



Hyperactivity and inattention (ADHD)

Last update: May 2023

Topic Editor:

Russell Schachar, MD, University of Toronto, Canada

Table of content

Synthesis 4

ADHD and Neuroscience 7

¹HICRAN DOĞRU, MD, ²F. XAVIER CASTELLANOS, MD, ³SAMUELE CORTESE, MD, PHD, ⁴YUTA Y AOKI, MD, PHD, DECEMBER 2021

Attention Deficit Hyperactivity Disorder and Cognition 16

NANDA ROMMELSE, PHD, FEBRUARY 2010

Genetic contributions to ADHD 22

JOANNA MARTIN, PHD, APRIL 2023

Children with Attention Deficit Hyperactivity Disorder: Epidemiology, Comorbidity and Assessment 30

ALICE CHARACH, MSC, MD, APRIL 2020

ADHD and Treatment 39

¹MEGHAN MILLER, PHD, ²STEPHEN P. HINSHAW, PHD, SEPTEMBER 2019

Synthesis

How important is it?

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition defined by atypical, persistent and impairing restlessness, impulsiveness and inattentiveness starting from an early age. There are three presentations of ADHD, based on the type of behaviours that are most prominent: 1) predominantly inattentive; 2) hyperactive-impulsive; and 3) combined. The disorder is diagnosed when the child's symptoms are present and impairing in more than one context such as in school, at home or in the community. ADHD is estimated to affect 5 to 10% of school-age children worldwide, and boys show higher rates than girls. In 50 to 66% of cases, ADHD tends to co-occur with other psychiatric or developmental disorders, such as anxiety, mood disorders, learning or language disabilities, conduct disorders and sleep difficulties. ADHD often persists into adulthood.

For children, ADHD symptoms and concurrent disorders interfere with academic and behavioural functioning at school, resulting in lower rates of high school completion. Symptoms can also affect peer and family relationships. As they grow older, these individuals are more likely to experience difficulties with employment, relationships, and physical and mental health. Adults with childhood history of ADHD are at greater risk of psychiatric hospitalizations and incarcerations, divorce, risky sexual and driving behaviours, increased emergency room visits, serious injuries and death. In sum, ADHD represents an important public health concern and may engender high personal and societal costs.

What do we know?

ADHD is believed to be caused by an interaction of genetic and environmental factors. Symptoms of ADHD are highly heritable (76%), and emerging discoveries implicate genetic variants that play a key role in brain development. Studies also indicate that ADHD shares genetic risk factors with other conditions such as autism, depression and diabetes. Furthermore, insights from neuroscience have unequivocally shown that the brains of children with ADHD differ from those of healthy comparisons. Among environmental risk factors, researchers have noted the negative influence of prenatal maternal smoking and drinking, maternal depression, low birth weight, poor

parenting practices, and living in a disadvantaged neighbourhood.

Children with ADHD experience more academic problems than their schoolmates due to their neuro-cognitive impairments and behaviour. ADHD is often associated with deficits in executive functioning (e.g., planning, organizing, paying attention to important details, and inhibiting impulses). Accordingly, children identified with this disorder are more likely to exhibit learning and/or language disabilities. Results from studies examining the working of the brain suggest that ADHD is associated with atypical activity in the frontal cortex, the brain area responsible for cognitive processes. That said, it is important to note that only a subgroup of school-aged children with ADHD (30%) has executive functioning weaknesses, suggesting it is neither necessary nor sufficient to cause the disorder.

What can be done?

Diagnosis

ADHD is usually first identified and treated among school-age children. However, the presence of hyperactive-impulsive or inattentive symptoms during the preschool years is considered central to establishing the diagnosis. Direct observation of the child can suggest the diagnosis but even the most symptomatic child can be calm and attentive in an unusual setting such as in the doctor's office. Consequently, assessment should focus on obtaining a history of the child's behaviour at home, at play and in school from early childhood to the time of the assessment. A typical clinical interview allows an opportunity to discuss how parents and teachers have responded to the child's difficulties and to identify strategies that have worked and those that have not. Assessment should not be limited to ADHD symptoms but should enquire about associated symptoms that might also be evident such as anxiety, mood or conduct problems. Parents are not always aware of how much stressful circumstances can upset their child; therefore, a direct interview with the child can be an important part of the assessment. Concurrent disorders are an important focus of treatment and their presence can alter the effectiveness of therapy.

Many clinicians find that parent and teacher rating scales are helpful in the diagnostic process as a way of obtaining a description of the child's behaviour that can readily be compared to age norms. Some children with high levels of restlessness, inattentiveness and impulsiveness have medical problems or developmental delays that must be identified as part of the assessment. Children with learning difficulties may be symptomatic at school and during homework sessions

because they are struggling with the academic material. Other children may be symptomatic at home only suggesting some parenting, social or environmental problem. It can be very difficult to identify which children have specific learning difficulties in the doctor's office. Consequently, consultation with an educational psychologist can be very helpful in getting a complete picture of the child's strengths and difficulties.

Interventions

Current evidence-based treatments for ADHD include medication and behavioural interventions. Stimulant medication (such as methylphenidate, i.e. Ritalin™) in various short and long acting preparations plays an important role in the treatment of ADHD. More recently, non-stimulant medications, such as Atomoxetine, have also become available. These medications can help a large number of affected individuals by improving their attentiveness, impulse control and reducing their activity level. Also effective are intensive behavioural interventions that involve a combination of self-control training for the child and education in parenting strategies for the parents. Positive parental attention, rewards for appropriate behaviours, and negative consequences for misbehaviours (e.g., prohibiting children from playing with their favourite toy) are recommended procedures in behavioural treatments. Teachers can also apply similar strategies within their classrooms.

Available evidence indicates that the best interventions are a combination of medication, behavioural interventions and school-based programming for behaviour and learning. These treatments have to be intensive and long term to have their optimal impact. That said, some issues with these treatments are that their effects are generally not long-term and tend not to generalize across settings. Future research examining factors that affect treatment outcomes (individual and contextual) should be conducted to improve children's treatment gains over time and in different contexts.

ADHD and Neuroscience

¹Hicran Dođru, MD, ²F. Xavier Castellanos, MD, ³Samuele Cortese, MD, PhD, ⁴Yuta Y Aoki, MD, PhD

¹Independent Scholar, New York, NY, USA, ²Nathan Kline Institute for Psychiatric Research, USA, ^{2,3}NYU Grossman School of Medicine, USA, ³Centre of Innovation in Mental Health, University of Southampton, UK, ⁴Medical Institute of Developmental Disabilities Research, Showa University, Tokyo, Japan

December 2021

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent childhood neuropsychiatric condition, estimated to affect 5%-10% of school-age children worldwide.¹ Because of ADHD core symptoms and frequently associated psychiatric comorbidities, individuals with ADHD are at risk for cognitive, academic, behavioural, emotional, and social functioning.¹ Therefore, ADHD exacts an enormous psychosocial and psychiatric burden on the individual, their family and the community.²

Problems

- Currently, ADHD is diagnosed according to a set of behavioural criteria,¹ fostering controversy because of the subjective nature of the diagnosis.
- Individuals with ADHD are heterogeneous from a phenomenological standpoint, leading to confusion in clinical as well as in research settings.
- The expression of symptoms varies with the child's developmental stage and social and academic contexts.³
- Current classification does not consider developmental variations in symptoms sufficiently.
- No long-term curative treatments are currently available.⁴
- Medication choice remains based on personal experience and empirical trials.⁴

Subject

Insights from the emerging field of pediatric neuroscience are beginning to provide foundations for delineating the physiological principles of brain function and dysfunction.⁵ These advances are expected to lead to objective characterization of patients with more precisely defined “presentations” of ADHD and to the eventual development of effective physiopathology-based treatments *en route* to precision psychiatry.⁶

Research Context

The most fruitful contributions to understanding ADHD are likely to derive from a multidisciplinary translational research framework including physiology, psychology, neurology, psychiatry, bioinformatics, neurogenetics, cellular and molecular biology, and systems neuroscience.

Key Research Questions

Among the issues amenable to investigation by neuroscience methods, the following are pivotal:

1. Is the brain of individuals with ADHD morphologically different from non-ADHD controls?
2. Does the brain of individuals with ADHD function differently?
3. Does brain neurochemistry differ in ADHD?
4. What are the causes of the underlying dysfunctions?
5. What are the developmental pathways of abnormal brain structure and function?

Recent Research Results

1) *Is the brain of individuals with ADHD morphologically different?*

Large-scale neuroimaging studies have begun to address brain structure in ADHD with appropriate statistical power. The Enhancing Neuro-Imaging Genetics Through Meta-Analyses (ENIGMA) consortium compared 1713 patients with ADHD to 1429 healthy participants and found a significantly smaller intracranial volume (Cohen's $d=-0.10$) in ADHD after adjusting for sex, age, and site.⁷ Additionally, smaller volumes, at the group level, were found in the ADHD group in **amygdala** ($d=-0.19$), **accumbens** ($d=-0.15$), **caudate** ($d=-0.11$), hippocampus ($d=-0.11$), and **putamen** ($d=-0.11$) even after adjusting for covariates including intracranial volume.

In a subsequent ENIGMA-ADHD study comprising 36 centers, lower cortical surface area values were found, especially in the frontal, **cingulate** and temporal regions; total surface area yielded

the largest effect (Cohen's $d=-0.21$). Fusiform gyrus and temporal pole cortical thickness were also lower than in controls.⁸

Traditional voxel-based morphometry meta-analyses have revealed reduced gray matter volume in ventromedial orbitofrontal cortex and right **basal ganglia** including globus pallidus, putamen and caudate.^{9,10}

A meta-analysis of diffusion tensor imaging studies found both higher and lower fractional anisotropy in multiple white matter (WM) tracts (right inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus) with atypical interhemispheric connection in the **corpus callosum** being the most common finding.¹¹

Does the brain of individuals with ADHD function differently?

The functional imaging literature on ADHD is too voluminous to be systematically explored here. We report results of the main available systematic review/meta-analyses.

A meta-analysis of 55 task-based fMRI studies using inhibitory control, working memory, and attention tasks reported underactivation of the frontostriatal, frontoparietal, and ventral attention networks, and hyperactivation of the somatomotor and visual systems.¹² Interestingly, these findings mirror, in general, the anatomy implicated by structural imaging studies.

Also, impaired functional abnormalities in the default mode network¹³ and the cingulo-opercular network¹⁴ have also been reported in individuals with ADHD. A recent longitudinal study showed that worse response to stimuli was significantly associated with an atypical increase in cingulo-opercular resting-state functional connectivity with increasing age.¹⁵ Stimulants are thought to have a role in stabilizing these networks.

Meta-analyses of EEG data also found differences in ADHD such as elevation in the theta/beta ratio¹⁶ and age-related differences in slow wave activity which were significantly higher in early childhood and lower in late childhood/adolescence in ADHD vs. controls, with an inversion point at 10 years of age.¹⁷

Taken together, the structural and functional findings suggest widespread anomalies encompassing multiple brain structures and atypical functional connectivity affecting multiple large-scale brain networks.

2) *Does brain neurochemistry differ in ADHD?*

Empirical findings from neurobiological studies suggest that, rather than changes in any neurotransmitter system at the molecular level, the disorder has been linked to dysfunctions in various systems, including dopaminergic, adrenergic, serotonergic, and **cholinergic** pathways.¹⁸

In addition, magnetic resonance spectroscopy studies have shown altered glutamatergic signaling (**glutamate**, glutamine, and **GABA**) in frontostriatal pathways.¹⁹

3) *What are the causes of the supposed dysfunctions?*

ADHD is highly heritable (heritability ~ 0.74)²⁰ with many genetic and environmental risk factors likely contributing. The first genome-wide significant loci has identified several genetic variants, each with a small effect on the risk for ADHD.²¹ A recent meta-analysis implicated several risk genes (ADGRL3, ANKK1, BAIAP2, DAT1, DRD4, LRP5, LRP6, and SNAP25) although their mechanisms remain unclear.²²

A meta-analysis classified environmental correlates of ADHD as 1) exposure to toxic substances (lead, maternal smoking, maternal use of acetaminophen or valproate, etc.), 2) nutrient deficiencies (iron, omega-3, vitamin D, etc.), 3) events during pregnancy and birth (preterm or low birth weight) and 4) deprivation, infection, poverty, stress, and trauma,²² although these factors are contributory, not diagnostic.

4) *What are the developmental pathways of brain abnormalities?*

A meta-analysis showed that the most prominent and reproducible structural abnormalities in ADHD are located in the basal ganglia.²³ Structural changes are particularly pronounced in untreated populations.²⁴ A relationship among the effect of advancing age, the use of stimulant drugs and normalization of structural abnormalities has been suggested.²³ However, a follow-up study revealed abnormalities in white matter tracts which connect various regions involved in sensorimotor and higher-level cognitive functions, regardless of remission status in adulthood.²⁵

In addition, the absence of childhood-ADHD history in 90% of adult-ADHD cases²⁶ has led to questioning the syndromic nature of adult-ADHD and its continuity with the neurodevelopmental disorder.²⁷

Research Gaps

- How are structural and functional connectivity abnormalities related?
- At which developmental stages do disruptions in neural networks first emerge and manifest clearly?
- How best can the interactions of genes and environmental (biopsychosocial) variables be understood?
- How do various etiological factors lead to neural anomalies?
- How to conceptualize emotion dysregulation in ADHD?
- What are the potential benefits of pathophysiology-based interventions?
- Is there a clear cut-off on the transdiagnostic diagnosis of ADHD-brain relationships? Can machine learning algorithms capture specific dimensions of ADHD-related psychopathology in neuroimaging datasets?

Conclusions

Insights from neuroscience have unequivocally shown that the brains of children with ADHD differ from those of healthy comparisons. Research on the neurobiological bases of ADHD seeks to provide a better understanding of brain circuit changes associated with etiology, pathophysiology, and treatment response, and to develop illness-specific neural therapy targets. Particularly important are multimodal approaches and mega-analyses that integrate genetic, imaging, and phenotypic data. These reflect the increasing adoption of both open science and best reporting practices.

Although technical and methodological obstacles remain, the genetic bases of dysfunctions in ADHD and the interacting environmental factors are increasingly coming into focus. Challenging and expensive longitudinal studies have begun to yield insights into the developmental pathways of brain abnormalities and their relationships with ADHD symptoms. As these elements become clearer, the field will be better able to design etiopathophysiologically-based interventions for ADHD with the potential for long-term effectiveness.

Implications for Parents, Services and Policy

Although neuroscience has helped to advance our knowledge of the etiopathophysiology of ADHD, so far we have not found sensitive and specific neurobiological markers. However, research in this field has mainly begun to take a “group-level approach”; normative modeling can bring the field

forward in terms of precision psychiatry.²⁸

Future work will primarily focus on the biological and cognitive features of the disorder,²⁹ improving behavioural diagnosis of ADHD and setting the stage for new treatments supported by biomarker technologies in the long term, as described in the Research Domain Criteria project of the US National Institute of Mental Health.³⁰ The dimensional approach provides the basis for a broader assessment of the child's potential needs and strengths, and is intended to facilitate linking behaviours and symptoms to underlying brain mechanisms and neuronal circuits. These ambitious goals will not be attained rapidly. In the interim, practitioners and parents must continue to collaborate to understand and support each child's development, with the goal of minimizing the most pernicious sequelae of ADHD, particularly during adolescence.³¹

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. 5th ed. American Psychiatric Association; 2013.
2. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Archives of Disease in Childhood*. 2005;90(suppl 1):i2-i7. doi:10.1136/ADC.2004.059006
3. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, Rohde LA, Sonuga-Barke EJ, Tannock R, Franke B. Attention-deficit/hyperactivity disorder. *Nature Reviews. Disease Primers* 2015;1:15020. doi:10.1038/nrdp.2015.20
4. Cortese S. Pharmacologic treatment of attention deficit-hyperactivity disorder. Ropper AH, ed. *The New England Journal of Medicine*. 2020;383(11):1050-1056. doi:10.1056/NEJMra1917069
5. Castellanos FX. A biased perspective on brain imaging of ADHD. *American Journal of Psychiatry*. 2021;178(8):694-700. doi:10.1176/appi.ajp.2021.21060609
6. Cortese S. Setting the foundations of developmental precision psychiatry for ADHD. *American Journal of Psychiatry*. 2021;178(8):677-679. doi:10.1176/appi.ajp.2021.21050549

7. 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. *The Lancet Psychiatry*. 2017;4(4):310-319. doi:10.1016/S2215-0366(17)30049-4
8. Hoogman M, Muetzel R, Guimaraes JP, et al. Brain imaging of the cortex in ADHD: a coordinated analysis of large-scale clinical and population-based samples. *American Journal of Psychiatry*. 2019;176(7):531-542. doi:10.1176/APPI.AJP.2019.18091033
9. Lukito S, Norman L, Carlisi C, Radua J, Hart H, Simonoff E, Rubia K. Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. *Psychological Medicine*. 2020;50(6):894-919. doi:10.1017/S0033291720000574
10. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal of Psychiatry*. 2011;168(11):1154-1163. doi:10.1176/appi.ajp.2011.11020281
11. Aoki Y, Cortese S, Castellanos FX. Research Review: Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2018;59(3):193-202. doi:10.1111/JCPP.12778
12. Cortese S, Kelly C, Chabernaud C, Proal E, Di Martino A, Milham MP, Castellanos FX. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*. 2012;169(10):1038-1055. doi:10.1176/appi.ajp.2012.11101521
13. Sutclubasi B, Metin B, Kurban MK, Metin ZE, Beser B, Sonuga-Barke E. Resting-state network dysconnectivity in ADHD: A system-neuroscience-based meta-analysis. *The World Journal of Biological Psychiatry*. 2020;21(9):662-672. doi:10.1080/15622975.2020.1775889
14. Cortese S, Aoki YY, Itahashi T, Castellanos FX, Eickhoff SB. Systematic review and meta-analysis: resting-state functional magnetic resonance imaging studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2021;60(1):61-75. doi:10.1016/j.jaac.2020.08.014

15. Norman LJ, Sudre G, Bouyssi-Kobar M, Sharp W, Shaw P. A longitudinal study of resting-state connectivity and response to psychostimulant treatment in ADHD. *American Journal of Psychiatry*. 2021;178(8):744-751. doi:10.1176/appi.ajp.2021.20091342
16. Arns M, Conners CK, Kraemer HC. A decade of EEG Theta/Beta Ratio Research in ADHD: A Meta-Analysis. *Journal of Attention Disorders*. 2012;17(5):374-383. doi:10.1177/1087054712460087
17. Biancardi C, Sesso G, Masi G, Faraguna U, Sicca F. Sleep EEG microstructure in children and adolescents with attention deficit hyperactivity disorder: a systematic review and meta-analysis. *Sleep*. 2021;44(7). doi:10.1093/sleep/zsab006
18. Cortese S. The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): What every clinician should know. *European Journal Of Paediatric Neurology*. 2012;16(5):422-433. doi:10.1016/j.ejpn.2012.01.009
19. Naaijen J, Lythgoe DJ, Amiri H, Buitelaar JK, Glennon JC. Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: A review of magnetic resonance spectroscopy studies. *Neuroscience & Biobehavioral Reviews* 2015;52:74-88. doi:10.1016/j.neubiorev.2015.02.009
20. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*. 2018;24(4):562-575. doi:10.1038/s41380-018-0070-0
21. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*. 2018;51(1):63-75. doi:10.1038/s41588-018-0269-7
22. Faraone S V., Banaschewski T, Coghill D, et al. The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews* 2021;128:789-818. doi: 10.1016/j.neubiorev.2021.01.022
23. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. *American Journal*

of Psychiatry. 2011;168(11):1154-1163. doi:10.1176/appi.ajp.2011.11020281

24. Frodl T, Skokauskas N. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatrica Scandinavica*. 2012;125(2):114-126. doi:10.1111/j.1600-0447.2011.01786.x
25. Cortese S, Imperati D, Zhou J, et al. White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2013;74(8):591-598. doi:10.1016/j.biopsych.2013.02.025
26. Moffitt TE, Houts R, Asherson P, et al. Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study. *American Journal of Psychiatry*. 2015;172(10):967-977. doi:10.1176/appi.ajp.2015.14101266
27. Castellanos FX. Is adult-onset ADHD a distinct entity? *American Journal of Psychiatry*. 2015;172(10):929-931. doi:10.1176/appi.ajp.2015.15070988
28. Marquand AF, Rezek I, Buitelaar J, Beckmann CF. Understanding heterogeneity in clinical cohorts using normative models: beyond case-control studies. *Biological Psychiatry*. 2016;80(7):552-561. doi:10.1016/j.biopsych.2015.12.023
29. Cortese S, Coghill D. Twenty years of research on attention-deficit/hyperactivity disorder (ADHD): looking back, looking forward. *Evidence-Based Mental Health*. 2018;21(4):173-176. doi:10.1136/ebmental-2018-300050
30. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *American Journal of Psychiatry*. 2014;171(4):395-397. doi:10.1176/APPI.AJP.2014.14020138
31. Klein RG, Mannuzza S, Olazagasti MAR, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry*. 2012;69(12):1295. doi:10.1001/archgenpsychiatry.2012.271

Attention Deficit Hyperactivity Disorder and Cognition

Nanda Rommelse, PhD

Radboud University Medical Center, Department of Psychiatry, Netherlands

February 2010

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by a triad of symptoms of inattention, hyperactivity and impulsivity.¹ The disorder is highly heritable and affects around 3-5% of school-aged children.^{2,3} In recent decades, the cognitive problems of ADHD have been widely studied. Cognition can be defined as gaining knowledge and comprehension, including thinking, knowing, remembering, judging and problem solving.

Subject

Several causal pathway models have been proposed, trying to combine the findings of biological and cognitive abnormalities frequently found in ADHD. The cognitive models all have in common that deficits in executive functioning (EF) are one of the most prominent characteristics of ADHD. EF has been defined as "those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour".⁴ EF impairments have been reported in many studies with ADHD patients, with problems in inhibition and working memory being the most frequently replicated.⁵ Deficits in EF are strongly linked to abnormalities in the *prefrontal lobe* and *frontal-subcortical circuitry* found in patients with ADHD.^{6,7}

Problem

Even though most causative models of ADHD incorporate deficits in EF as an important factor, it is actually unknown if and to what extent deficits in EF *cause* ADHD. In other words, given that ADHD is a highly heritable disorder, is EF a heritable trait that increases the risks of developing ADHD and in what percentage of patients may it pose a causal factor?

Key Research Questions

Two issues are central in order to examine whether EF deficits are causally related to ADHD:

- Given that ADHD is strongly heritable, are EF problems themselves also heritable and linked to the same genes as ADHD?
- What percentage of children with ADHD actually suffers from EF problems?

Recent Research Results

Are EF problems heritable and linked to the same genes as ADHD?

A necessary first step in determining if EF deficits are heritable is to study EF performance in a twin design. A twin design allows for disentangling the influence of heritable and environmental influences on EF. Several twin studies have examined EF performance.¹²⁻¹⁶ At ages 5 and 12, about 50% of performance on several EF tasks appeared attributable to genetic factors.¹⁶ Other studies have yielded similar percentages of around 40% to 50%,^{12,13,15} suggesting performance on EF tasks is moderately heritable. Furthermore, genetic factors appear an important mediator of *stability* of EF during childhood.¹⁴

A second step in determining if EF deficits are heritable and linked to the same genes as ADHD is to study the EF performance in relatives of ADHD patients. This sheds light on the familiarity of EF deficits in ADHD. Siblings, for instance, share on average 50% of their genes. It is therefore likely that non-affected siblings of a child with ADHD carry risk genes for ADHD without having the phenotypic expression of ADHD. If EF deficits are indeed familiarly linked to ADHD, non-affected siblings will show the same EF deficits, probably to a somewhat lesser extent, than their ADHD affected siblings.

Several studies have targeted EF within ADHD families and results support the hypothesis that EF deficits are familial and also present (to a lesser extent) in non-affected relatives of ADHD patients.^{5,17-21} Studies that have specifically targeted inhibition or interference control as an executive function have also reported promising results, with non-affected relatives displaying subtle deficits in this area and relatives resembling each other in their performance.²²⁻²⁶ These findings suggest that EF deficits are familial. Although this is not sufficient to suggest that EF problems are heritable; it is at least consistent with it.

A final step in examining whether EF deficits are linked to the same genes as ADHD is to examine EF performance in relation to ADHD candidate genes and/or to use EF performance in linkage analyses using ADHD pedigrees. Both of these strategies have rarely been carried out due to the

large sample sizes that are required to generate sufficient power for the analyses. Preliminary results indicate that *polymorphisms* in a gene (*Dopamine Receptor D4* gene) that has been most frequently replicated in relation to ADHD indeed also relates to EF.^{15,27-30} One linkage study found a genome-wide significant linkage signal on chromosome 13q12.¹¹ using an EF measure (verbal working memory) in ADHD pedigrees, suggesting genes on this location may influence both ADHD and EF performance.³¹ In addition, another linkage study indicated that a region on chromosome 3q13 was related to both a composite measure of EF and to inattention symptoms of ADHD, suggesting these EF deficits may relate to the same genes as ADHD.³²

What percentage of children with ADHD suffer from EF problems?

The percentage of children suffering from EF problems strongly depends on the definition of an executive function deficit (EFD).⁸ There is no consensus on what actually constitutes an EFD, but most definitions entail a performance below the 10th percentile of a matching control group on at least one, two or three EF tasks. On a group level, children with ADHD virtually always perform worse on EF measures than children in the control group. However, on an individual level, a proportion of children with ADHD outperform a proportion of the children in the control group.⁹ In other words, not every child with ADHD suffers from an EFD. EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD.⁹ Rather, other cognitive functions, motivational problems or, in some cases, response to family distress or peer problems, may constitute pathways to ADHD.^{10,11} About a third of the children show a moderately severe EFD, defined as being impaired on three or more EF measures.¹¹

Research Gaps

In order to determine whether EF deficits found in a proportion of ADHD patients are indeed causative of ADHD in this group, a more comprehensive approach is required than that has currently been undertaken. That is, only a few studies examined EF in a familial context and most studies have been underpowered for genetic analyses. An even larger problem is that results are difficult to compare because of the use of different tasks and methods to measure the same executive function. This is particularly troublesome for attempts to combine cognitive datasets across sites for increased statistical power in genetic analyses. Thus, in order to determine whether EF deficits found in a proportion of ADHD patients are indeed causative of ADHD, it is necessary to administer EF tasks that have good validity, reliability, heritability and norm data. Using the same “golden standard” tasks would make it possible to combine different samples

across research sites. This would greatly enhance comparability of data and would boost power for genetic analyses, leading to more robust results hopefully applicable in clinical practice.

Conclusions

Performance on EF tasks is moderately heritable and genetic factors appear an important mediator of *stability* of EF during childhood. EF deficits are familially linked to ADHD and are possibly related to, amongst others, the Dopamine Receptor D4 gene, which is also related to ADHD. In other words, (partly) genetically-based deficits in EF may *cause* ADHD. However, only a subgroup of ADHD patients (about 30%) suffers from moderately severe EF problems, suggesting EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD.

Implications for Parents, Services and Policy

Cognitive tests are still not sensitive or specific enough to be used in daily practice for diagnosing ADHD. We still have to rely on parents' and teachers' reports (or self report in adolescents and adults with suspected ADHD) for diagnosis. However, recent longitudinal data indicates that childhood EF predicts future academic achievement, social functioning and global functioning in ADHD patients.³³ These results suggest it may benefit clinical practice when EF impairments are assessed and treated, particularly in those at high-risk for negative outcomes, in order to prevent long-term difficulties across a range of important functional domains.³³ Intervention strategies for EF deficits are still in their primary phase of development, but already positive results have been obtained.^{34,35} A subgroup of children with ADHD that suffers from moderately severe EF deficits (+/- 30%) may benefit from these interventions.

References

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV*. 4th ed. Washington, DC.: American Psychiatric Association; 1994.
2. Faraone S, Biederman J, Mick E. The age dependent decline of attention-deficit/hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine* 2006;36(2):159-165.
3. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313-1323.
4. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment*. 4th ed. New York, NY: Oxford University Press; 2004.
5. Rommelse NN, Altink ME, Oosterlaan J, Buschgens CJ, Buitelaar J, Sergeant JA. Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. *Psychological Medicine* 2008;38(11):1595-1606.
6. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience* 2002;3(2):617-628.

7. Durston S. A review of the biological bases of ADHD: what have we learned from imaging studies? *Mental Retardation and Developmental Disabilities Research Reviews* 2003;9(3):184-195.
8. Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, Morgan CL, Faraone SV. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children *Journal of Consulting and Clinical Psychology* 2004;72(5):757-766.
9. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Journal of Abnormal Child Psychology* 2009;37(11):551-564.
10. Wåhlstedt C, Thorell LB, Bohlin G. Heterogeneity in ADHD: neuropsychological pathways, comorbidity and symptom domains. *Journal of Abnormal Child Psychology* 2009;37(4):551-564.
11. Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biological Psychiatry* 2005;57(11):1224-1230.
12. Anokhin AP, Heath AC, Ralano A. Genetic influences on frontal brain function: WCST performance in twins. *Neuroreport* 2003;14(15):1975-1978.
13. Taylor J. Heritability of Wisconsin Card Sorting Test (WCST) and Stroop Color-Word Test performance in normal individuals: implications for the search for endophenotypes. *Twin Research and Human Genetics* 2007;10(6):829-834.
14. Polderman TJ, Posthuma D, De Sonneville LM, Stins JF, Verhulst FC, Boomsma DI. Genetic analyses of the stability of executive functioning during childhood. *Biological Psychology* 2007;76(1-2):11-20.
15. Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID, Pennington BF, Peart J, Biederman J. Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? *Journal of Child Psychology and Psychiatry* 2005;46(7):774-803.
16. Polderman TJ, Gosso MF, Posthuma D, Van Beijsterveldt TC, Heutink P, Verhulst FC, Boomsma DI. A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. *Acta Neurologica Belgica* 2006;106(4):191-207.
17. Seidman L, Biederman J, Monuteaux M, Weber W, Faraone SV. Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *Journal of Abnormal Psychology* 2000;109(2):252-265.
18. Nigg JT, Blaskey LG, Stawicki JA, Sachek J. Evaluating the endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with ADHD combined and inattentive subtypes. *Journal of Abnormal Psychology* 2004;113(4):614-625.
19. Waldman ID, Nigg JT, Gizer IR, Park L, Rappley MD, Friderici K. The adrenergic receptor alpha-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotypes for childhood ADHD. *Cognitive, Affective, & Behavioral Neuroscience* 2006;6(1):18-30.
20. Bidwell LC, Willcutt EG, DeFries JC, Pennington BF. Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2007;62(9):991-998.
21. Uebel H, Albrecht B, Asherson P, Börger NA, Butler L, Chen W, Christiansen H, Heise A, Kuntsi J, Schäfer U, Andreou P, Manor I, Marco R, Miranda A, Mulligan A, Oades RD, van der Meere J, Faraone SV, Rothenberger A, Banaschewski T. Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child Psychology and Psychiatry* 2010;51(2):210-218.
22. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Buitelaar J. Familial clustering of executive functioning in affected sibling pair families with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44(4):385-391.
23. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Van der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;42(10):1242-1248.

24. Crosbie J, Schachar R. Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry* 2001;158(11):1884-1890.
25. Schachar RJ, Crosbie J, Barr CL, Ornstein TJ, Kennedy J, Malone M, Roberts W, Ickowicz A, Tannock R, Chen S, Pathare T. Inhibition of motor responses in siblings concordant and discordant for Attention Deficit Hyperactivity Disorder. *American Journal of Psychiatry* 2005;162(6):1076-1082.
26. Goos LM, Crosbie J, Payne S, Schachar R. Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. *American Journal of Psychiatry* 2009;166(6):711-717.
27. Boonstra AM, Kooij JJS, Buitelaar JK, Oosterlaan J, Sergeant JA, Heister JG, Franke B. An exploratory study of the relationship between four candidate genes and neurocognitive performance in adult ADHD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2008;147(3):397-402.
28. Altink ME, Rommelse NNJ, Slaats-Willemse DIE, Arias Vasquez A, Franke B, Buschgens CJM, Fliers EA, Faraone SV, Sergeant JA, Oosterlaan J, Buitelaar JK. The dopamine receptor D4 7-repeat allele influences neurocognitive functioning, but this effect is moderated by age and ADHD status. *Journal of Child Psychology and Psychiatry*. In press.
29. Durston S, de Zeeuw P, Staal WG. Imaging genetics in ADHD: a focus on cognitive control. *Neuroscience and Biobehavioral Reviews* 2009;33(5):674-689.
30. Loo SK, Rich EC, Ishii J, McGough J, McCracken J, Nelson S, Smalley SL. Cognitive functioning in affected sibling pairs with ADHD: familial clustering and dopamine genes. *Journal of Child Psychology and Psychiatry* 2008;49(9):950-957.
31. Rommelse NN, Arias-Vásquez A, Altink ME, Buschgens CJ, Fliers E, Asherson P, Faraone SV, Buitelaar JK, Sergeant JA, Oosterlaan J, Franke B. Neuropsychological endophenotype approach to genome-wide linkage analysis identifies susceptibility loci for ADHD on 2q21.1 and 13q12.11. *American Journal of Human Genetics* 2008;83(1):99-105.
32. Doyle AE, Ferreira MA, Sklar PB, Lasky-Su J, Petty C, Fusillo SJ, Seidman LJ, Willcutt EG, Smoller JW, Purcell S, Biederman J, Faraone SV. Multivariate genomewide linkage scan of neurocognitive traits and ADHD symptoms: suggestive linkage to 3q13. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2008;147B(8):1399-1411.
33. Miller M, Hinshaw SP. Does childhood executive function predict adolescent functional outcomes in girls with ADHD? *Journal of Abnormal Child Psychology*. In press.
34. Papazian O, Alfonso I, Luzondo RJ, Araguez N. Training of executive function in preschool children with combined attention deficit hyperactivity disorder: a prospective, controlled and randomized trial. *Revista de Neurologia* 2009;48(suppl 2):S119-S122.
35. Klingberg T, Fernell E, Olesen PJ, Johnson M, Gustafsson P, Dahlström K, Gillberg CG, Forsberg H, Westerberg H. Computerized training of working memory in children with ADHD--a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44(2):177-186.

Genetic contributions to ADHD

Joanna Martin, PhD

Centre for Neuropsychiatric Genetics and Genomics & Wolfson Centre for Young People's Mental Health, Cardiff University, Cardiff, United Kingdom

April 2023

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition, affecting about 5% of children globally. Although considered a childhood condition, the symptoms and associated impairment can be life-long. In children, ADHD is more commonly diagnosed in males, but the sex ratio decreases in adults.¹ ADHD is associated with cognitive difficulties, especially executive functions (e.g., working memory, inhibitory control). ADHD commonly co-occurs with other neurodevelopmental conditions, including autism, motor coordination difficulties, and learning difficulties. Similarly to other neurodevelopmental conditions, ADHD is highly heritable.

The last decade of genetic research has seen significant breakthroughs in our understanding of the genetic contributions to ADHD and how these risks exert their effects in the population.

Subject

Recent genetic studies have begun to identify robustly associated variants which increase ADHD risk. Another major advance has been studies examining the population-level impact of ADHD-linked genetic variants, including in clinical and general population samples.

Problems

One big hurdle to genetic discovery is not unique to ADHD; given the vastness and complexity of the human genome, genetic information from a large number (10,000s or even 100,000s) of individuals is needed to enable discovery. Another challenge is that ADHD is heterogeneous, meaning that people with ADHD differ in terms of their diagnostic subtype, symptom severity, symptom persistence, co-occurring conditions, and long-term outcomes.

Research Context

ADHD is associated with a significant negative impact on mental health (e.g., anxiety, depression, substance misuse), educational attainment, relationships, employment, and physical health. A better understanding of the genetic contributions and how they impact on heterogeneity is needed to inform clinical practice and improve outcomes for individuals with ADHD.

Key Research Questions

What are the specific genetic risk factors that increase risk for ADHD? What can explain the high levels of comorbidity between ADHD and other neurodevelopmental and psychiatric conditions? What is the impact of ADHD genetic risk at a population level? Can genetic factors help us better understand the heterogeneity in ADHD?

Recent Research Results

Given the high heritability of ADHD (estimated at about 76%),² numerous genome-wide association studies (GWAS) have sought to identify specific genetic variants contributing to ADHD risk. GWAS compare the population frequency of millions of genetic variants in individuals with and without ADHD, using a hypothesis-free approach. The first of these studies to succeed in identifying robustly associated markers, analysed data from 20,183 individuals with ADHD (primarily children) and 35,191 comparison individuals.³ This GWAS identified 12 loci^a consisting of common single nucleotide polymorphisms^b that showed a different population frequency in individuals with and without ADHD. The study estimated that common variants collectively account for about 21.6% of ADHD risk, with further genetic markers to be identified. Indeed, a more recent study built on this work with the inclusion of genetic data from 38,691 individuals with ADHD and 186,843 comparison individuals,⁴ identifying 27 genomic loci linked to ADHD. Both studies highlighted that ADHD is highly polygenic, with likely thousands of variants contributing to ADHD risk. They also examined the expression of the implicated genes in a variety of cell types, tissues, and brain development stages, concluding that implicated variants were important for key neurological processes, including central nervous system tissue, embryonic brain development, and dopaminergic neurons.

Significant progress has also been made in identifying rare genetic variants linked to ADHD. These include copy number variants (CNVs)^c, which are large sections of chromosomes with fewer or more copies than usual (i.e., deletion or duplication), and rare single nucleotide exonic mutations that disrupt or alter protein formation. While large CNVs have been linked to ADHD for over a

decade,⁵ recent studies have linked specific CNV regions to ADHD (examples include deletions at 15q11.2 and 22q11.21 and duplications at 16p11.2 and 16p13.11).⁶ Studies have also implicated rare exonic mutations^{d,7} as well as de novo (i.e., non-inherited) CNVs,⁸ but samples have been too small to identify specific risk variants within these classes of variation.

The large GWAS have contributed to our understanding of ADHD beyond discovery of specific risk factors. Studies indicate that there are high degrees of shared genetic risks between different definitions of ADHD (e.g., diagnosis and continuously assessed population traits,³ male and female ADHD,⁹ and childhood and adulthood diagnoses¹⁰). It is now also abundantly clear that ADHD genetic risks are shared with other neurodevelopmental conditions, notably autism,^{7,11} and psychiatric disorders, notably depression.¹² ADHD also shares a substantial proportion of genetic risks with other disorders and traits, including type 2 diabetes, smoking behaviours, insomnia, and low educational attainment.³ This widespread shared aetiology is likely to at least partly explain the co-occurrence of ADHD with these conditions and traits.

Another noteworthy contribution from GWAS analyses is that discoveries can be taken forward to examine the impact of ADHD genetic risk at a population level. Information from discovery GWAS can be used to calculate ‘polygenic risk scores’ (PRS) in an independent sample; these PRS indicate an individual’s genetic predisposition towards ADHD. For example, in the latest ADHD GWAS, PRS were derived in a clinical sample of children and adults who had undergone cognitive testing; ADHD PRS were associated with lower abilities in working memory, attention, and cognitive reasoning.⁴ A systematic review of ADHD PRS studies found widespread evidence of association with population level traits, including in the domains of cognition, education, psychopathology, brain structure, physical health, and socioeconomic factors.¹³

One useful application of PRS includes examining the impact of genetic risks on heterogeneity within ADHD clinical samples. It is clear that genetic risks contribute to whether an individual will develop ADHD or not. A key question is whether genetic risk additionally impacts on severity, co-occurring conditions, and long-term outcomes in those diagnosed with ADHD. Indeed, higher ADHD PRS are associated with co-occurring conduct disorder,¹⁴ substance use (e.g., alcohol and cannabis),¹⁵ emotional dysregulation,^{16,17} and executive function difficulties.^{18,19} These studies suggest that the presence of specific co-occurring difficulties may be clinical markers of a greater genetic predisposition to ADHD in diagnosed individuals.

Research Gaps

Larger samples are needed for continued discovery of genetic contributions to ADHD. Additionally, analysis of genetically diverse samples is urgently needed. Existing studies primarily consist of individuals of European ancestry and genetic findings may differ across populations.²⁰ A limitation of existing PRS methods is that predictive ability is highly reduced in samples that do not match the ancestry of the discovery data used to calculate scores.²¹ The inclusion of ancestrally diverse samples may also aid fine mapping to pinpoint the causal mechanisms of genomic regions linked to ADHD. With a rapidly growing number of implicated regions, much more work is needed to fully understand the impact of causal genetic factors on biological function. Further work is also needed to understand the environmental context for ADHD symptom onset and progression.

Conclusions

ADHD is a highly heritable, neurodevelopmental condition, with emerging discoveries implicating genetic variants that play a key role in brain development. It is the extreme end of a dimensional population trait, with genetic risks shared across sub-threshold symptoms and diagnosis. ADHD often persists into adulthood, with shared genetic factors between childhood and adulthood, as well as between males and females. Genetic risks are also shared with other conditions and related traits. This could explain the high level of co-occurrence with varied conditions such as autism, depression, and diabetes. Genetic risk factors may also help explain the clinical heterogeneity seen with regards to co-occurring neurodevelopmental and mental health outcomes in individuals with ADHD. Recent genetic studies provide a solid foundation for continued discovery and understanding of the aetiology of ADHD, with a view towards a precision medicine approach to support people impacted by ADHD.

Implications for Parents, Services and Policy

The widespread evidence of high levels of shared genetic risk factors between ADHD and other conditions, has important implications. Firstly, when young people are experiencing mental health difficulties, they may benefit from parents and teachers considering whether these difficulties could indicate underlying neurodevelopmental difficulties such as ADHD. Similarly, clinicians working within child and adolescent mental health services should be aware of these strong biological links across different conditions. Given the lifelong consequences of ADHD, more resources are needed to decrease waiting lists for ADHD assessment and treatment, for educational support for those with ADHD, as well as for training of teachers and doctors to recognise ADHD and its heterogeneous presentation. Finally, given emerging evidence of ADHD-

implicated genetic risk factors, future policies related to genetic testing and counselling could consider ADHD amongst other genetic conditions (such as autism and intellectual disability).

References

1. Faheem M, Akram W, Akram H, Khan MA, Siddiqui FA, Majeed I. Gender-based differences in prevalence and effects of ADHD in adults: A systematic review. *Asian Journal of Psychiatry*. 2022;75(March):103205. doi:10.1016/j.ajp.2022.103205
2. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*. 2019;24(4):562-575. doi:10.1038/s41380-018-0070-0
3. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*. 2019;51(1):63-75. doi:10.1038/s41588-018-0269-7
4. Demontis D, Walters GB, Athanasiadis G, et al. Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*. 2023;55(2):198-208. doi:10.1038/s41588-022-01285-8
5. Williams NM, Zaharieva I, Martin A, et al. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet*. 2010;376(9750):1401-1408. doi:10.1016/S0140-6736(10)61109-9
6. Gudmundsson OO, Walters GB, Ingason A, et al. Attention-deficit hyperactivity disorder shares copy number variant risk with schizophrenia and autism spectrum disorder. *Translational Psychiatry*. 2019;9(1):258. doi:10.1038/s41398-019-0599-y
7. Satterstrom FK, Walters RK, Singh T, et al. Autism spectrum disorder and attention deficit hyperactivity disorder have a similar burden of rare protein-truncating variants. *Nature Neuroscience*. 2019;22(12):1961-1965. doi:10.1038/s41593-019-0527-8
8. Martin J, Hosking G, Wadon M, et al. A brief report: de novo copy number variants in children with attention deficit hyperactivity disorder. *Translational Psychiatry*. 2020;10(1).

doi:10.1038/s41398-020-0821-y

9. Martin J, Walters RK, Demontis D, et al. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*. 2018;83(12):1044-1053. doi:10.1016/j.biopsych.2017.11.026
10. Rovira P, Demontis D, Sánchez-Mora C, et al. Shared genetic background between children and adults with attention deficit/hyperactivity disorder. *Neuropsychopharmacology*. 2020;45(10):1617-1626. doi:10.1038/s41386-020-0664-5
11. Mattheisen M, Grove J, Als TD, et al. Identification of shared and differentiating genetic architecture for autism spectrum disorder, attention-deficit hyperactivity disorder and case subgroups. *Nature Genetics*. 2022;54(10):1470-1478. doi:10.1038/s41588-022-01171-3
12. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell*. 2019;179(7):1469-1482.e11. doi:10.1016/j.cell.2019.11.020
13. Ronald A, de Bode N, Polderman TJC. Systematic Review: How the Attention-Deficit/Hyperactivity Disorder Polygenic Risk Score Adds to Our Understanding of ADHD and Associated Traits. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2021;60(10):1234-1277. doi:10.1016/j.jaac.2021.01.019
14. Demontis D, Walters RK, Rajagopal VM, et al. Risk variants and polygenic architecture of disruptive behavior disorders in the context of attention-deficit/hyperactivity disorder. *Nature Communications*. 2021;12(1):576. doi:10.1038/s41467-020-20443-2. Erratum in: *Nature Communications*. 2021;12(1):1166.
15. Wimberley T, Agerbo E, Horsdal HT, et al. Genetic liability to ADHD and substance use disorders in individuals with ADHD. *Addiction*. 2020;115(7):1368-1377. doi:10.1111/add.14910

16. Riglin L, Eyre O, Cooper M, et al. Investigating the genetic underpinnings of early-life irritability. *Translational Psychiatry*. 2017;7(9):e1241. doi:10.1038/tp.2017.212
17. Nigg JT, Karalunas SL, Gustafsson HC, et al. Evaluating chronic emotional dysregulation and irritability in relation to ADHD and depression genetic risk in children with ADHD. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2020;61(2):205-214. doi:10.1111/jcpp.13132
18. Nigg JT, Gustafsson HC, Karalunas SL, et al. Working memory and vigilance as multivariate endophenotypes related to common genetic risk for attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2018;57(3):175-182. doi:10.1016/j.jaac.2017.12.013
19. Chang S, Yang L, Wang Y, Faraone S V. Shared polygenic risk for ADHD, executive dysfunction and other psychiatric disorders. *Translational Psychiatry*. 2020;10(1):182. doi:10.1038/s41398-020-00872-9
20. Yang L, Neale BM, Liu L, et al. Polygenic transmission and complex neuro developmental network for attention deficit hyperactivity disorder: Genome-wide association study of both common and rare variants. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*. 2013;162B(5):419-430. doi:10.1002/ajmg.b.32169
21. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature Genetics*. 2019;51(4):584-591. doi:10.1038/s41588-019-0379-x

Notes:

^a **Locus (plural: loci):** The physical site or location of a specific gene on a chromosome.

^b **Single nucleotide polymorphisms:** A small genetic variation in a human's DNA.

^c **Copy number variants (CNVs):** Genes were thought to exist in 2 copies in our DNA. However, it is not always so. Some genes are sometimes present in 1, 3 or 4 copies in some individuals. This is what is called copy number variation.

⁴ **Exonic mutations:** Exonic variants are the parts of genes which typically code for proteins. Mutations in these regions cause a genetic alteration in the DNA sequence and can impact on the proteins that are formed.

Children with Attention Deficit Hyperactivity Disorder: Epidemiology, Comorbidity and Assessment

Alice Charach, Msc, MD

Hospital for Sick Children, Canada

April 2020, Éd. rév.

Epidemiology of ADHD

Children with Attention Deficit Hyperactivity Disorder (ADHD), characterized by developmentally excessive levels of inattention, over-activity and impulsiveness, are most frequently identified and treated in primary school. Studies worldwide identify a prevalence rate for ADHD equivalent to 5.29% (95% Confidence Interval: 5.01-5.56) of children and adolescents.¹ Rates are higher for boys than for girls, and for children under 12 years of age compared with adolescents.^{1,2} Prevalence estimates vary based on method of ascertainment, diagnostic criteria used, and whether functional impairment criteria are included.¹ Overall, estimates are remarkably similar from country to country with the exception of African and Middle Eastern countries where rates are lower compared with North America and Europe.¹

Symptoms generally interfere with academic and behaviour functioning at school, and often disrupt family and peer relationships.^{3,4} Children with ADHD use more health services and sustain more injuries than those without.^{5,6} While hyperactivity symptoms lessen in adolescence, the majority of children with ADHD continue to show some cognitive impairment, (eg, poor executive functioning, impaired working memory) relative to same-age peers through their teen years and into adulthood.^{7,8} Childhood hyperactivity is associated with subsequent onset of other psychiatric disorders, including anxiety, conduct problems, mood disorders and suicidal behaviour and antisocial personality disorder.⁹⁻¹¹ Adults with childhood history of ADHD are at greater risk of psychiatric hospitalizations and incarcerations, divorce, risky sexual and driving behaviours, increased emergency room visits, serious injuries and death.^{12,13} In addition, adults with ADHD documented in childhood show anatomical decrements in brain gray matter.¹⁴ Positive factors include parent involvement through high-school and attendance at college or university as these are associated with improved functioning at age 25.¹⁵

ADHD is an important public health concern, not only for the long-term impairments facing individuals and families but also for the heavy burden on educational, health and criminal justice systems.^{16,17}

Population studies identify that childhood inattention and hyperactivity are more common in single parent families, with low parent education attainment, parent unemployment, and low family income.^{18,19} Evidence from family studies identify that symptoms of ADHD are highly heritable,²⁰ however, early environmental factors contribute as well. History of prenatal maternal smoking and drinking, low birth weight, and developmental problems are associated with high levels of inattention and hyperactivity.²¹ Prenatal maternal smoking, maternal depression, poor parenting practices and living in a disadvantaged neighbourhood in the first year of life are all associated with later childhood behaviour problems, including inattention and hyperactivity four years later.²²⁻²⁴

Clinical identification and treatment of ADHD in North America can vary geographically, apparently reflecting differences in community practices or access to services.^{25,26} Treatment with stimulant medications for inattentive and hyperactive symptoms increased in the early to mid 1990s, and likely reflects longer periods of use with treatment extended into adolescent years as well as an increased number of girls identified and treated.²⁷⁻²⁹ Stimulant medications remain the first line pharmacological intervention for addressing symptoms of ADHD. However, combining medications with behavioural and other non-pharmacological interventions is recommended.³⁰

Concurrent (or Comorbid) Disorders

Half to two thirds of school children identified with ADHD also have concurrent psychiatric and developmental disorders, including oppositional and aggressive behaviours, anxiety, low self esteem, tic disorders, motor problems, and learning or language disabilities.³¹⁻³⁴ Sleep difficulties, including enuresis (bed-wetting), are common, with sleep-disordered breathing, a potentially correctable reason for increased inattention.^{35,36} Global impairment in children with ADHD increases with increasing numbers of concurrent disorders.³⁷ The concurrent conditions also increase the likelihood of additional difficulties developing as children become adolescents and young adults.³⁸⁻⁴¹

Neurocognitive difficulties are an important source of impairment in children with ADHD. Areas of executive functioning and working memory as well as specific language and learning disorders are

common in clinic groups.⁴²⁻⁵⁰ Approximately a third of children referred for psychiatric, often behaviour problems, may have previously unrecognized language difficulties.⁵¹ Whenever possible the potential for cognitive, language and developmental problems requires evaluation so that appropriate academic interventions can be implemented.

ADHD in Preschoolers

Attention Deficit Hyperactivity Disorder usually begins before children enter school. However in the preschool age group ADHD is characterized not only by impairment in attention span, excessive impulsivity and over-activity but also is frequently accompanied by severe temper tantrums, demanding, uncooperative behaviour and aggressiveness that can interfere with attendance at daycare or preschool, avoidance of family gatherings, and high family burden of care and distress.⁵²⁻⁵⁴ These disruptive behaviours are often the target of parental concern, and many receive a diagnosis of oppositional defiant disorder. Initial interventions should address parenting challenges using behavioural interventions rather than medication in preschool-aged children.⁵⁵

Assessment of ADHD in School-Age Children

Among primary school children, concerns about learning style and behaviour difficulties are often brought to the parents' attention by classroom teachers. Educators generally anticipate that by senior kindergarten and grade 1, children should be able to follow classroom routines, follow simple instructions, play cooperatively with peers, and remain focused for 15 to 20 minutes at a time on academic tasks. Concerns raised by teachers, especially experienced ones, provide important details about a child's academic and social functioning.

The formal diagnosis of ADHD reflects pervasive and detrimental levels of inattention, distractibility, overactivity and impulsiveness. The child's symptoms must be developmentally excessive and cause impaired functioning, most often in academic or social skills, peer or family relationships. Difficulties generally have been present since preschool, although not always recognized. The troublesome behaviours are present in more than one context, at home, at school or in the community, for example on outings to the park or to a grocery store.

There are two sets of formal diagnostic rules used in Canada, DSM 5 (Diagnostic and Statistical Manual, Fifth Edition) and ICD-11 (International Classification of Disorders, Eleventh Edition, accepted in 2019 and in effect in 2022). Both sets of formal diagnostic rules classify ADHD as a

neurodevelopmental disorder, in the ICD-11, the term ADHD replaces hyperkinetic disorder from ICD-10.^{56,57} There are three presentations of ADHD, predominantly inattentive presentation, where the child shows six of nine prescribed inattentive symptoms, predominately hyperactive-impulsive presentation, where the child shows six out of nine hyperactive-impulsive symptoms, and combined presentation, where the child shows high levels of both types of symptoms (see Chart 1 for diagnostic symptoms).

The clinical assessment of a child with ADHD is best done by a health professional familiar with pediatric mental health and psychosocial assessments. Since young children frequently respond to stressful circumstances with increased levels of activity and distractibility as well as difficulties in learning and social relationships, assessments of developmental, family and social contexts are required to identify alternative explanations for the impairing symptoms where appropriate. Physical contributions such as poor sleep, or chronic medical conditions should also be evaluated as explanations for or contributors to the child's difficulties. Ideally, the clinician can obtain information about the child's social and academic functioning from more than one informant who knows the child in different situations, for example, the child's parent and a teacher. Self-report surveys for parents and teachers are widely used to elicit information about specific child's behaviours in the home or school settings, respectively.⁴ In addition, a detailed clinical interview with the parents of younger children, and, for older children, with the child or youth themselves, is essential. Reviewing school reports over several years is also helpful to provide a longitudinal perspective from several teachers. An important aspect of the assessment includes identification of concurrent disorders, including learning and language disorders, as reviewed in the section above. Psychosocial or developmental concerns should also be identified as they may complicate treatment of the ADHD and impact the long-term prognosis.

Chart 1: DSM 5 Criteria for Attention Deficit Hyperactivity Disorder⁵⁷

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by **(1)** and/or **(2)**:

(1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic activities:

Inattention

- a. often fails to give close attention to details or makes careless mistakes
- b. often has difficulty sustaining attention in tasks or play activities
- c. often does not seem to listen when spoken to directly
- d. often does not follow through on instructions and fails to finish schoolwork, chores or duties
- e. often has difficulty organizing tasks and activities
- f. often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
- g. often loses things necessary for tasks or activities
- h. is often easily distracted by extraneous stimuli
- i. is often forgetful in daily activities

(2) six or more of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic activities:

Hyperactivity and Impulsivity

- a. often fidgets with or taps hands or feet or squirms in seat
- b. often leaves seat in situations where remaining seated is expected
- c. often runs about or climbs excessively in situations in which it is inappropriate
- d. often unable to play or engage in leisure activities quietly
- e. is often “on the go”, acting as if “driven by a motor” (unable to be still for extended time)
- f. often talks excessively
- g. often blurts out an answer before a question has been completed
- h. often has difficulty waiting his or her turn
- i. often interrupts or intrudes on others

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (eg, at school and home, in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia, or another psychotic disorder and are not better explained by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

References

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry* 2007;164(6):942-948.
2. Waddell C, Offord DR, Shepherd CA, Hua JM, McEwan K. Child psychiatric epidemiology and Canadian public policy-making: the state of the science and the art of the possible. *Canadian Journal of Psychiatry* 2002;47(9):825-832.
3. American Academy of Pediatrics. Subcommittee on Attention-Deficit/ Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108(4):1033-1044.
4. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2007;46(7):894-921.
5. Bruce B, Kirkland S, Waschbusch D. The relationship between childhood behaviour disorders and unintentional injury events. *Paediatrics & Child Health* 2007;12(9):749-754.
6. Leibson CL, Katusic SK, Barbaresi WJ, Ransom J, O'Brien PC. Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. *JAMA-Journal of the American Medical Association* 2001;285(1):60-66.
7. Brassett-Harknett A, Butler N. Attention-deficit/hyperactivity disorder: an overview of the etiology and a review of the literature relating to the correlates and lifecourse outcomes for men and women. *Clinical Psychology Review* 2007;27(2):188-210.
8. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *Journal of Pediatric Psychology* 2007;32(6):631-642.
9. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry* 1990;29(4):546-557.
10. Biederman J, Faraone S, Milberger S, Guite J, Mick E, Chen L, Mennin D, Marris A, Ouellette C, Moore P, Spencer T, Norman D, Wilens T, Kraus I, Perrin J. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Archives of General Psychiatry* 1996;53(5):437-446.
11. Copeland WE, Miller-Johnson S, Keeler G, Angold A, Costello EJ. Childhood psychiatric disorders and young adult crime: a prospective, population-based study. *American Journal of Psychiatry* 2007;164(11):1668-1675.
12. Klein RG, Mannuzza S, Olazagasti MA, Roizen E, Hutchison JA, Lashua EC, Castellanos FX. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry* 2012;69(12):1295-1303. doi:10.1001/archgenpsychiatry.2012.271
13. Ramos Olazagasti MA, Klein RG, Mannuzza S, Belsky ER, Hutchison JA, Lashua-Shriftman EC, Castellanos FX. Does childhood attention-deficit/hyperactivity disorder predict risk-taking and medical illnesses in adulthood? *Journal of the American Academy of Child and Adolescent Psychiatry* 2013;52(2):153-162.e4. doi:10.1016/j.jaac.2012.11.012

14. Proal E, Reiss PT, Klein RG, Mannuzza S, Gotimer K, Ramos-Olazagasti MA, Lerch JP, He Y, Zijdenbos A, Kelly C, Milham MP, Castellanos FX. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. *Archives of general psychiatry* 2011;68(11):1122-1134. doi:10.1001/archgenpsychiatry.2011.117
15. Howard AL, Strickland NJ, Murray DW, Tamm L, Swanson JM, Hinshaw SP, Arnold LE, Molina B. Progression of impairment in adolescents with attention-deficit/hyperactivity disorder through the transition out of high school: Contributions of parent involvement and college attendance. *Journal of Abnormal Psychology* 2016;125(2):233-247. doi:10.1037/abn0000100
16. Birnbaum HG, Kessler RC, Lowe SW, Secnik K, Greenberg PE, Leong SA, Swensen AR. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. *Current Medical Research & Opinion* 2005;21(2):195-206.
17. Secnik K, Swensen A, Lage MJ. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. *Pharmacoeconomics* 2005;23(1):93-102.
18. Fergusson DM, Boden JM, Horwood LJ. Exposure to single parenthood in childhood and later mental health, educational, economic, and criminal behavior outcomes. *Archives of General Psychiatry* 2007;64(9):1089-1095.
19. St Sauver JL, Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Early life risk factors for attention-deficit/hyperactivity disorder: a population-based cohort study. *Mayo Clinic Proceedings* 2004;79(9):1124-1131.
20. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313-1323.
21. Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Archives of General Psychiatry* 1998;55(8):721-727.
22. Romano E, Tremblay RE, Farhat A, Cote S. Development and prediction of hyperactive symptoms from 2 to 7 years in a population-based sample. *Pediatrics* 2006;117(6):2101-2110.
23. Elgar FJ, Curtis LJ, McGrath PJ, Waschbusch DA, Stewart SH. Antecedent-consequence conditions in maternal mood and child adjustment: a four-year cross-lagged study. *Journal of Clinical Child & Adolescent Psychology* 2003;32(3):362-374.
24. Kohen DE, Brooks-Gunn J, Leventhal T, Hertzman C. Neighborhood income and physical and social disorder in Canada: associations with young children's competencies. *Child Development* 2002;73(6):1844-1860.
25. Brownell MD, Yogendran MS. Attention-deficit hyperactivity disorder in Manitoba children: medical diagnosis and psychostimulant treatment rates. *Canadian Journal of Psychiatry* 2001;46(3):264-272.
26. Jensen PS, Kettle L, Roper MT, Sloan MT, Dulcan MK, Hoven C, Bird HR, Bauermeister JJ, Payne JD. Are stimulants overprescribed? Treatment of ADHD in four U.S. communities. *Journal of the American Academy of Child & Adolescent Psychiatry* 1999;38(7):797-804.
27. Miller AR, Lalonde CE, McGrail KM, Armstrong RW. Prescription of methylphenidate to children and youth, 1990-1996. *CMAJ-Canadian Medical Association Journal* 2001;165(11):1489-1494.
28. Robison LM, Sclar DA, Skaer TL, Galin RS. National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990-1995. *Clinical Pediatrics* 1999;38(4):209-217.
29. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. *Pediatrics* 1996;98(6 Pt 1):1084-1088.
30. Feldman ME, Charach A, Bélanger SA. ADHD in children and youth: Part 2-Treatment. *Paediatrics and Child Health* 2018;23(7):462-472. doi:10.1093/pch/pxy113
31. Fliers E, Vermeulen S, Rijdsdijk F, Altink M, Buschgens C, Rommelse N, Faraone S, Sergeant J, Buitelaar J, Franke B. ADHD and Poor Motor Performance From a Family Genetic Perspective. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009;48(1):25-34.

32. Drabick D, Gadow K, Sprafkin J. Co-occurrence of conduct disorder and depression in a clinic-based sample of boys with ADHD. *Journal of Child Psychology and Psychiatry* 2006;47(8):766-774.
33. Kadesjo B, Gillberg C. The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry* 2001;42(4):487-492.
34. Shreeram S, He JP, Kalaydjian A, Brothers S, Merikangas KR. Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among U.S. children: results from a nationally representative study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009;48(1):35-41.
35. Corkum P, Moldofsky H, Hogg-Johnson S, Humphries T, Tannock R. Sleep problems in children with attention-deficit/hyperactivity disorder: impact of subtype, comorbidity, and stimulant medication. *Journal of the American Academy of Child & Adolescent Psychiatry* 1999;38(10):1285-1293.
36. Owens JA, Maxim R, Nobile C, McGuinn M, Msall M. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine* 2000;154(6):549-555.
37. Biederman J, Milberger S, Faraone SV, Kiely K, Guite J, Mick E, Ablon JS, Warburton R, Reed E, Davis SG. Impact of adversity on functioning and comorbidity in children with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 1995;34(11):1495-1503.
38. Fischer M, Barkley RA, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: II. Academic, attentional, and neuropsychological status. *Journal of Consulting & Clinical Psychology* 1990;58(5):580-588.
39. Fischer M, Barkley RA, Fletcher KE, Smallish L. The adolescent outcome of hyperactive children: predictors of psychiatric, academic, social, and emotional adjustment. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993;32(2):324-332.
40. Fergusson DM, Horwood LJ. Early conduct problems and later life opportunities. *Journal of Child Psychology and Psychiatry* 1998;39(8):1097-1108.
41. Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Klein KL, Price JE, Faraone SV. Psychopathology in females with attention-deficit/hyperactivity disorder: a controlled, five-year prospective study. *Biological Psychiatry* 2006;60(10):1098-1105.
42. Solanto MV, Gilbert SN, Raj A, Zhu J, Pope-Boyd S, Stepak B, Vail L, Newcorn JH. Neurocognitive functioning in AD/HD, predominantly inattentive and combined subtypes. *Journal of Abnormal Child Psychology* 2007;35(5):729-744.
43. Hinshaw SP, Carte ET, Fan C, Jassy JS, Owens EB. Neuropsychological functioning of girls with attention-deficit/hyperactivity disorder followed prospectively into adolescence: evidence for continuing deficits? *Neuropsychology* 2007;21(2):263-273.
44. Thorell LB, Wahlstedt C. Executive functioning deficits in relation to symptoms of ADHD and/or ODD in preschool children. *Infant and Child Development* 2006;15(5):503-518.
45. Loo SK, Humphrey LA, Tapio T, Moilanen IK, McGough JJ, McCracken JT, Yang MH, Dang J, Taanila A, Ebeling H, Jarvelin MR, Smalley SL. Executive functioning among Finnish adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2007;46(12):1594-1604.
46. Barkley RA, Edwards G, Laneri M, Fletcher K, Metevia L. Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). *Journal of Abnormal Child Psychology* 2001;29(6):541-556.
47. Beitchman JH, Brownlie EB, Inglis A, Wild J, Ferguson B, Schachter D, Lancee W, Wilson B, Mathews R. Seven-year follow-up of speech/language impaired and control children: psychiatric outcome. *Journal of Child Psychology and Psychiatry* 1996;37(8):961-970.
48. Clark C, Prior M, Kinsella G. The relationship between executive function abilities, adaptive behaviour, and academic achievement in children with externalising behaviour problems. *Journal of Child Psychology and Psychiatry* 2002;43(6):785-

796.

49. Calhoun SL, Dickerson Mayes S. Processing speed in children with clinical disorders. *Psychology in the Schools* 2005; 42(4):333-343.
50. Rabiner D, Coie JD, Conduct Problems Prevention Research Group. Early attention problems and children's reading achievement: a longitudinal investigation. *Journal of the American Academy of Child & Adolescent Psychiatry* 2000;39(7):859-867.
51. Cohen NJ, Davine M, Horodezky N, Lipsett L, Isaacson L. Unsuspected language impairment in psychiatrically disturbed children: prevalence and language and behavioral characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993;32(3):595-603.
52. Cunningham CE, Boyle MH. Preschoolers at risk for attention-deficit hyperactivity disorder and oppositional defiant disorder: family, parenting, and behavioral correlates. *Journal of Abnormal Child Psychology* 2002;30(6):555-569.
53. Keown LJ, Woodward LJ. Early parent-child relations and family functioning of preschool boys with pervasive hyperactivity. *Journal of Abnormal Child Psychology* 2002;30(6):541-553.
54. Greenhill LL, Posner K, Vaughan BS, Kratochvil CJ. Attention deficit hyperactivity disorder in preschool children. *Child & Adolescent Psychiatric Clinics of North America* 2008;17(2):347-366.
55. Charach A, Carson P, Fox S, Ali M, Beckett J, Lim CG. Interventions for preschool children at high risk for ADHD: A comparative effectiveness review. *Pediatrics* 2013;131(5):e1584-606
56. 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(1):3-19. doi:10.1002/wps.20611
57. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington D.C.: 2013.

ADHD and Treatment

¹Meghan Miller, PhD, ²Stephen P. Hinshaw, PhD

¹University of California, Davis, USA

²University of California, Berkeley and University of California, San Francisco, USA

September 2019, Éd. rév.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neurodevelopmental disorder that originates in childhood and tends to persist across the lifespan. ADHD is strongly heritable, affects approximately 5-8% of young persons, and occurs more commonly in males than females. As described in the Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition,¹ ADHD consists of symptoms that are developmentally extreme, highly impairing and cross-situationally displayed. Such symptoms fall into two categories: (a) inattention-disorganization and (b) hyperactivity-impulsivity. Individuals who display significant symptoms of inattention-disorganization (but not hyperactivity-impulsivity) are considered to have the Inattentive Presentation; those who display significant symptoms of hyperactivity-impulsivity (but not inattention) are categorized in Hyperactive-Impulsive Presentation. The most common clinical presentation of ADHD is the Combined Presentation, in which the individual displays significant symptoms from both symptom domains. Current evidence-based interventions for ADHD consist of psychotropic medications and behaviour therapy.^{2,3,4,5}

Subject

Determining the most effective intervention strategies for ADHD is highly relevant. It is critically important to determine which components of evidence-based treatments are most effective (including evaluation strategies for making this determination), to identify how treatment strategies can optimally be combined, to determine ways in which to individualize treatments in order to achieve optimal results, to establish the best means of promoting generalization and maintenance of treatment gains, and to determine the factors that contribute to ideal treatment outcomes.

Problems

Years of intervention research have identified and honed evidence-based treatments for ADHD, including behavioural interventions and medication treatment. Yet such treatments, although evidence-based, are not curative and do not result in significant improvements for all who are treated. Additionally, effects of current evidence-based treatments are not generally long-term and tend not to generalize across settings.

Research Context

The voluminous research on risk factors, correlates, long-term outcomes and underlying processes related to ADHD has still not been fully translated into mechanism-specific interventions. Still, a number of well-controlled single-case reports and randomized, controlled clinical trials attest to the viability of behaviour therapy and medication interventions for ADHD.

Key Research Questions

A key research question involves evaluating the effectiveness of interventions for ADHD, including behavioural, medication and combined behavioural-medication interventions. Additional critical research issues focus on identifying factors that explain how and how well treatments work, and for whom.⁶ Such factors may include sex, ADHD subtype, developmental level, comorbidity, parental factors, medication dosage, cognitive changes, and family discipline styles.^{6,7,8,9,10}

Recent Research Results

Current evidence-based treatments for ADHD include medication and behavioural interventions. Medication treatments for ADHD typically consist of psychostimulants, although other types are often concurrently prescribed in order to address comorbid disorders. Psychostimulants used to address ADHD symptoms include methylphenidate, dextroamphetamine, and mixed amphetamine salts, which all enhance the transmission of dopamine. Atomoxetine, a norepinephrine reuptake inhibitor, has also been found to be effective. Both dopamine and norepinephrine are neurotransmitters (messengers in the brain) that are involved in many mental processes. Whereas such medications have been shown to reduce ADHD-related symptoms and functional impairments across settings,⁴ effects tend to last only as long as the medication is active within the body and brain.

As a result, and to promote active skill-building, non-medication treatments are often recommended as well. Behaviour therapy is the only consistently evidence-based intervention for

childhood ADHD aside from medication. Behavioural treatments typically involve interventions with parents, teachers, and the child.^{2,11} Specific components of behavioural interventions for ADHD include direct contingency management and clinical behaviour therapy. Direct contingency management consists of teachers or counselors directly rewarding target skills and employing effective consequences when problems arise. More commonly-used clinical behaviour therapy procedures involve (1) parent training on topics including behaviour management (e.g., positive parental attention, rewards for appropriate behaviour, negative consequences for misbehaviour) and (2) teacher training on topics such as use of prompts and rewards in the classroom. Across most relevant investigations, the greatest likelihood of symptom reduction occurs when medication and behavioural treatments are combined, particularly with respect to functional outcomes.^{12,13,14}

Although evidence-based interventions for ADHD have been identified, few randomized controlled trials have focused on identifying specific individual factors that influence treatment outcome. Key factors emerging from the Multimodal Treatment of children with ADHD (MTA) Study included the presence of a comorbid anxiety disorder, family public assistance, ethnicity/race, severity of ADHD, parental depressive symptomatology, child IQ, attendance, medication use in the community and negative/ineffective parental discipline.⁶

Finally, cognitive enhancements of contingency-based interventions (e.g., social skills training with parent training) as well as cognitive training to ameliorate neuropsychological deficits commonly associated with ADHD (i.e., executive function deficits, which include difficulties planning, staying organized, inhibiting inappropriate responses, setting and carrying out goals) may be viable but evidence is currently limited. A critical issue with the current evidence-based behavioural interventions for ADHD – including combination treatments of medication and behavioural interventions – is that treatment gains often are not maintained over periods of time, nor are gains generalized across settings.³

Research Gaps

A major issue with current evidence-based treatments for ADHD concerns generalization.¹⁶ Specifically, individuals with ADHD tend not to translate gains obtained in one setting to other key life settings. Thus, future treatment development efforts should focus on determining components of interventions that promote long-lasting maintenance of treatment gains across settings. An additional issue involves developing treatments that can address functional impairments that

often accompany ADHD (e.g., social difficulties, academic struggles, organizational skills deficits). Successful interventions in these domains may have significant long-term effects, with the potential for contributing to the elusive goal of maintaining gains. Finally, a critical gap in the literature pertains to early, preventive interventions. Such interventions, if successful, could alter the trajectory of ADHD from the start, preventing later problems. Although this approach is being used in other neurodevelopmental disorders (e.g., autism spectrum disorder), such methodology has rarely been used in the study of ADHD.¹⁷ One key problem relates to false-positives: how many preschool-aged children at risk for ADHD will actually proceed to the full disorder?

Conclusions

ADHD is a common and impairing neurodevelopmental disorder that requires intensive intervention. Much research has focused on identifying evidence-based interventions for ADHD. Current evidence-based treatment options include behavioural interventions and medication treatment. Medication treatment provides the greatest reduction of core ADHD symptoms (inattention, hyperactivity-impulsivity) whereas evidence exists that the combination of medication and behavioural interventions results in the greatest improvement in associated impairments (e.g., parent-child relations, academic problems, anxiety). Although these treatment options are useful for decreasing core symptomatology, they do not appear to remediate core deficits related to ADHD, and they tend not to produce long-term, generalized gains. It will be essential to promote translational research linking biological and contextual risk factors to development of improved treatment strategies. Important areas for future research include identifying specific factors that influence treatment outcome, developing of interventions that produce effects that can be generalized and maintained over time, determining ways to address the functional impairments commonly present in individuals with ADHD, and ascertainment of the potential benefits of preventive measures.

Implications for Parents, Services and Policy

Professional organizations (e.g., American Association of Child and Adolescent Psychiatry and American Academy of Pediatrics)^{18,19} have published assessment and treatment guidelines for ADHD, but there is little or no enforcement of such professional guides, nor is it clear that reimbursement always or even usually covers such standards. Families need to be aware of the need for relevant health professionals to have demonstrated expertise in ADHD and its common comorbidities and impairments; policy-makers need to assure adequate assessment and

treatment standards. Furthermore, large regional variation in rates of diagnosis and treatment of ADHD exists within the U.S.²⁰ and internationally.²¹ Policy-related factors such as high-stakes achievement testing, training of professionals, insurance coverage, and advertisements for treatment (particularly medication) may all be relevant regarding this wide variation. Overall, knowledge of ADHD, reduction of stigma regarding its identification and treatment, enlightened policies that provide for evidence-based services, and proper means of assessing treatment-related gains are essential goals if youth and their families are to receive optimal services.²²

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: Author; 2013.
2. Piffner LJ, Haack LM. Nonpharmacologic treatments for childhood ADHD and their combination with medication. In: Nathan PE, Gorman JM, eds. A guide to treatments that work, 4th ed. New York: Oxford University Press; 2015:55-84.
3. Miller M, Hinshaw SP. Treatment for children and adolescents with ADHD. In: Kendall PC, ed. Child and Adolescent Therapy, 4th Edition: Cognitive-Behavioral Procedures. New York: Guilford Press; 2011:61-91.
4. Kass E, Posner J, Greenhill LL. Pharmacological treatments for attention-deficit/ hyperactivity disorder and disruptive behavior disorders. In: Nathan PE, Gorman JM, eds. A guide to treatments that work, 4th ed. New York: Oxford University Press; 2015:85-140.
5. Evans SW, Hoza B, eds. Treating attention deficit hyperactivity disorder: Assessment and intervention in developmental context. Kingston, NJ: Civic Research Institute; 2011.
6. Hinshaw SP. Moderators and mediators of treatment outcome for youth with ADHD: Understanding for whom and how interventions work. *Journal of Pediatric Psychology*. 2007;32(6):664-675.
7. Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Abikoff HB, Conners CK, et al. ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(2):147-158.
8. MTA Cooperative Group. Moderators and mediators of treatment response for children with ADHD: The MTA Study. *Archives of General Psychiatry*. 1999;56(12):1088-1096.
9. Owens EB, Hinshaw SP, Kraemer HC, Arnold LE, Abikoff HB, Cantwell DP, et al. Which treatment for whom for ADHD? Moderators of treatment response in the MTA. *Journal of Consulting and Clinical Psychology*. 2003;71(3):540-552.
10. Kazdin AE, Weisz JR. Identifying and developing empirically supported child and adolescent treatments. *Journal of Consulting and Clinical Psychology*. 1998;66(1):19-36.
11. Evans SW, Owens JS, Wymbs BT, Ray AR. Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child & Adolescent Psychology*. 2018;47(2):157-198.
12. Conners CK, Epstein JN, March JS, Angold A, Wells KC, Klaric J, et al. Multimodal treatment of ADHD in the MTA: An alternative outcome analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(2):159-167.
13. Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, et al. Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(2):168-179.
14. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 1999;56(12):1073-1086.

15. Hinshaw SP, Owens EB, Wells KC, Kraemer HC, Abikoff HB, Arnold LE, et al. Family processes and treatment outcome in the MTA: Negative/ineffective parenting practices in relation to multimodal treatment. *Journal of Abnormal Child Psychology*. 2000;28:555-568.
16. Abikoff H. ADHD psychosocial treatments: Generalization reconsidered. *Journal of Attention Disorders*. 2009;13(3):207-210.
17. Sonuga-Barke EJS, Halperin JM. Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: Potential targets for early intervention? *Journal of Child Psychology and Psychiatry*. 2010;51(4):368-389.
18. American Association of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007;46(7):894-921.
19. American Academy of Pediatrics. ADHD: Clinical practice guidelines for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1022.
20. Fulton BD, Scheffler RM, Hinshaw SP, Levine P, Stone S, Brown TT, et al. National variation of ADHD diagnostic prevalence and medication use: Health care providers and educational policies. *Psychiatric Services*. 2009;60(8):1075-1083.
21. Hinshaw SP, Scheffler RM, Fulton BD, Aase H, Banaschewski T, Cheng W, et al. International variation in treatment procedures for ADHD: Social contexts and recent trends. *Psychiatric Services*. 2011;62(5):459-464.
22. Hinshaw SP. Attention deficit-hyperactivity disorder (ADHD): Controversy, developmental mechanisms, and multiple levels of analysis. *Annual Review of Clinical Psychology*. 2018;14:291-316.