substance-of-choice for teenagers and hence early alcohol initiation remains one of the major social problems of the 21st century [13, 14]. Prospective studies in adults describe a bidirectional association between HD/ADHD and substance use disorders (SUD) [15, 16]. Molecular genetics research indicates a shared genetic basis underlying both conditions [17].

DIAGNOSTIC CRITERIA

Worldwide, the diagnosis of attention deficit disorder (ADD) and/or hyperactivity disorder is based on 2 medical classifications – ICD-10 and DSM-5. Diagnosis of ADHD according to ICD-10 requires meeting criteria from 3 groups of symptoms, in accordance with established guidelines: 6 out of 9 attention deficit symptoms, 3 out of 5 hyperactivity symptoms, and 1 out of 4 impulsivity symptoms [2]. In addition, symptoms must persist for at least 6 months prior to diagnosis, with the onset before the age of 7. Clinical presentation cannot meet criteria for pervasive developmental disorders, anxiety disorders, manic or depressive episodes, schizophrenia, or other psychoses. In addition, symptoms must appear in more than one setting – e.g., an individual suspected of HD should manifest attention-related difficulties both at work and at home. Moreover, their presence should be corroborated by reports from other informants (e.g., family, partner, friends).

To be diagnosed with ADHD according to the DSM-5 [3], a person must exhibit a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, with the presence of symptoms listed in the inattention domain – at least 6 of all listed symptoms – and/or in the hyperactivity/impulsivity domain, persisting for at least 6 months to a degree inconsistent with the developmental level of the individual and adversely affecting social or academic functioning. In addition, several symptoms of inattention or hyperactivity/impulsivity must have been present before the age of 12. Several symptoms of inattention or hyperactivity/impulsivity must also be present in 2 or more settings (e.g., at home, school, work; with friends or relatives; or in other contexts). There must be clear evidence that the symptoms interfere with or reduce the quality of social, academic, or occupational functioning. Importantly, the symptoms do not occur exclusively during the course of schizophrenia or other psychotic disorders, nor can they be more accurately explained by another mental disorder (e.g., mood disorders, anxiety disorders, dissociative disorders, or personality pathology). Of note, the DSM distinguishes 3 ADHD subtypes: inattentive (6 out of 9 inattention symptoms), hyperactive-impulsive (6 of 9 symptoms), and mixed type (6 inattention and 6 hyperactivity/impulsivity, 12 symptoms in total). Hyperkinetic disorder according to ICD-10 corresponds to the mixed ADHD type according to DSM-5 [4].

CHALLENGES FACED BY PEOPLE WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Given the diagnostic criteria for HD/ADHD outlined above, it is important to underscore the heightened probability of significant difficulties the diagnosis may entail. Among those are an elevated risk of developing SUD, attributable to greater impulsivity [18]; an increased likelihood of developing behavioral addictions, associated with greater impulsivity, a stronger need for novelty seeking, and poorer impulse control [19]; and a higher risk of loneliness, depression, and anxiety disorders. It has been suggested that all these stem from the social challenges commonly encountered by individuals with HD/ADHD [20]. On top of that, they typically report lower self-esteem, a stronger tendency toward procrastination, and frequent difficulties with emotion regulation [21]. Considering all these issues and their negative effects on overall life satisfaction [22], researchers have proposed that HD/ADHD may increase the likelihood of relying on maladaptive coping strategies. This, in turn, elevates the risk of developing one or more of the aforementioned "problems", which then further diminish life satisfaction and increase the probability of the emergence or exacerbation of maladaptive behaviors or disorders.

HISTORY OF HYPERKINETIC DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

History consistently shapes contemporary perspectives, and the evolution of conceptualizations of HD and ADHD is no exception [23]. To this day, psychiatrists, neurologists, psychologists, and educators continue to debate the fundamental nature of both conditions [6, 24]. Diagnostic approaches also vary across major medical classifications, i.e. the ICD-10 and DSM-5. Researchers from diverse scientific fields remain engaged in ongoing discussions aimed at achieving a more unified understanding of the symptoms and identifying the most effective treatment strategies. Descriptions of symptoms resembling hyperactivity and attention deficits appear in children's educational literature of the 19th century. Heinrich Hoffmann – today regarded as a pioneer of German child psychiatry – authored children's rhymes depicting behaviors likely inspired by disorders he observed in his practice [23, 25]. Although these stories cannot serve as parenting guides, they were well received in the medical community, including by Freud, as "authentic characterizations of children devoid of the romanticized notion of innocence" typical of the 19th century [24, 26]. The most renowned literary allegory of a hyperactive child is the character "Fidgety Philip" ("Zappel-Philipp") from Hoffmann's tale *The Story of Fidgety Philip* [23, 25], whose behavior aligns with what would today be interpreted within the diagnostic framework of the combined presentation of HD/ADHD (mixed type).

The earliest descriptions corresponding to the inattentive HD/ADHD subtype are linked to Crichton's 1798 work *An Inquiry into the Nature and Origin of Mental Derangement:*

Comprehending a Concise System of the Physiology and Pathology of the Human Mind and History of the Passions and Their Effects. In chapter 2, *On Attention and Its Diseases*, Crichton categorizes the origins of attention disorders into 2 pathological extremes involving either heightened or diminished "sensibility of the nerves" [24, 25, 26]. Excessive sensitivity, he argues, results in persistent distraction – an "inability to attend to one object for the required length of time". According to Crichton, such distractibility may stem from innate temperament or may emerge secondarily as a consequence of exhaustion. Diminished sensitivity, in contrast, produces a generalized difficulty in activating attention – what Crichton describes as "a total suspension of attention in the brain". He associates this weakened attentional capacity with various bodily states, including poor diet, illness, head injuries or tumors, and epilepsy. Crichton also emphasizes individual differences in attention and the lack of a single normative standard. Notably, he observes that congenital attention difficulties undermine persistence in learning, yet do not impede the ability to understand instructions. Overall, his work represents an early medical attempt to conceptualize mental disorders in both children and adults [24, 25, 26].

In 1902, Sir George Still – often regarded as the father of English pediatrics – published *The Goulstonian Lectures: On Some Abnormal Psychical Conditions in Children*, delivered at the Royal College of Physicians in London. In these lectures, Still described children who exhibited attention deficits, excessive motor activity, and marked emotional reactivity. His young patients struggled to follow social norms, failed to learn from consequences, and showed little responsiveness to punishment. They acted impulsively and sought immediate gratification. Still referred to this cluster of symptoms as a "defect in moral control", which he believed depended on comparative reasoning, moral awareness, and volition. Because he considered the first 2 components to be intellectual in nature, he concluded that a defect in moral control was characteristic of individuals with intellectual impairment. However, Still also recognized children without intellectual impairment who nonetheless warranted careful diagnostic consideration, dividing them into 2 groups: those whose moral control deficits were linked to prior physical illnesses (e.g., meningitis, epilepsy, brain tumor, or head trauma), and those who displayed pathological behaviors in the absence of intellectual disability or physical disease – what he described as "A Morbid Manifestation, Without General Impairment of Intellect and Without Physical Disease". Still suggested that the latter condition was partly hereditary, noting that mothers were more frequently depressed and fathers alcohol-dependent. In addition, some of the children in this group had histories of early brain disturbances ("History of Severe Cerebral Disturbance in Early Infancy") [24, 25].

In 1908, Tredgold, in his work on mental deficiency, described children who only began to exhibit functional difficulties – such as hyperactivity and learning problems – upon reaching school age. He proposed that these symptoms might result from subtle perinatal hypoxia and the increased environmental demands placed on children at this stage [27]. The psychopathological profile of encephalitis lethargica (von Economo's disease), which reached epidemic proportions in Europe and the United States during the 1920s, further contributed to the development of the concept of "minimal brain damage" (MBD) or "minimal brain dysfunction" [27]. Following the illness, affected children frequently exhibited emotional lability, irritability, cognitive impairment, learning difficulties, sleep-related anxiety, and motor abnormalities [24, 25].

The Polish researcher Pitz also investigated behavioral outcomes in children recovering from encephalitis [24, 28]. In 1932, German researchers Kramer and Pollnow published *Über eine hyperkinetische Erkrankung im Kindesalter* ("On a Hyperkinetic Disease of Childhood"), drawing on observations of post-infectious behavioral changes. They described a syndrome encompassing nearly all 3 of the diagnostic criteria used for modern ADHD. The authors highlighted that hyperactivity was particularly disruptive during the preschool years and distinguished childhood hyperkinetic disease from encephalitis lethargica, noting that sleep disturbances were consistently observed in the latter but were not characteristic of all hyperactive children. Their collaboration was ultimately cut short due to the anti-Jewish policies of the Third Reich.

Subsequent research on both sides of the Atlantic, including animal studies, explored the previously observed link between hyperactive behavior and infection, leading to the hypothesis that frontal lobe damage was its underlying cause [24, 29]. Over time, observations led researchers to conclude that attention and behavioral deficits in children could result from CNS injury at birth. Because intellectual development typically remained unaffected, the syndrome came to be known as MBD [23, 25]. Meanwhile, Bradley observed that administering Benzedrine to children with brain injuries improved their behavior, social functioning, and cognitive performance following diagnostic pneumoencephalography. Initially, these findings attracted little scientific attention. It was only with Pannizoni's development of Ritalin in 1955 – originally intended to treat narcolepsy – that stimulant-based therapy for attention disorders and hyperactivity began to gain traction [24, 25]. At the turn of the 1950s and 1960s, the concept of MBD faced criticism, as similar symptoms were observed in children without any history of perinatal injury. Researchers began to attribute the disorder to CNS dysfunction – either immaturity or differences in neurotransmitter functioning – prompting a shift in terminology to "minimal brain dysfunction". During this period, transatlantic differences in conceptualization became more pronounced, with American researchers emphasizing the systematic description of patient behaviors and refinement of terminology [24].

A historically significant contribution was Chess's article, which, while acknowledging a biological basis for hyperactivity, stressed the importance of objective verification of symptoms (beyond parental or teacher reports), rejected the notion that the disorder stemmed from poor parenting, and distinguished hyperactivity symptoms from brain injury [30].

In 1968, the second edition of the DSM introduced the diagnosis "Hyperkinetic Reaction of Childhood", reflecting the

prevailing view that hyperactive behaviors tended to decline in adulthood. Recommended treatments included short-term stimulant therapy and psychological interventions. In contrast, in Europe, the dominant perspective persisted until the 1980s, linking hyperactivity to CNS damage and associating symptoms with other neurological conditions. Diagnoses such as encephalopathy or childhood psychoorganic syndrome were more commonly applied [30].

By the late 1970s and early 1980s, American researchers increasingly focused on attention deficits, a shift reflected in the DSM-III's introduction of ADD, with or without hyperactivity [23, 25], whereas European approaches continued to emphasize hyperactivity. ICD-9 (1978) classified the disorder as "Hyperkinetic Syndrome of Childhood" [31].

By 1994, DSM-IV, drawing on neurobiological, neuroimaging, and population genetic research, identified 3 ADHD subtypes: inattentive, hyperactive-impulsive, and combined. Studies supporting this classification highlighted differences in developmental trajectories among subtypes and spurred further neurobiological investigation into their etiological distinctions. Family and genetic observations reinforced the view that ADHD is not exclusively a childhood disorder. DSM-IV also permitted comorbid diagnoses, acknowledged sex-related differences in symptom presentation, and recognized variability in symptom severity [23, 24, 25]. ICD-10 (1993) provided diagnostic criteria for HD similar to those of DSM-IV, but distinguished 3 symptom domains – attention deficit, hyperactivity, and impulsivity – and applied them differently in the diagnostic process. Its criteria align most closely with the combined subtype of ADHD. Unlike DSM-IV, ICD-10 does not permit comorbid diagnoses. Hyperkinetic disorder/Attention deficit hyperactivity disorder remains a clinical diagnosis, as no specific biomarker can determine its etiology. Symptoms are not always pathognomonic, may occur in other conditions, and their assessment can vary across caregivers, teachers, and patients themselves. Consequently, further research is needed to clarify the classification of HD/ADHD as a distinct nosological entity [25, 32].

EPIDEMIOLOGY OF HYPERKINETIC DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

The reported prevalence of HD/ADHD varies widely across studies and regions. A meta-analysis of 102 international studies conducted 1978–2005 estimated the global mean prevalence among children and adolescents at 5.29%. When accounting for differences in diagnostic criteria, prevalence estimates range from 1–2% using ICD-10 criteria to 3–5% using DSM-IV criteria [32]. A German study of 2,452 children and adolescents aged 7–17 years found that 1% met ICD-10 criteria, whereas 5% met DSM-IV criteria [33]. Other studies report prevalence rates of 5–10% among school-aged children, 2.5–4% among adolescents, and 2.5–4.4% among adults [34]. Polish epidemiological studies estimate the prevalence of HD/ADHD at 5.17% [32]. According to DSM-IV, the combined presentation is the most common subtype, accounting for 50–75% of cases, while the predominantly inattentive presentation occurs in 20–30%, and the predominantly hyperactive-impulsive presentation in approx. 15% [33]. During childhood, the male-to-female ratio is roughly 5:1, with girls more frequently presenting with the inattentive subtype, while boys with the combined subtype. Notably, these sex differences tend to diminish with age [5, 35]. Most researchers estimate that ADHD persists into adolescence in approx. 70% of cases and into adulthood in 30–66% of individuals diagnosed during childhood [9, 36]. A 2009 WHO study identified several childhood factors that predict the persistence of ADHD into adulthood, including the combined subtype, greater symptom severity, a history of parental psychopathology, and comorbid mental disorders such as depression [9]. Persistence of ADHD in adults has also been associated with elevated familial rates of the disorder. Genetic studies involving adopted children and twins indicate that familial occurrence is more strongly influenced by heredity than by environmental factors, suggesting that ADHD can affect an individual's functioning across the lifespan [17].

ETIOLOGY OF HYPERKINETIC DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

The etiology of HD/ADHD is considered multifactorial. Current research aims to elucidate causal mechanisms by examining the relationship between behavioral symptoms and underlying biological changes in the CNS, both at structural-anatomical and functional-operational levels, while also considering the contributions of genetic and environmental factors.

NEUROPSYCHOLOGICAL PERSPECTIVE ON FUNCTIONING IN HYPERKINETIC DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

The core deficit in HD/ADHD is thought to involve reduced inhibitory control. Neuropsychological models explaining the associated functional impairments vary according to their conceptualization of the underlying pathomechanism and can be broadly positioned along 2 poles [37]. Barkley's model, representing a "top-down" perspective, posits that the impulsivity, hyperactivity, and inattention observed in HD/ADHD arise from prefrontal cortex dysfunction, which underlies inhibitory processes. According to Barkley, deficits in inhibition subsequently lead to secondary impairments in executive functions, including working memory, event reconstruction, internal self-talk, emotional self-regulation, and motor control. As a result of executive dysfunction, a child with HD/ADHD may struggle to perceive the relationship between past and future events, assess situations independently, initiate goal-directed behaviors, and integrate new experiences with prior knowledge, all of which undermine effective functioning [5, 37]. Some authors contend, however, that Barkley's model does not adequately differentiate behaviors specific to HD/ADHD from those observed in other childhood disorders [37, 38].

Authors of the Cognitive-Energetic Model [38] propose that problems also arise from the underlying energetic systems (i.e. arousal and activation), affecting the initiation of inhibitory processes, whose activation depends on physiological arousal, vigilance, and readiness to act. Anatomically, they are linked to activation of the basal ganglia and their connections with the prefrontal cortex and the anterior portion of the corpus callosum. Quay's model, by contrast, emphasizes the mechanisms underlying reduced inhibition in individuals with HD [39]. It distinguishes between the behavioral inhibition system (BIS) – comprising the septum, hippocampus, and their projections to the prefrontal cortex, and responsive to signals of punishment or absence of reward – and the behavioral activation system (BAS) – consisting of hypothalamic connections and the ventral tegmental area, and responsive to reward or absence of punishment. Quay proposes that the inhibitory deficit in HD/ADHD depends on motivation and the presence of reinforcements. Individuals with HD/ADHD generate fewer internal cues signaling the need to inhibit a response and struggle to sustain task engagement without external reinforcement. This pattern is associated with a hypoactive BIS, reflecting low sensitivity to punishment, and a hyperactive BAS, reflecting an increased need for reward [37, 39].

In the delay-aversion model, Sonuga-Barke, investigating the impact of gratification on task performance in children with ADHD, suggested that hyperactive individuals experience aversive feelings toward delaying responses, rather than exhibiting a pure inhibition deficit. This hypothesis is supported by observations that hyperactive children, when given a choice between a smaller immediate reward and a larger delayed reward, tend to choose the immediate option; however, in the absence of such a choice, they are capable of waiting for longer periods of time. The anatomical circuits implicated in these processes include: the orbitofrontal cortex, cingulate gyrus, nucleus accumbens, and thalamic connections with the orbitofrontal cortex, with dopamine as the principal neuromodulator [39].

ANATOMICAL AND STRUCTURAL CHANGES IN HYPERKINETIC DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Evidence for the biological basis of HD/ADHD comes from neuroimaging studies of the CNS, which have advanced rapidly since the 1970s. Meta-analyses of structural neuroimaging have primarily examined total brain volume, the cerebellum, and the caudate nucleus. The most pronounced structural differences between individuals with HD/ADHD and controls have been observed in the corpus callosum, total brain volume, and the right caudate nucleus [40, 41]. Most studies report a reduction in total brain volume of approx. 3–5% compared with controls [40]. Individuals with ADHD also show reduced volume in the right frontal lobe, both frontal lobes, or asymmetry between the left and right frontal lobes relative to control groups [40, 42]. A Scandinavian meta-analysis, encompassing both children and adults, confirmed that structural differences in CNS volumes are present in ADHD across different age groups compared with respective control populations [40]. Structural differences between children and adults with ADHD have also been investigated. Reduced volume of the anterior cingulate gyrus within the prefrontal cortex was observed primarily in adults compared with controls, whereas children showed significantly reduced gray matter volume in the right globus pallidus and putamen. Reductions in the anterior cingulate gyrus and amygdala observed in some children were predominantly seen in treatment-naive individuals following a diagnosis of HD. Longitudinal analyses of the caudate nucleus in children revealed volume reductions of 7% on the left and 8% on the right relative to controls. Comparisons between treated and untreated children indicated that those who received treatment exhibited larger caudate volumes [41].

Seidman et al. reported that gray matter alterations in subcortical nuclei tend to diminish as individuals with ADHD transition from childhood to adulthood; however, adults with ADHD continued to exhibit reduced volume of the right caudate nucleus compared with controls [40]. Corpus callosum volumes were generally smaller in children with HD/ADHD, although results varied across studies and across callosal regions. Some investigations found reductions in the posterior portion, while others observed decreases in both anterior and posterior segments [40]. Morphological studies of the limbic system indicated enlargement of the hippocampal head in children with ADHD, which was associated with lower symptom severity and interpreted as evidence of compensatory CNS plasticity [41]. Although overall amygdala volume did not differ between children with ADHD and controls, surface analyses revealed reductions in specific amygdalar regions in the ADHD group, which correlated with greater symptom severity. Disrupted connectivity between the amygdala and the orbitofrontal cortex has also been observed [43]. Some studies have reported reduced cerebellar volume, particularly in the posterior – inferior lobules. Additionally, decreased temporal cortex volumes have been found to correlate with greater ADHD symptom severity [44].

FUNCTIONAL AND PHYSIOLOGICAL CHANGES IN HYPERKINETIC DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Advances in neuroimaging techniques now allow for the assessment not only of brain structure but also of regional activity, neurotransmitter pathways, and metabolic disturbances. Functional magnetic resonance imaging, also known as blood-oxygen-level – dependent magnetic resonance imaging, enables the evaluation of brain function, e.g. by visualizing changes in regions involved in cognitive processes in response to treatment. Positron emission tomography (PET), using appropriately prepared isotopic tracers, allows for the visualization and quantification of metabolic and functional processes in specific CNS regions, as well as the analysis of neurotransmitter

and receptor pathways. Single-photon emission computed tomography (SPECT), employing radiolabeled pharmaceuticals, facilitates the assessment of cerebral blood flow in targeted brain areas. Magnetic resonance spectroscopy is used to analyze chemical compounds produced in tissues during metabolic processes, based on the principle that the proton spectrum remains stable in healthy tissue, while deviations may indicate biochemical alterations [45]. Functional magnetic resonance imaging studies show that the activity of attention-related brain regions in individuals with HD/ADHD does not always align with task demands. During tasks requiring sustained concentration, reduced activation is observed in the right anterior cingulate gyrus. During attentional reorientation, the fronto-striatal network becomes active, but its activation decreases during executive control. Cognitive and motivational difficulties are associated with reduced connectivity within the fronto-striatal network, whereas hyperactivity is linked to decreased activity in the primary motor and occipital cortices. Functional studies of the cerebellum have demonstrated reduced cerebellar activity in response to expected signals presented at unexpected times. Conversely, activity in the anterior cingulate decreases in response to unexpected signals presented at expected times. These findings suggest that dysfunction in the connections between the prefrontal cortex and cerebellum may contribute to difficulties in planning and time management. Some researchers also propose that reduced cerebellar activity may impair the anticipation of behavioral consequences, contributing to adaptive difficulties and impulsivity [45]. Functional PET and SPECT studies assessing cerebral circulation have reported reduced glucose perfusion in the frontal regions and striatum [44]. Investigations of dopamine transporter (DAT) density in the striatum have yielded mixed findings: some studies show increased DAT density in individuals with ADHD compared with controls, whereas Volkow et al. reported decreased DAT density, which has been interpreted as either down-regulation of dopaminergic neurotransmission or reduced dopamine availability [46]. Abnormalities in dopamine release have also been observed in the hippocampus and amygdala [47]. Magnetic resonance spectroscopy has revealed disruptions in glutamatergic metabolism within the prefrontal cortex and striatum. Given that glutamate plays a key regulatory role in dopaminergic neurotransmission in the CNS, these findings suggest a mechanistic link between glutamatergic and dopaminergic dysfunction in HD/ADHD [47].

ENDOPHENOTYPES IN HYPERKINETIC DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER

An endophenotype is a heritable biological marker linked to a disorder, occurring more frequently in unaffected relatives of affected individuals than in the general population [47]. In HD/ADHD, the core deficit is thought to be impaired response inhibition, which leads to secondary neuropsychological abnormalities. Studies of patients and their siblings have identified similar deficits in response inhibition, providing a potential tool for risk assessment. Neuropsychological testing has linked specific gene polymorphisms with clinical symptoms. For example, the DAT1 10/10 genotype is associated with attention deficits, whereas the presence of 7 or more VNTR repeats in the *DRD4* gene may correlate with impulsive performance on psychological tasks. These findings have led to a proposed distinction between 2 ADHD subtypes based on dopaminergic activity: one linked to mesocortical projections in the prefrontal cortex, characterized by impairments in thinking and behavior specifically related to inhibitory control; and another, in which impulsivity and motivational difficulties are associated with mesolimbic dopaminergic pathways [48]. Neuroimaging studies, particularly those combining imaging with genetic analysis, have also been applied to endophenotype research, allowing the investigation of neurobiological mechanisms by which specific gene polymorphisms may influence behavior [49].

GENETIC FACTORS IN HYPERKINETIC DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Evidence from historical, epidemiological, neuroanatomical, and neurophysiological studies supports the heritability of HD/ADHD. Family genetic studies indicate that first-degree relatives of affected individuals have a fivefold increased risk of exhibiting symptoms compared with the general population. Approximately 30–50% of relatives of individuals with ADHD have a personal history of the disorder, and 20–40% of parents of children with ADHD report residual symptoms themselves. Relatives also show elevated rates of other psychiatric disorders. Twin studies further confirm the genetic contribution, with concordance rates of approx. 80% for monozygotic twins and 29% for dizygotic twins. In line with these findings, 18% of biological parents of children with ADHD exhibit symptoms, compared with 6% of adoptive parents [50]. Advances in molecular genetics have facilitated the identification of genetic factors involved in the development of ADHD. Strategies employed include linkage studies, which scan the genome for markers associated with DNA regions potentially harboring disorder-related genes, and association studies, which examine polymorphisms in candidate genes and their correlation with the condition. More recently, genome-wide association studies (GWAS) have enabled the genotyping of large numbers of gene polymorphisms and replication analyses, allowing for the identification of variants not previously linked to ADHD [47]. A 2010 GWAS meta-analysis did not pinpoint specific gene polymorphisms definitively associated with the disorder, but candidate gene analyses suggest potential associations [51]. Analysis of rare copy number variants has indicated that duplications at *15q13.3* may be associated with ADHD and comorbid behavioral disorders [52]. Candidate gene studies are closely integrated with neurobiological, psychopharmacological, and biochemical research, offering insights into brain development and CNS responses to pharmacological treatments. These studies link HD/ADHD to dysfunction in dopaminergic, noradrenergic,

serotonergic, and glutamatergic systems. Investigations typically focus on genes involved in the encoding, synthesis, or metabolism of these neurotransmitters, as well as on proteins critical for CNS development [50, 53, 54].

ENVIRONMENTAL FACTORS IN HYPERKINETIC DISORDER AND ATTENTION DEFICIT/ HYPERACTIVITY DISORDER

Some authors estimate that environmental factors contribute to HD/ADHD in approx. 10–40% of cases [54]. Analyses of prenatal exposure to substances such as tobacco, alcohol, heroin, and caffeine, including findings from earlier studies, provide inconclusive evidence regarding their role as risk factors for HD/ADHD symptoms in children. This uncertainty may partly stem from difficulties in accurately measuring exposure, as most studies rely on maternal self-report, which limits understanding of gene – environment interactions. Review articles suggest potential interactions between genetic factors and prenatal exposure to tobacco and alcohol, including paternal exposures, in the etiology of ADHD. Recent research also implicates exposure to persistent organic pollutants, heavy metals (e.g., lead, manganese), organophosphate compounds, and phthalates, with some studies indicating an elevated risk particularly among boys. Deficiencies in zinc and omega-3 fatty acids may also contribute to the onset or severity of HD/ADHD symptoms. Maternal obesity has been linked to an increased risk of symptom development. Growing attention is given to maternal psychological factors, including stress during pregnancy, early traumatic experiences, and maternal rejection, although methodological limitations have been noted in these studies [55]. Numerous investigations focus on the interaction between genetic and broad environmental factors. A meta-analysis by Nigg et al. underscores the interplay between specific gene polymorphisms and environmental exposures in the manifestation of HD/ADHD symptoms [54].

SUMMARY

Hyperkinetic disorder/Attention deficit/hyperactivity disorder is regarded as one of the most heritable psychiatric conditions. Nonetheless, its multifactorial etiology makes it challenging to identify specific genes contributing to its pathogenesis [52]. It is also recognized that HD/ADHD may be influenced by environmental factors, including pre- and postnatal conditions, CNS disorders, exposure to toxic substances, and socio-economic circumstances [55, 56]. Contemporary research increasingly emphasizes the integration of genetic and environmental factors in elucidating the mechanisms underlying the disorder [54, 57].

Evidence indicates that HD/ADHD is strongly associated with other disorders in youth. Numerous studies highlight the comorbidity of HD/ADHD with emotional and behavioral problems, underscoring the importance of differentiating it from other conditions in both children and adults [5, 9, 55]. While a comprehensive discussion is beyond the scope of this review paper, it is essential to examine the core symptoms that may manifest during the course of HD. Of note, differences often emerge in perceptions of mental health problems between parents/caregivers and adolescents, as observed by physicians during assessments. Impulsivity represents a significant health and emotional concern in adolescents and has been identified in some studies as a key factor in early alcohol initiation. A meta-analysis by Lee et al., reviewing literature 1980–2009, confirms that the symptoms most frequently accompanying HD are oppositional defiant disorder and conduct disorder, both of which are linked to an increased risk of substance abuse in affected individuals [58].

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