Twenty years of research on attention-deficit/hyperactivity disorder (ADHD): looking back, looking forward

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ABSTRACT

In this clinical review we summarise what in our view have been some the most important advances in the past two decades, in terms of diagnostic definition, epidemiology, genetics and environmental causes, neuroimaging/cognition and treatment of attention-deficit/hyperactivity disorder (ADHD), including: (1) the most recent changes to the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders and International Classification of Diseases; (2) meta-analytic evidence showing that, after accounting for diagnostic methods, the rates of ADHD are fairly consistent across Western countries; (3) the recent finding of the first genome-wide significant risk loci for ADHD; (4) the paradigm shift in the pathophysiological conceptualisation of ADHD from alterations in individual brain regions to a complex dysfunction in brain networks; (5) evidence supporting the short-term efficacy of ADHD pharmacological treatments, with a different profile of efficacy and tolerability in children/adolescents versus adults; (6) a series of meta-analyses showing that, while non-pharmacological treatment may not be effective to target ADHD core symptoms, some of them effectively address ADHD-related impairments (such as oppositional behaviours for parent training and working memory deficits for cognitive training). We also discuss key priorities for future research in each of these areas of investigation. Overall, while many research questions have been answered, many others need to be addressed. Strengthening multidisciplinary collaborations, relying on large data sets in the spirit of Open Science and supporting research in less advantaged countries will be key to face the challenges ahead.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children, with an estimated worldwide prevalence around 5%.[1] Although it has for a long time been considered a childhood disorder, it is now established that impairing ADHD symptoms persist in adulthood in a sizeable portion of cases (around 65%),[2] although there is variability in the estimate due to methodological heterogeneity across studies.[3]

As for other mental health conditions there has, over the past two decades, been an increasing body of research on ADHD. Reasons for this increase include: increased recognition of the impact of ADHD on functioning; advances in research methodology and technology; and interest from pharmaceutical companies.

Here, we provide an overview of what we deem have been some the most important advances, in the past two decades, in ADHD research. We also discuss key areas for future research.

METHODS

Given the large body of literature and space constraints, this review is selective rather than systematic and comprehensive. We relied mostly on meta-analyses, retrieved with a search in PubMed using the following syntax/terms (update: 8 August 2018): (ADHD OR Attention Deficit OR Hyperkinetic Disorder) AND (meta-analy* OR metaanaly).

PRESENTATION

Diagnostic definition

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[4] published in 2013, introduced several significant changes in relation to the DSM Fourth Edition Text Revision (DSM-IV-TR)[5] criteria. First, the threshold in the number of symptoms (criterion A) necessary for the diagnosis in older adolescents and adults was reduced from 6 to 5. This change is in keeping with the notion that, despite a reduction in the number of symptoms over development, adults with ADHD in childhood can still present with impairment.[2] The required age of onset was increased from 'prior to 7' to 'prior to 12'. The purpose of these changes was well intended and designed to facilitate the diagnostic process in adults, who often have trouble pinpointing the exact age of onset, especially if early in the development. Unfortunately, neither change was based on empirical evidence, and methods used for diagnostic ascertainment in adults are still under debate.[3] Another pivotal change in DSM-5 is the removal of the veto around the dual diagnosis of ADHD and autism spectrum disorders (ASD) that was present in previous editions of the DSM. Unlike the age of onset and symptom number changes this change is supported by a significant body of research (see ref 6). Finally, the *(sub) types* of ADHD defined in the DSM-IV-(TR) were replaced by the notion of different *presentations*. This acknowledges the instability in the phenotypic manifestation of inattention or hyperactive/impulsive symptoms over time,[7] in contrast to the more static notion of a *subtype*.

With regard to the International Classification of Diseases (ICD), it appears that the veto to diagnose ASD in the presence of ADHD will be retained in the upcoming ICD 11th Revision (https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f821852937).

Overall, while these changes to a degree reflect recent empirical evidence and/or practical needs in the diagnostic process, there are still issues that need to be addressed. First, current criteria still focus on the number of symptoms rather than on a more precise definition of functional impairment. This should be a priority for the field and efforts, such as the development of the International Classification of Functioning, Disability and Health: Child and Youth version, are already ongoing.[8] Second, while currently each of the symptoms listed in the DSM criterion A carries the same weight, it has been argued that inattention should be more heavily weighted than hyperactivity/impulsivity.[9] Supporting evidence, which comes from clinical samples, needs to be replicated in population-based studies. Third, from a practical standpoint, it is unclear on how to best integrate different information sources (eg, parents, teachers, etc). Addressing this challenge is pivotal. Fourth, although proposed as a

separate type of ADHD or even a separate diagnostic entity, the extent to which the construct of sluggish cognitive tempo (impairment of attention in hypoactive-appearing individuals) overlaps with ADHD *inattentive presentation* remains still unclear.[10 11] Finally, one of the most controversial topics in the entire field of ADHD research is currently around the possibility that ADHD can emerge de novo in adulthood, in contrast to its conceptualisation as a neurodevelopmental disorder. Despite an increasing number of important studies, the controversy is far from being solved[12] and we expect it will be a major focus of research in the field in coming years.

We also expect that proposed radical, although controversial, changes in the nosographic approach to mental health conditions, such as the Research Domain Criteria will significantly influence future research on ADHD.[13]

Epidemiology

One of the most controversial questions in relation to the epidemiology of ADHD has been around possible differences in the prevalence of the disorder in different countries. In particular, the differential rates of clinical diagnosis in North America and Europe are cited by detractors of ADHD, as supporting the notion that ADHD is not a 'real' disorder but rather a social construct.[14] However, a meta-analysis published in 2007[1] found that diagnostic criteria, source of information, requirement of impairment for diagnosis and geographic origin of the studies significantly impacted on the estimated pooled rate of ADHD (5.29%). A significant difference in prevalence emerged only between North America and both Africa and the Middle East, although evidence from non-Western countries was limited. However, as there were only a limited number of studies available for Africa and Middle East, these findings should be considered with caution. By contrast, no significant differences emerged between Europe and North America, suggesting that when using the same diagnostic approach the rates of the disorder are fairly consistent in Western countries, with variability in the prevalence accounted for primarily by methods used to diagnose ADHD. Another more recent meta-analysis[15] found no evidence to support an increase in the epidemiological prevalence of ADHD over the past three decades when standardised diagnostic procedures are followed. This implies that the trend for increased rates of diagnosis[16] are not accounted for by actual increases in prevalence. Rather, the mismatch between administrative and epidemiological rates of the disorder, which varies between the USA and Europe, is likely accounted for by cultural and social factors.[16]

As the bulk of the available epidemiological studies focus on school-age children from North America and Europe, further population-based studies from other continents as well as in preschoolers and adults should be encouraged. Additionally, longitudinal epidemiological studies aimed at better understanding the developmental trajectories and predictors of remission/persistence of ADHD in adulthood will be instrumental, alongside other clinical, neuropsychological, genetic and neuroimaging studies, to inform prevention programmes. Development of a standardised definition of caseness and remission will be pivotal for this body of research to be fruitful.

Genetics and environmental causes of ADHD

Studies of twins and adopted children indicate a high heritability for ADHD (60%–90%).[17] Efforts to find the genes underpinning this heritability have been more challenging than initially anticipated. As for other mental health conditions, it became clear that ADHD aetiology is accounted for by a complex interaction of many genes each with a relatively small effect and by gene × environment interactions.[18]

The first approach to finding the genes involved in ADHD was the 'candidate gene' approach. This approach focuses on identifying the variants in genes coding for proteins hypothesised, a priori, to be involved in the pathophysiology of ADHD. These studies identified only about 10 genes as having significant support,[19] which together accounted for only a small fraction of the total ADHD heritability. The next major approach, 'genome-wide association studies' (GWAS), which allows the analysis of a large number of common (ie, present at greater than 5% frequency in the population) single-nucleotide polymorphisms across the entire genome, was initially unsuccessful in ADHD, as the available sample was too small to show a meaningful effect. However, in a major breakthrough, the first 12 independent loci have been recently identified through GWAS.[20] Associations were enriched in loss-of-function intolerant genes and brain-expressed regulatory marks, paving the way for a number of novel lines of investigation on the neurobiology of ADHD.

A further recently developed approach focuses on rare (ie, a frequency in the general population below 1%) 'copy number variants' (CNV). These are defined as replications or deletions of the DNA with a length of at least 1 kb. CNVs over-represented in ADHD have been detected, but their contribution can so far only explain 0.2% of ADHD heritability.[21]

As for environmental aetiological factors, there have been, over the past years, considerable data suggesting that prenatal and postnatal factors, such as maternal smoking and alcohol use, low birth weight, premature birth and exposure to environmental toxins, such as organophosphate pesticides, polychlorinated biphenyls and zinc, are associated with increased risk for ADHD.[17 22] However, except for preterm birth, genetics studies have implicated unmeasured familial confounding factors, which are not in line with a causal role of environmental factors.[23]

Severe maternal deprivation has also been related to the development of ADHD-like symptoms.[24]

The study of the causes of ADHD still has many unanswered questions. We need a better understanding of how genes interact with each other, and of the interplay between environmental factors and genes. Genetics has the potential to offer many other exciting future avenues of research in ADHD. We will only mention briefly here: (1) the use of induced pluripotent stem cell derived from peripheral tissue of patients with ADHD and used to generate brain cells with the aim to model brain circuits and responses to medications or other stressors; (2) the use of zebrafish and fruit fly models to augment currently available animal models of ADHD.

Neuroimaging and neurocognition

Initial pathophysiological models of ADHD published 20 years ago[25] were based on dysfunctions in a limited number of brain areas, namely the frontal cortex and the basal ganglia. Over the past two decades, and similar to other mental health conditions, a major paradigm shift from alterations in individual brain regions to dysfunction in brain networks has begun to reshape our understanding of the pathophysiology of ADHD. Structurally, meta-analyses and mega-analyses of the structural MRI studies conducted over the past two decades pointed to consistently replicated alterations in the basal ganglia,[26] and in a number of other subcortical areas.[27] Functionally, a comprehensive meta-analysis[28] found that the majority of the ADHD-related hypoactivated areas were related to the ventral attention and the frontoparietal networks. By contrast, the majority of ADHD-related hyperactivated areas fell within the default mode network and other hyperactivated areas were within the visual network. This is in line with the hypothesis that the attentional lapses that characterise ADHD result from an inappropriate intrusion of the default network in the activity of task-positive networks frontoparietal, ventral or dorsal attention networks,[28] according to the *default network hypothesis of ADHD*,[29] which has been arguably one of the most inspiring proposals in the neuroscience of ADHD over the past two decades.

While we have gained insight into the brain networks that are dysfunctional in ADHD and in the delay in cortical maturation,[30] we look forward to the next generation of neuroimaging studies which we hope will start to translate these findings into the clinical practice. The introduction of machine learning approaches, such as support vector machine, has been welcomed in the field of clinical neuroscience as a way to translate

neuroscientific findings at the individual patient level, thus overcoming the main limitation of current studies that can only provide results valid at the group, rather than individual, level.[31] An increasing number of studies have used machine learning based on MRI data to validate the diagnosis of ADHD with varying degrees of success.[32 33]

Neurocognitive studies have made a considerable contribution to our understanding of ADHD. In recent years, the field has moved away from linear single-cause models of ADHD towards multipathway models that emphasise the heterogeneity inherent to ADHD and provide a link between individual differences at the brain level and clinical presentation.[34 35]

We believe that an interesting line of research for the future will be to combine genetics, clinical, neurocognitive and neuroimaging data to define, via machine learning approaches, response to treatment, tolerability profiles and functional trajectory of the disorder over time. This will be a crucial step towards personalised and precision approaches to treatment.

Treatment

Over the past two decades, there has been a marked increase in the number of randomised controlled trials (RCT) aimed at testing the short-term efficacy and tolerability of pharmacological treatments for ADHD (both stimulant and non-stimulant medications). Most have been sponsored by Big Pharma and were designed to support the licence of the medication. In parallel, due to concerns around possible side effects of medications and lack of clarity around their long-term effects, several lines of research on non-pharmacological interventions have been developed. Recent important methodologically sound meta-analyses allow us to summarise and critically discuss this large body of evidence.

For the pharmacological interventions, a comprehensive network meta-analysis[36] of 133 double-blind RCTs demonstrated high to moderate effect sizes (in terms of efficacy) for the different medications versus placebo. Standardised mean differences (SMD) ranged from −1.02 (95% CI −1.19 to −0.85) for amphetamines to −0.56 (95% CI −0.66 to −0.45) for atomoxetine (methylphenidate: −0.78, 95% CI −0.93 to −0.62). In children/adolescents, methylphenidate was the only drug with better acceptability than placebo; in adults this was the case only for amphetamines (with no difference between placebo and other active drugs). Taking into account both efficacy and safety, evidence from this meta-analysis supported methylphenidate as preferred first-choice medication for the short-term treatment of ADHD in children/adolescents and amphetamines for adults.

As for non-pharmacological options, a comprehensive synthesis on non-pharmacological treatments for children and adolescents with ADHD has been provided in a series of meta-analyses by the European ADHD Guidelines Group (EAGG). In 2013, they published a first systematic review/meta-analysis[37] addressing the efficacy of behavioural interventions, diet interventions (restricted elimination diets, artificial food colour exclusions and free fatty acid supplementation), cognitive training and neurofeedback on ADHD core symptoms (ie, inattention, hyperactivity and impulsivity). The systematic review included only RCTs and considered two contrasting outcomes: those rated by individuals not blinded to the treatment condition (active vs control) and those rated by individuals who were probably blinded to treatment (eg, teachers in trials assessing a behavioural intervention implemented with parents). The results were strikingly different depending on the type rater. When considering not blinded ratings, all interventions resulted significantly more efficacious than the control condition in terms of reduction of ADHD core symptoms. However, when considering the more rigorous probably blinded ratings, only free fatty acid supplementation and artificial food colour exclusion remained significantly more efficacious than the control conditions, with small effect sizes (SMD=0.16 and 0.42, respectively), indicating that the clinical impact of these treatments on ADHD core symptoms is, at the group level, modest.

Subsequent EAGG meta-analyses focused on ADHD core symptoms and on ADHD-related problems. A meta-analysis[38] specifically focusing on behavioural interventions showed that, even when considering probably blinded ratings, the behavioural interventions were efficacious at improving important aspects related to ADHD, namely parenting (SMD for positive parenting 0.63; SMD for negative parenting 0.43) and conduct problems (SMD 0.31). Another updated meta-analysis[39] on cognitive training, which was found efficacious in improving verbal and visual working memory, which are impaired in a sizeable portion of children with ADHD and have been demonstrated to dissociate from ADHD symptoms.[40] These meta-analyses also suggest that training which targets several neuropsychological aspects may be more efficacious at improving ADHD symptoms, than training targeting only one aspect of cognitive functioning. The most recent meta-analysis[41] by the EAGG on neurofeedback did not provide support for the efficacy of neurofeedback on any of the neuropsychological and academic outcomes. Overall, this body of research does not provide solid evidence to routinely recommend non-pharmacological interventions as highly effective treatments for ADHD core symptoms, although some of them (eg, behavioural interventions or cognitive training) may be effective for important associated impairments (oppositional behaviours and working memory deficits, respectively). The role of fatty acid supplementation and artificial food colours exclusion as possible treatment strategies should be considered cautiously given the small effect size, with CIs close to non-significance.

Probably, the most crucial area of future treatment research in ADHD will be to gain insight into the long-term positive and negative effects of treatments, using randomised trials with withdrawn designs, as well as additional population-based studies with self-controlled methodologies and longitudinal follow-up studies. These should clarify the conclusions from the various follow-up waves of the Multimodal Treatment of ADHD (MTA) study, showing that neither the type and intensity of treatment received during the initial 15-month randomised phase of the study (treatment as usual medication (MED), behavioural therapy (BEH), medication plus behavioural therapy (COMB)) nor exposure to medication over the subsequent observational periods predicted the functional outcome at follow-up which has now extended to 16 years. Of note, in the MTA, the treatments received in the three experimental arms (MED, BEH, COMB) during initial 15-month randomised phase were carefully crafted in an attempt to achieve optimal outcomes. After this initial phase all participants were free to choose the type of treatment they received from their regular provider. As it is likely that these treatments were not as carefully optimised and monitored as the three experimental groups during the randomised phase, these longer term findings of the MTA are not easily interpretable and might be, to some extent, misleading.

CONCLUSIONS

Many questions have been successfully answered in the field of ADHD. Many others remain to be addressed. Additional multidisciplinary collaborations, use of large data sets in the spirit of Open Science and support of research activities in less advantaged countries are key to address the challenge.

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