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Adult ADHD: it is old and new at the same time – what is it?

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Abstract: Even though the number of studies aiming to improve comprehension of ADHD pathology has increased in recent years, there still is an urgent need for more effective studies, particularly in understanding adult ADHD, both at preclinical and clinical levels, due to the increasing evidence that adult ADHD is highly distinct and a different entity from childhood ADHD. This review paper outlines the symptoms, diagnostics, and neurological mechanisms of ADHD, with emphasis on how adult ADHD could be different from childhood-onset. Data show a difference in the environmental, genetic, epigenetic, and brain structural changes, when combined, could greatly impact the behavioral presentations and the severity of ADHD in adults. Furthermore, a crucial aspect in the quest to fully understand this disorder could be through longitudinal analysis. In this way, we will determine if and how the pathology and pharmacology of ADHD change with age. This goal could revolutionize our understanding of the disorder and address the weaknesses in the current clinical classification systems, improving the characterization and validity of ADHD diagnosis, specifically those in adults.

Keywords: attention-deficit/hyperactivity disorder (ADHD); adult ADHD; preclinical ADHD studies; clinical ADHD studies; ADHD presentations

1 Introduction

Attention-deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder characterized by cognitive deficits, such as the inability to sustain attention, or behavioral disturbances, including the inability to regulate motor and impulse behavior, forming the core symptoms of inattention, hyperactivity, and impulsivity. ADHD is acknowledged today as a more dimensional rather than a categorical disorder (Hoogman et al. 2012; Lubke et al. 2009; Shaw et al. 2011). As per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5th ed.), several inattentive or hyperactive-impulsive ADHD symptoms must be present before the age of twelve, present in two or more settings, including home, school, or work, with friends or relatives, which interfere with or reduce the quality of the social, school, or work functioning (APA 2013). ADHD neurobiology is underscored by a high level of genetics and heritability (Demontis et al. 2019; Li and He 2021) and functional and structural neuropathology (Albajara Sáenz et al. 2019; Samea et al. 2019; Van Dessel et al. 2019). Although thought to be a highly familial disorder, environmental factors may also play in ADHD susceptibility (Fröelich et al. 2011). Further, ADHD is also thought to emerge from a developmentally dynamic and complex interplay of genetic and environmental influences, as early as fetal life (Cecil and Nigg 2022), indicating that epigenetic changes can be a key molecular mediator and marker of ADHD. However, the exact etiology of the disorder is still poorly understood.

ADHD is typically considered a childhood disorder. However, findings identified that it could persist into adulthood in 40–60 % of cases (Barkley 2009; Gascon et al. 2011).
2 Onset of adult ADHD

Although most adults receive ADHD diagnosis in childhood, their manifestations upon diagnosis are sometimes misinterpreted and ignored in the worst cases. Regardless of whether ADHD symptoms were present as early as childhood (<12 years), these individuals would still receive an adult ADHD diagnosis. Importantly, in adults, ADHD symptoms may seem distinct from those observed in children and adolescents. One reason may be that everyday life and daily tasks of adults differ from those of children and adolescents, regardless of their psychiatric history. In addition, children and adolescents are more explorative than adults due to their greater risk-taking behavior, which is why ADHD is largely diagnosed at a younger age. However, ADHD also affects adults, which may become apparent as they age, affecting their daily living performance (Harpin 2005). Based on the literature, the following manifestations exist among adults with ADHD:

- complications and failure to excel in school (college or university) or job.
- challenges or failure in forming relationships with family members, friends, partners, or co-workers.
- periodic accidents or injuries.
- problems with substance use and misuse, primarily with alcohol and stimulants.
- issues with general mental health.

These manifestations observed in adults with ADHD seem to be more severe and impairing compared to the common presentations observed in children, including an inability to focus on any activity and easy distractibility, short attention span during play or schoolwork, trouble with sitting still or fidgeting, unrestrained movement and running around, loud and disruptive engagements in any activity, excessive talkativeness and highly likely to interrupt people (see Figure 1 for the comparison of childhood and adult ADHD manifestations).

Also, research findings show brain structural differences in ADHD that persist into adulthood, even in cases where people previously diagnosed with ADHD no longer meet the diagnostic criteria for the condition (Roman-Urrestarazu et al. 2016). Such findings suggest that while ADHD symptoms may become less apparent as people get old, they may still experience a variety of neurological differences, such as disorganization, impulsive decision-making, internal restlessness, wandering attention, and procrastination, that can influence their behavior, thereby impairing their daily living, wellbeing as well as work ability. For instance, adults with ADHD may struggle to manage job-related tasks or behave impulsively in situations demanding discretion (Geffen and Forster 2018). This can lead to more frequent job changes or unemployment, resulting in the personal economic downturn of these individuals. They may even have a failure to maintain long-term relationships. It seems that ADHD symptoms change with age. Indeed, there is evidence suggesting that ADHD symptoms may affect adults differently (Ginsberg et al. 2014), but do not necessarily worsen with age, given that adults tend to have better resources to manage and cope with their symptoms than children and adolescents.

The question, therefore, arises if adult ADHD is really a childhood-onset neurodevelopmental disorder or rather a distinct disorder different from childhood ADHD. Researchers explored (and answered) this question with a four-decade longitudinal study published in the American Journal of Psychiatry in 2015 (Moffitt et al. 2015). This study analyzed ADHD cases diagnosed in childhood and adulthood from a cohort of 1037 individuals and evaluated using various data sources, including participants, parents, teachers, informants, neuropsychological test results, and administrative records. This study accounted for several factors, including ADHD symptoms, associated clinical features, comorbid disorders, neuropsychological deficits, genome-wide association studies (GWAS)-polygenic risks, and life impairment indicators. This study is probably among the most comprehensive adult ADHD data ever reported, with four important findings noted here:

- Childhood ADHD had a prevalence rate of 6 %, occurred primarily in male subjects, was associated with neurocognitive deficiencies and childhood comorbid conditions with polygenic risks and residual adult life impairment.
- Adult ADHD showed a low, gender-balanced prevalence rate of 3 % and is typically associated with adult substance dependence, life impairment, and treatment contact.
– 90% of adult ADHD subjects lacked a history of childhood ADHD, indicating nonoverlapping backgrounds.
– Adult ADHD group did not display neuropsychological deficits during childhood or show polygenic risk for childhood ADHD.

From these findings, adult ADHD seems to represent an entity different from childhood ADHD and does not appear to be a childhood-onset neurodevelopmental disorder, a deduction that, if supported by more extensive findings, would revolutionize our knowledge of ADHD disorder. However, if definitions of adult ADHD are amended in the DSM-5th ed. criteria for ADHD, qualified mental health care professionals or general practitioners are bound to follow these guidelines. Therefore, the end goal should be to generate a valid ADHD classification that is highly objective, reliable, and biologically founded, which unfortunately remains unavailable.

Additionally, it should be noted that the American Psychiatric Association introduced a subtle but important change in the criteria in 2013 when they published the DSM-5th ed. (APA 2013), an update from the DSM-4th ed.-text revision (TR) edition (Epstein and Loren 2013). This includes modifications to the criteria (A–E) for ADHD diagnosis, namely criterion A (ADHD symptoms), criterion B (age of onset), criterion C (disorder pervasiveness), criterion D (degree of impairment), and criterion E (other exclusionary conditions). For criterion A, additional examples of ADHD symptoms and how they may manifest during adolescence and adulthood are now covered, as well as the requirement of five symptoms in any of the symptom domains to be diagnosed with ADHD in older adolescents and adults. Meanwhile, for criterion B, the onset of several inattentive or hyperactive-impulsive ADHD symptoms has been increased at least before the age of twelve. For criterion C, evidence of the presentation of ADHD symptoms has now been extended to two or more settings, for example at home, at school or work, with friends or relatives or in other activities. In addition, there is clear evidence that ADHD symptoms interfere with or reduce the quality of social, academic, or occupational functioning (criterion D). Lastly, criterion E indicates that ADHD symptoms are separate from other psychiatric disorders, such as autism spectrum disorder, obsessive-compulsive disorder, or depression with distinct signs and symptoms. Overall, the new changes made in DSM-5th ed. emphasize the requirement of age-appropriate diagnostic tools for use in adolescents and adults and the acknowledgment of ADHD as a neurodevelopmental disorder, indicating the nervous system functions and developmental alterations caused by ADHD. Regarding ADHD classification of diseases, the previously termed “types” or “subtypes” are now referred to as “presentations”, identified as predominantly hyperactive (ADHD-H), predominantly inattentive (ADHD-PI), and combined (ADHD-C). Furthermore, severity of the disorder can now be specified mild, moderate, or severe.

More recently, in March 2022, DSM-5th ed.-TR was published, and no updates on adult ADHD information from the previous version were provided. One recent review
paper critiquing the text revision indicated that only a little has changed but was considered insignificant (Koutsoldenis and Honkasila 2022). So, there appear to be age influences on ADHD, but they were not thoroughly presented and discussed. This issue may have resulted from the present lack of information regarding the age-dependent analysis of ADHD, and specific parameters or markers for the successful and effective diagnosis of ADHD are not yet available.

3 Adult ADHD screening and diagnosis

Given the differences between childhood and adult ADHD, we will next address the question how this disorder can be screened in adults? To address this, the Adult ADHD Self-Report Scale (ASRS) symptom checklist was materialized in 2003 in conjunction with the World Health Organization (WHO) and the adult ADHD workgroup (including researchers from New York University Medical School and Harvard Medical School). The ASRS-version 1.1 (ASRS-v1.1) consists of 18 questions, of which six served as ASRS screeners. These questions are consistent with the DSM-4th ed.-TR criteria and address ADHD symptoms in adults (Kessler et al. 2005b). One investigation has revealed that the six-question ASRS screener is as useful and effective as the eighteen-question ASRS in the ADHD diagnosis among the general population (Brevik et al. 2021), suggesting its reliability and validity as a self-report scale for use in adults with ADHD.

Patients fill out the ASRS-v1.1 symptom checklist that would allow the healthcare professional to understand and evaluate the presenting symptoms experienced by the patient that identify the presence of core symptoms of ADHD: inattention, hyperactivity, and impulsivity (refer to Kessler et al. 2005b). The ASRS-v1.1 symptom checklist is now available in over 25 languages. Comprehensive information on the ASRS instruments is available on the National Comorbidity Survey website (https://www.hcp.med.harvard.edu/ncs/asrs.php). An update to the ASRS symptoms checklist, published by the same group in 2017 (Ustun et al. 2017), presents the modifications made to reflect ADHD diagnosis based on the DSM-5 criteria. The ASRS checklist included an updated six-item questions of the ASRS, replacing two of the six items with items on executive functioning (i.e., not part of the ADHD-defining symptoms) (Ustun et al. 2017). These updates have good psychometric properties as a screener for the general adult population that can identify ADHD with high sensitivity and specificity. Also, it could discriminate well between patients presenting for evaluation and those needing special treatment. This allows expansion of our knowledge and understanding of adult ADHD as being characterized by deficiencies in executive functioning, needed to regulate and guide human behavior. The brain therefore requires a central coordinating system known as the executive system. This system is responsible for the synchronization of cognitive processes responsible for attention and memory function, goal-directed and task-oriented behaviors, as well as self-regulation and behavior inhibition (Hosenbocus and Chahal 2012). This system incorporates the executive function required for preparation and execution of complex behaviors. In fact, ADHD is essentially a cognitive disorder of developmental impairments in brain executive functions. They are complex in nature and when impaired, constitute a pattern that can be recognized readily in clinical practice. This can be a form of hyperactivity, impulsivity, and inattention, which can impair daily tasks among patients.

In general, the ASRS symptom checklists improve the clinician's ability for faster preliminary identification of adult patients requiring a further comprehensive ADHD diagnostic evaluation and for other comorbid neuropsychiatric disorders (Adler et al. 2006). Furthermore, the checklist shows validity for use in the ADHD-specialized mental health care facilities and general health facility, thus, supporting both mental health and general practitioners. Overall, the identification and diagnosis of adult ADHD are paramount, given the negative effects of this neuropsychiatric disorder in the major aspects of human personal, familial, and societal life. Thus, it is important to have a standardized tool catered to the needs of clinicians that could better assist them in properly diagnosing patients that will help in symptoms management and treatment. Also, other tools may be used to supplement the main checklist or standardized diagnostic tool, such as patient's past and present medical records and interview forms to be used by parents and other family members or significant others, and even workmates, among others (Culpepper and Mattingly 2008; Martel et al. 2017). This will not only help in the detection of the disorder, but also allow proper utilization of treatment modalities whether pharmacologically or non-pharmacologically. The fraudulent reporting of symptoms to obtain the ADHD diagnosis for reasons of obtaining stimulants prescription is another issue leading to the difficulty in diagnosing adult ADHD (Sansone and Sansone 2011). Therefore, supportive evidence coming from someone (other's perspective) besides the patient helps to address this challenge.

To establish adult ADHD diagnosis, various other structured diagnostic interview instruments were designed for use by clinicians (Abrams et al. 2018). The objective of
these adult ADHD diagnostic tools is to determine the existence of ADHD in this age group by using a structured interview guide founded on DSM criteria. Among the existing and generally used diagnostic tools these include the Adult ADHD Clinical Diagnostic Scale (ACDS v1.2) (Kessler et al. 2010), Conner’s Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein et al. 2001), and the Diagnostic Interview for ADHD in adults (DIVA-5) (Zamani et al. 2021). In addition to making the diagnosis of ADHD, these structured and systematized tools can help to document the chronology (history) and observance of symptoms and provide an exhaustive examination of clinical symptoms and overall functional impacts (i.e., on personal, familial, societal life) of the disorder in adults. Again, a more intense discussion on the basics of adult ADHD, its screening and diagnosis, the onset of symptoms, and overall neurobiology appears necessary to better understand this disorder in the future.

4 Adult clinical ADHD symptoms

Factor analyses in ADHD divide the behavioral symptoms into two separate domains, reflecting inattention and the other a combination of hyperactivity/impulsivity. However, of these symptom domains, inattention or attaintive behavior has become the hallmark of ADHD that persists or is present during adulthood (Döpfner et al. 2015; Kessler et al. 2010). Several studies have identified the persisting impairment in attention and memory in adults with ADHD. Firstly, deficits in adults with ADHD are much more pronounced on complex attentional tasks than the simpler ones (Báltin et al. 2009; Schoechlin and Engel 2005), also with high errors of omission and reaction time. Secondly, when exposed to memory tests measuring multiple aspects of memory, such as working versus long-term memory, adults with ADHD show greater impairment in long-term memory, with deficits in recall and recognition, highlighting the impairment in encoding rather than retrieval induced by ADHD in adults (Skodzik et al. 2017). However, despite these findings of impaired memory, adults with ADHD still showed the same accuracy level as controls in predicting memory in a meta-memory performance test (Knouse et al. 2012) which captures the knowledge of one’s memory capabilities. This highlights another challenge of disentangling memory deficits from attentional deficits. Working memory impairments are common in ADHD which creates diverse challenges with other functional dimensions (Fassbender et al. 2011). Remarkably, impaired general executive function/working memory, rather than its individual sub-components (reordering, updating, dual processing) has been found to predict ADHD and its severity (Fosco et al. 2020). This indicates that total rather than specific working memory processes is essential in understanding ADHD and its symptoms. Alternatively, these discrepancies may rather be a result of behavioral inhibition (Boonstra et al. 2005), as it was found that adults with ADHD are more susceptible to proactive interference (where old memories interfere with the retention of new learning) but not in spatial working memory tasks (White 2007). Also, adults with ADHD have a higher rate of incorrect responses on a modified serial reaction-time task involving distracting stimuli to investigate implicit sequence learning in ADHD and control participants, revealing unimpaired implicit learning performance in adults with ADHD (Pedersen and Ohrmann 2018). This further supports previous findings of impaired behavioral inhibition in adult ADHD. It should be noted that attention and working memory are both keys to learning novel information. Attention allows information to be taken in, while working memory enables the brain to make sense of it. In the case of ADHD, those who have the disorder and struggle to learn have attention issues, working memory issues, or both. Furthermore, these findings allow us to identify ADHD as a brain disorder, given that various parts of the brain, including the amygdala, the hippocampus, the cerebellum, and the prefrontal cortex, govern attention and memory functions. The frontal lobe, which covers the prefrontal cortex, an area of the brain responsible for higher-order cognitive functioning such as problem-solving, was found using computational neuroanatomic techniques, to have maturational delays in children with ADHD (Shaw et al. 2007). However, regional maturational progress remains similar in both children with and without ADHD, with primary sensory areas attaining peak cortical thickness earlier than the polymodal high-order association areas. Although data from adults were not studied, it was posited that in adults with ADHD, attaining cortical maturational development may also be delayed. Interestingly, in another study, the use of fronto-central NoGo P3 event-related potential (ERP), a neurophysiological index in ADHD, and a biomarker for response inhibition and aging was used in adults (Kakuszi et al. 2020). Young adults with ADHD were shown to have delayed developmental P3-trajectory which was also reduced across all emotional valences, and this reduction was mostly pronounced in this age group when compared to advanced ages. Interestingly, these P3 differences weakened in middle adulthood but started to resurge with advancing age. Overall, these findings illustrate a mirroring pattern between brain development and aging, suggesting that the brain areas with delayed development tend to degenerate relatively early. These factors may also be the reason why
adult ADHD appears to be distinct from childhood ADHD. Overall, ADHD may induce neuroanatomical and neurological impairments that could affect behavior.

Studies indicated that inattention tends to endure with age (Döpfner et al. 2015; Kessler et al. 2010); at the same time, the hyperactive/impulsive symptoms wane with age. They also showed that hyperactivity may become suppressed in the form of restlessness, sometimes misinterpreted as anxiety. Also, it was shown that the hyperactive/impulsive symptoms may become less apparent due to changing behavioral constraints and environment. Recently, a study proposed to subdivide symptoms of impulsivity into four dimensions (Lopez et al. 2015):

- perseverance (ability to stay on task when bored),
- premeditation (ability to consider consequences of actions),
- sensation seeking (need for excitement and stimulation), and
- urgency (tendency to act rashly).

Results show that compared with controls, adults with ADHD who were not exposed to any addictive substance had lower perseverance and premeditation, and urgency. Another common behavior reported by adults with ADHD is risky driving behaviors (i.e., high rates of vehicle collisions, citations, and arrests) (Cox et al. 2011). This study identified the contributions of impaired attentional control, greater fatigue, and elevated daytime sleepiness in the observed behavior (Bioulac et al. 2015); unfortunately, these are not mentioned in the DSM-5th ed. diagnostic criteria (APA 2013).

Along with normal development, ADHD symptoms display important normative changes. Among these changes include the presence of hyperactivity in school-age children as a predominant ADHD symptom which normatively decreases until reaching the peak of childhood age (Sandberg 2002). In contrast, inattention becomes noticeable as children enter school, but remains relatively more stable over time (Hart et al. 1995). These are consistent with the ADHD prevalence rates in preschool to school-age children of around 5–6% (Egger and Angold 2006; Polanczyk et al. 2007) and then fall marginally to around 3–4% in adulthood (Kessler et al. 2006). On the other hand, adults with ADHD were shown to have persistence of inattention and a decline in hyperactive and impulsive symptoms. The inattention in adults with ADHD is prominent in their activities of daily living including work, which is commonly seen as inorganization, doing careless mistakes, inattention to details, inability to follow-through with instructions, and being overall forgetful in their daily life. They also try to multi-task without completing any of them. Moreover, it was shown that hyperactivity in adults with ADHD becomes more of an internal experience rather than being observed externally. This hyperactive manifestation may be observed as a general feeling of restlessness which can be seen as fidgeting or becoming easily bored when tasks become mastered. Furthermore, impulsive symptoms in adults with ADHD can manifest as engagement in risky behaviors, intruding other people’s conversations, and use of inappropriate remarks. While these behaviors seem normal for others, these behaviors become abnormally frequent and constant in adults with ADHD which can impair their ability to function well, leading them to struggle with personal, professional, and social functioning, and increases their higher risk for other behavior and psychiatric comorbidities. This includes increased rates of conduct and antisocial personality disorder (APD) and oppositional defiant disorder (ODD). Many adults with ADHD are also at higher risk of having mood disorders with depression and bipolar disorder commonly diagnosed (Goodman and Thase 2015; Klassen et al. 2010). Repeated patterns of failures and frustrations coupled with anxiety due to ADHD in adults can worsen depression (Knouse et al. 2013).

5 Neurobiology and genetics of ADHD

Concepts of ADHD shifted from an assertion that the disorder is a cluster of few sequestered dysfunctions to more elaborate models combining the heterogeneity of ADHD clinical behavioral presentations. Observations from neuroimaging studies demonstrate structural and functional impairments in brain networks involved in the development and function of cognitive functions (e.g., attention, memory), sensorimotor functions, and emotion regulation (Cortese and Castellanos 2012). Neurophysiological findings revealed the presence of brain functioning alterations with ADHD. ADHD patients tend to exhibit brain functional hypo-arousal and pronounced cortical slowing, indicated by increased slow waves (theta) and decreased fast waves (beta) in the quantitative electroencephalography (qEEG) (Barry and Clarke 2009), with the theta/beta ratio (TBR) suggested as a marker to help diagnose ADHD (Lubar 1991). A large-scale study consisting of 482 patients (6–30 years old) reported 98% specificity and 86% sensitivity of the use of scalp vertex (Cz) TBR in diagnosing ADHD (Monastra et al. 1999) and was further confirmed in a meta-analysis displaying an effect size of 3.08 predicting a specificity and sensitivity of 94% (Snyder and Hall 2006). Given these findings, TBR was suggested for use as a complementary
tool along with self-reported scales for ADHD clinical evaluation (Snyder et al. 2008). Hence, in 2013, the U.S. Food and Drug Administration (FDA) approved the use of EEG-based methods to diagnose ADHD, such as the Neuropsychiatric EEG-Based Assessment Aid (NEBA) System (Thomas and Gaffney 2017). This noninvasive neurophysiological scan test gauges an increased brain oscillatory TBR in ADHD. Previously, in an eyes-open EEG condition using spectral analysis of absolute ($\mu$V$^2$) and relative power (%) carried out for four frequency bands (delta (2–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–21 Hz)), adults with ADHD did not show changes in the absolute power of slow waves (theta and beta) when compared with age-matched controls. However, ADHD children were found with increased theta and beta waves absolute power whereas the relative power did not differ from that of controls. However, across groups, children showed greater delta and theta waves relative power than adults, but adults have higher alpha and beta (higher) frequencies. From this experiment, only ADHD children, but not ADHD adults, showed a greater TBR. Now, the question is aimed at understanding whether these discrepancies stem from maturational processes (age discrepancies) or if there is a core difference in cortical arousal between ADHD children and adults (Markovska-Simoska and Pop-Jordanova 2017). Until 2010, TBR consistently showed a high diagnostic value as a biomarker candidate for ADHD. However, rising concern over accuracy and reliability is increasing as some studies have failed to replicate TBR differences between ADHD and non-ADHD samples in children (Ogrim et al. 2012) and adults (van Dongen-Boomsma et al. 2010). Moreover, a cross-sectional analysis only identified an accuracy of 49.2–54.8% on the use of TBR in predicting ADHD (Buyck and Wiersema 2014). This is, in part, caused by the high heterogeneous nature of ADHD as a mental disorder. Therefore, future studies must evaluate this heterogeneity applying various tools, including MRI and genetic studies in addition to EEG analysis.

At a molecular level, ADHD has been correlated to dysfunctions in the dopaminergic systems, a.k.a. dopamine reward pathway, showing its complexities as a disorder. Meanwhile, genetic studies show about 74% of heritability in ADHD (Faraone and Larsson 2019), higher than most other neuropsychiatric disorders, and heritability is estimated to impact about 22% of single nucleotide variants (SNPs) presentations (Gudmundsson et al. 2019). Given these findings, there is a need for the inclusion of not only the neurophysiological tools but, more importantly, the use of genetic markers studies in the clinical setting for the diagnosis of ADHD, which will not only improve the understanding of its high-heterogeneous background but will also ensure adequate long-term treatment and support to patients with ADHD.

ADHD neurobiology is complex and affects numerous brain pathways and neurotransmitter systems. Among these are dopamine, a neurotransmitter, and a hormone (peripheral). In the brain, dopamine plays a major role in encoding and consolidating memory, attention, movement, pleasure, motivation, and reward. Abnormalities in dopamine levels (being too low or too high) have a high association with various neuropsychiatric disorders. Converging proof has involved dopamine neurotransmission abnormalities in ADHD pathology.

Interestingly, in ADHD, dopamine levels are low, possibly due to very high levels of dopamine transporters. Neuroimaging studies (Stevens et al. 2018; Volkow et al. 2009) revealed that distinct pathways are involved in specific ADHD symptoms, including the involvement of the brain’s major dopaminergic systems, comprising the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular systems that play vital roles in regulating many important physiological functions (Figure 2). ADHD findings (Johansen et al. 2002; Sagvolden et al. 2005) show deficiencies in attention and poor behavioral organization due to the hyperfunctioning mesocortical system, impaired motor functions, and poor nondeclarative habit learning caused by the hyperfunctioning nigrostriatal system. Meanwhile, the mesolimbic system, the main behavioral selection mechanism for reinforcement and extinction, is associated with enhanced dopaminergic neuronal activity. In ADHD, the mesolimbic system, at a neurobiological level, may constantly be programming and re-programming neuronal connections (reinforcements) by strengthening connections associated with the reinforced behavior (adaptive) while at the same time decreasing other neuronal connections associated with non-reinforced behavior (maladaptive) (Johansen et al. 2002). It should be noted that this reinforcement process operates briefly from the behavioral occurrence to the consequential perception of the behavior. Moreover, the tuberoinfundibular pathway plays a role in the neuronal control of the hypothalamic-pituitary endocrine system, a.k.a. hypothalamic-pituitary-adrenal (HPA) axis. Though not comprehensively studied, factors such as suppressed HPA axis induce low cortisol levels, especially in the hyperactive-impulsive ADHD presentation (Pauli-Pott et al. 2023; Pinto et al. 2016). Moreover, the thyroid hormones regulated by the HPA axis were dysregulated in ADHD (Weiss et al. 1993; Weiss and Refetoff 2000), particularly those with hypothyroidism and generalized resistance to thyroid hormone (GRTH). Transgenic mice which express human mutant beta1 thyroid receptor gene (Siess et al. 2006), with hallmarks of GRTH, are hyperactive, impulsive,
and inattentive, showing the relationship between GRTH and ADHD. Further, a more recent clinical study identified that patients with Thyroid hormone beta-receptor mutations show ADHD-like phenotype (Uter et al. 2020). Hypothyroidism during fetal and postnatal periods causes developmental delays, while in adulthood, it induces neuronal network abnormalities, resulting in profound behavioral and neurological defects, including inattention and memory impairment (Custodio et al. 2021; Custodio et al. 2023a,b; Fedotova 2000; Turic et al. 2010; Vallortigara et al. 2008). Also, it should be noted that thyroid hormone and dopamine share the same basic unit, tyrosine (Kohlmeier 2003), so it is conceivable that abnormalities in thyroid hormone levels and function may affect dopamine function; for instance, hypothyroidism often leads to the loss of DA neurons (Kincaid 2001).

Furthermore, GWAS have already been identified; among these is the discovery of two dopamine-related genes, the dopamine transporter (DAT) (Brown et al. 2011; Grünblatt et al. 2019; Hansen et al. 2014) and D4 dopamine receptor subtype (DRD4) (Bonvicini et al. 2020; Leung et al. 2017; Tovo-Rodrigues et al. 2013), particularly in the key dimensions of adult ADHD (Hasler et al. 2015). Other candidate genes have also been identified besides these gene targets, such as the norepinephrine transporter (NET; SLC6A2 polymorphisms) (Sigurdardottir et al. 2016), serotonin transporter (SERT; 5-HTTLPR polymorphisms) (Grevet et al. 2007), and brain-derived neurotrophic factor (BDNF; Val66Met polymorphism) (Mei et al. 2022), among others. Of these genes, the NET and SERT belong to a group of monoamine transporters, and like DAT, are responsible for the reuptake of their associated amine neurotransmitters (NET = norepinephrine; SERT = serotonin; DAT = dopamine). However, findings (Farah and Mick 2010; Sigurdardottir et al. 2021; Yadav et al. 2021) indicate that NET, SERT, and BDNF polymorphisms do not raise the risk for adult ADHD, nor can they prove or exclude their role in adult ADHD. Therefore, further studies are needed to identify their role in the disease process, given their important role in brain function. However, previous review analysis identified that the catecholamines, dopamine and norepinephrine, were found to influence prefrontal cortical functions relevant to ADHD treatment (Arnsten and Pliszka 2011), particularly by enhancing postsynaptic α2A-adrenoceptors and dopamine D1-receptors activity. A previous study shows that atomoxetine at lower-optimal levels, enhanced the ‘signal’ (preferred neuronal direction) by indirectly increasing norepinephrine stimulation of α2A-adrenoceptors, while reduced the ‘noise’ (nonpreferred neuronal direction) by indirectly increasing dopamine stimulation of D1 receptors (Gamo et al. 2010). In the prefrontal cortex, dopamine complements norepinephrinergic functions which reduce prefrontal cortical neuronal activity in response to irrelevant stimuli. All currently approved ADHD medications enhance catecholamine neurotransmission in the prefrontal cortex. The stimulants methylphenidate and amphetamine block DAT and NET reuptake, while the non-stimulant atomoxetine more selectively prevents NET reuptake.

Overall, given the data on the roles of DAT and DRD4 gene polymorphisms, and possibly the NET, SERT, and BDNF,
it would be worthwhile to extend studies on these genes on preclinical animal models to understand adult ADHD pathology and pharmacogenetics better. After all, ADHD is a condition with a solid connection to impaired neurotransmission. Also, longitudinal analysis approach should be carried out to evaluate the developmental changes occurring in an ADHD model. This in turn, will provide us with answers whether adult ADHD is indeed a disorder different from childhood-onset ADHD.

The solute carrier family 6, member three gene, mostly known as the dopamine transporter (also dopamine active), is a membrane-spanning protein that pumps the dopamine out of the synaptic gap back into the cytosol. In the cytosol, other transporters sequester dopamine into vesicles for storage and later release. The DAT gene is in chromosome region 5p15.33 and comprises 372 amino acids. This gene encodes a dopamine transporter, a member of the sodium- and chloride-dependent transporter family. The 3′ untranslated region (UTR) of DAT contains a 40 bp tandem repeat, known as variable number tandem repeat (VNTR), which can be present in 3–11 copies. Studies show that variations in the number of repeats are associated with ADHD (Faraone and Larsson 2019).

Several meta-analyses showed a 9-repeat allele was suggested to confer as a risk allele in the DAT1 gene in 3′-untranslated region variant number tandem repeat polymorphism adult ADHD (Gründblatt et al. 2019). Interestingly, recent evidence indicated that the long-allele variants (10 repeats and longer) might confer to lower expression of the transporter than the short-allele. In addition, another study investigating a correlation between driving risks with ADHD and DAT gene VNTR polymorphisms (DAT1 9 R; rs28363170) showed that drivers with more self-reported ADHD symptoms also reported more risk-taking in traffic and had more recorded traffic accidents and violations. DAT1 9 R carriers had a higher probability of high traffic-risk behavior only if they also had ADHD symptoms. Leading concepts on ADHD suggest that hyperactivity, impulsivity, and inattention are caused by deficiencies of the ‘neuroanatomic network’ of attention, including alerting, orienting, and executive control and functioning (Swanson 2003). Studies at preclinical and clinical levels support that executive function is altered in ADHD (Karama et al. 2008; MacDonald et al. 2009; Meneses et al. 2011; Yang et al. 2012; Wilson 2000). This is because dopamine, the main neurotransmitter of the executive system, playing an essential role in the frontal cortex in mediating executive function, is commonly found altered in ADHD pathology. Also, executive function deficits have been proposed as an endophenotype for ADHD (Doyle et al. 2005). Moreover, resting-state striato-frontal functional connectivity is sensitive to the DAT1 genotype, predicts executive function, and is altered in adults with ADHD (Gordon et al. 2015). In addition, allelic variation in polymorphisms of the DAT gene (i.e., rs37020, rs4600000) predicted individual differences in measurements of response inhibition (for example in behavioral stop-signal reaction-time tasks). Furthermore, activity in frontal regions (anterior frontal, superior frontal, and superior medial gyri) and caudate varied additively with the T-allele of rs37020. The influence of genetic variation in DAT on the development of fronto-striatal inhibition networks may represent a key risk mechanism for disorders of behavioral inhibition. Furthermore, A novel gene-brain-behavior association between the DAT1 rs27048 (C)/rs429699 (T) haplotype with the left dorsal caudate functional connectivity and visual memory performance denotes a differential influence of DAT1 genotype in altering specific brain function yielding neuropsychological dysfunction in ADHD (Shang et al. 2021).

The DRD4 gene encodes the D4 subtype of the dopamine receptor. DRD4 is a G-protein coupled receptor belonging to the D2-like subfamily of dopamine receptors, consisting of the D2, D3, and D4 receptors. DRD4 receptors are found in both the pre- and post-synaptic neurons, which interferes with adenylyl cyclase, and mutations in this gene have been associated with many behavioral phenotypes, particularly ADHD. The DRD4 gene is highly expressed in brain regions associated with attention and inhibition, including the anterior cingulate cortex. A highly polymorphic functional VNTR in DRD4, consisting of 48 bp in exon 3, is frequently studied in ADHD. Different DRD4 genotypes are associated with differential treatment responses in pharmacogenetic studies; interestingly, a 7R allele encodes a defective dopamine receptor gene, diminishing treatment response. That 7R allele may even constitute a subgroup of ADHD. However, recently it was found that the DRD4 4R homozygosity is most prevalent in ADHD patients without sluggish cognitive tempo (SCT; impairments across social, emotional, and academic functioning). In these tests, they found that ADHD patients without SCT were found to perform worse on all neuropsychological domains evaluated (Bolat et al. 2020). Furthermore, DRD4 SNPs (rs916457) are highly linked to perceptual organization and working memory, usually impaired with ADHD (Cervantes-Henriquez et al. 2021). Furthermore, adults with a 7-repeat allele of the DRD4 gene that are diagnosed with ADHD had smaller superior frontal cortex and cerebellum mean volume compared to ADHD subjects not harboring this allele, suggesting that volumetric abnormalities in the dorsolateral prefrontal cortex and cerebellum may illustrate a neuroanatomical phenotype and the clinical expression of ADHD in adults induced by DRD4.
genotype (Monuteaux et al. 2008). The dopaminergic system, which is involved in behavioral control, reward, pleasure-seeking, and emotional inhibition, is one of the principal targets of ADHD genetics, with the most explored genes being the DAT and DRD4 genes (Prince 2008; Turic et al. 2010), in specific regions of the brain covered by the prefrontal cortex, basal ganglia, and limbic system, and cerebellum (Figure 3) (Yadav et al. 2021). Thus, further evaluating the genetic variants of DAT and DRD4 genes could provide insights into the underlying pathophysiology of ADHD and its treatments. In a recent publication (2023) in Nature Genetics, authors identified a high association of ADHD genetic risk with several brain-specific neuronal subtypes, particularly dopaminergic neurons, refining the genetic architecture and implicating dopaminergic systems and functions with ADHD pathology (Demontis et al. 2023).

Although ADHD is a highly heritable disorder with high genetic factors, it is also influenced by environmental factors (Froehlich et al. 2011). Among the proposed environmental factors include complications during perinatal period, substance exposures, nutrition, chemical (heavy metals) exposures, and lifestyle and psychosocial factors. These factors can further increase ADHD risks in genetically susceptible individuals. Moreover, ADHD is also caused by the interplay of environmental and genetic factors (epigenetics). Epigenetic changes do not change your DNA sequence, unlike genetic changes, but they can change how DNA sequence is read by your body (Van Vliet et al. 2007). Studies have demonstrated a role of epigenetic modifications (Meijer et al. 2020; Mirkovic et al. 2020; Neumann et al. 2020), including DNA methylation in ADHD. Basic cellular processes, including synaptic plasticity in learning and memory consolidation (Gräff and Mansuy 2008), are accomplished through regulation of gene transcription via epigenetic mechanism, particularly DNA methylation. Moreover, previously, associations between epigenetic markers and ADHD

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**Figure 3:** ADHD-implicated brain regions. ADHD research suggests that hyperactivity, impulsivity, and inattention are caused by deficiencies of the ‘neuroanatomic network’ of attention, including alerting, orienting, and executive control and functioning. This network covers different regions of the brain including the prefrontal cortex, basal ganglia, limbic system, and cerebellum. The Figure was created using BioRender.com.
were investigated (Xu et al. 2015). Results determined expression profiles of specific histone modifying genes, such as HDAC1, MeCP2, MYST4, and p300 on top of the identified expressions of dopamine-related genes, DAT1, DRD4, and DRD5, including their methylation gene promoters. A multivariate logistic regressions model resulted in an accuracy level of 0.93 which indicates a high role in ADHD development.

In addition, presence of epigenetic mechanisms in biological aging (senescence) profiles also exist (Horvath 2013; Levine et al. 2018), showing hypoactivation of DNA repair pathways and hyperactivation of interferon and pro-inflammatory, indicating evidence of associations between age biomarkers and neurodevelopmental diseases, such as ADHD. Interestingly, a recent study (Arpawong et al. 2023) identified that ADHD genetic burden is associated with older epigenetic age, by investigating roles of education, behavioral, and sociodemographic factors in adult samples (50 years and above). This data shows that genetic burden and symptoms of ADHD can enhance risks of accelerated aging and shortened lifespans, when indexed by an epigenetic biomarker. Also, the short lifespans associated with ADHD are likely mediated by a higher polygenic score (presence of increased behavioral and sociodemographic factors) related with accelerated physiological aging. These factors include a higher body mass index, increased depressive symptoms, frequent cigarette smoking, low educational attainment and income, and more cognitive challenges relative to the general population. Overall, these results show the significant role of gene-environment interactions (epigenetics) in ADHD.

6 Current understanding of adult ADHD: can mouse models help bridge the gap?

Investigations of human disorders using alternatives, such as animals, particularly mouse models, have been a widely used methodology in biomedical research. The use of the mouse model has become beneficial in understanding human disorders, given the similarities between mice and humans regarding genetics, anatomy, and physiology (Bryda 2013). Generally, humans and mice are biologically very similar and get most of the same diseases, for similar genetic reasons. On average, the protein-coding regions of human and mouse genomes are 90% identical (Breschi et al. 2017), making mouse genetic research valuable for understanding human disorders. Moreover, structurally, although the human brain is larger and more complex than the mouse brain due to a greater number of specialized areas and neocortical invaginations, however, individual neuronal types and connections, both human and mouse brains are very similar (Wong et al. 2023). Also, animal models, particularly mouse models, remain valuable and powerful tools used to answer and address practical challenges in ADHD research. In addition, the use of genetically modified mouse models (transgenics) has become useful in neuroscience research, particularly in understanding ADHD pathology (de la Peña et al. 2018), and their subtypes: predominantly inattentive (ADHD-PI) (Custodio et al. 2018; Custodio et al. 2021; Custodio et al. 2023a,b), hyperactive-impulsive (ADHD-HI) (dela Peña et al. 2019), and combined (ADHD-C) (Ha et al. 2020; Hong et al. 2014). This methodology contributes to interpreting the genotype–phenotype associations in ADHD. Animal models of ADHD are validated based on the face validity (similarity of symptoms between human and animal models), construct validity (similarity in underlying mechanisms; dopaminergic impairment), and predictive validity (similarity of treatment responses) (de la Peña et al. 2018). The spontaneously hypertensive (SHR/Ncrl) rat is the most-validated animal model for ADHD, showing inattention, hyperactivity, and impulsivity in an array of behavioral tests. They also showed improvement in behaviors following treatments for ADHD, such as methylphenidate, amphetamine, and atomoxetine, indicating involvement of impaired neurotransmission in the pathophysiology of ADHD (Sagvolden et al. 2009). Furthermore, several animal models have been proposed, particularly using transgenic mouse models allowing better understanding of the roles of genes in understanding ADHD. These models are identified as either highly validated or still warrant further validation (potential animal models). Among the most validated mouse models is the DAT-KO mice, showing all core symptoms of inattentiveness, hyperactivity, and impulsivity, with presenting dopaminergic alterations (hypodopaminergic). Moreover, treatment with methylphenidate, amphetamine, and atomoxetine improved the behavior in mice (Del’Guidice et al. 2014; Gainetdinov et al. 1999; Takamatsu et al. 2015). These findings support the role of DAT gene in ADHD, both in mice and humans. Furthermore, DRD4 signaling is essential for the expression of hyperactivity and impaired behavioral inhibition in a mouse model lacking DRD4 (DRD4-KO) (Avale et al. 2004), however, further studies are needed to validate the use of DRD4-KO mice in modeling clinical ADHD.

Most, if not all, studies in preclinical (animal) and clinical (human) ADHD research focus on understanding the disorder’s pathology in younger individuals, given that most documented findings show that ADHD occurs earlier in
life, classifying this disorder as a neurodevelopmental disorder, due to its early onset. Given that adult ADHD appears to be distinct from childhood ADHD, focus should also go towards understanding adult ADHD pathology due to its severity in symptoms and behavior impact. Evidence suggests that genetic factors of adult ADHD play a more prominent role than childhood ADHD. Thus, to bridge the gap in understanding adult ADHD, animal research, particularly the use of mouse models, should also delve into this life cycle; thus, determining whether the current understanding of the pathology and pharmacology of ADHD is similar in older animals.

7 Conclusions

There are still no certainties about what causes ADHD; however, it is accepted to have multifactorial origin. Several authors have suggested the involvement of different brain areas in the etiology of ADHD, especially those involving the dopaminergic systems. More recently, several genetic propensities for ADHD have been proposed. There is also evidence of environmental exposure as a factor of influence. Further, epigenetic processes modulating gene expressions have been proposed as a key molecular mediator and marker of genetic and environmental influences on ADHD. While genes increase a person’s risk for acquiring certain disorders, such as ADHD, the entire genetic system is highly effective and responsive to inputs, indicating that certain environmental changes can regulate and impact the expression of ADHD genes.

Given the increasing evidence that adult ADHD is distinct from childhood ADHD, and due to its severity in symptoms and behavior impact, focus should go towards a better understanding of adult ADHD pathology. While recent studies show that adult ADHD may not be a childhood-onset neurodevelopmental disorder, and if supported by additional important findings, this may revolutionize our understanding of the disorder. Therefore, addressing these weak points and challenges in the current clinical classification systems could improve the characterization and validity of ADHD diagnosis, particularly those of adult form.

8 Future directions

The new changes made in the current DSM-5th ed., with the emphasis on the age-appropriate diagnostic tools requirement for use in adolescents and adults, though considered a milestone, seemed so subtle for some and for most, but are considered unimportant and not-well thought of, and fails to answer the problems and issues of previous DSM versions tackling ADHD as a disorder. The DSM-5 reduced the symptom criteria threshold for adults from six to five in either hyperactive/impulsive or inattention (APA 2013). However, this did not address the issues on developmental changes (as well as normative changes) in the ADHD structure and presentations. Thus, it shows that the current ADHD criteria may not be sensitive to adult ADHD symptom diagnosis. Therefore, we propose that future version (DSM-6th) have more empirical work or bases such as the conduct and use of network analyses to systematically compare ADHD symptoms across key developmental periods, in a form of longitudinal analyses, from the earliest possible time a child can be diagnosed, though mostly and commonly done during preschool, until adulthood (and even old-adult age). Also, with this, we may also be able to understand the interrelationship between individual symptom structures. Another issue to be addressed is emotional dysregulation/impulsivity, though found to be present in patients with ADHD, yet is still to be considered in the diagnostic criteria of the disorder. Emotional dysregulation/impulsivity is core feature of ADHD linked to the impulsivity dimension of the disorder (Barkley 2015). Failure in adaptive emotion regulation and negative affect were found to be distinct and are indicative dimensions of adult ADHD (Hirsch et al. 2019). Difficulties in this domain of emotional control forms part of the larger inattentive/executive dimension dysregulation found in ADHD. Thus, the inclusion of emotional dysregulation/impulsivity as a symptom domain impaired in ADHD would allow understanding of this other facet of the disorder.

It is apparent that the diagnostic criteria for all disorders, especially psychiatric disorders, continue to evolve as new research is produced and new treatments become available. The DSM is no different in this regard as more research continues, diagnostic criteria become updated. The hurdles faced in the field of psychiatry are the lack of definite objective criteria (i.e., blood tests, X-rays and scans, biopsies) to diagnose different illnesses, including ADHD, reflected in the current DSM version. This is worrisome given that biological factors were identified in GWAS and SNPs analyses, yet no useful markers have been fitted on its criteria. Given that, diagnosis relies primarily on subjective criteria, although some integrate qEEG (TBR) results; however, this does not produce definite and consistent results. Hopefully, with the continuous research in ADHD, objective measures will soon be developed, so our understanding of its pathophysiology will be improved, as the diagnostic methods. Considering all these, the DSM, however, should be praised for its high reliability, allowing clinical work and research in psychiatry to improve so much over these years.
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