ENCYCLOPEDIA
on Early Childhood
Development

Hyperactivity and inattention (ADHD)

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Synthesis

How important is it?

Attention-Deficit/Hyperactivity disorder (ADHD) is a neuropsychiatric disorder defined by developmentally atypical, persistent and impairing restlessness, impulsiveness and inattentiveness starting from an early age. ADHD can be broken down into three subtypes based on the type of behaviours that are most prominent: 1) the inattentive type; 2) the hyperactive-impulsive type; and 3) the combined type depending on the nature of the symptoms. 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 outside of the home. ADHD is estimated to affect 3 to 7% of school-age children worldwide, and boys show higher rates of ADHD than girls. ADHD tends to co-occur with other psychiatric or developmental disorders (e.g., anxiety, mood disorder, learning or language disabilities, conduct disorder and sleep difficulties) in 50 to 66% of cases. ADHD persists into adulthood in more than half of affected individuals. ADHD symptoms and its concurrent disorders interfere with academic and behavioural functioning at school and so children have lower rates of high school completion. They are also more likely to experience employment difficulties as they grow older. Other negative consequences relating to ADHD include difficult interpersonal relationships and higher prevalence of accidental injuries, driving accidents and teen pregnancy. 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%), yet the nature of the genetic influence is still unknown. Results from published studies indicate that ADHD shares genetic influences with other conditions so, for example, one finds shared genetic influences between inattentive symptoms and dyslexia, hyperactive-impulsive symptoms and oppositional problems, and ADHD with symptoms of autism. Furthermore, genes responsible for cell division, cell adhesion, and neuronal migration are thought to be related to the onset of ADHD. 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

Stimulant medication (such as methylphenidate, 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 become available and play an important role in treatment. 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. Direct training of cognitive functions such as working memory (that ability to hold and manipulate information in short-term memory) has shown promise as a potentially effective intervention. Some children may show improved behaviour upon removal of certain foods from their diet although the generality of this effect is not known and training of the brains electrical activities may improve alertness and behaviour in some children. That said a major issue with these treatments pertains to the generalization of improvements 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

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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 network[13] and the cingulo-opercular network[14] 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 ratio[16] 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 cases[26] 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]

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Attention Deficit Hyperactivity Disorder and Cognition

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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 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 familiality 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 familially 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.

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ADHD and Genetics

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood onset disorder that frequently persists into adulthood and is associated with the development of cognitive and functional deficits and comorbid disorders. The disorder tends to run in families and numerous twin studies find that ADHD is highly heritable, indicating the predominance of genetic influences in the aetiology of the disorder. While such studies do not exclude the importance of environmental factors they suggest that in most cases these interact with genetic factors; although exceptional environments such as severe early deprivation,[1] or exceptional genetic risk factors such as rare *copy number variants*[2] may exert large effects on disease risk in some cases. The nature of the genetic influences on ADHD is largely unknown although it is thought that this largely results from additive and interactive effects of common genetic variation.

Subject

Genetic studies of ADHD are relevant in two main ways. First, quantitative genetic studies enable the investigation of the extent of genetic effects on ADHD and the extent to which these are shared with associated cognitive impairments, brain function deficits and comorbid disorders and traits. Second, molecular genetic studies enable the identification of the specific risk factors involved, enabling a detailed understanding of the underlying molecular and neurobiological mechanisms involved.

Key Research Questions

What are the genetic influences on ADHD and the mechanisms that mediate genetic effects on behaviour? How do genetic and environmental factors interact in the aetiology of ADHD and associated behavioural and cognitive traits?

Recent Research Results

Family and twin studies delineate a disorder that tends to run in families with a risk to first degree relatives in the order of five- to tenfold the population rate.[3,4] The proportion of phenotypic variance explained by genetic factors (heritability) averages around 76%.[5] The analysis of population twin and ADHD *proband-sibling* samples suggest that genetics influence levels of ADHD throughout the population and that ADHD is best perceived as the extreme of one or more continuously-distributed traits.[3] The two symptom domains of ADHD – inattention and hyperactivity-impulsivity – share most but not all their genetic influences, suggesting that unique as well as common genetic and neurobiological processes are involved.[6] Further studies have investigated the degree to which genetic influences are shared between ADHD and associated disorders and traits. These find that ADHD, particularly inattentive symptoms, share genetic influences with dyslexia;[7] hyperactive-impulsive symptoms with oppositional problems;[8] and ADHD with symptoms of autism spectrum disorder.[9] These are thought to be *pleiotropic* effects of genes that are expressed in more than one clinical disorder.

More recently the overlap of familial effects on ADHD and cognitive performance deficits identified two familial cognitive factors.[10] The larger factor, reflecting 85% of the familial variance of ADHD, captured all familial influences on mean reaction time and reaction time variability on a speeded reaction time task; while a second smaller factor, reflecting 12.5% of the familial variance of ADHD, captured all familial influences on omission errors and 60% on commission errors on a *go/no-go task*. Moreover, the cognitive factors were found to be independent of shared genetic effects between ADHD and IQ.[11] These two cognitive performance factors therefore seem to index most of the familial influences on ADHD and are thought to result primarily from genetic factors. As such, further work is now needed to delineate the genetic factors that underlie these two familial cognitive factors and the neurobiological processes involved, and to clarify whether these mediate the genetic effects on behaviour or whether they represent pleiotropic effects.

Molecular genetic studies on ADHD started with candidate gene association studies in the mid-1990s, with the first two reported associations between genetic variants in the *dopamine D4 receptor* (DRD4) and dopamine transporter (DAT1) genes. Subsequently, association was reported with a microsatellite marker near to the dopamine D5 receptor gene (DRD5). Since then there have been numerous replication studies with only a few independent replications, however meta-analysis of available data reported strong evidence for the association with DRD4 and DRD5 that reached genome-wide levels of significance in the study of Li and colleagues.[12] Evidence for the association with DAT1 has been far less consistent, with generally only weak evidence of

association,[12] although there are several potential sources of heterogeneity that might account for this, including: specific association with ADHD that is not comorbid with conduct disorder,[13] association with specific haplotypes (correlated sequences of correlated genetic variation),[14,15] and the interaction with environmental measures such as maternal smoking during pregnancy.[16-18] These candidate gene findings are important because they were the first direct evidence that genes regulating neurotransmission, particularly dopamine regulation, are involved directly in risk for ADHD; and confirmed a priori hypotheses derived from the immediate and marked effects of stimulants on ADHD symptoms that are thought to relate to the effects of stimulants on dopamine availability at neuronal synapses.

There have been numerous other candidate gene studies focusing mainly on the *dopamine*, *serotonin* and *noradrenalin* systems. These were recently reviewed by Gizer and colleagues[19] who reported significant association following meta-analysis for several genes (DRD4, DAT1, DRD5, DBH, ADRA2A, 5HTT, TPH2, MAOA, and SNAP25). Previous research had estimated the overall impact of the most replicated gene findings and found that around 3.3% of the variance was explained by the additive effects of these genes; accounting for only 4.3% of the estimated heritability of ADHD of 76%.[20] Additional work is clearly needed to explain the rest of the genetic influences on ADHD.

Further studies have taken advantage of *single nucleotide polymorphism (SNP) arrays* that enable genotyping of genetically informative markers across the entire human genome. Depending on the density of the arrays these may account for 80% or more of common genetic variation. In ADHD, genome-wide association studies (GWAS) have yet to establish confirmed novel associations, since no individual SNP has yet to reach genome-wide levels of significance. The problem is that conventional levels of significance in the region of .05 to .001 would be found by chance with SNPs throughout the genome, due the very large number independent haplotypes (correlated sequences of correlated genetic variation) across the genome. As a result, higher levels of significance, in the region of 5×10^{-8}, are recommended to adjust for the low prior odds of association.[21] This has meant that for most common complex disorders, 12,000 or more samples are needed to reliably identify a few associated SNPs, since in nearly all cases only small genetic risks have been identified for specific risk *alleles* with odds ratios in the region of 1.1 – 1.4 or less. The first GWAS study of ADHD investigated 438,784 SNPs in 958 combined type ADHD proband-parent trios. No genes of moderate to large effect were identified[22] and no findings passed genome-wide levels of significance. However, when a set of 51 candidate genes was investigated,

there was significant group evidence for association from the selected SNPs, implicating mainly dopamine, noradrenalin and serotonin neurotransmitter genes. Similar findings were subsequently reported in a study that combined genome-wide association data from several studies.

Of particular interest is the Cadherin gene (CDH13), which has been found to be associated with ADHD in more than one GWAS study and lies within the only region that reached genome-wide significance in a meta-analysis of linkage studies of ADHD.[23-25] This finding and other hints from GWAS indicate that genes involved in cell division, cell adhesion, neuronal migration and neuronal plasticity may also confer risk for ADHD.[26]

Overall there is a long way to go to delineate the specific genetic factors that explain the high heritability of the disorder. This is, however, a common phenomenon in common disorders research and several potential explanations for the so called ‘dark-matter’ of heritability has been put forward. Potential reasons include numerous genes of very small effect, genetic heterogeneity with risk conferred by many different genes and variants within genes, higher order interactions between genes and with environment and aetiological heterogeneity. In addition, we do not yet understand the contribution made to ADHD from rare copy number variants (CNVs) or other types of rare genetic variation; although recent data suggest that in a few cases CNVs may be the main cause of the disorder.[2]

Finally, the focus of much of the genetic research has moved to the identification of intermediate phenotypes, measures of neurobiological function that mediate genetic effects on ADHD and may be more proximal to gene function. For example there is evidence from a few *fMRI* studies for greater effect sizes from specific genetic variants.[27,28] Were this also to be the case for cognitive variables sharing genetic effects with ADHD it might be possible to identify genetic variants associated with ADHD following genetic investigations of the intermediate phenotypes. As mentioned genetic influences on ADHD appear to be indexed mainly by two familial cognitive factors measured by poor performance leading to slow and variable reaction times and an increase in commission and omission errors on cognitive performance tasks,[10] so that intermediate phenotype could usefully focus on the processes that underlie these cognitive performance impairments in ADHD.

Interestingly, the most replicated genetic association with cognitive performance measures in ADHD is an inverse association between cognitive function and ADHD risk allele from DRD4. Among children with ADHD the high risk 7-repeat allele for ADHD is associated with less cognitive

impairment that those carrying non-risk alleles.[29] This unexpected finding has also been found with the gene ZNF804A and schizophrenia,[30] suggesting that this may be a common finding in neuropsychiatric disorders. These findings suggest that cognitive performance may indicate important sources of heterogeneity with the cognitively less impaired group indicating a discrete molecular pathogenesis.

Research Gaps

Further work is needed to identify both common and rare genetic variants that account for the heritability of ADHD; using very large samples and future whole genome sequencing technologies. Neurobiological research needs to focus on measures that are genetically correlated with ADHD and use genetic association data to determine the nature of the cognitive, neuronal and cellular processes that mediate genetic risks on behaviour. Genetic studies of ADHD in adults are only just beginning, but it is expected that some genetic factors will influence risk for persistence and remission of the disorder during the transitional years from childhood to adulthood. Finally, further work is needed to identify environmental risks that act in an additive or interactive way with genetic risks for ADHD.

Conclusions

ADHD is a highly heritable disorder that starts in childhood and often persists into adulthood. Quantitative genetic studies help us to understand the aetiological links between ADHD and co-occurring disorders and traits; and the cognitive processes that mediate genetic effects on behaviour. Further work is needed to understand the processes that underlie the associated cognitive performance deficits such as reaction time and errors performance deficits. Dopamine system genes have been implicated in the aetiology of ADHD, particularly the DRD4 and DRD5 genes, and there is evidence from GWAS studies that other genes regulating neurotransmission and neurodevelopment, such as SNAP-25 and CDH13, are involved. Recent studies have identified rare copy number variants as a major risk for ADHD, but these only appear to affect a few cases. Further work is needed to explain the ‘dark matter’ of heritability which is yet to be explained by the genetic variants associated with ADHD to date.

Implications

Family, twin and adoption studies have had a major influence on the way that we perceive ADHD, and this in turn has influenced clinical decision making. We know that the disorder is largely

inherited and that the genetic influences account for stability of ADHD over time. Furthermore genetic studies have helped our understanding of the development of comorbid disorders. Future work will use genetic data to identify aetiologically distinct sub-groups with the aim of improving the prediction of clinical outcome and developing novel targeted intervention strategies to treat the disorder and prevent its progression into adulthood. These are critical strategies because of the very high personal and societal costs of ADHD, including education and employment problems, high accident rates and risk for the development of anxiety, depression, drug and alcohol addiction and antisocial behaviour.

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

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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 themself, 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 Disorder[57]

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).

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ADHD and Treatment

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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]

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