Attention-deficit hyperactivity disorder

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Attention-deficit hyperactivity disorder (ADHD), like other psychiatric disorders, represents an evolving construct that has been refined and developed over the past several decades in response to research into its clinical nature and structure. The clinical presentation and course of the disorder have been extensively characterised. Efficacious medication-based treatments are available and widely used, often alongside complementary psychosocial approaches. However, their effectiveness has been questioned because they might not address the broader clinical needs of many individuals with ADHD, especially over the longer term. Non-pharmacological approaches to treatment have proven less effective than previously thought, whereas scientific and clinical studies are starting to fundamentally challenge current conceptions of the causes of ADHD in ways that might have the potential to alter clinical approaches in the future. In view of this, we first provide an account of the diagnosis, epidemiology, and treatment of ADHD from the perspective of both the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders and the eleventh edition of the International Classification of Diseases. Second, we review the progress in our understanding of the causes and pathophysiology of ADHD on the basis of science over the past decade or so. Finally, using these discoveries, we explore some of the key challenges to both the current models and the treatment of ADHD, and the ways in which these findings can promote new perspectives.

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Introduction

Attention-deficit hyperactivity disorder (ADHD), like other psychiatric syndromes, has been refined and developed over the past 50 years, from its first contemporary description in the Diagnostic and Statistical Manual of Mental Disorders (second edition; DSM-II) as a hyperkinetic reaction of childhood to its current inclusion in DSM-5[1] as a lifespan neurodevelopmental condition with specific criteria for children and adults, a change reflected in its counterpart, the International Classification of Diseases (11th revision; ICD-11).[2] This process of diagnostic evolution has been the result of periodic review and reformulation shaped by both research and clinical drivers. From a research perspective, the ADHD diagnostic formulation can be considered a part of a larger working hypothesis about the nature and structure of the disorder.[3] As such, this diagnostic formulation is tested against empirical evidence so that it represents an increasingly accurate approximation of nosological reality as reflected in established research findings. Because the primary purpose of diagnostic systems is to provide intuitive and implementable guides for clinical decision making, the threshold for diagnostic innovation is set high and the pace of diagnostic evolution has been incremental in nature.[4] Furthermore, as diagnostic systems in psychiatry have adopted a descriptive or phenomenological approach, considerations of the underlying causes of ADHD have been excluded from this process of re-evaluation and refinement. However, this diagnostic framework might be set to change. Progress in the aetiology and pathophysiology of ADHD challenges our current ways of thinking about the condition, while raising the prospect of new and potentially more effective clinical approaches.

Developing a broader range of more effective clinical approaches for people with ADHD, through the use of scientific discoveries, represents an important goal for the field.

ADHD is a prevalent, impairing condition that is frequently comorbid with other psychiatric disorders and creates a substantial burden for the individual, their family, and the community.[5] Medication-based treatment strategies have proven efficacious and cost-effective in the short term and a number of compounds are available, recommended, and widely used.[6,7] However, the long-term effectiveness of these treatments on key educational, vocational, and social outcomes remains uncertain.[8,9] Furthermore, such effects are compounded by low adherence, especially after extended use in adolescence.[10] These limitations are probably the result of both biological and psychosocial processes (eg, the build up of medication tolerance, ADHD-related stigma, and social resistance to medication).[8,11] Clearly, there is a pressing need for better long-term treatments for ADHD. By changing the way the field thinks about the causes of ADHD, scientific progress might help stimulate the development of new strategies for increasing the effectiveness of current treatments or the evolution of new alternatives. This Seminar will explore the issue of long-term treatment in three sections. The first section provides an account of the consensus about the clinical

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1980, and March 1, 2019, with an emphasis on the previous 10 years. English and non-English language publications were considered in our search. We included primary and review articles resulting from these searches, along with relevant references cited within those articles. Given the broad scope, yet restricted space, of our review, we occasionally cite review papers in place of primary reports. We used the search terms: "ADHD", "neurobiolog*", "neural circuits", "brain imaging", "genetics", "endophenotypes", "impulsivity", and "psychostimulant".

condition of ADHD, its diagnosis, epidemiology, developmental course, and treatment. The second section presents an up-to-date overview of ADHD science, focusing on advancements in aetiology and pathophysiology. The final section briefly explores how some of the most important scientific discoveries are beginning to challenge conceptions of ADHD in specific ways and examines the prospect that they will encourage new clinical perspectives and approaches.

Clinical consensus

Diagnosis

ADHD is a clinical diagnosis requiring a detailed evaluation of current and previous symptoms and functional impairment. A full family, gestational, and developmental history should be taken.[12] The American Psychiatric Association's DSM-5 defines ADHD in children (younger than age 17 years) as the presence of six or more symptoms in either the inattentive or hyperactive and impulsive domains, or both (panel 1). Fewer symptoms (ie, at least five symptoms in either domain) are required to meet the adult diagnostic criteria. The age of symptom onset was modified from before age 7 years in DSM-IV to before age 12 years in DSM-5 to permit greater flexibility when diagnosing adults. Additionally, whereas DSM-IV divided ADHD into three subtypes on the basis of the predominant symptomatology (inattentive, hyperactive and impulsive, or combined), DSM-5 replaced the term "subtype" with "presentation" to emphasise that symptom clusters can change as patients mature and develop.[14] The ICD has updated its diagnostic formulation to bring it into line with DSM-5, moving ADHD from the disruptive to the neurodevelopmental disorder domain, exchanging the label hyperkinetic disorder with ADHD, and including inattentive and hyperactive–impulsive presentations of symptoms.[15] Distinct from DSM-5 and ICD-10, ICD-11 describes the essential features of the disorder, without giving a precise age of onset, duration, or number of symptoms.[15] We reviewed the diagnostic challenges, common comorbidities, and the role of neuropsychological tests (appendix pp 1–3).

See Online for appendix

Panel 1: **Criteria for attention-deficit hyperactivity disorder**

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders criteria

Inattention

- Often cannot give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities
- Often has trouble holding attention on tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and does not finish schoolwork, chores, or duties in the workplace (eg, loses focus, or is side-tracked)
- Often has trouble organising tasks and activities
- Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework)
- Often loses things necessary for tasks and activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, and mobile telephones)
- Is often easily distracted
- Is often forgetful in daily activities

Hyperactivity and impulsivity

- Often fidgets with or taps hands or feet, or squirms in seat
- Often leaves seat in situations when remaining seated is expected
- Often runs about or climbs in situations where it is not appropriate (adolescents or adults might be limited to feeling restless)
- Often unable to play or take part in leisure activities quietly
- Is often "on the go" or acting as if "driven by a motor"
- Often talks excessively
- Often blurts out an answer before a question has been completed
- Often has trouble waiting their turn
- Often interrupts or intrudes on others (eg, conversations or games)

The eleventh edition of the International Classification of Diseases criteria

- Persistent pattern (at least 6 months) of inattention,* hyperactivity–impulsivity,* or both
- Onset typically in early to mid-childhood
- Symptoms interfere with academic, occupational, or social functioning

*Additional descriptors of inattention, hyperactivity, and impulsivity are provided in the International Classification of Diseases, 11th revision.[13]

Although ADHD is chronic in nature, and treatment is typically provided over several years, the course of the disorder can vary from one patient to the next. Longitudinal studies suggest the possibility of at least four developmental trajectories: early onset (preschool ADHD [3–5 years]), middle childhood (6–14 years) onset with a persistent course, middle childhood onset with adolescent offset, and adolescent or adult onset (16 years and older).[16–18] Treatment approaches and particular medications overlap substantially across these trajectories (as we discuss later), but prognosis might differ and understanding these disease courses might aid in treatment planning (eg, whether a child with ADHD no longer needs medication when they reach adolescence). Efforts are underway to predict the onset and course of ADHD across the lifespan. For example, on the basis of four longitudinal cohorts, Caye and colleagues[19] developed a risk calculator of childhood characteristics, such as intelligence quotient (IQ) and childhood maltreatment, that collectively estimates risk for adult ADHD. Establishing of robust predictors of clinical course would aid treatment decisions, informing, for instance, the duration of interventions and periods of elevated risk.

Epidemiology

Accurately estimating the number of individuals affected by ADHD in a population is essential to health service planning. This estimate allows the burden associated with the disorder to be approximated and then the required investment to be made. Furthermore, accurate epidemiological data across time and countries can help test the validity of the ADHD diagnosis, and might provide indications about its causes and pathophysiology.[20] Initial studies in the 1970s and 1980s provided

a wide range of prevalence estimates, which, when interpreted in the context of the rapidly increasing number of children treated with medication at the time, raised societal concerns about inconsistent and excessive diagnosis. These studies also created disputes about the validity of the diagnosis. Some suggested the disorder was nothing more than a cultural product of competitive developed societies, its increasing use spurred on by the influence of the pharmaceutical industries trying to build market share. Meta-analytic studies investigating the factors responsible for this variability in prevalence were important in resolving such disputes. Two studies were especially influential and aggregated 102 studies[21] (and then an additional 41 studies)[20] involving community samples of children and adolescents from 35 countries in six continents worldwide and estimated the prevalence of ADHD as 5·29% (95% CI 5·01–5·56).[21] Follow-up meta-regression analyses indicated that the variability in previously reported ADHD prevalence was, in fact, attributable to methodological differences between studies, specifically in the diagnostic criteria, sources of information, and the requirement of functional impairment for diagnosis factors that varied between regions and countries.[21,22] Point prevalence from Europe, Oceania, South America, Asia, Africa, and the Middle East did not differ from those from North America, nor did the prevalence change across time from 1985 to 2012.[21,22] These data suggest that ADHD prevalence worldwide is stable when study methods are consistent. In general, studies done in the same populations with equivalent rating scales do not detect temporal changes in the number or severity of symptoms,[23] supporting the meta-analytical data, with only some studies pointing to decreasing[24] and fewer to increasing rates of subthreshold symptoms.[25]

Meta-analyses have estimated the prevalence of ADHD in adults aged 19–45 years at 2·5% (95% CI 2·1–3·1).[26] Longitudinal studies following clinical samples of children with ADHD document a general decline of symptoms; meta-analytic data estimate that 15% of patients will persist with full diagnostic criteria in adulthood and 40–60% of patients will be classified as partial remitters.[27] Prevalence in adults is higher than would be expected by the persistence rates from children, suggesting the emergence of new cases during development. In fact, studies of prospectively followed up, representative community samples showed the emergence of ADHD during adolescence and adulthood, indicating a new developmental subtype of the disorder,[28] a finding discussed further in subsequent sections of this Seminar.

Treatment

ADHD seldom affects only one functional domain but impacts many aspects of an individual's wellbeing, including physical health, and academic, social, and occupational functioning. Often arising in childhood, ADHD can also be chronic in nature, frequently continuing through adolescence and beyond, at least at the level of impairment. Evaluation of treatment outcomes therefore should incorporate multiple components, such as psychoeducation, learning and academic support, school accommodation, intervention for management of symptoms, parental practices, and assessment and treatment of associated disorders. Treatment approaches are also likely to evolve as a patient matures. For example, parental practices have a large role in the treatment of a child aged 6–12 years, whereas psychoeducation regarding the risk of substance abuse and motor vehicle accidents becomes more central when a patient reaches adolescence. In our proceeding discussion of different approaches to managing ADHD, the degree of unmet clinical need in many countries where only a small percentage of individuals with the condition receive any treatment should be acknowledged.[29]

With respect to the management of ADHD symptoms, US,[30] Canadian,[31] Latin American,[32] and European[33] medical organisations all recommend the use of psychostimulant medications. Many of these ADHD resources and guidelines can be found online.[33,34] However, most of these organisations recommend beginning with psychoeducation and behavioural management, particularly for individuals with mild symptoms and impairment.[6,35] US guidelines differ and suggest that medication is considered with initial treatment.[30] For children younger than 6 years old, there is consensus that treatment should start with behaviour management in the form of parent training and that medication should be reserved for more severe or unresponsive cases. The National Institute for Health and Care Excellence (NICE) guidelines,[33] for example, recommend that medication management for children younger than 5 years be considered only when parent training has been attempted and a second opinion has been obtained from a provider with expertise in ADHD in young children.

Medication

Medications for ADHD are categorised into stimulants (or psychostimulants) and non-stimulants, with several different formulations, delivery systems, and pharmacokinetic profiles available (table). Importantly, the availability of medications varies worldwide, with very few options accessible in some countries.

First used in children in the 1930s, psychostimulants continue to be first-line medications for management of ADHD symptoms and consist of formulations of methylphenidate and amphetamine. Mechanisms of action for both are similar. Methylphenidate blocks presynaptic dopamine and norepinephrine transporters, thereby increasing catecholamine transmission; amphetamine also inhibits both transporters, but additionally increases the presynaptic efflux of dopamine.[36] The efficacy of psychostimulants in reducing ADHD symptoms in short-term treatment has been shown in numerous clinical trials

	Dose range (mg)	Delivery
Stimulants		
Methylphenidate (short; duration of 4 h)		
Methylphenidate, immediate release	10–60	Tablet
Methylphenidate, oral solution	10–60	Liquid
Dexmethylphenidate, immediate release	2·5–20	Tablet
Methylphenidate (intermediate; duration of 6–8 h)		
Methylphenidate hydrochloride, sustained release	10–60	Tablet
Methylphenidate, long-acting	10–60	Capsule; contents can be sprinkled onto soft food
Methylphenidate (long; duration of 8–12 h)		
Dexmethylphenidate, extended release	5–30	Capsule; contents can be sprinkled onto soft food
Methylphenidate, oral solution, extended release	20–60	Liquid or chewable tablet
Methylphenidate, osmotic release	18–54 for children; 18–72 for adults	Tablet; osmotic-release oral system
Methylphenidate, transdermal	10–30	Patch
Methylphenidate hydrochloride, extended release	10–60	Capsule; contents can be sprinkled onto soft food
Amphetamine (short; duration of action 4–6 h)		
Dextroamphetamine	5–40	Tablet and liquid
Dextroamphetamine-amphetamine	5–30	Tablet
Amphetamine (long; duration of action 8–12 h)		
Dextroamphetamine-amphetamine, extended release	5–30	Capsule; contents can be sprinkled onto soft food
Dextroamphetamine, sustained release	5–40	Capsule
Lisdexamfetamine	10–70	Capsule; contents can be dissolved in liquid
Non-stimulants (duration of action 24 h)		
Atomoxetine	0·5–1·4 mg/kg; maximum 100 mg	Capsule
Guanfacine, extended release	1–4	Tablet
Clonidine, extended release	0·1–0·4	Tablet

Table: **Medications for attention-deficit hyperactivity disorder**

of both children and adults with ADHD. For instance, a meta-analysis including more than 10 000 children and adolescents (with trials lasting approximately 3 months) found that methylphenidate and amphetamine both had moderate-to-large effect sizes when symptom change was rated by clinicians (SD for methylphenidate 0·78; SD for amphetamine 1·02) and teachers (SD for methylphenidate 0·82; data not available for amphetamine).[37] A meta-analysis of 18 studies suggested that methylphenidate is also efficacious in adults, with an effect size of 0·6 based on self-reported and clinician-reported symptom change.[38] Moreover, another meta-analysis encompassing more than 8000 adult participants showed moderate effect sizes for both methylphenidate (0·49) and amphetamine (0·79).[37] An additional meta-analysis of children with ADHD across 22 trials and adolescents with ADHD across nine trials compared methylphenidate and amphetamine and found both interventions highly efficacious, with slightly larger effects sizes for amphetamine (0·99) relative to methylphenidate (0·72).[39] The side-effect profiles of these drugs are similar, with the most common side-effects being appetite suppression, insomnia, dry mouth, and nausea, but amphetamine might be somewhat more prone to side-effects.[40] Side-effects are generally similar for adults and children, but might be more common in young children (ie, aged 5 years and younger).[41] NICE guidelines[33] recommend that medication treatment should begin with methylphenidate for children older than 5 years, but to then switch to amphetamine if the response is inadequate. For adults aged 18 years and older, the NICE guidelines recommend starting with either methylphenidate or the amphetamine formulation, lisdexamfetamine.

Three additional areas of concern with stimulant medications merit further consideration. First, there are the effects of long-term stimulant treatment on growth, specifically height and weight velocity. Although studies have yielded mixed results, most suggest that consistent stimulant use over several years can affect growth trajectories.[42,43] Based on childhood growth models, consistent long-term stimulant use might lead to modest reductions in adulthood height (approximately 1–3 cm), but more substantial increases of weight and body-mass index (although initial treatment can cause modest weight loss).[41] These effects, however, are potentially attenuated by introducing so-called drug holidays (eg, not taking medication over holiday periods or summers) and are arguably outweighed by the benefits of treatment.[44,45] Second, given the potential euphorigenic effects of stimulants, concern that stimulant use might increase the likelihood of subsequent substance abuse and dependence has been considerable.[46] However, this concern is not reflected in longitudinal research as studies have either suggested that stimulant use has no effect on, or can even lower, substance abuse risk.[46–48]

In many developed countries, stimulant diversion is a related concern, by which individuals without ADHD acquire stimulants, often with the goal of increasing academic or vacation productivity.[49] Further research is needed to understand the prevalence and impact of such use. Finally, a third concern is that stimulants, with their sympathomimetic properties, increase the likelihood of cardiovascular events. Although initial research from small, retrospective samples indicated the presence of associations between stimulant use and sudden cardiac death,[49] large scale registry studies have generally been reassuring, showing no relationship between serious cardiovascular events and stimulant use.[51,52]

Relative to stimulants, non-stimulant medications have lower responses and effect sizes and thus are typically reserved for patients who respond poorly or have intolerable side-effects to trials of stimulant formulations. Non-stimulant medications include the norepinephrine transporter inhibitor, atomoxetine, and the α-2 agonists, guanfacine and clonidine (table). Most treatment guidelines deem non-stimulant medications second-line treatments to be considered if treatment with stimulants proves inadequate. NICE guidelines,[33] for example, suggest that children with ADHD are switched to atomoxetine or guanfacine if their response to methylphenidate or amphetamine is poor; for adults, the recommendation is to switch to atomoxetine, as there is less evidence for α-2 agonists in adult ADHD.

A meta-analysis of 25 trials of atomoxetine in children with ADHD indicated a moderate effect size (SD 0·64); however, a large portion of patients (approximately 40%) had persistent symptoms requiring additional clinical intervention.[53] Atomoxetine is also effective in adults, albeit with a more modest effect size (approximately 0·33) based on a meta-analysis of 12 trials.[54] Trials of long-acting α-2 agonist formulations (extended-release guanfacine and extended-release clonidine) in children indicated medium effect sizes (0·5–0·6).[55,56] These formulations are often used as adjuvants to stimulants in patients with inadequate response to monotherapy, or in patients with comorbid aggression, insomnia, or tic disorders.[57] A clinical trial of extended-release guanfacine suggested similar effect sizes for adults with ADHD, but additional research is still needed to confirm these results.[58] In summary, the efficacy of ADHD medications has been clearly shown in the short term, with effect sizes and side-effects generally similar for adults and children. However, non-medication interventions do often differ between the age groups. Cognitive behavioural therapy and occupational coaching have a more substantial role in adult management, whereas home-based and school-based behavioural treatments are recommended for children (as we discuss later).

In the context of well controlled randomised controlled trials (RCTs), medications undoubtedly show short-term efficacy; however, their more general clinical value has been questioned. For example, once out of the rigorous context of an RCT, adherence is generally low, especially in adolescence, which undermines the practical effectiveness of medication treatments.[59] Long-term, naturalistic follow-up studies also cast doubt on the persistence of treatment effects, perhaps because of the development of tolerance with chronic dosing.[60] Taking academic-related outcomes as an example, a meta-analysis including 34 trials found that methylphenidate had only small and inconsistent effects on academic performance, improving general productivity, and accuracy in mathematics, but not reading.[61] Furthermore, in a sample of 370 children with ADHD followed up prospectively, stimulants were observed to have no effect on the number of school dropouts.[62] Similarly, in an 8-year, naturalistic follow-up of the Multimodal Treatment of ADHD (MTA) study,[8] null effects of psychostimulant treatment were reported across several functional domains, including academic achievement, social function, and overall levels of impairment. Findings from national registries have been more encouraging. For example, a Swedish registry found a substantial lowering of criminality during periods of stimulant use,[63] a US-based insurance registry described a reduction in motor vehicle accidents,[64] and a Taiwanese registry suggested a lowering of depression risk.[65] Additional positive effects on shorter-term outcomes such as traumas and injuries notwithstanding,[66] long-term functional outcomes are an essential area for further attention in the clinical management of ADHD.

The limitations of medication treatment for ADHD highlight the importance of the continued search for new and improved approaches to its management. In this regard, several new compounds are being explored. For example, the association between ADHD and de novo mutations in genes related to the expression of metabotropic glutamate receptors[67] has led to trials of glutamate modulators (eg, fasoracetam) in children with ADHD.[68] Trials are also underway to examine the effects of agents targeting nicotinic acetylcholine receptors, because of the putative role of acetylcholine in regulating arousal and attention.[69] Small studies of transdermal nicotine in adults and children with ADHD have shown promising initial results, but still require confirmation with larger RCTs.[70,71]

Psychosocial and non-pharmacological approaches

Non-pharmacological approaches have either been adapted from other clinical areas or newly developed to complement medication treatment, and are recommended as part of the multimodal approach.[33] Access to effective non-pharmacological approaches is especially important for children aged 3–5 years for whom medication is not recommended, when there is a preference against medication expressed by families, or when there is resistance to medication use from clinicians and national organisations.[29] The MTA[72] study has provided important evidence about the value of generic psychosocial treatments when applied to ADHD. The MTA was a

US-based, multisite study of young children aged 7–9·9 years with ADHD that allowed for comorbid conditions other than bipolar, autism, or psychosis, as long as the comorbidity did not require treatment incompatible with the study treatments. The MTA study found that treatment with either methylphenidate alone or in combination with psychosocial treatment (including home-based and school-based behavioural treatments and a summer school-based treatment) provided similar effects on ADHD symptoms after 14 months. However, combined treatment was superior to methylphenidate alone in improving some other functional outcomes, such as academic performance, parent–child relations, and social skills.[72] Analogous findings from other studies have led to recommendations that combined treatment (a stimulant and parent training) is preferable to medication alone for most children with ADHD.[35] Conversely, the benefits of parent training as the sole intervention are less clear. One meta-analysis suggested that symptom improvement with parent training is minimal when assessments are based on raters probably masked to treatment allocation (eg, teachers).[73] Similarly, neurofeedback, another popular non-pharmacological intervention, has shown promise in single arm or uncontrolled studies, but the effects do not separate from placebo with rigorous placebo control (eg, mock or sham neurofeedback) and masked raters.[74] Attentional and executive functioning training with interactive computer games (eg, Cogmed Working Memory Training) produces robust performance improvements on the training tasks.[75] However, the translation of these effects to improvements in ADHD symptoms has not been replicated,[75,76] despite promising findings from initial studies.[77] Placebo-controlled trials of dietary treatments (such as the exclusion of additives or supplements with free fatty acids) have shown value;[78] however, the effects are generally modest, although larger for exclusions when food intolerance is present. Interventions like physical exercise and meditation might have complementary benefits, but evidence for their short-term or long-term control of symptoms remains sparse.[79,80] Because of the equivocal effects of non-pharmacological interventions on ADHD symptoms to date, additional research is needed to show the efficacy of these interventions, and their combination, within the context of multimodal treatments.[81]

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Scientific progress in understanding the causes of ADHD

Having reviewed the clinical consensus about ADHD as represented in DSM-5 and ICD-11, we now provide an overview of scientific developments in our understanding of the pathogenesis, causes, and pathophysiology of ADHD. Through this overview, we want to convey the great strides made by researchers in understanding the disorder. These developments will create a platform for our exploration of the ways in which science is challenging our conceptions of ADHD and how these insights might stimulant new treatment approaches.

Aetiology

A more thorough review of the published literature on genetic influences in ADHD is provided in the appendix (pp 3–4) but, briefly, the heritability for ADHD is high and most estimates range between 70% and 80%.[82] Genome-wide association studies have successfully identified 12 genome-wide significant risk loci, yet these associations account for approximately 22% of the disorder's heritability (as discussed later). Studies have also shown enrichment of certain copy-number variants in ADHD,[83,84] but these results require replication.

Numerous environmental exposures are associated with ADHD and have been suggested as putative causal factors. Nevertheless, given the complexity of the causal process (including the correlations between genetic and environmental exposures) and the reliance on observational (rather than experimental) study designs, most of these associations have yet to be shown as causal. In this context, many prenatal and perinatal risk factors, such as prematurity and low birthweight, have been more consistently associated with ADHD, with family studies suggesting that these effects cannot be explained by genetic confounding.[85–87] Intrauterine exposure to tobacco, and maternal stress and obesity during pregnancy, are also associated with ADHD, but they can be explained, at least in part, by confounding genetic factors.[88] Evidence is inconclusive or insufficient in relation to intrauterine exposure to alcohol and drugs and prenatal and perinatal birth-related complications.

Postnatal factors and social determinants have also been implicated in ADHD. For instance, experimental evidence shows that exposure to artificial food colourings and flavourings increases the severity of ADHD symptoms, but the effects are small.[89] The links between ADHD and exposure to pollutants and pesticides are largely correlational in nature. Innovative designs such as mendelian randomisation are starting to be used to test causal interpretations of these effects, albeit initial attempts have been disappointing.[90] Although associations between ADHD and parenting style have been noted, they are likely to be due to an evocative gene–environment correlation whereby a child's behaviour elicits harsh and unsupportive parenting, which leads to an escalation of problems and the development of coercive cycles within families.[91] Evidence that supports social determinants of ADHD comes from a naturally created experiment: the adoption of children exposed, from soon after birth, to extreme deprivation in state institutions before the fall of the Communist regime in Romania in the late 1980s. Following on from earlier studies showing an association between institutional neglect and ADHD, Kennedy and colleagues[92] reported a 7-times increase in ADHD in individuals who had experienced more than

6 months of deprivation as children compared with those who experienced less than 6 months. The magnitude of this effect, combined with the strength of the design (contrasting those with more and less than 6 months deprivation), means that this result is unlikely to be attributable to pre-existing genetic or intrauterine risk.[93] However, the severity of the adversity experienced by these children is an extraordinary, or rare, environmental variant and the effect of less extreme exposures on ADHD risk is not as clear.

The mismatch between twin-based estimates of ADHD heritability (approximately 70–80%) and the estimates of genetic contribution based on the aforementioned genome-wide association study (about 22%) challenges researchers to account for the approximate 50% gap in the familial transmission of ADHD. Clearly, this gap cannot be explained by rare de novo mutations, which, by definition, are not inherited. To answer this question, some have looked to the study of gene–environment interactions. The plausibility of this hypothesis (ie, that gene–environment interactions account for the gap between heritability estimates and genetic contributions based on the genome-wide association study), in part, rests on the fact that the standard twin heritability model pools genetic main effects with gene–environment interactions into a single heritability term. To differentiate gene–environment interactions from genetic main effects, studies have combined specific risk alleles (mainly relating to neurotransmitter genes) and specific exposures (eg, social stressors such as intrauterine exposure to substances and psychosocial risk factors). Despite some studies finding suggestive results, to date convincing replications are absent.[94] Another approach focuses on epigenetic modifications in individuals with ADHD. Although this approach cannot, by itself, account for missing heritability, it has so far indicated differential DNA methylation in genes related to monoaminergic and GABAergic systems, and also in genes involved in neurodevelopmental processes.[95] However, partly because of their reliance on the harvesting of genetic material from peripheral tissues (which might not reflect changes in the brain), the actual extent to which these modifications are causal remains to be seen.[96] To improve our understanding of gene–environment interactions, and presumably ADHD causality, large-scale prospective studies such as the UK Biobank and the US-based ECHO and ABCD studies might prove helpful. These studies include biospecimens for genome-wide sequencing, detailed measures of phenotypic variance, and longitudinal assessments of environmental exposures, with adequate power to detect interactions and small effects. Over the next 5–10 years, we anticipate that these efforts will yield good results.

Pathophysiology

ADHD is associated with deficits across a range of cognitive domains (panel 2). Global cognitive effects, as reflected in IQ below population norms, are well documented,[97] as are more circumscribed cognitive and motivational correlates. For example, laboratory studies have found replicated evidence of deficits in executive functions such as behavioural inhibition, working memory, set-shifting, and planning and organisation in groups of individuals with ADHD compared with non-affected controls.[98,99] However, within such groups, the specific pattern of individual executive function impairment varies dramatically from one individual with ADHD to another. This variation means that, although some individuals will show a pervasive pattern of impairment across different executive functions, others will display profound impairment in a particular executive function (eg, working memory) but be unaffected in other areas (eg, the ability to inhibit). Some patients will show no executive function impairment at all. This further emphasises the importance of issues of heterogeneity for current conceptions of ADHD.[100,101] Moreover, deficits in executive functions are by no means specific to ADHD and are similarly reported in many other psychiatric conditions.[102–104]

Other cognitive domains, separable from (although potentially interacting with) executive functions, have also been implicated in ADHD. These include difficulties in regulating one's psychological state in response to changing environmental circumstances by, for instance, trying to moderate one's degree of arousal (so-called cognitive energetic factors). Clinically, this means that ADHD symptoms are exacerbated during lengthy and seemingly mundane tasks.[105] Furthermore, some people with ADHD show altered patterns of motivation[106] and respond differently to positive and negative reinforcement.[107,108] In this regard, difficulties in delaying gratification or waiting for important outcomes are motivational hallmarks for many with ADHD. These could be the result of either an inability to curb behavioural urges (ie, behavioural inhibition), or atypical responses to the expectation of future rewards, which often present as a heighted aversion to delay.[109] Once again, there is great heterogeneity in the expression of these motivational and cognitive impairments.[100]

Panel 2: **Cognitive domains associated with attention-deficit hyperactivity disorder**

- Arousal: preparedness for action or behavioural activation
- Executive functions: a broad range of higher-order cognitive processes, including decision making, planning, and working memory
- Behavioural inhibition: capacity to restrain one response, or urge, in favour of another, often more automatic, response
- Motivation: pursuing outcomes of potential value on the basis of subjective determinations
- Set shifting: changing behavioural patterns to meet new environmental demands (eg, adjusting to new rules or expectations)
- Working memory: short-term memory that allows for mental operation of information (eg, mental arithmetic) and often considered one type of executive function

For more on the **UK Biobank** see https://www.ukbiobank.ac.uk

For more on **ECHO** see https://www.nih.gov/echo

For more on **ABCD** see https://abcdstudy.org

By highlighting the context-specific and dynamic nature of cognitive deficits in ADHD, the growing evidence of cognitive–energetic and motivational problems in ADHD has changed the way the pathophysiology of ADHD is considered. An especially important emergence has been the idea that ADHD is not always the result of a fixed deficit that affects performance across all settings, but rather it varies considerably from setting to setting.[110,111] For instance, ADHD symptoms and associated cognitive problems are much more common on tasks that are long and repetitive (with a low amount of stimulation) than they are on interesting tasks, in which there are frequent and engaging things happening. The most robust laboratory indication of the power of context, or setting, to shape the performance of people with ADHD is seen in how reaction time and accuracy change as the rate of stimulus presentation is varied. Patients with ADHD make more mistakes than controls only under very fast and very slow conditions.[112]

Regarding brain structure and function, findings from neuroimaging research complement the cognitive and motivational profiles associated with ADHD. Because of its important role in executive functions, early neuroimaging research focused principally on the prefrontal cortex, showing functional and maturational abnormalities associated with ADHD.[113,114] For example, youth with ADHD show on average a 2–3 year delay in reaching peak thickness of much of the cerebrum, including the prefrontal cortex.[115] Over the last decade, neuroimaging research in ADHD, along with other psychiatric disorders, has shifted its focus of inquiry away from discrete neural substrates and towards the role of distributed neural circuits, recognising the importance of understanding the function, organisation, and development of interacting brain regions.[116] Emerging from this work, several large neural networks have been implicated in ADHD, including the default mode network (DMN), dorsal and ventral attentional networks, salience networks, and frontostriatal and mesocorticolimbic circuits (or the dopaminergic mesolimbic system).[5] Functional neuroimaging studies have shown reduced connectivity within the DMN of children aged 6–17 years with ADHD and a pattern suggestive of delayed DMN neuromaturation,[117] consistent with earlier structural MRI studies pointing to delayed maturation of the cerebral cortex.[115] The function of the DMN is hypothesised to underlie the normative capacity for mind-wandering and introspection, but in ADHD might reflect a tendency towards distractibility, potentially due to impaired regulation of attentional resources.[118] Similar research highlights atypical interactions between the DMN and the dorsal and ventral attentional networks, and the salience network, suggesting that the DMN, and its relationship to mind-wandering, might interfere with, or disrupt, attentional networks' capacity to maintain externally, focused attention.[5,118]

For more on **ENIGMA** see http://enigma.ini.nsc.edu

In addition to the DMN and attentional networks, individuals with ADHD also manifest abnormalities within the dopaminergic mesolimbic system, a neural circuit associated with motivated behaviours, anticipated outcomes, and reinforced learning.[98] For example, relative to healthy controls, individuals with ADHD show reduced volumes of the nucleus accumbens (a key node within the mesolimbic system),[119,120] reduced activation of the mesolimbic system when anticipating rewarding outcomes,[121] and reduced fractional anisotropy (a diffusion MRI indicator of white matter organisation) within white matter tracts of the mesolimbic system.[122]

Despite these advances in our understanding of the neurobiology of ADHD, several concerns persist. First, most neuroimaging studies of ADHD have been cross-sectional in design, and thus unable to reach causal interpretations. For example, adaptations to a disorder versus underlying causes cannot be disambiguated from cross-sectional, case-control designs. Combining neuroimaging and RCTs is a potentially fruitful approach to overcome the limitations of correlational neuroimaging research, identifying causal effects of interventions (although not causal factors that give rise to the disorder itself) on brain structure and function.[123] Second, neuroimaging studies of ADHD often have small samples and poor reproducibility. False findings might have arisen from inadequate control over multiple statistical comparisons, imaging confounds such as head motion and partial averaging, and inadequate clinical phenotyping (eg, relying solely upon parental reports for diagnostics). By contrast, one mega-regression analysis of structural MRI studies from more than 1700 youth with ADHD reported reduced volumes in multiple subcortical structures, including those associated with the aforementioned attentional and reward systems.[120] However, the effect sizes across all regions were small (Cohen's d <0·2), highlighting the fact that many previous neuroimaging studies were underpowered and risked false-positive results. Finally, the small effect sizes reported by large mega-analyses, such as ENIGMA, suggest that neuroimaging is unlikely to have clinical use as a diagnostic tool, at least not until substantial methodological advances have been made.

What are the prospects for clinical advances in response to scientific advances?

In this final section, we briefly discuss four means by which scientific findings are challenging the way ADHD is conceptualised and explore the prospect that these can improve the diagnosis and treatment of ADHD in the future.

Dimensionality

All evidence confirms that ADHD is best understood as the extreme end of a continuum and that people with ADHD differ from those without ADHD by degree rather than in kind. Yet, both DSM-5 and ICD-11 continue to

operationalise ADHD as a categorical diagnosis: a syndrome defined by symptom thresholds that suggest the existence of discrete boundaries between health and disorder, and between unaffected and impaired. However, there is no evidence that this definition of ADHD is correct, and so current clinical boundaries are somewhat arbitrary, built on clinical experience about the number and severity of symptoms or degree of impairment that warrants intervention. Are there viable alternatives to the current categorical models that better reflect the underlying reality of the condition? Despite concerns about clinical applicability, several different dimensional models have been proposed, but none have been judged to have the simplicity and immediacy of the current approaches.[124]

Heterogeneity

As aforementioned, science leaves us in no doubt that ADHD is a complex and heterogeneous disorder. Individuals with the condition differ from one another in myriad ways and at multiple levels, such as in their genetic risks, environmental exposures, brain structures, and cognitive and motivational profiles. Recognising that ADHD is a heterogeneous disorder presents appreciable challenges to researchers (studies designed to explore this heterogeneity require large samples, multiple measures that capture the full range of deficits, and the use of sophisticated multivariate analytical approaches), but also offer potential clinical opportunities. Acknowledging heterogeneity might lead to the adoption of precision medicine: the tailoring of treatments to target an individual's underlying cognitive and brain processes.[125] For instance, executive training might be efficacious for individuals with ADHD and executive dysfunctions, but not for those with motivational or cognitive energetic abnormalities. Neuropsychological subtyping of ADHD populations has been proposed to facilitate this sort of approach.[98,125] However, progress is hampered by a lack of consensus regarding the pathophysiological dimensions of greatest clinical relevance and whether individuals cluster along these dimensions to form identifiable subgroups. Addressing the challenges of heterogeneity is central to the Research Domain Criteria (RDoC) initiative of the US-based National Institute of Mental Health.

Development

ADHD is a lifespan disorder with roots in early childhood[126] and branches extending into adolescence and adulthood.[127] We've previously highlighted evidence that several different developmental forms of ADHD appear to exist, which are currently not distinguished in diagnostic approaches. The developmental core of the ADHD phenotype will remain marked by childhood onset and adulthood persistence, but four developmental types with potential clinical relevance are starting to emerge. However, much still needs to be learned about differential prognosis or treatment response of individuals with these distinct developmental phenotypes. Taking a developmental perspective focuses attention on the likely value of early intervention and prevention strategies.[128] Interventions aimed at delaying the initial onset or reducing the impact of ADHD continue to be hindered by a lack of understanding of the early cognitive and behavioural precursors and predictors of later ADHD that would allow for the cost-effective early identification of at-risk individuals.[129] We are also devoid of effective interventions that can be implemented during the first years of life, although novel approaches to strengthening underlying brain networks are being trialled.[130] Additional strategies, aimed at reducing the escalation and effect of the disorder, have effectively focused on the use of parent training, psychoeducation, and support to reduce the risk of emergence of comorbid conditions and associated impairment.[131]

Overlapping causes

Our Seminar highlights a surprising degree of overlap between ADHD and other psychiatric conditions in terms of both aetiology and pathophysiology. This overlap, like evidence of dimensionality and heterogeneity, challenges current diagnostic systems, and lends conceptual support for approaches that attempt to identify common pathophysiological processes that cut across traditional diagnostic boundaries (eg, RDoC initiative), rather than those that diverge at the level of the clinical DSM or ICD phenotypes.[132] The assumption of a transdiagnostic framework, such as RDoC, is that shared vulnerability processes can be successfully targeted to treat different clinical conditions. For example, where similar executive deficits are present across a range of different neurodevelopmental conditions (ADHD, autism spectrum disorder, and psychosis), the same executive control training approaches could have clinical value.[133] Similarly, a transdiagnostic framework might provide some insight into why causal factors can give rise to ADHD, and other psychiatric conditions. For instance, gestational diabetes is associated with increased risk for ADHD in the offspring.[134] Although genetic confounding has not been excluded, preclinical research suggests that this observation might be attributable, at least in part, to the effects of maternal hyperinsulinaemia or adiposity on the development of the fetal mesolimbic system.[135,136] One could therefore hypothesise that this same prenatal exposure has transdiagnostic implications, increasing risk for other conditions related to mesolimbic dysfunction, such as Tourette's syndrome and substance use disorders.[135,137] However, to date, evidence supporting treatment or causal implications of a transdiagnostic framework is largely absent.

Conclusions

ADHD is a common, highly heritable, and impairing condition. Efficacious treatments are available but

limited in many ways. We believe that the enormous strides made over the past 10 years by scientists in understanding the nature and causes of ADHD challenge accepted models of ADHD and might have the potential to encourage new clinical improvement. However, this advancement will take both time and considerable investment to identify the specific processes and systems to target, develop new and innovative interventions to target these processes, and discover the best ways to tailor them to a patient's individual needs.

Contributors

All authors contributed equally to the writing of the manuscript.

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References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th edn. Arlington, VA: American Psychiatric Association, 2013.

2 WHO. International statistical classification of diseases and related health problems, 11th edn. Geneva: World Health Organization, 2018.

3 Smoller JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS. Psychiatric genetics and the structure of psychopathology. *Mol Psychiatry* 2019; **24:** 409–20.

4 Coghill D, Sonuga-Barke EJS. Annual research review: categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders: implications of recent empirical study. *J Child Psychol Psychiatry* 2012; **53:** 469–89.

5 Gallo EF, Posner J. Moving towards causality in attention-deficit hyperactivity disorder: overview of neural and genetic mechanisms. *Lancet Psychiatry* 2016; **3:** 555–67.

6 Pliszka SR, Crismon ML, Hughes CW, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006; **45:** 642–57.

7 Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. *J Health Affairs* 2007; **26:** 450–57.

8 Molina BSG, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 2009; **48:** 484–500.

9 Chang Z, Ghirardi L, Quinn PD, Asherson P, D'Onofrio BM, Larsson H. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. *Biol Psychiatry* 2019; **86:** 335–43.

10 Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. *Postgrad Med* 2010; **122:** 184–91.

11 Bussing R, Zima BT, Gary FA, Garvan, CW. Barriers to detection, help-seeking, and service use for children with ADHD symptoms. *J Behav Health Serv Res* 2003; **30:** 176–89.

12 Barkley R.A. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2002; **63** (suppl 12): 10–15.

13 WHO. ICD-11 for mortality and morbidity statistics (ICD-11 MMS), 2018 version. https://icd.who.int/browse11/l-m/en (accessed Dec 23, 2019).

14 Lahey BB, Pelham WE, Loney J, Lee SS, Willcutt E. Instability of the DSM-IV subtypes of ADHD from preschool through elementary school. *Arch Gen Psychiatry* 2005; **62:** 896–902.

15 Reed GM, First MB, Kogan CS, et al. Innovations and changes in the ICD-11 classification of mental, behavioural and neurodevelopmental disorders. *World Psychiatry* 2019; **18:** 3–19.

16 Moffitt TE, Houts R, Asherson P, et al. Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study. *Am J Psychiatry* 2015; **172:** 967–77.

17 Sibley MH, Rhode LA, Swanson JM, et al. Late-onset ADHD reconsidered with comprehensive repeated assessments between ages 10 and 25. *Am J Psychiatry* 2018; **175:** 140–49.

18 Krasner AJ, Turner JB, Feldman JF, et al. ADHD symptoms in a non-referred low birthweight/preterm cohort: longitudinal profiles, outcomes, and associated features. *J Atten Disord* 2018; **22:** 827–38.

19 Caye A, Agnew-Blais J, Arseneault L, et al. A risk calculator to predict adult attention-deficit/hyperactivity disorder: generation and external validation in three birth cohorts and one clinical sample. *Epidemiol Psychiatr Sci* 2019; **29:** e37.

20 Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry* 2015; **56:** 345–65.

21 Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007; **164:** 942–48.

22 Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol* 2014; **43:** 434–42.

23 Collishaw S. Annual research review: secular trends in child and adolescent mental health. *J Child Psychol Psychiatry* 2015; **56:** 370–93.

24 Safer DJ. Is ADHD really increasing in youth? *J Atten Disord* 2015; **22:** 107–115.

25 Rydell M, Lundström S, Gillberg C, Lichtenstein P, Larsson H. Has the attention deficit hyperactivity disorder phenotype become more common in children between 2004 and 2014? Trends over 10 years from a Swedish general population sample. *J Child Psychol Psychiatry* 2018; **59:** 863–71.

26 Simon V, Czobor P, Bálint S, Mészáros Á, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009; **194:** 204–11.

27 Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006; **36:** 159–65.

28 Asherson P, Agnew-Blais J. Annual research review: does late-onset attention-deficit/hyperactivity disorder exist? *J Child Psychol Psychiatry* 2019; **60:** 333–52.

29 Wright N, Moldavsky M, Schneider J, et al. Practitioner review: pathways to care for ADHD — a systematic review of barriers and facilitators. *J Child Psychol Psychiatry* 2015; **56:** 598–617.

30 Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007; **46:** 894–921.

31 Canadian ADHD Resource Alliance. Canadian ADHD practice guidelines, 4th edn. Toronto, ON: Canadian ADHD Resource Alliance, 2018.

32 Palacio JD, De la Peña-Olvera F, Palacios-Cruz L, Ortiz-León S. Algoritmo latinoamericano de tratamiento multimodal del trastorno por déficit de atención e hiperactividad (TDAH) a través de la vida. *Revista Colombiana de Psiquiatria* 2009; **38:** 35–65.

33 NICE. Attention deficit hyperactivity disorder: diagnosis and management. March, 2018. https://www.nice.org.uk/guidance/ng87 (accessed Dec 23, 2019).

34 World Federation of ADHD. The World Federation of ADHD guide. 2019. http://cpo-media.net/ADHD/2019/ebook/HTML (accessed Dec 23, 2019).

35 Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007; **46:** 894–921.

36 Posner J, Greenhill LL. Attention-deficit/hyperactivity disorder. In: McVoy M, Findling RL, eds. Clinical manual of child and adolescent psychopharmacology, 2nd edn. Arlington, VA: American Psychiatric Association, 2013.

37 Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018; **5:** 727–38.

38 Castells X, Ramos-Quiroga JA, Rigau D, et al. Efficacy of methylphenidate for adults with attention-deficit hyperactivity disorder: a meta-regression analysis. *CNS Drugs* 2011; **25:** 157–69.

39 Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry* 2010; **19:** 353–64.

40 Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ* 2001; **165:** 1475–88.

41 Greenhill L, Kollins S, Abikoff H, et al. Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry* 2006; **45:** 1284–93.

42 Greenhill LL, Swanson JM, Hechtman L, et al. Trajectories of growth associated with long-term stimulant medication in the multimodal treatment study of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2019; published online Aug 15. DOI:10.1016/j.jaac.2019.06.019.

43 Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: a review of the literature. *J Am Acad Child Adolesc Psychiatry* 2008; **47:** 994–1009.

44 Klein RG, Landa B, Mattes JA, Klein DF. Methylphenidate and growth in hyperactive children. A controlled withdrawal study. *Arch Gen Psychiatry* 1998; **45:** 1127–30.

45 Ibrahim K, Donyai P. Drug holidays from ADHD medication: international experience over the past four decades. *J Atten Disord* 2015; **19:** 551–68.

46 Chang Z, Lichtenstein P, Halldner L, et al. Stimulant ADHD medication and risk for substance abuse. *J Child Psychol Psychiatry* 2014; **55:** 878–85.

47 Molina BS, Hinshaw SP, Eugene Arnold L, et al. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. *J Am Acad Child Adolesc Psychiatry* 2013; **52:** 250–63.

48 Biederman J. Pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) decreases the risk for substance abuse: findings from a longitudinal follow-up of youths with and without ADHD. *J Clin Psychiatry* 2003; **64** (suppl 11)**:** 3–8.

49 Rabiner DL. Stimulant prescription cautions: addressing misuse, diversion and malingering. *Curr Psychiatry Rep* 2013; **15:** 375.

50 Gould MS, Walsh BT, Munfakh JL, et al. Sudden death and use of stimulant medications in youths. *Am J Psychiatry* 2009; **166:** 992–1001.

51 Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med* 2011; **365:** 1896–904.

52 Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 2011; **306:** 2673–83.

53 Schwartz S, Correll CU. Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: results from a comprehensive meta-analysis and metaregression. *J Am Acad Child Adolesc Psychiatry* 2014; **53:** 174–87.

54 Cunill R, Castells X, Tobias A, Capella D. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. *Pharmacoepidemiol Drug Saf* 2013; **22:** 961–69.

55 Wilens TE, Robertson B, Sikirica V, et al. A randomized, placebo-controlled trial of guanfacine extended release in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adoles Psychiatry* 2015; **54:** 916–25.

56 Sallee FR, McGough J, Wigal T, Donahue J, Lyne A, Biederman J. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2009; **48:** 155–65.

57 Scahill L, Chappell PB, Kim YS, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. *Am J Psychiatry* 2001; **158:** 1067–74.

58 Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol* 2001; **21:** 223–28.

59 Charach A, Fernandez R. Enhancing ADHD medication adherence: challenges and opportunities. *Curr Psychiatry Rep* 2013; **15:** 371.

60 Greydanus DE, Nazeer A, Patel DR. Psychopharmacology of ADHD in pediatrics: current advances and issues. *Neuropsychiatric Dis Treat* 2009; **5:** 171.

61 Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E, Oosterlaan J. Does methylphenidate improve academic performance? A systematic review and meta-analysis. *Eur Child Adolesc Psychiatry* 2019; **28:** 155–64.

62 Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Modifiers of long-term school outcomes for children with attention-deficit/hyperactivity disorder: does treatment with stimulant medication make a difference? Results from a population-based study. *J Dev Behav Pediatr* 2007; **28:** 274–87.

63 Lichtenstein P, Larsson H. Medication for attention deficit–hyperactivity disorder and criminality. *N Engl J Med* 2012; **367:** 2006–14.

64 Chang Z, Quinn PD, Hur K, et al. Association between medication use for attention-deficit/hyperactivity disorder and risk of motor vehicle crashes. *JAMA Psychiatry* 2012; **74:** 597–603.

65 Lee MJ, Yang KC, Shyu YC, et al. Attention-deficit hyperactivity disorder, its treatment with medication and the probability of developing a depressive disorder: a nationwide population-based study in Taiwan. *J Affect Disord* 2016; **189:** 110–17.

66 Chang Z, Ghirardi, Quinn PD, Asherson P, D'Onofrio BM, Larsson H. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. *Bio Psychiatry* 2019; **86:** 335–43.

67 Elia J, Glessner JT, Wang K, et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. *Nat Genet* 2011; **44:** 78–84.

68 Elia J, Ungal G, Kao C, et al. Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. *Nature Commun* 2018; **9:** 4.

69 Whitehouse PJ. Paying attention to acetylcholine: the key to wisdom and quality of life? *Progress Brain Res* 2004; **145:** 311–17.

70 Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology (Berl)* 2004; **176:** 182–94.

71 Shytle RD, Silver AA, Wilkinson, BJ, Sanberg PR. A pilot controlled trial of transdermal nicotine in the treatment of attention deficit hyperactivity disorder. *World J Biol Psychiatry* 2002; **3:** 150–55.

72 The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal treatment study of children with ADHD. *Arch General Psychiatry* 1999; **56:** 1073–86.

73 Rimestad ML, Lambek R, Zacher Christiansen H, Hougaard E. Short-and long-term effects of parent training for preschool children with or at risk of ADHD: a systematic review and meta-analysis. *J Atten Disord* 2019; **23:** 423–34.

74 Cortese S, Ferrin M, Brandeis D, et al. Neurofeedback for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *J Am Acad Child Adolesc Psychiatry* 2016; **55:** 444–55.

75 Cortese S, Ferrin M, Brandeis D, et al. Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *J Am Acad Child Adolesc Psychiatry* 2015; **54:** 164–74.

76 Chacko A, Feirsen N, Bedard AC, Marks D, Uderman JZ, Chimiklis A. Cogmed Working Memory Training for youth with ADHD: a closer examination of efficacy utilizing evidence-based criteria. *J Clin Child Adolesc Psychol* 2013; **42:** 769–83.

77 Klingberg T, Fernell E, Olesen PJ, et al. Computerized training of working memory in children with ADHD—a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 2005; **44:** 177–86.

78 Stevenson J, Buitelaar J, Cortese S, et al. Research review: the role of diet in the treatment of attention-deficit/hyperactivity disorder–an appraisal of the evidence on efficacy and recommendations on the design of future studies. *J Child Psychol Psychiatry* 2014; **55:** 416–27.

79 Krisanaprakornkit T, Ngamjarus C, Witoonchart C, Piyavhatkul N. Meditation therapies for attention-deficit/hyperactivity disorder (ADHD). *Cochrane Database Syst Rev* 2010; **16:** CD006507.

80 Wigal SB, Emmerson N, Gehricke JG, Galassetti P. Exercise: applications to childhood ADHD. *J Atten Disord* 2013; **17:** 279–90.

81 Duric NS, Assmus J, Gundersen D, Duric Golos A, Elgen IB. Multimodal treatment in children and adolescents with attention-deficit/hyperactivity disorder: a 6-month follow-up. *Nord J Psychiatry* 2017; **71:** 386–94.

82 Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005; **57:** 1313–23.

83 Martin J, O'Donovan MC, Thapar A, Langley K, Williams N. The relative contribution of common and rare genetic variants to ADHD. *Transl Psychiatry* 2015; **5:** e506.

84 Thapar A. Discoveries on the genetics of ADHD in the 21st century: new findings and their implications. *Am J Psychiatry* 2018; **175:** 943–50.

85 Nigg JT, Knottnerus GM, Martel MM, et al. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. *Biol Psychiatry* 2008; **63:** 325–31.

86 Nigg JT, Breslau N. Prenatal smoking exposure, low birth weight, and disruptive behavior disorders. *J Am Acad Child Adolesec Psychiatry* 2007; **46:** 362–69.

87 Class QA, Rickert M, Larsson H, Lichtenstein P, D'Onofrio BM. Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison. *Br J Psychiatry* 2014; **205:** 355–61.

88 Knopik VS, Sparrow EP, Madden PA, et al. Contributions of parental alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: a female twin study. *Psychol Med* 2005; **35:** 625–35.

89 McCann D, Barrett A, Cooper A, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007; **370:** 1560–67.

90 Nigg JT, Elmore AL, Natarajan N, Friderici KH, Nikolas MA. Variation in an iron metabolism gene moderates the association between blood lead levels and attention-deficit/hyperactivity disorder in children. *Psychol Sci* 2016; **27:** 257–69.

91 Harold GT, Leve LD, Barrett D, et al. Biological and rearing mother influences on child ADHD symptoms: revisiting the developmental interface between nature and nurture. *J Child Psychol Psychiatry* 2013; **54:** 1038–46.

92 Kennedy M, Kreppner J, Knights N, et al. Early severe institutional deprivation is associated with a persistent variant of adult attention-deficit/hyperactivity disorder: clinical presentation, developmental continuities and life circumstances in the English and Romanian Adoptees study. *J Child Psychol Psychiatry* 2016; **57:** 1113–25.

93 Lugo-Candelas C, Monk C, Duarte CS, Lee S, Posner J. Shared genetic factors, fetal programming, and the transmission of depression. *Lancet Psychiatry* 2018; **5:** 771–73.

94 Nigg J, Nikolas M, Burt SA. Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2010; **49:** 863–73.

95 Walton E, Pingault JB, Cecil CA, et al. Epigenetic profiling of ADHD symptoms trajectories: a prospective, methylome-wide study. *Mol Psychiatry* 2017; **22:** 250–56.

96 Barker ED, Walton E, Cecil CAM. Annual research review: DNA methylation as a mediator in the association between risk exposure and child and adolescent psychopathology. *J Child Psychol Psychiatry* 2018; **59:** 303–22.

97 Kuntsi J, Eley TC, Taylor A, et al. Co-occurrence of ADHD and low IQ has genetic origins. *Am J Med Genet B Neuropsychiatr Genet* 2004; **124B:** 41–47.

98 Posner J, Rauh V, Gruber A, Gat I, Wang Z, Peterson BS. Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Res* 2013; **213:** 24–30.

99 Brown TE. ADD/ADHD and impaired executive function in clinical practice. *Curr Atten Disord Rep* 2009; **1:** 37–41.

100 Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biol Psychiatry* 2005; **57:** 1224–30.

101 Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends Cogn Sci* 2006; **10:** 117–23.

102 Velligan DI, Bow-Thomas C. Executive function in schizophrenia. *Semin Clin Neuropsychiatry* 1999; **4:** 24–33.

103 Mur M, Portella MJ, Martínez-Arán A, Pifarré J, Vieta E. Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit. *J Clin Psychiatry* 2007; **68:** 1078–86.

104 O'Hearn K, Asato M, Ordaz S, Luna B. Neurodevelopment and executive function in autism. *Dev Psychopathol* 2008; **20:** 1103–32.

105 Kofler MJ, Raiker JS, Sarver DE, Wells EL, Soto EF. Is hyperactivity ubiquitous in ADHD or dependent on environmental demands? Evidence from meta-analysis. *Clin Psychol Rev* 2016; **46:** 12–24.

106 McInerney RJ, Kerns KA. Time reproduction in children with ADHD: motivation matters. *Child Neuropsychol* 2003; **9:** 91–108.

107 Sonuga-Barke E, Bitsakou P, Thompson M. Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2010; **49:** 345–55.

108 Sergeant J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. *Neurosci Biobehav Rev* 2000; **24:** 7–12.

109 Sonuga-Barke EJ. Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition. *Behav Brain Res* 2002; **130:** 29–36.

110 James SN, Cheung CHM, Rijsdijk F, Asherson P, Kuntsi J. Modifiable arousal in attention-deficit/hyperactivity disorder and its etiological association with fluctuating reaction times. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2016; **1:** 539–47.

111 Straub M, Ulke C, Paucke M, et al. Brain arousal regulation in adults with attention-deficit/hyperactivity disorder (ADHD). *Psychiatry Research* 2018; **261:** 102–08.

112 Metin B, Roeyers H, Wiersema JR, van der Meere J, Sonuga-Barke E. A meta-analytic study of event rate effects on go/no-go performance in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2012; **72:** 990–96.

113 Castellanos FX, Giedd JN, Marsh WL, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 1996; **53:** 607–16.

114 Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* 1997; **48:** 589–601.

115 Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA* 2007; **104:** 19649–54.

116 Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. *Neuropsychol Rev* 2014; **24:** 3–15.

117 Fair DA, Posner J, Nagel BJ, et al. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2010; **68:** 1084–91.

118 Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neurosci Biobehav Rev* 2007; **31:** 977–86.

119 Cha J, Fekete T, Siciliano F, et al. Neural correlates of aggression in medication-naive children with ADHD: multivariate analysis of morphometry and tractography. *Neuropsychopharmacology* 2015; **40:** 1717–25.

120 Hoogman M, Bralten J, Hibar DP, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *Lancet Psychiatry* 2017; **4:** 310–19.

121 Plichta MM, Scheres A. Ventral–striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. *Neurosci Biobehav Rev* 2014; **38:** 125–34.

122 Konrad A, Dielentheis TF, El Masri D, et al. Disturbed structural connectivity is related to inattention and impulsivity in adult attention deficit hyperactivity disorder. *Eur J Neurosci* 2010; **31:** 912–19.

123 Wang Y, Bernanke J, Peterson BS, et al. The association between antidepressant treatment and brain connectivity in two double-blind, placebo-controlled clinical trials: a treatment mechanism study. *Lancet Psychiatry* 2019; **6:** 667–74.

124 Swanson JM, Wigal T, Lakes K. DSM-V and the future diagnosis of attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep* 2009; **11:** 399–406.

125 Posner J. The role of precision medicine in child psychiatry: what can we expect and when? *J Am Acad Child Adolesc Psychiatry* 2018; **57:** 813–17.

126 Campbell SB, Halperin JM, Sonuga-Barke EJS. A developmental perspective on attention-deficit/hyperactivity disorder (ADHD). In: Lewis M, Rudolph KD, eds. Handbook of developmental psychopathology. Boston, MA, USA: Springer, 2014: 427–48.

127 Franke B, Michelini G, Asherson P, et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. *Eur Neuropsychopharmacol* 2018; **28:** 1059–88.

128 Halperin JM, Bédard AC, Curchack-Lichtin JT. Preventive interventions for ADHD: a neurodevelopmental perspective. *Neurotherapeutics* 2012; **9:** 531–41.

129 Smith E, Meyer BJ, Koerting J, et al. Preschool hyperactivity specifically elevates long-term mental health risks more strongly in males than females: a prospective longitudinal study through to young adulthood. *Eur Child Adolesc Psychiatry* 2017; **26:** 123–36.

130 Goodwin A, Salomone S, Bolton P, et al. Attention training for infants at familial risk of ADHD (INTERSTAARS): study protocol for a randomised controlled trial. *Trials* 2016; **17:** 608.

131 Daley D, Van Der Oord S, Ferrin M, et al. Practitioner review: current best practice in the use of parent training and other behavioural interventions in the treatment of children and adolescents with attention deficit hyperactivity disorder. *J Child Psychol Psychiatry* 2018; **59:** 932–47.

132 Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biol Psychiatry* 2014; **76:** 350–53.

133 Johnson MH, Gliga T, Jones E, Charman T. Annual research review: infant development, autism, and ADHD – early pathways to emerging disorders. *J Child Psychol Psychiatry* 2015; **56:** 228–47.

134 Nomura Y, Marks DJ, Grossman B, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. *Arch Pediatr Adolesc Med* 2012; **166:** 337–43.

135 Peleg-Raibstein D, Sarker G, Litwan K, et al. Enhanced sensitivity to drugs of abuse and palatable foods following maternal overnutrition. *Transl Psychiatry* 2016; **6:** e911.

136 Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. *Prenat Diagn* 2017; **37:** 95–110.

137 Buse J, Schoenefeld K, Münchau A, Roessner V. Neuromodulation in Tourette syndrome: dopamine and beyond. *Neurosci Biobehav Rev* 2013; **37:** 1069–84.