

ADHD: A true neurodevelopmental disorder?

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders. First described in 1798 by Alexander Crichton, ADHD became widely known outside the medical profession with the publication of the story of Fidgety Phil ('Zappelphilipp') in Heinrich Hoffman's book 'Struwwelpeter' in 1846. Since then, scientists and clinicians have been struggling to understand its causes. To date, there is neither a genetic test nor a brain scan to diagnose ADHD due to the fact that it is a heterogeneous collection of behaviours that appear to have different causes and symptoms. In view of the lack of an objective diagnostic method, the major difficulty that specialists face is to decide where to set the threshold between behaviours and states of mind that require medication or behavioural treatment and differences that can be left alone. The increased rate in diagnosis and stimulant use in ADHD recently raises several issues, notably, are we setting lower diagnostic thresholds because of societies' intolerance of behaviours and impairments associated with ADHD? This article discusses some of the controversies in ADHD diagnosis and treatment, including many medical, social, and ethical aspects.

Keywords: Attention deficit hyperactivity disorder, ADHD, Impulsivity, Stimulant, Methylphenidate, Atomoxetine

Attention-deficit/hyperactivity disorder (ADHD) is a highly disruptive childhood-onset disorder, characterized by inappropriate hyperactivity, inattention, and impulsivity that onsets before the age of seven and often persists into adolescence and adulthood.^{1,2} It is the most common neurodevelopmental disorder of childhood, estimated to affect

1.4–6% of school children, and probably the most controversial.³

The major clinical features are severe impulsiveness, lack of concentration, and motor hyperactivity, observed in at least two distinct settings, for example, home, school, and social settings. ADHD is often accompanied by other psychiatric and developmental disorders, including learning impairments, oppositional defiant disorder, conduct disorder, autism, and dyslexia.¹ These impairing symptoms put children at risk of education failure and can severely disrupt family, teacher, and peer relationships.

From a public health perspective, the cost of ADHD is significant in terms of academic underachievement, later unemployment, and often comorbid substance abuse and antisocial behaviour.⁴ In England and Wales, children with ADHD place a significant cost on health, social, and education services, reaching £23 million for initial specialist assessment and £14 million annually for follow-up care. In 2006, the total annual cost of prescribed stimulants and other drugs for ADHD in England was roughly £29 million.⁵ And the costs keep rising....

Molecular genetics of ADHD

Given the impact of ADHD on society as a whole and particularly on children's quality of life, it is imperative to understand the aetiology and pathophysiology of this disorder. At present, little is known about either the causes or the mechanisms of ADHD, but family, twin, and adoption studies provided strong evidence that ADHD is hereditary.^{1,6} Twin studies showed that disease concordance was much higher in identical twins compared to non-identical twins, with 60–90% of the phenotypic variance being explained by inherited factors. There is evidence for shared inherited

factors with a wide range of psychiatric disorders. Another interesting aspect is that ADHD prevalence is higher in males than in females, but at present a genetic explanation for this phenomenon is lacking.¹

Interestingly, the high-heritability estimates are similar to those found in other psychiatric disorders such as schizophrenia and autism. As with these disorders, genetic effects are not 100%, indicating additional contribution from non-shared environmental factors, epigenetic effects, random events, or measurement inaccuracies. ADHD, like other common medical and psychiatric disorders, is considered a complex genetic trait, influenced by multiple genes, non-inherited factors, and the interaction between them.

With this high heritability, much effort has been, and still is being, directed towards searching for specific susceptibility genes. The search has consisted of identifying common DNA variation. Whole-genome linkage studies were not able to point to regions harbouring susceptibility genes, probably reflecting the fact that there are no common susceptibility genes of large effect sizes for ADHD.

Candidate gene association studies have been more promising, and a small number have been shown to consistently withstand replication and meta-analysis, including genes involved in the dopaminergic pathway, long hypothesized to be involved in ADHD; the 7-repeat allele of the D4 dopamine receptor gene (*DRD4*), a microsatellite repeat in the D5 dopamine receptor gene (*DRD5*), and a 480 bp variable number tandem repeat in the dopamine transporter gene, *DAT1*.¹ There is considerable sample heterogeneity reported for the *DAT1* allele, which could be the result of multiple polymorphisms in this gene. There is also evidence that the gene encoding a protein responsible for the degradation of dopamine (*COMT*) could have a modifying effect on the ADHD phenotype (reviewed by Thapar *et al.*⁷).

Genome-wide association studies are still at an early stage for ADHD and have provided some interesting genes to investigate further. However, all association studies have failed to find a common gene variant and have not provided support for previous candidate genes. This is probably a reflection of the extremely large sample sizes required for the small effect size expected and sample heterogeneity. Another possibility is that disorders such as ADHD may be better explained by the effect of rare genetic variants, for example, rare copy number variants (CNVs). CNVs are part of the normal variation of the human genome and are DNA segments of 1 Kb or

greater that vary in number when the genomes of different individuals are compared. They can be copy number gains (insertions and duplications) or subtractions (deletions) when compared to the control genome. Large and rare CNVs have been associated with neurodevelopmental disorders such as schizophrenia and autism.^{8,9} A UK study analysing rare CNVs and ADHD found a significantly increased rate in ADHD cases compared to controls and also reported an overlap of CNVs found in ADHD with both schizophrenia and autism, further supporting ADHD as a neurodevelopmental disorder.^{10,11}

Molecular genetic studies at best account for less than 5% of the estimated heritability in ADHD symptoms due in a large part to the heterogeneity of the clinical phenotype and the genetic architecture. Thus, future directions include finding ways of dividing subjects into more homogenous subgroups for use in genetic studies¹² and using intermediate phenotypes or endophenotypes. Endophenotypes are stable, heritable measurements that are closer to the biological aetiology of a disorder (e.g. the gene) than the clinical diagnosis itself. Examples of endophenotypes that measure simpler traits, likely to be influenced by a smaller number of genes, are magnetic resonance (MR)-based measured effects on brain structure.¹³ Importantly, some MR imaging studies provide evidence for differences in brain structure and/or function that may facilitate linkage studies as well as provide neurobiological mechanisms for how gene variants impact on the brain.^{14,15}

Environmental impact on ADHD

There are a number of environmental risk factors that have been associated with ADHD. Major associations have been seen with maternal-related prenatal risk (alcohol, smoking, drug use, stress in pregnancy), pregnancy and birth complications, including prematurity and low birth weight, and environmental exposures, including toxins (pesticides, polychlorinated biphenyl, and lead) and some virus infections. At present, although some studies have found positive association with an agent and ADHD, for example, an association between low-level prenatal organochlorine exposure and ADHD-like behaviours in childhood,¹⁶ no firm conclusions can yet be made for a link to ADHD behaviour outcome, with the exception of extreme situations including extreme prematurity, very low birth weight, and foetal alcohol syndrome. Similarly, despite many studies of diet and ADHD symptoms, there is no evidence yet to show that

diet plays a causal role, although some nutritional changes may help relieve some symptoms in children diagnosed with ADHD (see below). Adverse social and family environments have also been associated with ADHD, but none so far have been found to be causal, with the exception of children exposed to extreme early deprivation: the Romanian orphans who were studied after their adoption in the UK and were found to have a deprivation specific ADHD-like behaviour (reviewed by Thapar *et al.*⁷). Surprisingly, a study of television and video game use (whether total time spent or exposure to violent content) did not predict attention problems or influence school grades.¹⁷

No gene, no real disease?

At present, there is no single cause of ADHD, and identified risk factors are non-specific, as most of those found appear to affect a range of different neurodevelopmental and psychiatric phenotypes. The lack of common susceptibility genes/loci and the difficulties in a clear-cut diagnosis have led to debate in the scientific and medical community about ADHD aetiology, including a view from Szasz, who has argued that ADHD was ‘invented (by psychiatrists to give a medical explanation for antisocial human traits) and not discovered (behavioural interpretations do not represent a disease)’.¹⁸

Some believe that ADHD is selected for in evolution, for example, Hartmann, who developed the hunter-farmer theory of ADHD.¹⁹ Building on this, Jensen regards ADHD as a ‘disorder of adaptation’ and suggests that ‘many emotional and behavioural responses (particularly if relatively commonplace

within a given species) may not just be ‘symptoms’ of disorders, but they might instead reflect adaptive responses of the organism to environmental demands’.²⁰ Gallagher goes even further to suggest that ADHD may have evolved because it increases creativity and inventiveness of the population and that ‘if ADHD genes are selected for because they foster creativity, then ADHD is not a neurological ‘defect’, but rather a variant temperament (albeit one which may require intervention)’.²¹

Eisenberg provides evidence for the selection of an associated ADHD variant from a study of Ariaal men of northern Kenya, where the ADHD-associated allele of the *DRD4* gene promotes behavioural/psychological traits that are helpful in some social and ecological contexts, but detrimental in others.²² Williams and Taylor²³ conclude from a study using a neuropsychological test (simulations of the changing food group task) that ‘even individually impairing combinations of genes, such as those that may cause ADHD, can carry specific benefits for society, which can be selected for at that level, rather than being merely genetic coincidences with effects confined to the individual’.

Adherents of another theory, the social construct theory, believe that society has created ADHD by its specific demands on children and its perception of an individual group (see debate Timimi vs. Taylor),²⁴ and the neurodiversity theory proposes that ADHD is a normal human difference to be tolerated and respected as any other human difference.³ Other critics interpret ADHD as being the consequence of disturbances in the relationship between the primary attachment figure (usually the mother) and child, a view held by some



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psychoanalysts particularly in Germany, which usually leads to hot debates at congresses.

Diagnosis

ADHD is usually diagnosed using the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV), which defines three general subtypes:^{25,26}

1. Predominantly hyperactive-impulsive: a child who is excessively fidgety and restless, seems to always be ‘on the go’, and has difficulty waiting and remaining seated, acts immaturely, may not set physical boundaries, and may exhibit destructive behaviours.
2. Predominantly inattentive: a child who is easily distracted, forgetful, manifests day-dreaming, disorganization, poor concentration, and difficulty completing tasks.
3. Combined type.

However, there is mounting evidence that the ADHD/inattentive and ADHD/combined subtypes are separable disorders with different underlying pathology.²⁷⁻²⁹

The DSM-IV diagnostic criteria consist of two dimensions: symptoms and impairment, each with subtype-specific descriptions. Not only is a distinction between symptom and impairment often unclear,³⁰ but so is a symptom-based rating problematic due to the subjectiveness of judgements of what is ‘normal’ and ‘abnormal’ behaviour. Similarly, impairment is ambiguous and depends on the individual challenges and demands that patients face in daily life. Hence, assessment of behavioural characteristics is subjective and may be interpreted differently by different observers and in different cultures.^{26,31} According to Rousseau *et al.*,³¹ the literature does not provide a definite answer about the DSM-IV cultural validity in child psychiatry. On the one hand, it suggests that all diagnostic categories may be found universally. On the other, variations in prevalence rates support the hypothesis of a role for social and cultural factors in the diagnostic process, that is, the existence of diagnostic criteria biases. For instance, ADHD prevalence is higher in North America than in Europe, where the International Classification of Diseases – 10th Edition (ICD-10) diagnosis of ‘hyperkinetic disorder’ is more commonly used. In fact, diagnostic criteria of ADHD in DSM-IV and ICD-10 are heterogeneous, and a positive ADHD diagnosis is three to four times more likely with DSM-IV than with ICD-10.³²

ADHD often coexists with other conditions, and this makes its diagnosis more difficult. As many as one-third of children with ADHD have one or more co-morbidities, of which learning disabilities, oppositional defiant disorder, conduct disorder, anxiety, tics, and depressive disorders are the most common.^{26,33} Most of these disorders share common features, e.g. similarity in symptoms or age at onset. There are currently no biomarkers of ADHD that could help diagnosis and assessment of treatment efficacy. Nevertheless, it is important to recognize the limitations of the DSM-IV definitions by adding more objective means of assessment to the diagnostic process.²⁶ Berger²⁶ has pointed to the need to verify the DSM-IV diagnostic criteria of ADHD in a more specific way, which will take into account gender, cultural bias, and developmental variations.

Some rating scales have been developed to specifically assist diagnosis, score symptom severity, and rate improvements in various domains during intervention, both in primary care and clinical trial settings. The most widely used are: ADHD Rating Scale, Conners’ Parent and Teacher Rating Scales, Child Behaviour Checklist, Parent-rated Hyperactivity/Impulsivity Swanson Nolan and Pelham Ratings, and UPPS Impulsivity Scale.

Pharmacotherapies

There are pharmacological and non-pharmacological treatments for ADHD for both children and adults.³⁴ Pharmacological approaches are the most common and typically consist of stimulant medication, such as methylphenidate, dexamethylphenidate, mixed amphetamine salts, and lisdexamfetamine dimesylate. However, non-stimulants such as atomoxetine, clonidine, guanfacine, and reboxetine have also been found to be efficacious in treating ADHD, although their efficacy seems to be slightly lower than that of stimulants.^{35,36} Among the different substance classes, there is a large variety of delivery forms (liquid, sprinkle, tablet, capsule, or patch), formulations (active isomers, mixtures of active and less active isomers, or prodrugs), and release forms (immediate-, intermediate- or extended-release).

Adverse effects are a serious problem compromising treatment compliance for both stimulant and non-stimulant medications.³⁷ The most common side effects of stimulants are decreased appetite, sleeplessness, headache, abdominal pain, and nausea,^{38,39} whereas those of non-stimulants include decreased appetite, abdominal pain, vomiting, headache, sleepiness, and sedation.³⁹⁻⁴¹

Adverse effects on blood pressure, heart rate, and exercise parameters have also been reported for both stimulant and non-stimulant drugs, but usually do not reach clinical relevance.^{40–44} For instance, small but statistically significant changes in blood pressure and heart rate were observed at 6 weeks of treatment with high doses of extended-release methylphenidate in adolescents, without clinically meaningful changes in electrocardiogram and no serious cardiovascular adverse events.⁴² Although rare, serious cardiovascular adverse events (e.g. vasculopathy) have also been reported with stimulant use.⁴⁵ No cytogenetic side effects have been associated with the use of methylphenidate.⁴⁶ A black-box warning for suicidal ideation has been published in the US prescribing information of the non-stimulant atomoxetine, based on findings from a meta-analysis showing that the drug is associated with a significantly higher incidence of suicidal ideation than placebo.^{40,47}

Since ADHD medications are prescribed for long-term treatment, there is a need for longitudinal safety studies.³⁷ For instance, despite the frequent use of stimulants, there is still a lack of clarity on the effects of long-term use on growth and nutritional status of children.⁴⁸ As clinical trials in the paediatric population are limited, clinicians and health authorities must rely on spontaneous reports as the main source of information about previously unknown adverse drug reactions.³⁷ A recent systematic review of the safety information contained within the summaries of product characteristics (SPCs) of medications licensed in the UK for treating ADHD reported significant differences between the SPCs and national guidelines on prescription, partly due to the ongoing reactive process of amending the SPCs as new information becomes available.⁴⁹ This may confuse clinicians seeking advice on drug prescription for their ADHD patients.

Alternative treatments

Complementary and alternative approaches are also used to ameliorate ADHD symptoms or combat its causes.⁵⁰ They include dietary modifications (diets rich in low glycaemic index carbohydrates, proteins, and essential fatty acids), nutritional supplementation (e.g. with essential fatty acids, vitamin B6, magnesium, zinc, L-carnitine, and different amino acids), herbal medicine (e.g. rhodiola, chamomile, and St John's wort), homeopathy, and physical exercise. Some of them have proven to be beneficial in ADHD patients.⁵⁰ Although the biological rationale for using them is clear from the possible causes of

ADHD and their relationship with diet, an objective assessment of their efficacy is difficult, a problem inherent to all dietary studies, not to forget the placebo effect.

A systematic review of 34 studies published in the Chinese literature found that traditional Chinese medicine (TCM) may have equal or better effectiveness than methylphenidate, but the quality of the clinical trials does not support any particular recommendation of TCM for treating ADHD in children.⁵¹ Over the counter products used in Western medicine include *Ginkgo biloba* and short-chain fatty acids, but these substances have not been shown to be significantly superior to placebo or methylphenidate.^{52,53} In a small, placebo-controlled trial, omega-3/omega-6 fatty acids improved symptoms in a sub-population of children with ADHD of the inattentive subtype and co-morbid neurodevelopmental disorders.⁵⁴

In addition to medication, there are also non-pharmacological treatments. These are alternatives for patients who cannot or must not take the required medicines to adequately manage their disease, for instance because of contraindications and co-morbid conditions (e.g. anxiety and tic disorders), drugs' adverse effects, non-responsiveness, or reduced efficacy. Also, patients at risk of substance misuse should avoid stimulant medication. Alternative treatments include different forms of psychosocial interventions, e.g. cognitive and behavioural therapies. For instance, parent and teacher training in effective behaviour-management techniques – behavioural parent training programmes – may help reduce the problem behaviours associated with ADHD in children, and cognitive behavioural therapy is commonly used for adults with ADHD. Neurofeedback has also been proved efficacious in the treatment of ADHD, with a large effect on inattention and impulsivity and a medium effect on hyperactivity.⁵⁵ Computerized training of working memory is also beneficial, but current consensus is that the non-pharmacological therapies listed above are supportive for ongoing pharmacotherapies and should not be regarded as substitutions. However, this conception is controversial.

Pill or therapist?

The choice of treatment, whether pharmacological or psychosocial, is multifactorial. Brinkman and Epstein⁵⁶ found that, at the time of diagnosis, parents and children view psychosocial treatment as a more acceptable option than medication, and that medication acceptability is significantly higher

among Caucasian than among non-Caucasian parents. Also, actual experience with medication can increase parent-reported acceptability of medication treatment for ADHD. However, acceptability alone does not predict implementation and adherence, neither of psychosocial nor of pharmacological treatment. Both are influenced by a variety of factors, for instance, the former by service availability and feasibility of family attendance (e.g. time and affordability) and the latter by perception of needs and benefits weighed against side effects and costs, patient acceptance, and social support. The choice of treatment also depends on the type and severity of symptoms presented and the respective perceived needs of patients and their families. Treatment preferences are often dynamic and context-dependent, as family priorities and values change over time. It has been noted that pharmacotherapies alone are better in the short term, but cognitive and behavioural therapies deliver the best results in the long term. It is also worth noting that ADHD medicines do not have disease-modifying potential, that is, they only bring symptomatic benefits for as long as the therapy lasts.

Concluding remarks

As described above, ADHD is a controversial disorder for various reasons: its cause is unknown, its diagnosis subjective and the long-term efficacy and safety of its treatment are unclear. But is the mixture of complex aetiology and heterogeneous diagnostic criteria enough to refute its existence as a clearly identifiable and genuine neurodevelopmental disorder? Furman⁵⁷ argued in 2008 that evidence for a genetic or neuroanatomic cause of ADHD is insufficient and that ADHD is unlikely to exist as an identifiable disease. 'Inattention, hyperactivity and impulsivity are symptoms of many underlying treatable medical, emotional and psychosocial conditions affecting children', he says. Critics have described ADHD as a diagnosis used to label difficult children who are not ill but whose behaviour is at the extreme end of the normal range.⁵⁸ Controversy also continues to grow over medicines used to treat ADHD, their efficacy, tolerability, safety, long-term effects, and abuse potential, as well as social and ethical issues on ADHD diagnosis and treatment.

Are the arguments against ADHD being a real clinical condition still valid taking into account the most recent findings in genetics, pathophysiology, and neuroimaging? Even if yes, does this view help relieve suffering of symptoms and impairments

in ADHD patients? How can an unidentifiable disease be treated? Will the impact of undiagnosed ADHD on children's daily living in family, school, and social settings ever be measured? What is the psychological burden of parents believing that the abnormal behaviour of their children is biologically not explainable? Is ADHD a by-product of poor parenting or miseducation? The debate continues.

Singh noted that ADHD has served as a case study to illustrate the potential social and ethical consequences of psychiatric diagnosis and treatments; or macrolevel analyses of corporate, governmental, and institutional interactions that inhere in the take-up of psychiatric diagnosis and drug treatments.⁵⁹ She argued that neither bioethics nor sociology has yet managed to fully take on the complexity of ADHD. There is little attention to ADHD as a lived experience in local contexts, and this is particularly problematic because 'children carry this diagnosis in the midst of complex and highly contested social, political and medical territories', she says. The consequences of diagnosis for children's overall well-being have been neglected in scientific research, and much attention should be drawn to children's perceived experience of living with ADHD.

In contrast to the occasional denial of the existence of ADHD as a clinical entity, there is the risk of overdiagnosis and overtreatment, which refers to children who are diagnosed with ADHD but should not be (false positives). Global use of ADHD medications rose three-fold from 1993 through 2003, whereas global spending (2.4 billion US dollars in 2003) rose nine-fold.⁶⁰ Use and spending grew in both developed and developing countries, but spending growth was more pronounced in developed countries. In the United States, the number of physician outpatient visits, in which ADHD was diagnosed, increased by 66% (from 6.2 to 10.4 million) from 2000 to 2010.⁶¹ Sciutto and Eisenberg⁶² reviewed prevalence studies and research on factors affecting diagnostic accuracy in ADHD until 2007. They concluded that 'there does not appear to be sufficient justification for the conclusion that ADHD is being systematically overdiagnosed'. Nevertheless, they noted that this conclusion is generally not reflected in public perceptions or media coverage of ADHD. On the other hand, there are also misdiagnosis and underdiagnosis. For instance, girls are likely to be underdiagnosed because they more often suffer from the inattentive subtype without the disruptive hyperactive behaviour.⁴⁸

If left untreated, ADHD may persist into adulthood and be accompanied by a variety of

behavioural, social, and economic problems, including depression and anxiety disorders, antisocial behaviour, poor peer relationships, substance abuse/misuse, learning disabilities, low academic attainment, unemployment, etc. Substantial progress continues to be made in our understanding of the aetiology and pathophysiology of ADHD resulting particularly from genetics, neurophysiological, and neuroimaging studies. This may help us not only to improve diagnosis and treatment of this impairing disorder, but also to develop and implement preventive strategies in the near future. In view of the increasing numbers of diagnosed ADHD cases recently, such improvements will have a large impact on health economics globally.

After a critical analysis of the literature, whatever ADHD represents for us, the often heartrending stories from those diagnosed with ADHD and their relatives underline the necessity to understand the pathogenesis of ADHD to develop effective preventive and symptomatic interventions.

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