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Review article

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Neurobiology of attention-deficit hyperactivity disorder: historical challenges and emerging frontiers

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Abstract

Extensive investigations spanning multiple levels of inquiry, from genetic to behavioural studies, have sought to unravel the mechanistic foundations of attention-deficit hyperactivity disorder (ADHD), with the aspiration of developing efficacious treatments for this condition. Despite these efforts, the pathogenesis of ADHD remains elusive. In this Review, we reflect on what has been learned about ADHD while also providing a framework that may serve as a roadmap for future investigations. We emphasize that ADHD is a highly heterogeneous disorder with multiple aetiologies that necessitates a multifactorial dimensional phenotype, rather than a fixed dichotomous conceptualization. We highlight new findings that suggest a more brain-wide, 'global' view of the disorder, rather than the traditional localizationist framework, which asserts that a limited set of brain regions or networks underlie ADHD. Last, we underscore how underpowered studies that have aimed to associate neurobiology with ADHD phenotypes have long precluded the field from making progress. However, a new age of ADHD research with refined phenotypes, advanced methods, creative study designs and adequately powered investigations is beginning to put the field on a good footing. Indeed, the field is at a promising juncture to advance the neurobiological understanding of ADHD and fulfil the promise of clinical utility.

Sections

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is a prevalent and debilitating neurodevelopmental disorder characterized by persistent and developmentally inappropriate levels of overactivity, inattention and impulsivity[1]. Although first described well over 100 years ago[2,3], ADHD was not recognized in the psychiatric classification system of the USA (that is, the Diagnostic and Statistical Manual of Mental Disorders (DSM)) until DSM-II was published in 1965 (ref. 4) (Fig. 1). The definition of ADHD subsequently went through several revisions, including in DSM-III (published in 1980)[5], DSM-IV (1994) and DSM-5 (2013)[6]. The World Health Organization International Classification of Diseases 11th edition (ICD-11; published in 2022)[7] includes a substantially revised definition of ADHD (from that in ICD-10) that is now largely similar to the definition of the disorder in DSM-5. Most of the available literature on ADHD has used the DSM-IV definition of this condition.

ADHD is estimated to affect 2–7% of children[8,9], with a higher diagnosis rate in males than in females[10]. The actual rates of clinical identification of ADHD in children vary widely between and within countries, with nearly 10% of children identified to have this disorder in the USA[11]. Although ADHD is primarily characterized by age-inappropriate inattention and/or hyperactivity or impulsivity, it is associated with important secondary features, including problems with irritability, anxiety and disruptive behaviours. There is also marked heterogeneity in clinical presentation, outcomes and pathophysiology[12–16]. Although the onset and identification of ADHD usually takes place during childhood[17], its symptoms and associated impairments often persist across the lifespan[18]. ADHD leads to chronic social, occupational, interpersonal and health challenges even when treatment has been provided[19–21]. Indeed, ADHD increases the risk for depression, substance use, antisocial behaviour, under-employment, and shortened lifespan owing to accidental death, suicide or physical health complications[22,23], making it one of the most vital mental disorders to characterize and comprehend globally.

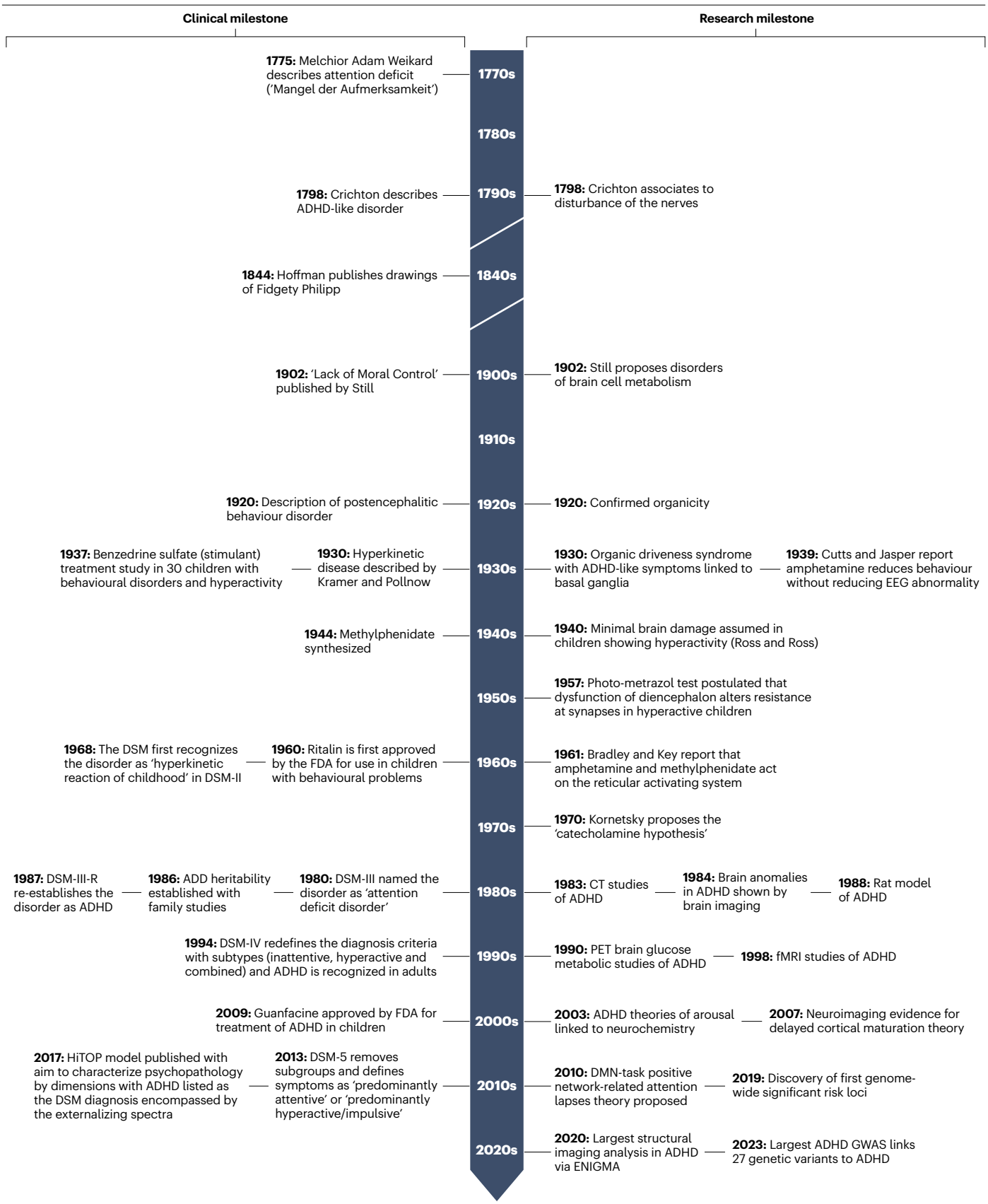
Decades of research has contributed to the concept of ADHD as a neurobiological disorder[2,24]. The earliest reference to ADHD in the medical literature was made by Melchior Adam Weikard, a German physician, in 1775 (ref. 25). Crichton (1798) then posited that attention disorders stemmed from disruptions in nerve function[26]. Later, Still (1902) attributed attention disorders to irregularities in brain cell metabolism[3]. Subsequent decades saw advancements in neuroimaging techniques[27,28], which were utilized to elucidate the neurobiological mechanisms underlying ADHD, with the ultimate aim of refining treatment approaches (Fig. 1). Currently, psychostimulants, such as methylphenidate, are considered the first-line treatment of ADHD in children and adolescents. The efficacy of methylphenidate was identified by Bradley serendipitously in 1937 (refs. 29,30) and it was first approved by the FDA in the USA to treat various mental disorders in 1954 (refs. 30,31). Investigations of the mechanisms of psychostimulants like methylphenidate have shaped much of our understanding of the neurobiology of ADHD (Fig. 1). Indeed, the investigative spotlight on the role of the dopaminergic system in ADHD pathophysiology has largely been driven by the mechanism of action of methylphenidate[32–34]. Nevertheless, many brain systems involved in attention, executive functions and reward have also been implicated in the symptomatology of ADHD[35]. The literature to date has provided some understanding of the neurobiological mechanisms at play in this disorder but attempts at further specification have too often failed to replicate. Subsequently, translating the emerging neurobiology of ADHD to substantive changes in clinical diagnosis and intervention has proven difficult.

Our aim in this Review is not to be comprehensive but to synthesize our current understanding of ADHD neurobiology, traversing varying levels of analysis, from brain-wide networks to neurotransmitter systems and genetic architecture. Studies have implicated alterations in various brain networks, dysregulation of catecholaminergic neurotransmission and several genes in the pathogenesis of ADHD. Yet, no uniform and conclusive understanding of the neurobiological aetiology of this disorder has been formed. Here, we emphasize three key points at play. First, neurobiology maps poorly onto diagnostic categories: neurobiological findings are generally not disorder or syndrome specific and are heterogeneous within disorders. As a result, it is not surprising that studies that have looked for a biological difference between cases and controls have often yielded very small effects. This dichotomous viewpoint has limited our understanding by not accounting for the heterogeneity that underlies ADHD pathophysiology. Second, much of the neurobiological investigations of ADHD have long been driven by a localizationist framework — reducing ADHD pathophysiology to specific brain regions, networks or genes — when global dysfunction might be implicated. Last, the field has been littered with underpowered studies, including small and unrepresentative samples, leading inevitably to significant but non-generalizable or irreplicable findings. Here, we provide recommendations to address these issues. We emphasize the importance of adopting a heterogeneous and multi-dimensional (subtypes) conceptualization of ADHD and broadening the scope of mechanistic investigations by considering a new 'global' model of the disorder. We also highlight the need to pair such concepts with advanced methods, creative study designs and adequately powered investigations to advance the field.

ADHD neurobiology: levels of analysis

As famously demonstrated by the diagram of neuroanatomical organization by Churchland and Sejnowski[36], the brain is organized across multiple spatial scales, ranging from large-scale brain systems or networks to functional areas, synapses and genes (Fig. 2). These different scales or levels of organization have guided research on the neurobiology of ADHD, as discussed in the sections below. Corresponding to the CNS scale (~1 m), we first discuss the various brain–behaviour relationships that have been explored. At a systems level (~10 cm), we explore the different brain-wide systems and focal systems that have been implicated in ADHD. At the level of maps (~1 cm), we discuss localized regions or areas that have been implicated in the disorder. At the synaptic, neuronal and circuit level (~1 mm), we discuss the

Fig. 1 | Timeline of key events and milestones in ADHD neurobiology research. Historical summary of select key research and clinical milestones occurring between 1798 and the early 2020s that have contributed to the current state of understanding of attention-deficit hyperactivity disorder (ADHD) neurobiology[1,2,5,24,100,196,197]. The timeline demonstrates the entanglement of research direction and novel clinical insights in the early stages of ADHD neurobiology discovery. Benzedrine is a brand name of amphetamine sulfate. Ritalin is a brand name of methylphenidate. ADD, attention-deficit disorder; DMN, default mode network; DSM, Diagnostic and Statistical Manual of Mental Disorders; fMRI, functional MRI; GWAS, genome-wide association study; HiTOP, hierarchical taxonomy of psychopathology.


Clinical milestone
Research milestone
1775: Melchior Adam Weikard describes attention deficit ('Mangel der Aufmerksamkeit')
1770s
1780s
1798: Crichton describes ADHD-like disorder
1790s
1798: Crichton associates to disturbance of the nerves
1844: Hoffman publishes drawings of Fidgety Philipp
1840s
1902: 'Lack of Moral Control' published by Still
1900s
1902: Still proposes disorders of brain cell metabolism
1910s
1920: Description of postencephalitic behaviour disorder
1920s
1920: Confirmed organicity
1937: Benzedrine sulfate (stimulant) treatment study in 30 children with behavioural disorders and hyperactivity
1930: Hyperkinetic disease described by Kramer and Pollnow
1930s
1930: Organic driveness syndrome with ADHD-like symptoms linked to basal ganglia
1939: Cutts and Jasper report amphetamine reduces behaviour without reducing EEG abnormality
1944: Methylphenidate synthesized
1940s
1940: Minimal brain damage assumed in children showing hyperactivity (Ross and Ross)
1950s
1957: Photo-metrazol test postulated that dysfunction of diencephalon alters resistance at synapses in hyperactive children
1968: The DSM first recognizes the disorder as 'hyperkinetic reaction of childhood' in DSM-II
1960: Ritalin is first approved by the FDA for use in children with behavioural problems
1960s
1961: Bradley and Key report that amphetamine and methylphenidate act on the reticular activating system
1970s
1970: Kornetsky proposes the 'catecholamine hypothesis'
1987: DSM-III-R re-establishes the disorder as ADHD
1986: ADD heritability established with family studies
1980: DSM-III named the disorder as 'attention deficit disorder'
1980s
1983: CT studies of ADHD
1984: Brain anomalies in ADHD shown by brain imaging
1988: Rat model of ADHD
1994: DSM-IV redefines the diagnosis criteria with subtypes (inattentive, hyperactive and combined) and ADHD is recognized in adults
1990s
1990: PET brain glucose metabolic studies of ADHD
1998: fMRI studies of ADHD
2009: Guanfacine approved by FDA for treatment of ADHD in children
2000s
2003: ADHD theories of arousal linked to neurochemistry
2007: Neuroimaging evidence for delayed cortical maturation theory
2017: HiTOP model published with aim to characterize psychopathology by dimensions with ADHD listed as the DSM diagnosis encompassed by the externalizing spectra
2013: DSM-5 removes subgroups and defines symptoms as 'predominantly attentive' or 'predominantly hyperactive/impulsive'
2010s
2010: DMN-task positive network-related attention lapses theory proposed
2019: Discovery of first genome-wide significant risk loci
2020s
2020: Largest structural imaging analysis in ADHD via ENIGMA
2023: Largest ADHD GWAS links 27 genetic variants to ADHD

investigation of the catecholaminergic neurotransmitter system. Last, at the molecular level (~1 Å), we discuss genetic associations with ADHD.

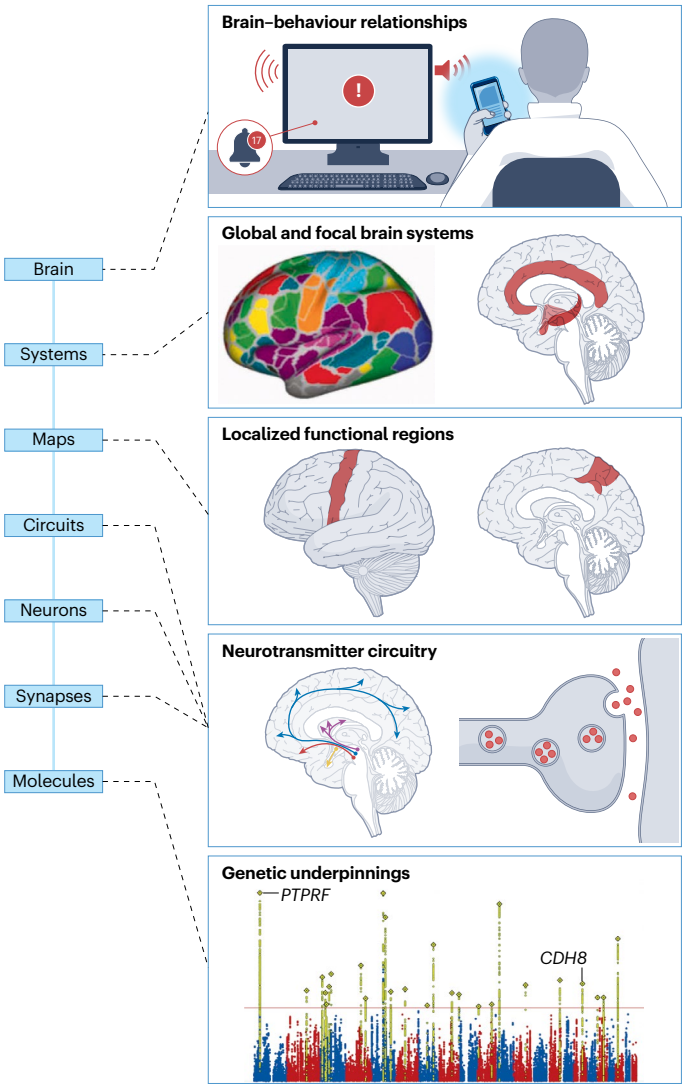


Fig. 2 | Spatial scales of the nervous system for ADHD neurobiology investigation. This schematic is inspired by the structural levels of organization in the nervous system as proposed by Churchland and Sejnowski[36] and is based on recent work by Petersen et al.[272]. The various scales of focus at which neurobiological investigation can occur (left) represented by specific mechanisms of focus at each scale (right). In this Review, we emphasize the focus, at each scale, that is most relevant to attention-deficit hyperactivity disorder (ADHD) neurobiology research. At the brain-wide level, we discuss how neurobiology manifests as brain–behaviour relationships; at the systems level, we discuss brain-wide systems[273] as well as well-established focal systems; at the level of maps, we discuss localized functional regions that have been implicated in the disorder; at the synaptic, neuronal and circuit level, we discuss the investigation of catecholaminergic neurotransmitter systems; and last, at the molecular level, we discuss the genetic underpinnings of ADHD that have been investigated thus far (the bottom image highlights two genes near the significant loci associated with ADHD in genome-wide association studies[197]). Adapted with permission from ref. 272, Elsevier. Brain parcellation image adapted with permission from ref. 263, Elsevier. Genome-wide association studies data image adapted from ref. 197, Springer Nature America Inc.

Brain–behaviour associations

Alterations in several psychological processes have been reported in ADHD. Such altered psychological processes have been the subject of investigation as refined phenotypes (or, formerly, 'endophenotypes') to assist in discovering relevant biology[14]. In recent years, the search for brain alterations related to such changes in psychological processes has accelerated, focusing largely on four main domains: reward response, arousal, executive functions and attention[37].

Reward system dysregulation in ADHD impacts the ability to process rewards, which can contribute to many of the symptoms observed in individuals with ADHD. Children with ADHD respond atypically to reinforcers, be they tangible rewards or social praise, are less able to delay gratification, and find it more difficult to modify their behaviours than children without ADHD[38–40]. They also respond more impulsively during delayed reinforcement, in that they are more likely than typically developing peers to choose small immediate reinforcers over larger delayed reinforcers[40–42]. Such dysregulation in reward responses has been associated with alterations in synaptic dopamine processing in the ascending dopaminergic system[43,44]. Brain studies suggest that the mesoaccumbens dopamine pathway, which projects from the ventral tegmental area in the midbrain to the nucleus accumbens, is critically involved in reward and motivation[45] and underlies the reward and motivational deficits observed in ADHD[12,46].

One of the most long-standing theories of ADHD is the failure to maintain optimal arousal of the cortical systems[47–50]. Arousal refers to the neural, behavioural and physiological mechanisms that regulate states of wakefulness and alertness[51,52]. It also refers to readiness to attend to relevant stimuli and to have available energy for a task. At the lowest arousal level, an individual is in a coma, whereas at the highest arousal level, they are in a panic. The neurobiology underlying arousal regulation probably involves the vigilance system[53] and involves ascending noradrenergic systems in the brain. The Yerkes–Dodson law[54] describes an inverted U-shaped relationship between arousal and task performance, with task-directed behaviour requiring optimal regulation of arousal to achieve good performance. Studies have suggested that reduction in vigilance and sustained attention seen in ADHD might be reflective of a tonically hypo-aroused state[55]. Furthermore, it has also been suggested that a general state of hypo-arousal in ADHD may be compensated through maladaptive strategies such as hyperactive motor behaviours and sensation seeking. Other features of ADHD that are suggestive of a disturbance in arousal regulation include emotional dysregulation[56], sleep disorders[57], dysregulation of the hypothalamus–pituitary–adrenal axis[58] and problems regulating appetite[59]. Several studies — involving EEG and various task-based manipulations such as reaction time variability[60,61] — have provided support for hypo-arousal in ADHD[62,63].

A vast body of literature has also linked dysregulation of executive functions to ADHD symptoms[64–67]. Executive functions are described as higher-level cognitive processes such as working memory, inhibitory and attentional control, cognitive flexibility, and goal-directed behaviours[68]. Individuals with ADHD show greater impairment in executive functions than individuals without ADHD[69]. Dysregulation of executive functions in ADHD suggests that deficits in top-down processing can lead to difficulties in controlling automatized responses to stimuli, planning and organizing. Consequently, individuals with ADHD may encounter challenges in monitoring the task relevance of stimuli and demands, disrupting regulatory cognitive control[70]. Several studies have highlighted differences in structure and function of executive function-linked brain regions in ADHD[70–72].

Another related theory — termed the interference hypothesis — focuses on a failure to sustain attention as a key impairment in ADHD. Studies examining altered reaction time cycles suggest that attentional 'lapses' seen in ADHD involve the default mode network (DMN)[73]. The interference hypothesis states that the expanded reaction time often seen in ADHD is the behavioural product of occasional lapses in attention owing to the emergence of random default mode brain activity while performing a task, thus impairing attentional control[73]. Brain studies have shown aberrant DMN connectivity within itself and also with other networks in individuals with ADHD, further supporting this theory[16].

None of these theories has reached consensus support, and it is clear that no single mechanism among those described above fully accounts for the symptoms of ADHD, with its unique mix of dysexecutive, impulsive, hyperactive and associated dysregulatory features. Indeed, there are well-documented strengths and weaknesses of all of these behavioural theories (and others) of ADHD[12,48,74–79]. Such theories may have simply emerged in the context of the varying presentations of ADHD or due to sampling variability (distinct subsets of the population for any given study), or perhaps all of these varied processes may be contributing to the ADHD phenotype in a more holistic sense.

Functional brain systems and networks

Many neural systems have been implicated in ADHD, most prominently the frontostriatal circuits, involved in reward, executive function and focused attention. These parallel neural circuits comprise projections from the cortex to the striatum, from the striatum to the thalamus and from the thalamus back to the cortex[80,81]. The circuits involve different cortical regions, with each loop thought to mediate different neurocognitive functions. The role of frontostriatal circuits in ADHD symptoms has been supported in part through lesion studies in both animals and human[82,83]. Multiple lines of evidence, including human neuroimaging studies and studies of animal models, suggest that ADHD involves functional and anatomical abnormalities within the cortico-striato-thalamo-cortical loops, particularly the cognitive and limbic loops[82–86]. In line with this work, studies have used task and resting-state functional MRI to examine the activity and connectivity between regions in frontostriatal circuits and have found support for their involvement in ADHD — albeit, at times, conflicting outcomes in both activity and connectivity have been documented. Most studies have reported a reduction in inferior frontostriatal activation during a motor inhibition task[87–89]. However, others have shown greater[90,91] or no differences[92] in frontostriatal activation in ADHD during response inhibition. A recent mega-analysis focusing on specific subcortical structures and their connectivity to the cortex showed that ADHD diagnosis and traits were associated with atypical connectivity between striatal regions and the inferior frontal, insular, supplementary motor and inferior parietal regions[93]. Although an abundance of research supports the involvement of frontostriatal circuits in ADHD, recent work has suggested that deficits in ADHD are subserved by multiple networks[94,95].

The frontoparietal network is also often studied in ADHD. This network is involved in executive functions and attentional control and includes areas that also feature in frontostriatal circuits, including the dorsolateral prefrontal cortex (PFC), anterior PFC, lateral frontal pole, anterior cingulate cortex, lateral cerebellum, caudate, anterior insula and inferior parietal lobe[96–98]. In individuals with ADHD, the frontoparietal network exhibited hyperconnectivity with regions of the DMN and hypoconnectivity with regions of the ventral attention and somatosensory networks[99]. In addition, investigations have also suggested that delay in both cortical[100] and functional[101] maturation in prefrontal regions (included within the frontoparietal network) contributes to the development of ADHD[100]. While frontoparietal circuits have been frequently studied in ADHD, several other networks have also been implicated in this disorder, including the dorsal attention and ventral attention networks, and even motor and visual networks[89,95,102–106].

More recently, in line with the interference hypothesis mentioned above, ADHD has been associated with dysregulation of the DMN[107]. Several lines of evidence have noted a stronger coactivation or weaker anticorrelation between the DMN and task-positive networks, including the dorsal attention and salience networks, which is thought to result in attention lapses, mind-wandering, and poorer performance on attention and executive function tasks[73]. Maturational lag in ADHD has also been shown to be relatively specific to the DMN and its interconnections with two task-positive networks: the frontoparietal and ventral attention networks[101]. Structural findings related to the DMN have also been highlighted, suggesting that delayed development of cortical areas in the DMN is linked to persistent ADHD throughout adolescence and into adulthood[108]. DMN dysregulation may be an important element of the neurobiological underpinnings of arousal regulation deficits in ADHD[109]. It has been suggested that arousal regulation deficits in ADHD might be rooted in altered low-frequency connectivity[110,111] between regions of the DMN. Lapses of attention owing to intrusions of this network could manifest in behavioural variability and unstable vigilance. Pharmacological studies have also implicated the DMN in ADHD. Indeed, methylphenidate treatment has been associated with the suppression of DMN activity during cognitive tasks[112,113]. Moreover, some studies have described an increase in intrinsic functional connectivity within the DMN in people with ADHD in response to this treatment[114,115]. Overall, multiple networks and systems have been shown to be involved in ADHD, suggesting that a global brain-wide perspective may be necessary to understand this disorder (discussed in more detail below).

Localized functional regions

Various local brain regions have been related to ADHD symptoms. Many studies have noted that ADHD is associated with under-function of the right inferior frontal cortex during cognitive control[99,116–119]. Functional anomalies in ADHD have also been observed in the left inferior parietal lobe and right lateral cerebellum in timing tasks[116,120], the supplementary motor area in motor response inhibition tasks[88], and the left anterior cingulate cortex in interference inhibition tasks[121]. Decreases in activation have also been observed in the putamen[122] and caudate[117,123], whereas the amygdala has shown increases in activation[124,125]. In addition to brain regions involved in higher-order processing, structural and functional differences have been noted in both the visual[103] and motor cortices[126,127]. In line with the current understanding of ADHD, subcortical structures like the striatum[128], nucleus accumbens and amygdala[129] exhibit altered activity during various reward-based tasks. Studies examining structural differences have also reported that children with ADHD present smaller volumes in different subcortical brain regions (that is, the nucleus accumbens, amygdala, caudate, hippocampus and putamen)[130,131].

Investigators have also examined tracts that are important for efficient communication between various brain regions by using diffusion tensor imaging techniques, which measure various forms of water diffusion such as fractional anisotropy. Reduced fractional anisotropy suggests reduced integrity of white matter tracts whereas increased

fractional anisotropy indicates enhanced tract integrity. Overall, investigations using fractional anisotropy in ADHD have reported mixed results. Some studies on the superior longitudinal fasciculus tract have shown a relationship between increased fractional anisotropy and ADHD[132], whereas others have suggested a relationship between decreased fractional anisotropy and ADHD[133,134]. Studies have also reported decreases in fractional anisotropy mainly within association tracts linking cognitive control and attentional cortical networks (for example, the right superior longitudinal fasciculus, linking the inferior parietal lobule and lateral prefrontal cortex) as well as in projection tracts integrating cortical and lower brain processing centres (for example, the corticospinal tract)[134,135]. More recent meta-analyses and mega-analyses have shown reductions in fractional anisotropy in the frontostriatal pathways, cingulum, and corpus callosum[136] as well as in the inferior longitudinal and left uncinate fasciculi[137]. Taken together, studies have shown that white matter microstructural organization is disrupted in many major fibre tracts in ADHD[138].

Overall, studies using various methodologies have converged on the idea that the brain is altered in ADHD, although what region or system in the brain is atypical is still inconclusive. Again, the variability in the findings might simply reflect examinations involving a vastly heterogeneous population. However, considering that many brain-wide association studies of ADHD have been underpowered (Fig. 3), this seemingly non-convergent yet consistent localization of findings across studies may paradoxically indicate a global, 'brain-wide' pathophysiology in ADHD.

Atypical neurotransmitter signalling and circuit-level alterations

The most discussed pathophysiological mechanism in ADHD is the dysregulation of the catecholaminergic system; that is, dopamine and norepinephrine transmission. Dopamine is a neurotransmitter that is involved in various cognitive functions, including attention, motivation and reward processing[139–141]. Long-standing work using animal models as well as pharmacological interventions in humans has elucidated the pathways of dopamine signalling and its influences on behaviour[142–144]. Electrophysiological studies have also shown how the tonic and phasic activation of the dopamine system can modulate the PFC and limbic afferent interactions within the nucleus accumbens[145], thereby elucidating communication within the cortico-striatal loops. Norepinephrine is involved in regulating alertness and arousal and influences the ability to concentrate and focus. Dopamine and norepinephrine exhibit an inverted U-shaped influence on cognitive functions, where either too little or too much of either transmitter impairs various cognitive abilities[146]. Electrophysiological studies in animals suggest that norepinephrine enhances 'signals', whereas dopamine decreases 'noise' in the PFC, thereby implicating their role in the optimal regulation of various cognitive functions[147,148]. Extensive research in monkeys has shown that catecholamine depletion in the PFC is as destructive as ablation of the tissue itself[149]. Dysregulated catecholamine transmission results in disorganized attention, poor concentration and distractibility, which are key symptoms seen in ADHD. Genetic knockout studies in rodents have supported specific genetic mechanisms in the catecholaminergic system as a contributing mechanism to mouse models of hyperactivity[150,151]. The first mega-analysis of functional connectivity in human brain focused specifically on related subcortical systems[93]. Several studies in both animals and humans have also revealed deficient dopaminergic and noradrenergic transmissions in ADHD[152].

The proposed role of catecholamines, such as dopamine and norepinephrine, in ADHD has largely been driven by pharmacological studies focusing on treatments for this disorder[24]. Stimulants such as methylphenidate, as noted above, have led to the focus on catecholamine neurotransmission in ADHD pathophysiology[144,153]. Methylphenidate blocks dopamine and norepinephrine transporters, thereby generating an increase in catecholaminergic availability in the synaptic terminal[154–159]. Such increments in dopamine and norepinephrine affect brain systems that subserve behaviours related to executive function[160–162], decision-making[163], emotional responsivity[164] and reward regulation[165,166]. Thus, dysfunction of the dopamine and norepinephrine systems compromises optimal cognitive functioning and likely accounts for some of the pathophysiology of ADHD[167–169].

Dopaminergic dysfunction in ADHD has also been implicated by work examining iron deficiency in the brain. Adolescents with iron deficiency have been shown to be as much as twice as likely to be diagnosed with ADHD[170,171]. Studies in preclinical rodent models of iron deficiency have found marked disruption to the dopamine system, including reductions in the concentrations of D1 and D2 dopamine receptors[172,173], impairments in dopamine transporter function, and as much as a 20% decrease in basal ganglia dopamine concentration[173–176]. In humans, changes in MRI indices of brain iron have been further linked to changes in PET indices of presynaptic dopamine availability[177] and frontostriatal connectivity[178], suggesting that a reduction in brain iron content during youth may impact cognition in part through its effect on the dopamine system. Elucidating whether the relationship between iron deficiency, dopaminergic deficits and ADHD symptomatology is casual or simply an exacerbating factor remains an important question for future studies.

More recently, the use of non-stimulants, such as guanfacine, for the treatment of ADHD[146] has revealed another pathophysiological mechanism underlying ADHD. The rise in use of such compounds has been driven by the fact that psychostimulants are either ineffective or poorly tolerated in 30–50% of adults with ADHD[179]. In addition, given their addictive properties, stimulants are associated with a marked risk of long-term misuse, especially in individuals with stimulant or cocaine abuse[155]. The mechanism of action of guanfacine, a norepinephrine α2A-adrenoceptor agonist, has implicated that stimulation of such receptors improves ADHD symptomatology[180]. Landmark work by Arnsten[181] showed that adequate levels of norepinephrine (and dopamine) are necessary for optimal function of the PFC and any alterations in the neurochemical levels can improve with α2A-adrenoceptor agonists (that is, guanfacine). In studies with monkey models, stimulation of α2A receptors strengthened the functional connectivity of PFC networks, whereas blockade of such receptors in the PFC resulted in a reduction in working memory, an increase in impulsivity and a rise in locomotor activity. Hence, various stimulant and non-stimulant medications, while having therapeutic effects, have also provided clues to the related pathophysiological mechanisms in ADHD. The impact of such findings has had a large influence on our current characterization of the molecular level underpinnings of ADHD and has guided important research in genetics.

Genetic studies

ADHD is a multifactorial disorder resulting from a combination of multiple genetic and environmental factors that are thought to affect neural development[182,183]. The reported heritability of ADHD ranges from 0.7 to 0.8, indicating that this condition is associated with substantial genetic liability[184–187]. At the same time, multiple environmental factors,

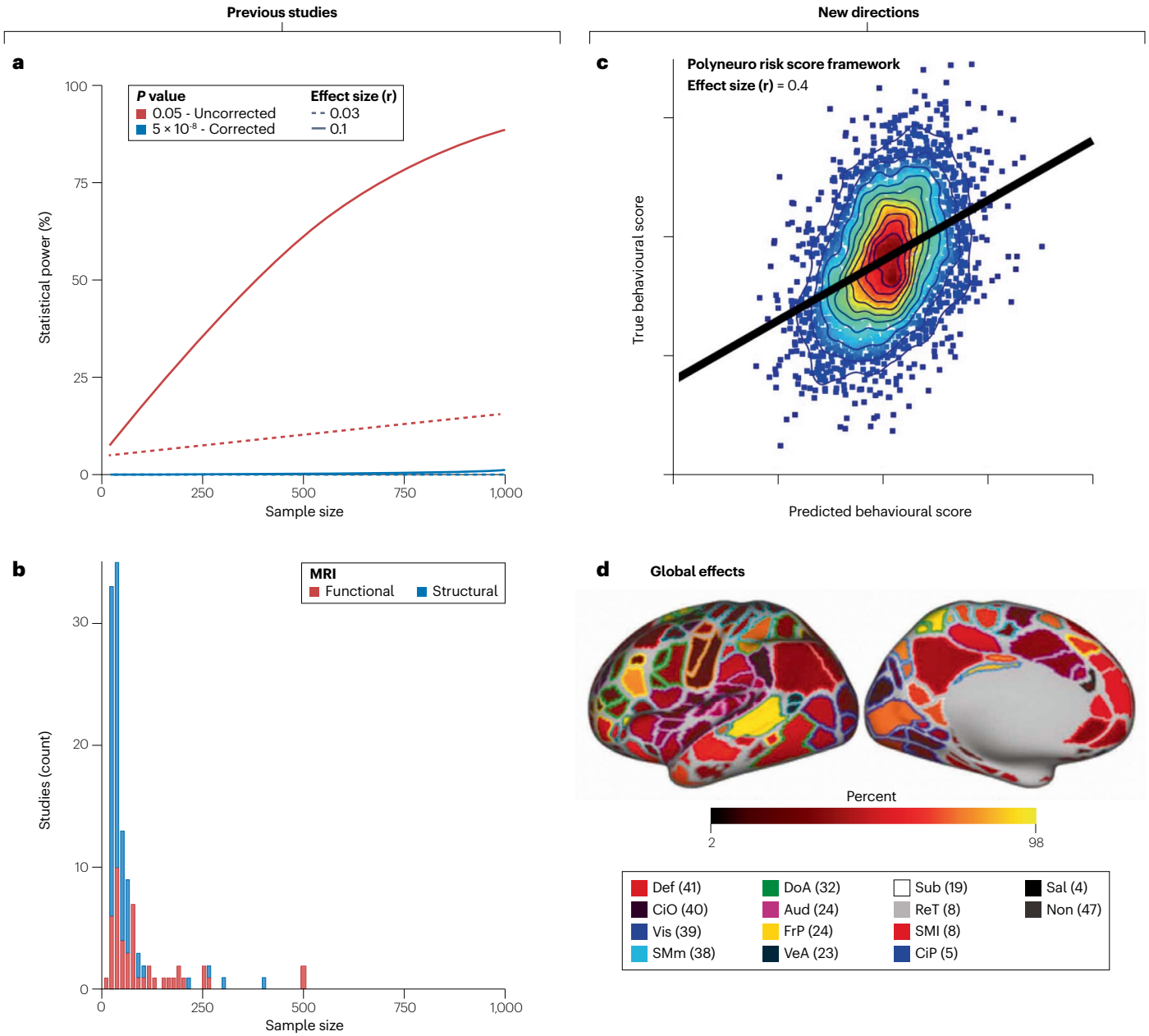


Fig. 3 | New directions to improve power in neuroimaging studies of ADHD. **a**, Brain–behaviour associations, especially in complex disorders like attention-deficit hyperactivity disorder (ADHD), have a small effect and require a large sample size to detect true relationships. Analytical power estimates were generated (*y* axis) as a function of sample size (*x* axis) using the pwr package (version 1.3-0) in R (version 4.4.0). Representative effect sizes were chosen from large-scale analyses of dimensional ADHD phenotypes and general brain–behaviour associations[93,274]. **b**, Current studies examining such relationships in ADHD have small sample sizes and are underpowered. Histogram of total sample sizes from neuroimaging studies of ADHD included in two recent meta-analyses[130,275]. **c**, Multivariate approaches that mimic the polygenic risk score (PRS) framework in genetics provide an opportunity in neuroimaging to combine many small effects in the brain to predict brain–behaviour relationships in neuroimaging (that is, polyneuro risk score), increasing effect sizes and lowering sample size requirements. Here, the relationship of connectivity across the whole brain to general ability in the ABCD sample is applied using the polyneuro risk score framework[263]. **d**, Effects from such studies are highlighting more global effects across the whole brain as opposed to localized effects to specific regions or networks[239,263]. Regions of interest defined by the Gordon parcellation schema with the corresponding number of parcels for each network (shown in brackets in the key)[263]. Regions of interest with brighter colours are more predictive of a given behaviour[263]. Aud, auditory; CiO, cingulo-opercular; CiP, cingulo-parietal; Def, default; DoA, dorsal attention; FrP, frontoparietal; Non, no assignment; ReT, retrosplenial temporal; Sal, salience; SMl, somatomotor lateral (mouth); SMm, somatomotor medial (hand); Sub, subcortical; VeA, ventral attention; Vis, visual. Parts **c** and **d** adapted with permission from ref. 263, Elsevier.

such as low birthweight and perinatal problems, have been linked to an increased risk for ADHD[188]. Further mechanisms of genetic transmission that may include the environment (for example, genetic nurturance) are beginning to be explored[189]. The relative familial risk has been shown to be similar for relatives of both boys and girls with ADHD[190] as well as the families of both white and Black probands[191]. Further work is still needed to characterize the root causes of familiality of ADHD across various demographic groups.

Investigators have sought to identify specific genes contributing to the genetic variance of ADHD. Many early studies used the candidate gene approach to examine polymorphisms in genes that influence the dopamine pathway and other catecholamine systems[192], specifically genes involved in dopamine signalling[193] (for example, *DRD4*, *DRD5* and *DAT1*), norepinephrine signalling (for example, *ADRA2A*) and serotonin signalling (for example, *HTT*). While initial findings seemed quite promising, only a handful of such associations have been replicated across studies. This difficulty in replication is probably due to the relatively small effect sizes of the associations and the field continually conducting underpowered studies. Hence, the field has progressively moved away from examining focal genes to exploring the influence of multiple genes in ADHD.

Family-based linkage analysis has been used to screen broad sections of the genome to identify regions that may contain additional genes that increase susceptibility to ADHD. Studies found no evidence anywhere in the genome for a gene with a large effect on ADHD, although they identified regions that may contain genes with smaller effects on certain chromosomes[194]. Of the candidate genes that were identified in previous association studies, only *HTT* and *DRD5* were found in regions of significant positive linkage. Many of the remaining candidate genes mapped to chromosomal regions that could be excluded statistically in the genome screen[194]. Hence, the genetic architecture of ADHD, with regards to early findings in the catecholamine systems, is still unclear as results from candidate gene approaches have rarely been validated in linkage studies.

Genome-wide association studies (GWAS), which look for associations between a disorder and hundreds of thousands to millions of common genetic variants (single nucleotide polymorphisms) across the entire genome have generated new ideas about the genetic origins of ADHD[187,195]. A GWAS meta-analysis conducted in 2019 of 20,183 cases and 35,191 controls discovered the first genome-wide significant risk loci – 12 in total – for ADHD[196]. None of the genome-wide significant loci contained any of the previously implicated candidate genes. Rather, several of the loci were located in or near genes that are implicated in neurodevelopmental processes such as synapse formation, neuronal wiring and neurotransmitter homeostasis. More recently, the largest ADHD GWAS to date (referred to here as the 2022 ADHD GWAS), with a sample of 38,691 individuals with ADHD and 186,843 controls, revealed 27 genome-wide loci associated with ADHD[197]. Out of the 12 genome-wide significant loci in the 2019 ADHD GWAS, 6 replicated in the 2022 ADHD GWAS. The integration of functional genomics data with these latest GWAS results suggests a set of ADHD-linked genes that are involved in early development and cognition and are linked to other psychiatric or neurodevelopmental disorders. For instance, genes such as *PTPRF, SORCS3 and DCC* encode components of the postsynaptic density membrane, whereas several transcription factor genes such as *FOXP1* and *FOXP2* have been associated with speech disorders and intellectual disability[197]. As with the brain imaging findings noted above, these functions are more consistent with brain-wide functions than localized systems. Nonetheless, while the replication of 6 loci is a positive sign of rigour, the lack of replication of the other loci potentially reveals continued power issues related to small effect sizes and other limitations of the overall approach.

The failure to replicate the traditional variants in the recent GWAS suggests that the associations from prior candidate gene studies may have been false positives. Still, GWAS also have limitations, and it remains unclear whether other forms of variation not assessed by GWAS, such as the variable number tandem repeat polymorphism in *DRD4* (a dopamine receptor gene identified as a candidate gene in early studies)[198], will replicate in future studies. Alternatively, it is possible that alternative mechanisms (for example, iron deficiency) modulate catecholamine dysregulation, leading to the emergence of ADHD symptoms, and implicating the dopamine system in the absence of a genetic finding. It is also a consideration that, given the polygenic nature of ADHD, multiple genes with small effects might converge to have effects on mechanisms that modulate catecholamine neurotransmission. However, while an intuitive expectation is that variants resulting in ADHD traits cluster in supposedly key pathways, such as the catecholaminergic system, in line with an omnigenic viewpoint[199], variants that contribute to ADHD might be spread across most of the genome and might not even be near genes with disease-specific functions. Taken together, recent findings and newer genetic conceptualizations have opened opportunities to question long-standing theories regarding catecholaminergic genes as well as to pose novel inquiries about the genetic underpinnings of ADHD.

Integration and advancement

As highlighted in the sections above, the neurobiology of ADHD has been extensively researched with growing urgency and major strides over the years. While various neurobiological factors, such as genetic components, dysregulated neurotransmitters and atypical brain systems, have been implicated in ADHD, an integrated picture has remained elusive. Hence, neurobiological findings have fallen short for clinical translation. In the following sections, we discuss new discoveries that may be underpinning some of the difficulties in characterizing the neurobiology of ADHD and how these findings are driving the field in exciting new directions.

Heterogeneity and a multi-dimensional perspective

Most studies of ADHD neurobiology have been guided by a binary, diagnostic conceptualization of the disorder. Such an approach relies upon an assumption of a clear and uniform distinction between individuals meeting diagnostic criteria and those who do not, and relative homogeneity within these groups. We, and others, have argued that one of the main obstacles to disentangling the neurobiological aetiology of ADHD is this dichotomous conceptualization of the disorder[14,15,200–205].

ADHD appears to be heterogeneous in its clinical profile, neuropsychology and neurobiology. Recent efforts suggest that ADHD is usefully viewed as the variable aggregation of dimensional traits continuously distributed in the population; such a dimensional perspective has been supported by studies examining ADHD phenotypes[15,206] as well as genomics[207]. ADHD is also clinically and mechanistically related to other psychiatric disorders such as autism spectrum disorder, obsessive-compulsive disorder, conduct disorder, depression and anxiety disorders[208,209]. Indeed, most children with ADHD will also meet criteria for a second disorder[210], highlighting the great variability in the ADHD population. Such comorbidity is also supported by the genetic overlap between disorders: ADHD shows the highest genetic correlation with post-traumatic stress disorder, cannabis and cocaine use, and major depression as well as a second-order moderate genetic

correlation with autism spectrum disorder and anxiety[208]. It has also been proposed that ADHD is an aggregation of dimensional traits, which are implicated in multiple disorders[211–213]. Indeed, a trait-based, dimensional approach to understanding psychopathology, including ADHD, appears to be a critically needed element to resolve ADHD pathogenesis in particular[14,214]. Additionally, as ADHD is a neurodevelopmental disorder, the developmental trajectories add another layer to the already complex issue of heterogeneity. For example, while in some cases ADHD is persistent into adulthood, it appears in a minority of cases to partially or fully abate in adolescence and adulthood[215] — highlighting how the phenotypic expression changes over time. Such developmental heterogeneity[216] makes it difficult, yet crucial[217], to precisely characterize the neurobiology of ADHD.

The phenotypic heterogeneity of ADHD means that the DSM diagnostic category may encompass biologically distinct or partially distinct entities, domains, dimensions or syndromes. Indeed, it is generally clear that a clean mechanistic separation between individuals with and without ADHD may not exist[218–221]. Not surprisingly, examination of neural underpinnings in ADHD has revealed brain differences in individuals with internalization and externalization problems[222], thereby challenging the assumption (as in case–control studies) that all individuals with ADHD have the same neurobiological aetiology. Furthermore, it is quite possible that the neural profile associated with a particular phenotype changes as the brain develops — even within an individual[100]. As such, adding the developmental axis challenges the reliability and stability of a neurobiological marker from one developmental time point to another, highlighting the importance of developmentally informed research and intervention.

Given the heterogeneity in phenotype and biology across development, we endorse the adoption of a dimensional conceptualization for ADHD. Recent frameworks in mental health, such as the Research Domain Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP), have re-energized interest in the dimensional organization of nosology[201,202,223]. However, such frameworks also have important limitations[224]. First, despite their promise and new ways of thinking about the biology of disorders such as ADHD, it has been challenging to convert findings into clinical decision-making. Second, while RDoC has just recently adopted a developmental dimension[225,226], HiTOP is still missing the developmental framework that is probably critical for characterizing all aspects of a neurodevelopmental disorder such as ADHD[227]. Nonetheless, HiTOP, RDoC and related approaches open opportunities to conceptualize trait-level phenotypes in human as well as animal models. While results from animal models do not always translate well into humans, they have been productive in ADHD research[228] and these frameworks may provide a new impetus to further attempts at translation.

In summary, the effort to clarify neurobiological mechanisms involved in ADHD might confer success only after we move beyond considering ADHD as a distinct unitary, homogeneous category. ADHD neurobiology is extremely heterogeneous. Multiple neurobiological mechanisms at different levels may drive ADHD symptoms for different subsets of individuals. In addition, long-term outcomes of, for example, treatment response, prognosis and symptom trajectory of the same ADHD symptom profile are equally vast and may reflect underlying heterogeneity in neurobiology. The current work involving the adoption of a multi-dimensional framework to understand the constituent processes of a syndrome as well as identifying useful and more neurobiologically homogeneous subgroups or biotypes appears promising (expanded on further in Box 1). However, we highlight here, as we have done previously[203], that it will be unlikely that any of these rubrics alone will constitute 'the answer'. Undoubtedly, distinct subgroups, unique features or dimensions of even the same individuals might be pertinent for different questions or outcomes (for example, prognosis, diagnosis or optimal therapy). Here, we focus specifically on heterogeneity as it pertains to neurobiology and note that, when trying to understand and parse the variance among multiple features (for example, genes, brain systems and behaviour) in typical and atypical populations, many distinct subpopulations might emerge. Thus, recent efforts have been and should continue to innovate and apply approaches to identify ADHD subtypes tied to the question of interest[203]. In summary, designing newer studies with the conceptualization of ADHD as a multifactorial, dimensional condition needs to garner momentum in the field to better address the heterogeneity that underlies ADHD neurobiology.

Box 1 | The heterogeneity problem and ADHD neurobiology

The heterogeneity problem in attention-deficit hyperactivity disorder (ADHD), as in all mental health disorders, is complex. It manifests on many levels, from symptoms to treatment response to biological underpinnings. While efforts to identify homogeneous subgroups have been long-standing, it is unlikely that 'one way' of subtyping can explain the vast heterogeneity in ADHD across its seemingly unlimited dimensions[203]. Nevertheless, such efforts have received renewed interest after recent research initiatives, including the Research Domain Criteria[276], which emphasizes finding behavioural stratifications or dimensions that are grounded in biological systems and that cut across current Diagnostic and Statistical Manual of Mental Disorders classifications. In ADHD, efforts to parse heterogeneity have been extensive, spanning multiple levels from brain systems to genes. At the systems level, group iterative multiple model estimation has been used to identify different brain connectivity subtypes linked to ADHD risk[277]. At the level of circuits, investigators have used other unsupervised approaches to characterize previously unknown ADHD temperament subtypes[206]. Similarly, at the level of genes, latent class analysis has identified multiple ADHD genomic risk trajectories[278]. However, a central limitation to such methods is a lack of a tie to a question of interest[203]. Alternative hybrid approaches, such as functional random forests[67,203], surrogate variable analysis[273] and normative modelling[279,280], have been utilized in ADHD (and other disorders) to identify neurobiological subtypes tied to an outcome. They can be specifically beneficial in subgrouping highly dimensional data at all levels of inquiry. Importantly, modern computational approaches are not the only methods at our disposal to parse the heterogeneous nature of ADHD neurobiology. ADHD subtypes have also been identified based on responses to methylphenidate treatment[281]. Animal models can be quite useful in modelling potential subtypes as well[282]. Characterizing the biological variance across ADHD at multiple levels of brain organization will be critical to understanding the underpinnings of the disorder.

Expanding the scope of investigation

Both early and modern neurobiological theories of ADHD have been deeply rooted in the mechanism of action of stimulants because of the

serendipitous discovery that stimulant medications can be useful in treating behavioural disorders in children. As the mechanism of action of stimulants, such as methylphenidate, is the modulation of catecholamines, research at various levels – from genomics to brain systems – has focused on understanding the catecholaminergic system. However, such focus on a specific system has potentially created a self-fulfilling loop and led to a narrow scope of investigation – useful at most for a subgroup. Thus, a broader scope of investigation is needed.

Given the heterogeneous nature of ADHD, it is possible that there are multiple pathophysiological mechanisms involved. A general finding from years of ADHD psychiatric genetic studies is that the risk attributed to genes involved in the regulation of catecholaminergic systems has not been replicated. The failure to implicate previously known candidate genes in ADHD suggests that prior models are either imprecise or are only useful for explaining mechanisms underlying a small subset of patients that exhibit the disorder. While current medications targeting catecholaminergic neurotransmission, such as methylphenidate, do indeed lead to improved outcomes in some patients with ADHD, at least in the short term, neither the effects nor the targeted pathways are specific to ADHD. Moreover, giving stimulant medications to individuals without ADHD has also been shown to have an impact on behaviour[229–231]. Despite a historical emphasis on catecholamine systems, several lines of research have suggested that other neurobiological systems are also of potential importance, including the cholinergic system and nicotinic receptors[232–234], glutaminergic transmission (also affected by stimulants)[153,235,236], and serotonin transmission[237]. More recently, advancements in genomics have revealed a number of variants involved in ADHD. A recent GWAS showed that the affected genome-wide loci often have a general function in areas such as neurite outgrowth, synaptic plasticity or glutamatergic signal transmission[197], suggesting that ADHD neurobiological aetiology extends beyond the catecholaminergic systems. Thus, the dysregulation of catecholaminergic systems might be a contributing factor to ADHD symptoms but it is unlikely to be the sole or causal mechanism for developing the disorder.

Non-invasive methods such as neuroimaging have further implicated brain systems beyond the catecholaminergic systems. It has now been suggested that biological and physiological correlates of ADHD are not simply localized alterations in brain function but, rather, implicate widely distributed functional brain systems[16,95,238,239]. While some studies show altered connectivity within the DMN in ADHD[110,240,241], other lines of work using resting-state functional MRI studies show that other networks are involved[242]. The fact that the literature highlights the involvement of many systems reinforces the idea that ADHD is probably not defined by one system or circuit, but that it might be distributed across many systems in the brain. A recent study revealed that cumulative effects of resting-state connectivity across various brain networks relate to ADHD symptoms[239], providing support for a neurobiological basis for the heterogeneity observed in ADHD presentation[243]. These findings emphasize that multiple brain networks, if not all, are likely involved to varying degrees (that is, a global view of the pathophysiology) and are consistent with the above-mentioned GWAS findings of genes implicated in biological functions that impact the entire brain.

A broader focus of investigation is necessary as the wider neural impacts of therapeutic drugs and the cross-modulation of neural systems are increasingly understood. Efforts should be placed to understand the convergence of multi-level findings, where genomics, neuroimaging, and other studies inform and validate each other. While prior work primarily focused on relating focal genes or brain regions to ADHD, recent studies confirm that ADHD does not stem from a singular cause. Thus, examination of ADHD neurobiology could greatly benefit from adopting the anti-localizationist and anti-reductionist philosophy that is currently emerging in neuroscience research[244].

Designs and methods that complement ADHD phenotyping

Biological features related to ADHD, such as genes or brain networks, have small effect sizes[239]. Signals related to complex traits such as ADHD phenotypes tend to spread across most of the genome as explained by various models[245,246]. Such genes with small effects contribute to the risk of developing the disorder in combination with environmental factors[247]. Similar small effect sizes for brain–behaviour studies have been shown by recent large-scale neuroimaging data[204,248–251]. Consequently, small effects link brain network connectivity changes to ADHD phenotypes[239].

Studies investigating the neurobiology of ADHD have often been underpowered to detect such small effects, owing to the very small sample sizes that are historically common in, for example, brain imaging studies[252] (Fig. 3). This issue is further exacerbated by ADHD heterogeneity, in both symptom presentation and potential underlying biological mechanisms. Efforts to subtype or create homogeneous groups of participants based on either phenotypes or brain features to address heterogeneity decrease the sample size even further, which on the one hand might increase effect sizes but, on the other, might exacerbate issues of studies generally being underpowered. Furthermore, owing to the reduced incidence of ADHD in girls compared with boys[10] and the historic underrepresentation of girls and minority groups in samples[253,254], traditionally small unrepresentative samples are a major issue for the field[250].

Overall, as Ioannidis noted back in 2005 (ref. 255), known biases in underpowered studies (for example, 'p-hacking'[256]) and publication biases have led to many highly significant but not generalizable findings. Even if some effects replicate, they are mostly inflated and suffer from the 'winner's curse'[257], which can subsequently lead to results from meta-analyses also being inflated. Thus, our scientific culture, which de-emphasizes null findings in favour of significant findings, biases the field in ways that might be misleading with regards to the neurobiology of ADHD. These challenges, while nevertheless ongoing, can be addressed through larger sample sizes, transparent reporting and changes in publication practices. In short, small underpowered studies are vulnerable to sampling variability and multiple potential statistical biases, including effect size inflation. A roadmap of the future will include global collaboration, open science, data sharing, standardization[258], consortium-style study investments, phenotype refinement and more, to overcome these challenges. Such challenges will dramatically decrease as sample sizes, and by extension statistical power, increases.

Even with larger sample sizes and improved phenotyping, examination of ADHD neurobiology will not find success unless paired with appropriate study designs, methods and measurements. Emerging frameworks in psychiatric neuroimaging suggest that there are two possible routes forward that represent distinct methodological[259] and clinical goals[260]. First, we need to establish or improve already existing large observational consortia studies. Such efforts can help understand population variability that may support clinical screening or ADHD prediction[260]. The field of genomics has already rendered success by pooling data to form large genomics consortiums that have yielded the discovery of newer genetic variants implicated in ADHD[196,197,208]. Given the polygenicity of ADHD and the inherent difficulty with finding

individual variants, genomics researchers have used large GWAS data to create a polygenic score, or as often referred to in studies of psychopathology, a polygenic risk score (PRS)[261]. A PRS can estimate the genetic liability of an individual for a particular disorder or trait, based on current knowledge of the genetic architecture of that trait. Studies have shown that ADHD PRS is reliable and robust, and operates in a dose-dependent manner: the higher the PRS, the higher the odds ratio for having ADHD[197,262]. Studies have also shown that common genetic variants underlying ADHD, as captured by the ADHD PRS, are associated not only with diagnosed ADHD but also with more dimensional ADHD traits. Such traits include externalizing behaviours, reduced working memory, impaired education attainment, reduced brain volume, higher body mass index and reduced socioeconomic status[262], which illustrates the shared genetic effects between various comorbid conditions. Newer methodologies in genetics have already begun to yield progress to better understand underlying biology.

In neuroimaging, large-scale population studies provide some early opportunities for such investigations[210,239]. In fact, similar to PRS in genomics, new approaches have begun to utilize a polyneuro risk score[239,263] to study effects across the entire brain in both structure[264] and function[263] related to ADHD phenotypes[239]. The creation and pooling of such large-scale studies have multiple benefits: first, the sample size is dramatically increased to conduct robust brain–behaviour association studies; second, unlike case–control studies with recruitment cutoffs, samples from consortia studies are more likely to be diverse and compatible for examining dimensional traits. In fact, such studies can prove beneficial to oversample for girls with ADHD given the lower diagnostic rates for girls[10]. Building from the principles of meta-analyses, pooling data allows researchers to examine the generalizability and heterogeneity of participant-level factors. However, it is important to note that even the 'largest samples' in the literature and currently available in the field are not guaranteed to be enough for certain findings to be generalizable. In our own work[249], we showed that the ABCD study (n = ~9,000) is small for some effects, which might require even larger UK Biobank size samples (n >30,000). To this end, future research should promote open international collaborations that allow cultural and regional variability of data. While such efforts will not be easy, a cultural shift in the field that recognizes that the only way to truly understand the biology of ADHD is with sufficiently diverse samples might encourage local funding agencies to support global work. Such examples already exist (for example, ENIGMA, OpenNeuro and the Psychiatric Genetics Consortium), are likely to expand and will increase the generalizability of findings.

In parallel to large, observational studies and consortia, the second approach can focus on smaller, targeted-sample longitudinal and interventional studies of people with ADHD[259,260]. Indeed, not all study designs require massive samples. Precision functional mapping techniques in neuroimaging studies can focus on improving brain–behaviour signals in an individual by using high-reliability neurobiological assessments and within-person designs. Such studies can inform researchers about the effects of ADHD and/or various interventions within individuals and can be useful to identify longitudinal mechanisms for treatment development. In such designs, the base-state of symptoms and neurochemistry for an individual can be considered to better understand the effects of interventions[144,265,266]. Samples as low as n = 3 have been extremely valuable in characterizing brain mechanisms under such within-person mechanistic intervention designs[267]. In this sense, each individual becomes their own 'mini' study, which can be replicated in more individuals. Smaller targeted studies using deep-phenotyping approaches can incorporate intensive and multi-dimensional tests, multiple longitudinal visits, as well as smartphone and ecological momentary assessments to focus on identifying person-specific neurobiological and phenotypic patterns of ADHD. While brain-wide association studies (for example, relating brain systems to attention phenotype) may require larger sample sizes to establish meaningful correlations, a comprehensive global brain-wide investigation (for example, examining all networks instead of a focal one) can still be conducted with smaller, more targeted samples. We think that leveraging these approaches is essential for accurately defining ADHD mechanisms, its heterogeneous subgroups and neurobiological profiles. Furthermore, ongoing methodological and study design advancements beyond what has already been described here will also be essential in the field to extend the conceptual progress we have made so far.

Glossary

Brain networks
Interconnected regions of the brain that communicate with each other.

Brain-wide association studies
Approach used to identify associations between brain-wide imaging measures and various behaviours.

Effect sizes
Magnitudes of the relationships observed between variables in a study.

Functional connectivity
Measures the degree to which the activity in one brain region is related to activity in another region.

Heterogeneity
Variability in symptoms, aetiologies, mechanisms and responses to treatment among individuals with the disorder.

Localizationist framework
The concept that specific brain functions can be attributed to specific regions of the brain.

Phenotypes
Observable characteristics or traits of an organism.

Conclusions

The field has come a long way in establishing the neurobiology of ADHD since the first description of an ADHD-like disorder and the implication of the CNS. While the definition of ADHD will continue to be redefined (DSM)[6,268], methodological and design advancements in genomics and neuroscience will continue to help map ADHD neurobiology and to bring clinical utility closer. In this Review, we summarized the current knowledge in ADHD neurobiology across multiple levels of inquiry, highlighted historical challenges and discussed potential paths forward. We contend that improved and refined phenotyping[269–271] will markedly contribute to our understanding. Simultaneously, broadening our investigative scope beyond isolating pathology within specific genes, regions or networks to a more comprehensive developmental and global perspective is crucial. This expansion, coupled with a full acknowledgement of the multi-dimensional heterogeneous nature of the disorder, will collectively establish a solid foundation for advancing our knowledge. By aligning such an approach with meticulously chosen study designs and methods, we anticipate propelling the field towards a comprehensive understanding of the neurobiology of ADHD.

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Competing interests
D.A.F. is a patent holder on the Framewise Integrated Real-Time Motion Monitoring (FIRMM) software. He is also a co-founder of Turing Medical Inc., which licenses this software. S.M.N. is a consultant for Turing Medical Inc., which commercializes FIRMM technology. These interests have been reviewed and managed by the University of Minnesota in accordance with its conflict-of-interest policies. The other authors declare no competing interests.

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