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S Clare Stanford
Emma Sciberras *Editors*

New Discoveries in the Behavioral Neuroscience of Attention-Deficit Hyperactivity Disorder

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S Clare Stanford • Emma Sciberras
Editors

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Editors
S Clare Stanford
Division of Biosciences
University College London
London, UK

Emma Sciberras
School of Psychology
Deakin University
Burwood, Australia

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Preface

It is nearly 10 years since the publication of the first edition of this book, as Volume 9 in the series of *Current Topics in Behavioral Neuroscience*. Much has happened in the field since then and so we were delighted to be invited to edit a second edition, to provide an update on all this progress.

As before, the content of this volume combines clinical and preclinical perspectives on the research and treatment of Attention-Deficit Hyperactivity Disorder (ADHD), so as to be informative and interesting to all readers, not just those with professional expertise in this field. Some authors of this volume contributed to the first edition, which pre-dated the publication of DSM-5, and have provided fascinating insights into how their field has developed over recent years. However, we were keen to recruit some new authors, not least to ensure that the content incorporated significant advances and promising developments in ADHD research, including new technologies.

This volume starts with a discussion of the clinical features of ADHD and an update of the diagnostic criteria, as well as risk factors for this disorder. This is followed by a series of three chapters that cover the efficacy and limitations of pharmacological treatments for ADHD. These consider not only the pharmacodynamics of established treatments but also the efficacy of different formulations, their pharmacokinetics and effects in different patient subgroups. These chapters are complemented by a detailed and comprehensive appraisal of the prospects for the successful development of new compounds that are already on the horizon. The last chapter in this cluster points the way to biological targets for methylphenidate that are comparatively under-explored, but could lead to completely new approaches for the drug treatment of ADHD in the future.

The next group of chapters covers co-occurring conditions. The strong associations between obesity and substance abuse with ADHD were discussed in Edition 1, but this topic has now been expanded to include the disruption of circadian and sleep rhythms and autism. This new material reflects the increased awareness of these co-occurring conditions as important elements of the clinical profile of ADHD.

The next two chapters describe research findings based on genetics and epigenetics. The former topic is discussed in a chapter that explains the exciting developments in technologies in this field, as well as providing an update on the knowledge-base for genes and polymorphisms that are implicated in ADHD. The inclusion of a whole chapter on epigenetics in this volume attests to how much progress has been made in this aspect of ADHD research in a comparatively short time. It is striking that this topic, which is still in its infancy, was not even mentioned in the first edition.

The next series of chapters deals with animal studies of ADHD. These start with an overview and critique of procedures for evaluating different aspects of cognitive performance in mammals (typically rodents). This is followed by a chapter covering the effects of drugs, which are used to treat ADHD patients, on the cognitive performance of rodents in these tests. The last chapter in this set considers the likely validity of claims that selective breeding, genetic alteration, or a neuronal lesion has produced in a rodent model of ADHD.

The final four chapters deal with new approaches to the research of ADHD. First, there is a critique of the use of zebrafish, as a substitute for mammals, in ADHD research. This important work holds great promise in the context of the ethical obligation to use the least sentient species in animal experiments. Then, there is a review of how the electro-encephalogram (EEG) is being used as a non-invasive approach for studying neural activity in the brain and how this work is providing evidence for altered functional circuitry in ADHD patients. This is complemented by a chapter describing the evidence for differences in brain functional connectivity between individuals with and without ADHD; this is another exciting technological approach, which offers a valuable alternative to the static, "snapshot" imaging studies that were prevalent 10 years ago. The final chapter of the book comprises a review of progress in research using pluripotent stem cells from ADHD patients in order to construct 2- and 3-dimensional models, in vitro, to study this disorder. This technology has yet to be incorporated extensively in ADHD research, but will surely make a vital contribution to the field in the future. Not only will it enable a better understanding of the neurobiology of ADHD but will also help with the development of in vitro alternatives for animal experiments.

The commissioning of these chapters preceded the emergence of COVID-19 and we were delighted to have assembled such an impressive team of experts. Every chapter covers an important topic and it would have been a pity to have any gaps in the series. It is a testament to the resilience and commitment of this team of authors that they all fulfilled their promise to contribute a chapter despite the huge personal and professional challenges arising from the pandemic. We are immensely relieved and grateful for their continued support, without which prospects for producing this book would have collapsed.

London, UK — S. Clare Stanford
Burwood, VIC, Australia — Emma Sciberras

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ADHD in Children and Adults: Diagnosis and Prognosis

Douglas Teixeira Leffa, Arthur Caye, and Luis Augusto Rohde

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Abstract Attention-Deficit Hyperactivity Disorder (ADHD) is a prevalent neuropsychiatric disorder associated with significant impairment and distress throughout the lifespan. Recent investigations have shed light on different aspects regarding the trajectory of ADHD, including reports on risk factors in childhood, that are associated with remission or persistence in adulthood. Despite significant advances in our understanding of the pathophysiology of the disorder, the diagnosis of ADHD remains strictly clinical and is based on behavioral symptoms of inattention, impulsivity, and hyperactivity. In this chapter we review the diagnostic process of ADHD, discuss the clinical presentation of the disorder across the lifespan, and examine patterns of comorbidity and longitudinal predictor of outcomes.

Keywords Attention-deficit hyperactivity disorder · Comorbidity · Diagnosis · Prognosis · Symptoms · Trajectory

D. T. Leffa and A. Caye
ADHD Outpatient Program and Developmental Psychiatry Program, Hospital de Clinica de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

L. A. Rohde (✉)
ADHD Outpatient Program and Developmental Psychiatry Program, Hospital de Clinica de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

National Institute of Developmental Psychiatry, São Paulo, Brazil

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Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CD	Conduct disorder
DSM-5	Diagnostic and statistical manual of psychiatric disorders (fifth edition)
EEG	Electroencephalogram (electroencephalography)
ICD-11	International classification of diseases (11th revision)
IQ	Intelligence quotient
MRI	Magnetic resonance imaging
MTA	Multimodal treatment of ADHD
ODD	Oppositional defiant disorder
PATS	Preschoolers with attention-deficit hyperactivity treatment study
PET	Positron emission tomography
SPECT	Single photon emission computerized tomography

1 Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterized by frequent, pervasive, and impairing symptoms of inattention and/or hyperactivity/impulsivity. Meta-analytic data suggest a worldwide prevalence rate of ADHD in children and adolescents of around 5.3% (Polanczyk et al. 2007), with a male-to-female ratio of roughly 2:1 (Polanczyk et al. 2007; Willcutt 2012). Discrepancies in prevalence estimates according to sex might result from referral biases among treatment-seeking patients or distinct pathophysiological mechanisms still poorly understood (Faraone et al. 2015). The heterogeneity observed among prevalence rates can be partially explained by methodological factors in the studies, such as the choice of diagnostic criteria, information sources, and the inclusion of a requirement for functional impairment for the diagnosis (Polanczyk et al. 2014). Although previously seen as a disorder specific to children, in the last two decades substantial work has documented the persistence of ADHD to adulthood. In this sense, the prevalence in adults has been estimated as 2.5% (Song et al. 2021). In adulthood, sex differences are almost nonexistent (Song et al. 2021).

In 2013, the DSM-5 introduced some revisions in the ADHD diagnostic criteria in order to better reflect the knowledge regarding the nature of the disorder and to make the diagnosis more reliable. Among those, the following changes potentially impact prevalence measures: First, the age-of-onset criterion was modified. The emphasis moved from age-of-onset of impairment to age-of-onset of symptoms, reflecting the difficulties to precisely define the source of impairment in a highly comorbid disorder as ADHD. The age-of-onset limit increased from 7 to 12 years. Second, the symptom threshold for older adolescents and adults (age 17 or more) was decreased from six to five symptoms, reflecting the evidence that even adults

with lower number of symptoms have clinically significant impairments. Third, the diagnosis of ADHD was allowed in the presence of Autism Spectrum Disorder (ASD) due to evidence of high comorbidity between the two disorders. The revised criteria were shown to have negligible impacts in the prevalence of ADHD in children, with a more considerable effect in adults (Polanczyk et al. 2010; Matte et al. 2015).

Recent investigations have shed light on different aspects regarding the trajectory of ADHD, including reports on risk factors in childhood associated with remission or persistence in adulthood. Here, we review the current knowledge on diagnostic criteria and clinical presentation of ADHD in children, adolescents, and adults, exploring changes in symptomatology across the lifespan.

2 Diagnosis

The diagnosis of ADHD relies on clinical assessment and it is performed based on diagnostic classification systems, predominantly the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5: American Psychiatric Association 2013) and the International Classification of Diseases 11th revision (ICD-11: World Health Organization 2018). While the DSM-5 approach is essentially structured on criteria, the ICD-11 has migrated to a prototype presentation. In this sense, while DSM-5 provides criteria to determine whether the patient qualifies for the diagnosis, ICD-11 relies mostly on the description of main elements of the most common presentations. DSM-5 criteria specify two dimensions of symptoms, namely inattention and hyperactivity/impulsivity, which define three presentations of the disorder: predominantly hyperactive-impulsive, predominantly inattentive, and combined presentation. Previous findings show that the combined and predominantly inattentive presentations are the most commonly observed (Willcutt 2012; Vitola et al. 2017). It is important to highlight that DSM-5 defines presentations and not types as did DSM-IV, due to the substantial evidence of low developmental stability of these presentations (Willcutt 2012; Vitola et al. 2017). The DSM-5 adopted the following criteria:

(a) *Presence of symptoms*. To meet this criterion, children and adolescents should present at least six out of the nine symptoms described for the inattentive and/or hyperactive/impulsive domains. For older adolescents (age 17 or more) and adults, at least five symptoms in one or both domains are required (the lower threshold is related to the fact that older adolescents and adults can experience impairment with fewer symptoms). It is essential to evaluate whether symptoms have persisted for at least 6 months and are inconsistent with the developmental level of the patient. Moreover, symptoms should not be exclusively a manifestation of oppositional behavior or failure to understand tasks and instructions.
(b) *Age of onset*. According to the DSM-5, symptoms should be present before 12 years of age.

(c) *Pervasiveness*. According to this criterion, several symptoms should be present in more than just one environment. The presence of symptoms in a single environment might point to a false positive. As an example, symptoms might be present just at home due to parental conflicts.
(d) *Impairment*. Symptoms should clearly interfere or reduce the quality of social, academic, or occupational functioning in order to constitute a diagnosis of ADHD.
(e) *Exclusionary criteria*. In order to diagnose ADHD, the symptoms should not be better explained by another mental condition, or by the use of medications.

The diagnosis of ADHD is performed by clinical history, using the diagnostic criteria previously mentioned. Evaluation for ADHD should consist of clinical interviews with the patients and other informants (including parents/family members and teachers). A detailed clinical interview should be performed in order to obtain information regarding the patient's school or work functioning, comorbid psychiatric disorders, complete medical and developmental history, and psychiatric family history (American Psychiatric Association 2013). In addition, a complete physical examination should be performed to exclude other clinical conditions that might cause symptoms of inattention, hyperactivity, or impulsivity. In this sense, it is imperative to carry out an assessment on auditory and visual acuities.

Attention problems are usually more prominent when individuals with ADHD are assigned boring, tedious, or repetitive tasks (American Psychiatric Association 2013). Moreover, inattention symptoms can increase while the patient is working on demanding tasks that challenge their cognitive processing abilities. Motivation, relevance, and attractiveness of the task for the child can influence the manifestations of symptoms. Poor sustained attention often results in difficulties with following instructions and organizing tasks, distractibility, and failing to give close attention to details. Hyperactivity can be observed as fidgeting with hands or feet, often leaving a seat in situations in which remaining seated is expected, and acting as if driven by a motor.

It is important to highlight that inattention, hyperactivity, and impulsivity symptoms might be the result of relationship problems with parents, or friends, or be derived from inappropriate educational systems or inadequate work environments. In this case, they often occur in a specific environment or situation and this situation should alert against the diagnosis of ADHD. For the diagnosis of ADHD, several symptoms should be present in more than one environment, besides clearly interfering with social, academic, or occupational functioning.

In order to diagnose ADHD, symptoms should not be better explained by other mental disorders. This is of particular interest since in both clinical and community samples about 50–80% of patients with ADHD present psychiatric comorbidities (Biederman and Faraone 2005; Jensen and Steinhausen 2015). Disruptive, impulse-control and conduct disorders, including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), are observed in 50–80% of patients with ADHD (Biederman and Faraone 2005; Jensen and Steinhausen 2015). About 10–30% of patients will have comorbid depressive and anxiety disorders (Biederman and

Faraone 2005; Jensen and Steinhausen 2015), and up to 25% will have learning or communication disorders (Biederman and Faraone 2005; Jensen and Steinhausen 2015). ASD is also highly prevalent in patients with ADHD, and meta-analysis demonstrated that 28% of patients with ASD have comorbid ADHD (Lai et al. 2019). In the DSM-5, ADHD can be diagnosed in the presence of ASD, while in the ICD-11 the diagnosis of ADHD is excluded in the presence of ASD. The change in DSM-5 is consistent with the reconceptualization of ADHD as a neurodevelopmental disorder rather than a disruptive behavior disorder.

It is known that different informants will not always have the same point of view and perspective related to ADHD symptoms in a patient (Rohde et al. 2019). This is not a surprise since they interact with the patient in different settings. In addition, some informants will be able to evaluate some of the symptoms better than others (e.g., parents will better report regarding their child's behavior at home, while teachers might be able to better evaluate on how the patient's behavior differs from his peers at school) (Rohde et al. 2019). Currently, neither the DSM-5 nor the ICD-11 provide a guideline on how to proceed when faced with contradictory information from different sources, and clinical experience suggests that the clinician's best-estimate diagnosis should be made based on as many sources as possible. In this sense, reports from informants should be taken into account in the evaluation of adolescents and adults, when available (Rohde et al. 2019).

The diagnosis of ADHD is based on clinical assessment and cannot be made by rating-scales alone, neuropsychological tests, or neuroimaging exams. There are no biomarkers with sufficient predictive power to confirm or exclude the diagnosis (Faraone et al. 2015). The QbTest, a non-invasive computer-based test that combines attention measurements with a simultaneous recording of activity, using a motion tracking system, has been approved by the Food and Drug Administration to be used to aid in the clinical assessment of ADHD. It provides objective measurements of attention, hyperactivity, and impulsivity, and results in quicker diagnostic decision-making when added to routine assessment (Hollis et al. 2018). However, it has demonstrated only moderate ability to identify ADHD (Hult et al. 2018) and therefore should be used cautiously in the clinical setting. Neuroimaging exams, including magnetic resonance imaging (MRI), positron emission tomography (PET) scan, single-photon emission computed tomography (SPECT), and electroencephalogram (EEG) might be used in differential diagnosis for specific cases, but should not be incorporated in the routine clinical evaluation since none of them has sufficient positive and negative predictive power in clinical settings (Faraone et al. 2015). Neuropsychological tests can be applied in order to better estimate intellectual impairment, executive functioning, and potential learning disorders, and also to better understand the child's relative strengths and weaknesses.

It is important to note that the majority of these complementary diagnostic tools had their diagnostic performance tested in clinical situations where groups of patients with severe combined ADHD symptoms were contrasted against groups of healthy controls without mental disorders, a situation that can be handled easily by clinicians without these tools (Rohde et al. 2019). The field awaits more investigations where the use of these diagnostic tools might improve clinicians' diagnostic

performance to deal with differential diagnosis between ADHD and anxiety disorders, bipolar disorder, and other neurodevelopmental disorders.

3 ADHD in Preschool Children

Despite still being less frequently diagnosed at this developmental period than in school-aged children, ADHD in preschoolers has been increasingly recognized over the years, with a recently estimated prevalence of 2.1% (Danielson et al. 2018). For instance, insurance claims data in the USA from 2008 to 2014 indicate a clear increase in the proportion of 2–5 year-olds that have been assessed or treated for ADHD, from 1.34% to 1.53% (Visser et al. 2016). This pattern might reflect the increasing awareness of the importance of early identification, which is a prerequisite for intervention in an otherwise adverse trajectory (Sonuga-Barke and Halperin 2010).

Nevertheless, the assessment of ADHD symptoms in very young children is particularly challenging because preschoolers who are developing normally commonly manifest marked hyperactivity and impulsivity, which could be deemed as benign and with a tendency to normalize throughout development (Harvey et al. 2009). Furthermore, the context of symptom expression in preschool children is much more variable in terms of structure and demand than that of primary or secondary school children, making it difficult to carefully evaluate the presence of symptoms across multiple settings (O'Neill et al. 2014). Finally, clinical presentation can be quite different in preschoolers than in later phases of development, and the current diagnostic manuals do not provide developmentally sensitive adaptations for the clinicians. For instance, there is no developmental adaptation on the number of symptoms or level impairment for diagnosing ADHD at this early stage of life (Curchack-Lichtin et al. 2014). The DSM-5 emphasizes, however, that hyperactive-impulsive symptoms are much more common in toddlers, while inattention symptoms tend to become more prominent during school years (American Psychiatric Association 2013).

Regardless of their young age, preschool children with ADHD have a similar pattern of impairment and comorbidity when compared to school-aged children with ADHD. Around 70% present with at least one comorbidity, the most common being ODD, followed by other comorbidities such as anxiety disorders, communication disorders, and ASD (Canals et al. 2018; Posner et al. 2007). Comorbidities play a role in the pattern of impairment and longitudinal course of symptoms: comorbid ODD or CD predicted the stability of an ADHD diagnosis after 6 years of follow-up in a large clinical trial of preschoolers (Riddle et al. 2013). While ODD is characterized by constant patterns of negativistic, hostile, and defiant behaviors that are persistent and inappropriate for the developmental level, CD is characterized by persistent antisocial behaviors including acts of aggression, destruction of property, deceitfulness, theft, and rule violations.

Behavioral problems during preschool years predict impairments in academic and social functioning throughout childhood and adolescence (Altszuler et al. 2016; Lahey et al. 2016; Meinzer et al. 2016; Sjöwall et al. 2017). Preschool-aged children with ADHD commonly present with persistently impaired relationships and functioning (Lahey et al. 2004), for instance, with a higher likelihood of being suspended from school or daycare (Egger and Angold 2006). Early reports showed that very young hyperactive children still presented disruptive and inattentive behaviors in multiple settings, combined with impaired cognition and reading abilities as they aged, in a 12-year follow-up study (McGee et al. 1991). Likewise, these hyperactive children frequently fail to complete high school and have a higher chance of being unemployed or reporting financial difficulties, relative to their unaffected peers in young adulthood (Altszuler et al. 2016; Barkley et al. 2006). Risky behavior is also a pattern shared by preschool-aged children: at age 5, the rate of injury of a child with ADHD is estimated at 19.3%, compared to 10.9% for children without the disorder (Dalsgaard et al. 2015a, b).

The literature addressing the course of ADHD symptoms with an onset in preschool age is scarce. Exactly as observed in studies of school-aged children, the estimates of ADHD persistence from preschool to school-age are markedly variable (Lahey et al. 2004; Riddle et al. 2013; O'Neill et al. 2014). Analyses conducted in the follow-up study of the Preschoolers with Attention-Deficit Hyperactivity Treatment Study (PATS – the largest clinical trial conducted in preschool-aged children with ADHD) revealed that the diagnosis of ADHD was fairly stable from preschool to school-aged children over 6 years, ranging from 77% to 89% persistence (Riddle et al. 2013).

4 ADHD in School-Aged Children

The diagnosis of ADHD in school-aged children involves the assessment of the presence of developmentally inappropriate symptoms of inattention, hyperactivity, and/or impulsivity assessed via multiple informants to assess pervasiveness (American Psychiatric Association 2013). The clinician usually interviews the patient alongside the parents, and the younger the child is, the more emphasis will be given to the parents' report. Teachers are also extremely important in the process. This is because of the demands imposed by the school that might reveal symptoms of inattention that are not present at home and because of their experience with children of similar age and development (Seixas et al. 2012). A complete clinical interview aims to establish the frequency and intensity, age at onset, and associated impairment of each of the 18 core symptoms of ADHD. Although executive dysfunction and emotional dysregulation are common in ADHD children, these are frequently part of other psychiatric disorders and are not part of the core diagnostic criteria for ADHD (Biederman et al. 2012; Surman et al. 2011).

Several assessment tools are available to assist the assessment and evaluation of response to treatment in children with ADHD (Epstein and Weiss 2012) including

the SNAP-IV (Swanson, Nolan and Pelham Scale-fourth revision) and SWAN (Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale) scales. However, recent research has shown that items are not equally informative as suggested by these rating-scales, as some symptoms are strongly associated with a more severe condition, such as being easily distracted and runs about or climbs excessively, while others are not (Arias et al. 2016). Furthermore, the best ADHD rating-scales are no more than 80% sensitive and 80% specific, meaning that while identifying eight out of ten children with ADHD in the population, they also generate many false-positive cases when applied as screening tools (Martel et al. 2015). This has at least two important implications: there is probably no benefit in universal screening of ADHD in the community or in schools; and even very high scores in the assessment tools are not sufficient criteria for a diagnosis, which still depend on a thorough clinical evaluation.

One of the clinical challenges in the diagnosis and management of children with ADHD is their pattern of comorbidity. Among the most frequent disorders that tend to co-occur in ADHD children are other neurodevelopmental disorders (such as ASD, intellectual disability, and specific learning disorders) and behavioral disorders (such as ODD and CD) (Akmatov et al. 2021; Jensen and Steinhausen 2015). However, research also reports higher rates of internalizing disorders, such as anxiety, and major depression, among children with ADHD (Arnold et al. 2011; Hammerness et al. 2010; Schatz and Rostain 2006; Youngstrom et al. 2010). Overall, although studies present variable estimates of the frequencies of specific disorders, depending on the origin of its sample and assessment methods, it is widely accepted that more than half of children with ADHD will present with at least one comorbidity, and a substantial proportion will have two or more comorbidities (Faraone et al. 2015). Furthermore, evidence supports the conclusion that comorbidities contribute independently to a more severe clinical impairment and worse prognosis (Faraone et al. 2015).

ADHD in school-aged children, as in other periods of development, is associated with significant distress and impairment. A meta-analysis including more than 5,000 children and adolescents revealed considerably worse quality of life in ADHD children compared to their typically developing peers, both when rated by themselves and their parents, and especially in social, emotional, and academic functioning (Lee et al. 2016). Importantly, the quality of life of the parents of ADHD children is also frequently affected (Dey et al. 2019). An example of how ADHD impacts the social and emotional domains is the moderate-to-large impairments in socializing with peers, with high levels of rejection and more frequent engagement in bullying behavior (Benedict et al. 2015; Ros and Graziano 2018). Children with ADHD are also at higher risk of suffering accidental injuries and visits to the emergency department (Ruiz-Goikoetxea et al. 2017; Yeh et al. 2020), which is probably the major cause behind the increased rate of premature death in this population (Dalsgaard et al. 2015a, b). Not surprisingly, ADHD is strongly associated with worse educational outcomes. In a large analysis of medical and educational records of more than 760,000 children, those with ADHD presented higher rates of

unauthorized absence and exclusion, more commonly had a record of special educational need and achieved lower academic attainment (Fleming et al. 2017).

5 ADHD in Adolescents

Most children diagnosed with ADHD will continue to have significant symptoms of the disorder through adolescence, when symptoms are usually associated with increased cognitive demands during middle and high school. In this sense, academic problems that might have been effectively managed during elementary school may become a significant issue (Bussing et al. 2010). Peer problems may become more evident as social interactions assume greater relevance during teenage years, and an increased vulnerability to engage in risk-taking behaviors might translate into a higher risk of substance use disorder (Faraone et al. 2021).

In adolescence, ADHD is associated with poor academic achievement, including higher incidence of failing grades and lower scores on standardized tests of achievement (Frazier et al. 2007). Besides lower academic achievement, adolescents with ADHD will present decreased employment rates and lower earnings (Fletcher 2014). During teenage years, ADHD is associated with fewer friends and less acceptance by peers, with higher rates of social rejection (Bagwell et al. 2001). Moreover, aggression in childhood appears to predict lower social acceptance in adolescence, and impairments in peer relationships is present even in youths who no longer meet diagnostic criteria in adolescence (Bagwell et al. 2001). Since peer groups' acceptance is especially important in adolescence, ADHD is clearly a risk factor for worse quality of life during this time (Faraone et al. 2021).

Adolescents with ADHD often present poor affect regulation, with displays of both excessive negative and positive responses for the situation, becoming easily frustrated and presenting sudden outbursts of anger and irritability (Barkley and Fischer 2010). In some situations, these symptoms might be a manifestation of comorbid ODD or CD. In this sense, about half of adolescents with ADHD also meet diagnostic criteria for ODD and/or CD, which can significantly increase clinical impairment (Tseng et al. 2011). The comorbidity of ADHD with ODD and CD is associated with increased conflicts, anger, poor communication, and negative interactive styles often seen in ADHD adolescents (Edwards et al. 2001; Harty et al. 2009; Tseng et al. 2011).

Adolescence is a period in which substance experimentation often emerges. In ADHD, increased vulnerability to engage in risk-taking behaviors like substance use in adolescence appears to be the result of social factors, including low self-esteem, peer pressure and curiosity, combined with poor inhibitory control and an immaturity of cognitive controls systems (e.g., prefrontal cortex) when compared to emotion and reward systems (Faraone et al. 2015). In ADHD, the risk of substance use disorder is substantially higher (Lee et al. 2011; Sundquist et al. 2015). Populational studies have shown that adolescents with ADHD have a risk of subsequent drug use disorders, which is three times higher than individuals without ADHD after

adjusting for sex and parental education (Sundquist et al. 2015). Individuals with ADHD are twice as likely to have a lifetime history of nicotine use and have increased risk for alcohol, marijuana, and cocaine use and abuse compared to those without ADHD (Lee et al. 2011). Vulnerability to engage in risk-taking behaviors can also manifest as increased likelihood to develop sexually-transmitted infections (Chen et al. 2018), higher rates of teenage pregnancies (Hua et al. 2021), and increased risk of accidents and injuries (Brunkhorst-Kanaan et al. 2021).

6 ADHD in Adults

ADHD is known to persist into adulthood, even though there is no consensus on the exact rate. Longitudinal studies have found persistence rates ranging from 4% to 76% (Caye et al. 2016b). Previous studies indicate that about 15% of childhood cases present full diagnostic criteria in adulthood, while 65% persist with symptoms causing impairment, but with no full diagnostic criteria, and 20% have no symptoms or impairment in adulthood (Faraone et al. 2006). A meta-analysis indicated that patients with severe ADHD and patients with comorbid conditions (including CD and Major Depressive Disorder) will have higher persistence rates (Caye et al. 2016b). In addition, persistence rates will vary depending on the diagnostic system or tool used and the characteristics of the samples (community or clinical), since clinical samples appear to be composed of more severe cases with more comorbidities, which will inflate persistence rates. Data from the Multimodal Treatment of ADHD (MTA) study also found that parental mental health problems are associated with persistence into adulthood (Roy et al. 2016). Recently, an international collaboration including three populational samples and one clinical sample in three continents developed a risk calculator to estimate the chance of persistence of ADHD from childhood into adulthood based on clinical criteria (Caye et al. 2019 – link: https://ufrgs.br/prodah/adhd-calculator).

In adulthood, inattention symptoms often persist, while hyperactive and impulsivity symptoms usually improve (Cheung et al. 2015). Emotional dysregulation, including low frustration tolerance, irritability, and mood lability, is commonly observed in adults with ADHD and is described by DSM-5 as an associated feature supporting diagnosis (American Psychiatric Association 2013). Studies have shown that emotional dysregulation is primarily related to ADHD itself, rather than comorbid conditions (Skirrow et al. 2014; Skirrow and Asherson 2013) and is also associated with increased impairment (Skirrow and Asherson 2013). It should also be noted that, in adults with ADHD, emotional dysregulation responds to pharmacological treatment with stimulants and atomoxetine (Reimherr et al. 2005; Rösler et al. 2010). Even though emotional dysregulation should be viewed as a core component of ADHD, it is not used as diagnostic criterion due to its frequent occurrence in other comorbid conditions (Asherson et al. 2016).

ADHD in adults is also associated with excessive mind-wandering, or mental restlessness (Seli et al. 2015), with dysfunctions of executive control, such as

inhibitory control and working memory (Pievsky and McGrath 2018), and with sleep problems (Van Veen et al. 2010). The symptoms of ADHD in adults may be more heterogeneous and subtle when compared to children and adolescents. For example, hyperactivity might be present as constant activity, overscheduling, or choosing a busy job while impulsivity can manifest through problems such as quitting jobs, ending relationships prematurely and being unwilling to wait in line. Inattention usually manifests as distractibility, difficulties in remembering appointments, and difficulties with time management.

Not surprisingly, ADHD in adulthood is associated with a wide range of negative outcomes. Among those are occupational failure with lower employment rates (Fletcher 2014), a 34% reduction in earnings relative to non-ADHD siblings (Fletcher 2014), and a higher likelihood of receiving disability pension (Jangmo et al. 2021). A study performed in a large population sample demonstrated that adults with ADHD present extensive financial problems even after controlling for income, education, psychiatric comorbidities, and substance use (Beauchaine et al. 2020); the financial distress is associated with higher rates of suicide (Beauchaine et al. 2020). A study with over 36,000 subjects, patients with ADHD showed increased risk of gambling problems and spending too much money (Bernardi et al. 2012). Diagnosis of ADHD was associated with being divorced and with emotional loneliness (Michielsen et al. 2015). Young adults with ADHD were 60% more likely to have been convicted of a crime, and 70% more likely to have been incarcerated (Mohr-Jensen et al. 2019). Patients with ADHD are 23% more likely to be involved in vehicular crashes (Vaa 2014), with increased risk of serious transport accidents (Chang et al. 2014) and higher mortality rates (Dalsgaard et al. 2015b). Patients with ADHD are also more likely to attempt suicide, with higher rates of death (Chen et al. 2019; Fitzgerald et al. 2019; Huang et al. 2018; Septier et al. 2019; Sun et al. 2019). ADHD is still highly comorbid in adulthood, including comorbid mood disorders, anxiety disorders, bipolar disorder, substance use disorder, and personality disorders (Katzman et al. 2017).

ADHD is traditionally conceptualized as a neurodevelopmental disorder, in which adults with the diagnosis should have experienced impairing symptoms since childhood. More recently, however, longitudinal data following individuals with and without ADHD from childhood to adulthood have suggested the existence of a significant proportion of adults with a late-onset of ADHD symptoms. In a Brazilian study, 84.6% of the young adults with ADHD did not meet criteria for ADHD at the age 11 (Caye et al. 2016a). Similar findings were observed in a study performed in New Zealand (Moffitt et al. 2015) and one performed in the United Kingdom (Agnew-Blais et al. 2016). Several possible explanations for these findings have been discussed, as reviewed elsewhere (Asherson and Agnew-Blais 2019; Caye et al. 2017). Among these are a change of the informant reporting ADHD symptoms, the possibility of symptoms being derived from other psychiatric conditions, subthreshold ADHD symptoms in childhood not captured in the longitudinal studies, heterotopic neurodevelopmental trajectories and childhood ADHD masked by family environment or high intelligence quotient (IQ). Although these factors appear to explain a relatively large portion of the late-onset cases, current evidence

appears to converge on the existence of a proportion of patients with ADHD in adulthood with no symptoms during childhood. Current investigations have been trying to explore the extent to which late-onset ADHD reflects the same pathophysiology as early childhood-onset form of ADHD. In this sense, recent findings point to lower genetic factors in late-onset ADHD, suggesting that environmental pressures might be more relevant for this population (Agnew-Blais et al. 2021).

Recent findings have highlighted new aspects regarding the longitudinal course of ADHD remission from childhood to adulthood. A study conducted by Sibley et al. (2021, personal communication) evaluated 558 children with ADHD from the MTA study, which originally compared 14 months of pharmacological and psychosocial treatments for children with ADHD (The MTA Copoperative Group 1999). Children were 7–10 years old at the beginning of the original study and were followed from childhood through young adulthood for a period of 16 years while submitted to serial clinical assessments. The authors observed that approximately one-third of children with ADHD experienced full remission at some point during the follow-up period (Sibley et al. 2021, personal communication). Most interestingly, about 60% of the fully remitted subjects experienced full or partial recurrence of ADHD after the initial period of full remission (Sibley et al. 2021, personal communication). Sustained remission to the study endpoint was observed in only 9% of the sample, while the majority of the 558 children with ADHD (64%) presented fluctuating periods of persistence and remission over time (Sibley et al. 2021, personal communication). These findings suggest that childhood-onset ADHD is a chronic, but waxing/waning disorder, characterized by a fluctuating nature, and highlight the need for future studies investigating environmental factors that could trigger symptom fluctuation.

7 Conclusion

In every period of the life span, ADHD is associated with significant impairment and distress to patients and their families. Decades of research consistently report strong links between ADHD and adverse life outcomes. Children with ADHD show an increased risk of accidental injuries, poor relationship with peers and parents, worse quality of life, and impaired school performance. Adolescents with ADHD show more school refusal and grade retention, earlier and more frequent use of marijuana, tobacco, and other drugs, earlier sexual engagement and more frequent teenage pregnancy. Adult ADHD is associated with lower education attainment, reduced job performance, and an increased risk of traffic accidents, criminality, unemployment, and substance abuse. A common denominator that encompasses all life periods is increased mortality by external and accidental causes. While the core features of the disorder remain the same throughout development, there are specificities of each stage of the life-cycle in the presentation of ADHD that should be considered in the clinical assessment of the disorder. While there is a pattern of mean symptom decrease from childhood to adolescence, persistence of the disorder occurs

in a substantial proportion of individuals with ADHD, and some even experience an increase in the level of symptoms and impairment after childhood.

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Current Pharmacological Treatments for ADHD

Madeleine J. Groom and Samuele Cortese

Contents

Abstract Attention-Deficit Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition associated with impaired function and increased risk of poor outcomes in children, young people and adults with the condition. Currently approved pharmacological treatments for ADHD include a range of

M. J. Groom (✉)
Academic Unit of Mental Health and Clinical Neurosciences, School of Medicine, Institute of Mental Health, University of Nottingham, Nottingham, UK
e-mail: Maddie.Groom@nottingham.ac.uk

S. Cortese
Faculty of Environmental and Life Sciences, Center for Innovation in Mental Health, School of Psychology, University of Southampton, Southampton, UK

Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK

Solent NHS Trust, Southampton, UK

Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York, NY, USA

Centre for ADHD and Neurodevelopmental Disorders Across the Lifespan, Institute of Mental Health, University of Nottingham, Nottingham, UK

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stimulant (methylphenidate, amphetamine) and nonstimulant (atomoxetine, guanfacine, clonidine) medications. All have been shown to be effective in treating the symptoms of ADHD and improving other functional outcomes including quality of life, academic performance, rates of accidents and injuries, and do not appear to be associated with significant adverse outcomes or side effects. In this chapter, we review medications for ADHD by summarising the mechanisms of action of each of the two main classes of compounds (stimulants and nonstimulants), the formulations of the most commonly prescribed medications within each class, their efficacy in treating ADHD symptoms and other outcomes, and other factors that influence treatment decisions including side effects and tolerability, comorbidities and medical history. We conclude with a summary of the treatment decisions made by clinicians and suggest some next steps for research. Further research is needed to understand the mechanisms of action of these medications and how exactly they improve symptoms, and to examine their effects on commonly occurring comorbidities.

Keywords ADHD · Amphetamine · Clonidine · Comorbidity · Efficacy · Functional outcomes · Guanfacine · Methylphenidate · Nonstimulant · Stimulant · Tolerability · Treatment

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
AMP	Amphetamine
ASD	Autism spectrum disorder
ATX	Atomoxetine
BP	Blood pressure
CD	Conduct disorder
CLON	Clonidine
CNS	Central nervous system
CNV	Copy number variation
DA	Dopamine
DAT	Dopamine transporter
EF	Executive functions
FDA	Food and Drug Administration (USA)
GXR	Guanfacine – extended release
HR	Heart rate
HRQoL	Health-related quality of life
LC	Locus coeruleus
LDX	Lisdexamfetamine
MAO	Monoamine oxidase
MPH	Methylphenidate
MR	Magnetic resonance
MRI	Magnetic resonance imaging

NE	Norepinephrine
NET	Norepinephrine transporter
NICE	National Institute for Health and Care Excellence (UK)
ODD	Oppositional defiant disorder
PFC	Prefrontal cortex
QoL	Quality of life
RCT	Randomised controlled trial
RTV	Reaction time variability
SNP	Single nucleotide polymorphism
SUD	Substance use disorder
WHO	World Health Organisation
WM	Working memory

1 Introduction

ADHD is associated with significant adverse outcomes in mental and physical health, and increased risk of criminality, substance misuse and long-term unemployment (Daley et al. 2019). The costs to healthcare and society are significant (Swensen et al. 2003; Gustavsson et al. 2011; Sciberras et al. 2020). Effective intervention can reduce the risks of these negative outcomes (Boland et al. 2020) and can therefore increase the potential for people with ADHD to live productive and satisfying lives.

Medication is recommended as a core component of treatment for ADHD in evidence-based national guidelines in a number of countries worldwide (see Table 1) and has been shown to be cost-effective (Jensen et al. 2005; Wu et al. 2012). The emphasis in these guidelines is on first-line treatment with medication in moderate to severe cases of ADHD aged 6 years and over, with psychosocial or behavioural therapies offered as an adjunct or as first-line treatment in those whose symptoms are mild or who are too young for medication.

Psychostimulant medications (methylphenidate (MPH) and amphetamines (AMP)), and the nonstimulant, atomoxetine (ATX), are now licensed for the treatment of ADHD in many countries throughout the world, including the UK, USA, Canada, Europe, Australia, India, Saudi Arabia and parts of Africa. Increasingly, medications licensed to treat children and adolescents (aged 6 to 17 years) are now also licensed for treatment of adults with ADHD. More recently, α_2-adrenergic nonstimulant treatments (clonidine and guanfacine) have been made available in some countries, although they are less frequently licensed than MPH, AMP and ATX. As shown in Table 1 stimulants are recommended as first-line medication in all the included guidelines, although some guidelines recommend offering a choice between MPH or AMP or the nonstimulant ATX. Medications for ADHD all influence central nervous system (CNS) function (Arnsten and Dudley 2005; Berridge and Arnsten 2013; Chandler et al. 2014; Arnsten 2020) and have been

Table 1 Treatment guidelines for ADHD in several countries. The table provides a representative overview of guidelines in different geographical regions of the world and the similarities and differences between them but is not an exhaustive list of all ADHD guidelines worldwide

Country	Organisation	Publication	Specification
UK	National Institute for Health and Care Excellence (NICE)	National Institute of Health and Care Excellence (2018)	*Children aged less than 5 years:* Offer parent-training. Only offer medication with advice from a specialist ADHD service *Children and young people aged 5 years and over*: Offer psychoeducation and parent-training. If symptoms persist, offer MPH first for 6 weeks. If no response, switch to LDX after 6 weeks or DEX if cannot tolerate LDX Offer ATX or GXR if no benefit from MPH or LDX/DEX Consider CBT for young people who have some benefit from medication but whose symptoms are still causing significant impairment in at least one domain *Adults (>17 years):* Offer medication to adults if environmental modifications have been tried but symptoms are still causing significant impairment. Offer MPH or LDX first for 6 weeks (switch from LDX to MPH or vice versa if no benefit) Offer DEX to adults whose symptoms are responding to LDX but cannot tolerate the longer effect profile Offer ATX if no response or cannot tolerate MPH or LDX after 6-week trials
USA	American Academy of Pediatrics (APA)	Wolraich et al. (2019)	*Children aged 4–5 years*: Consider MPH in children with moderate to severe symptoms for whom parent-training/behaviour modification has not been successful[a] *Children aged 6–11 years and adolescents aged 12–17*: Prescribe an FDA-approved medication in conjunction

(continued)

Table 1 (continued)

Country	Organisation	Publication	Specification
			with parent-training and classroom interventions. Try MPH or AMP first. If no response or families are concerned about abuse/diversion potential, offer nonstimulant. Combine stimulant and nonstimulant in those who show partial response to stimulants *Adults*: No recommendations
Canada	Canadian ADHD Resource Alliance (CADDRA)	Canadian ADHD Resource Alliance (2018)	*All age groups*: Psychoeducation and psychological interventions that are appropriate to the individual's developmental stage and circumstances are advocated First-line treatments: Long-acting stimulants (LDX, MPH, MAS) with an adequate trial to measure response before considering second-line treatment Second-line treatments: ATX, GXR and short/intermediate acting stimulants (MPH, DEX), or long-acting nonstimulants (GXR or ATX in children aged 6–17 years, GXR in adults aged 18 and over) in patients who experience significant side effects/no response to first-line medications. Combine these with first-line medications in sub-optimal responders Third-line treatments: Bupropion, CLON, imipramine, modafinil (reserved for treatment-resistant cases and require specialise input)
Australia	National Health & Medical Research Council	Australian Government National Health and Medical Research Council (2012)	*Children aged less than 7 years and aged 6 to 12 years:* Behaviour modification, family therapy, CBT recommended first. Only offer medication if these are ineffective *Adolescents:* CBT

(continued)

Table 1 (continued)

Country	Organisation	Publication	Specification
			recommended Only if psychosocial interventions are ineffective, offer stimulant medication (MPH or DEX) for 1 month Clinicians are referred to other sources, including NICE guidelines, for decisions around nonstimulant medication prescribing *Adults:* No recommendations
Spain[b]	Ministry of Health, Social Services and Equality	Alda et al. (2017)	*Children aged less than 6 years:* Pharmacological therapy not recommended *Children aged over 6 years:* Offer psychoeducational and/or psychological therapies first. When symptoms are severe, or if these interventions are not effective, offer MPH, LDX, GXR or ATX *Adults:* If symptoms are mild, offer non-pharmacological treatments. Pharmacological recommended for moderate to severe symptoms. If LDX and OROS-MPH were prescribed in childhood, continue these medications into adulthood. Otherwise, ATX
Germany[b]	Association of the Scientific Medical Societies in Germany	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, (AWMF) [Association of the Scientific Medical Societies in Germany] (2017)	*Children aged 6 years and over:* If symptoms are mild, offer psychosocial treatment and psychotherapy with supplementary pharmacotherapy only in isolated cases to treat residual symptoms. For moderate symptoms offer intensified psychosocial intervention/psychotherapy or pharmacological treatment. Severe symptoms: Intensive psychoeducation followed by pharmacotherapy with psychosocial therapy. In all cases, medication structure is stimulants first choice (MPH then DEX or LDX if inadequate response),

(continued)

Table 1 (continued)

Country	Organisation	Publication	Specification
			nonstimulants (ATX or GXR) as second choice if stimulants not suitable/tolerated *Adults:* Start with psychoeducation/psychotherapy and offer pharmacotherapy only for more severe symptoms or as an adjunct to non-pharmacological therapies. When medication is offered, offer MPH (delayed or extended release) or DEX or LDX as first-line and then offer ATX if stimulants are not sufficiently effective or tolerated
India	Indian Psychiatric Society	Shah et al. (2019)	*Children aged less than 6 years*: Offer psychosocial interventions. Only offer medication if significant impairment persists *Children aged 6+ years:* Offer environmental modifications first then parent-training if symptoms are not severe. If symptoms are severe or do not respond to these interventions, offer MPH for 6 weeks. If poor response, offer ATX or CLON, with preference for ATX *Adults:* No recommendations
Saudi Arabia	Saudi ADHD Society	Bashiri et al. (2021)	*Children < 5 years:* Offer psychosocial interventions. Do not offer medication without specialist advice *Children 5 years and older:* Offer group-based psychoeducation first, then CBT. Offer pharmacotherapy if symptoms persist. First-line: MPH. Second-line: LDX or DEX. Third-line: ATX or GXR *Adults:* Offer psychosocial therapies first. If symptoms persist, offer

(continued)

Table 1 (continued)

Country	Organisation	Publication	Specification
			pharmacotherapy. First-line: MPH or LDX. Second-line: DEX or ATX
South Africa	South African Society of Psychiatrists	Child guidelines: Flisher and Hawkridge (2013) Adult guidelines: Schoeman and Liebenberg (2017)	*Children:* If symptoms are mild/moderate with minimal impairment or family do not want medication, use behavioural interventions as first-line If symptoms are severe or behavioural treatment is not effective, offer medication trial. Offer MPH or ATX first. Switch to other one if no or limited response If still no response, check diagnosis is correct then offer CLON or tricyclic antidepressants *Adults:* Multimodal treatment is advocated, combining non-pharmacological and pharmacological therapies. Based on guidelines in other countries (e.g. NICE, APA, CADDRA), extended-release stimulants are recommended, in combination with immediate-release stimulants to 'top up' if the ER dose starts to wear off. ATX recommended as second-line. The alpha-adrenoceptor agonists are not available

MPH Methylphenidate, *AMP* Amphetamine, *LDX* Lisdexamfetamine, *DEX* dexamphetamine, *ATX* Atomoxetine, *GXR* Guanfacine-extended release, *CLON* Clonidine, *MAS* Mixed Amphetamine Salts, *CBT* Cognitive Behavioural Therapy

[a] MPH has not yet received FDA approval for treatment of children aged less than 6 years and use is therefore off-label

[b] Summaries of the guidelines were retrieved from the website of the ADHD Institute (ADHD Institute 2021)

shown to reduce core symptoms of ADHD (inattention, hyperactivity, impulsivity) with varying degrees of efficacy (Cortese et al. 2018). All are also associated with side effects and there are some contraindications to their use, including medical history and risk of substance misuse (Cortese et al. 2018; Cortese 2020). These factors, coupled with the preferences of the parent, child/young person, or adult with

ADHD, must be brought together to develop an appropriate treatment plan for each individual case.

2 Medications for ADHD and Their Mechanism of Action

2.1 Stimulant Medications

Stimulant medications include MPH and AMP. As shown in Table 1, national guidelines in several countries advocate the use of MPH and AMP as first-line treatments for moderate to severe ADHD symptoms in children and adolescents aged 6 years and over, and adults. Stimulants increase extracellular dopamine (DA) in the striatum and to a lesser degree, norepinephrine (NE) in the prefrontal cortex (PFC) (reviewed in: Faraone 2018). It is thought that these pharmacological effects are responsible for the clinically therapeutic effects of stimulant medications in treating ADHD symptoms, although the specific relationship between modulation of DA and NE transmission and ADHD symptoms has yet to be established (Childress et al. 2019).

2.1.1 Methylphenidate

MPH is a racemic mixture with a 50:50 ratio of *d*-threo-MPH and *l*-threo-MPH; the *d*-threo enantiomer affects extracellular concentration of DA in striatum, whereas the effects of *l*-MPH are not specific to the CNS and binding to the DAT is comparatively low (Markowitz and Patrick 2008; Childress et al. 2019). Plasma concentrations of *d*-threo-MPH correlate with the proportion of DAT blockade in the striatum in a dose-dependent manner. In seminal PET imaging studies in humans, Volkow et al. (1998) reported that peak DAT blockade is reached 60–90 min after oral administration and suggested that it is the time taken to reach this peak in plasma that likely explains why there is not usually a 'high' associated with these stimulant medications, unlike substances such as cocaine, which have a much more rapid effect (reviewed in: Swanson and Volkow 2002).

There are subtle (but potentially clinically important) differences in the ways that MPH and AMP influence DA and NE transmission. The primary action of MPH is to block DA transporters (DAT) in the striatum (Swanson and Volkow 2002; Martinez et al. 2020) where the largest concentration of DA receptors in the brain is located, thereby increasing extracellular dopamine in the striatum and activation of its afferent targets, including PFC. It should be noted that evidence is inconsistent as to whether these effects are primarily in ventral or dorsal striatum (see: Faraone 2018 for a review). Transporter blockade reduces reuptake of the neurotransmitter presynaptically thereby prolonging the effect of the neurotransmitter on the postsynaptic receptors (Swanson and Volkow 2002). MPH also blocks NE transporters (NET) in the PFC (Childress et al. 2019) with evidence of high affinity of MPH for NET

(Hannestad et al. 2010). It has been suggested that increases in both DA and NE following MPH administration occur because NE and DA compete to bind with the NET, which are significantly more abundant in PFC than DAT, resulting in increases in extracellular levels of both catecholamines in the PFC (Arnsten and Dudley 2005; Spencer et al. 2015). [See Chapters "New Drugs to Treat ADHD: Opportunities and Challenges in Research and Development" and "Effects of Methylphenidate on the Dopamine Transporter and Beyond" for a comprehensive overview of biological/pharmacological action of MPH.]

2.1.2 Amphetamine

AMP also increases extracellular levels of DA in the striatum and NE in the PFC but the mechanisms are slightly different to those of MPH. AMP reduces reuptake of DA and NE but, at higher doses, also interacts with vesicular monoamine transporter-2 (VMAT2) presynaptically to increase release of DA from synaptic vesicles and reverse DAT uptake (Faraone 2009; Hodgkins et al. 2012; Heal et al. 2013). These effects on presynaptic release occur at high doses and are unlikely to explain the clinically therapeutic effects on ADHD but they are associated with a drug 'high' and therefore with abuse potential, as well as impairing effects on cognition (Spencer et al. 2015). AMP also weakly inhibits monoamine oxidase (MAO), which is responsible for intraneuronal metabolism of DA and NE, thereby further increasing indirectly their availability at the postsynaptic receptor.

Similarities and differences in the way that MPH and AMP influence extracellular concentrations of DA and NE might partly account for a proportion of the inter-individual variability in treatment response between these two types of stimulant medication. Notably, Volkow et al. (2002a) suggested that individual differences in the amount of DA released into the synaptic space may then influence the rate of DAT blockade: those with lower amounts of DA release will be influenced more strongly by DAT blockade than those with higher rates of DA release. Similar to MPH, further research is needed to understand individual differences in DA and NE transmission following clinically therapeutic doses of AMP, to determine whether these differences are relevant for predicting treatment response.

Further research is also needed to establish the relative roles of DA and NE transmission in the therapeutic effects of stimulant medications for ADHD. In particular, individual differences in DAT and NET availability and distribution, mediated by genetic polymorphisms on the DAT and NET genes (Hahn et al. 2011; Sigurdardottir et al. 2016), might contribute to individual differences in response to MPH. Radioligands that are effective in competing for NET have been developed in recent years and indicate reduced NET availability in ADHD (Sigurdardottir et al. 2016; Ulke et al. 2019) (although see: Vanicek et al. (2014) who reported no significant difference between adults with ADHD and a typical control group). This means that knowledge of the effects of MPH and AMP on NET will increase and give a more accurate picture of the balance between DAT and NET, given that research to date has predominantly focused on the role of DA in understanding the effects of these medications. It has also been suggested that individual

differences in DA release, as well as DAT availability, may be crucial to understanding the effects of MPH on ADHD symptomatology (Volkow et al. 2002b). Furthermore, there is a need to map the effects of MPH and AMP on DA and NE in different brain regions and link these more systematically to cognitive and functional impairments in this population to better understand the mechanisms of action at the level of brain networks (Swanson et al. 2011). Gaining greater insight into individual differences in treatment response is an important aim for future research given the often slow, trial-and-error approach to identifying the right medication for each individual child or adult affected by ADHD.

2.2 Nonstimulants

As outlined above, stimulants are recommended as first-line treatments for ADHD, in those aged 6 years and over, in clinical guidelines. However, a substantial proportion of children with ADHD (up to 30%) do not respond to stimulant medication (Spencer et al. 1996; Bates 2009) and there are others who cannot tolerate the side effects which include loss of appetite, weight loss and disrupted sleep (Cortese et al. 2013; Connolly et al. 2015). Although the proportion of non-responders is small relative to the numbers of responders, in real terms this represents a significant number of children, adolescents and adults with ADHD worldwide who do not benefit from stimulant medication. In addition, where there is risk of misuse or diversion of stimulant medication, or where there are medical factors or other comorbidities that contraindicate stimulant use, an alternative treatment is needed. These alternative, nonstimulant therapies currently comprise atomoxetine and NE receptor agonists, guanfacine and clonidine. Others are available but are not yet commonly recommended in national guidelines so in this chapter we will consider only these three nonstimulant medications.

2.2.1 Atomoxetine

ATX is a selective NE reuptake inhibitor recommended for children and adolescents with ADHD who do not respond well to stimulants or who have comorbidities that preclude the use of stimulants (Hutchison et al. 2016). It was the first nonstimulant medication to be approved by the Federal Drug Administration (FDA (USA)) and recommended by national guidelines in several countries. Randomised Controlled Trials (RCTs) and meta-analyses indicate that the efficacy of ATX is lower than MPH or AMP (see Sect. 5), but it can be particularly useful when stimulant medications are contraindicated. ATX inhibits reuptake of NE by blocking presynaptic NET, thereby increasing synaptic concentrations of NE and stimulating postsynaptic α_2-adrenoceptors (Clemow and Bushe 2015). Relative to stimulant medications, ATX has a much higher affinity and selectivity for NE than DA transporters but it should be noted that it also inhibits DA reuptake in the PFC indirectly through its blockade of NET (Clemow and Bushe 2015).

2.2.2 Guanfacine and Clonidine

The extended-release versions of guanfacine (GXR) and clonidine (CLON) are nonstimulant medications approved for use as monotherapy and adjunctive therapy (most commonly as adjuncts to stimulant medications) to treat children and adolescents in the UK, the USA and Canada (see Table 1). Both are NE receptor agonists; unlike ATX, they stimulate postsynaptic receptors directly rather than by blocking reuptake of NE from the synaptic cleft (Huss et al. 2016). GXR is highly selective for the α_{2A}-adrenoceptor subtype, while CLON stimulates all α-adrenoceptor subtypes (α_{2A}, α_{2B} and α_{2C}) (Hirota 2014). Alpha$_{2A}$- and α_{2C}-adrenoceptors are found throughout the brain (although the PFC contains mostly the α_{2A} subtype) whereas the α_{2B}-subtype is most prevalent in thalamus (Huss et al. 2016).

In keeping with its properties as an α_{2A}-adrenoceptor specific agonist, guanfacine was initially designed to enhance PFC-dependent executive functions (EFs) including working memory (Wang et al. 2007). Evidence suggests that the cognitive-promoting benefits of guanfacine arise from stimulation of α_{2A}-adrenoceptors, predominantly located on the dendritic spines of PFC pyramidal neurons, where they stimulate intracellular communication by closing voltage-dependent hyperpolarisation-activated and cyclic nucleotide-gated (HCN) channels, thereby strengthening pre-frontal cortical networks (Arnsten 2009; Huss et al. 2016; Arnsten 2020). This increase in functional connectivity supports EFs and may also be fundamental to the positive effects of these medications on ADHD symptoms (Berridge and Arnsten 2013; Arnsten 2020). Antagonistic, but complimentary, roles of these medications on NE and DA signalling have been proposed by Arnsten (2020): specifically, stimulation of prefrontal D1 receptors (a subtype of DA receptors and the most abundant in the brain) stimulates voltage-dependent HCN channels causing them to open, leading to reduced network connectivity and thereby reducing 'noise', while NE receptor stimulation closes these channels and retains the integrity of task-specific functional networks, enhancing the 'signal' and supporting focused attention. Together, these two actions of NE and D1 receptor stimulation are proposed to enhance the 'signal to noise' ratio of stimulus processing during cognitive tasks (Chandler et al. 2014).

Further research is needed to understand the mechanisms through which ADHD medications ameliorate the clinical and cognitive impairments associated with the condition. The NE receptor agonists are a prime example of drug development driven by experimental work to first understand the mechanisms of action of specific compounds. Swanson et al. (2011) suggest that fuller examination of cognitive profiles of strengths and difficulties in ADHD may facilitate better understanding of the mechanisms of action of currently available medications but may also lead to new developments that target cognitive functions and their neural substrates more precisely. Similarly, Connolly et al. (2015) propose that the identification of functionally relevant copy number variations (CNVs) may drive forwards pharmacogenetic approaches that are driven by an understanding of the effects of specific single nucleotide polymorphisms (SNPs) on neuronal signalling, rather than

focusing on genes involved in DA and NE transmission, such as DAT and DRD4 which have offered limited success in understanding the mechanisms of medications for ADHD. In the next section, we briefly describe ways in which the design of specific medications can influence their mechanisms of action.

3 Pharmacokinetics of ADHD Medications

The speed of onset and duration of the effects of medications for ADHD differ depending on their precise formulation and drug design; these differences offer a significant amount of flexibility in selecting the right treatment for individuals. Table 2 summarises the main FDA-approved medications for ADHD, including their formulation, drug delivery mode and approximate duration of response. A fuller review of these different drug designs is beyond the scope of this chapter; the interested reader is referred to Brown et al. (2018); Childress et al. (2019); Cortese (2020) for further information on this topic. [See also: Chapters "The Benefits and Limitations of Stimulants in Treating ADHD" and "New Drugs to Treat ADHD: Opportunities and Challenges in Research and Development"].

Initially, MPH and AMP were available only as immediate-release formulations, which reach peak plasma concentrations rapidly (within 1–3 h). These are effective in reducing symptoms (Moreira Maia et al. 2017) but extended-release preparations are now often preferred and outnumber immediate-release options (see Table 2). The majority of extended-release preparations are designed to release the drug bi-phasically, mimicking the multi-dosing regimen of immediate-release formulations but without the disadvantages that arise from sustained exposure over long periods of time (Childress et al. 2019). To achieve this, they combine immediate- and extended-release components in varying ratios resulting in longer lasting effects (generally up to 9–12 h), whilst requiring only one daily dose, and thereby negating the difficulties of trying to adhere to multiple dosing during the school or working day. They also have lower abuse potential because of their slower action, although nonstimulants are still preferable for those deemed to be at significant risk of abuse or diversion (Martinez-Raga et al. 2017) (see Sect. 7 for further discussion).

The preparations of MPH (see Table 2) differ in the way they release the drug. For example, 'Osmotic-release oral system methylphenidate' (OROS-MPH) releases MPH via an osmotic pump that expands as water permeates the membrane. This drug delivery platform releases 22% of MPH immediately and the remainder is released gradually over the course of several hours. In contrast, the 'Controlled Delivery' formulations deliver approximately 30% immediately and the 'Spheroidal Oral Drug Absorption System' (SODAS) platform releases 50% immediately, with the remainder released over an extended time-period.

Similarly, AMP formulations comprise different drug delivery platforms such as 'extended release orally disintegrating tablet' (XR-ODT), which delivers AMP via an orally disintegrating tablet combining a 50:50 ratio of immediate to extended-release delivery. These drug delivery modes result in different peak plasma times and different response durations, which may be better suited to individual patients,

Table 2 Pharmacodynamics of extended-release stimulant medications and nonstimulant medications for ADHD

Medication class	Preparation	Drug delivery platform (IR:ER %)	Form	Approx duration of response (h)[b]
Stimulants				
	Methylphenidate	OROS-MPH (22:78)	Tablet	10–12
	Methylphenidate	MPH-CD (30:70)	Tablet[a]	8
	Methylphenidate	SODAS (50:50)	Capsule[a]	8
	Methylphenidate	Transdermal patch (N/A)	Transdermal patch	9
	Methylphenidate	LiquiXR (20:80)	Liquid suspension	8–12
	Dexmethylphenidate	SODAS (50:50)	Capsule[a]	9–12
	Mixed amphetamine salts	SODAS (50:50)	Capsule	8–12
	Lisdexamfetamine	Prodrug (N/A)	Capsule[a]	10–12
	Dexamphetamine sulphate	Bead capsule (50:50)	Capsule[a]	6–9
	Amphetamine	LiquiXR (NR)	Liquid suspension	8–12
	Amphetamine	XR-ODT (50:50)	Tablet	9–12
	Mixed amphetamine salts	Triple-bead MAS-ER (NR)	Capsule[a]	16
Nonstimulants				
	Atomoxetine	N/A	Capsule	24
	Guanfacine-ER	N/A	Tablet	12–24
	Clonidine-ER	N/A	Tablet	12–24

ER Extended Release, *OROS-MPH* Osmotic-release oral system methylphenidate, *MPH-CD* methylphenidate-Controlled Delivery, *SODAS* Spheroidal Oral Drug Absorption System, *XR-ODT* extended release orally disintegrating tablet, *MAS-ER* Mixed amphetamine salts extended release, *N/A* Not applicable, *NR* Not reported

[a] Capsule/tablet can be chewed or sprinkled on food or swallowed whole

[b] Information obtained from the website of chadd.org (CHADD 2021)

depending on the time of day when they need to gain the most benefit. It is worth noting that lisdexamfetamine (LDX), an amphetamine-based medication, has different pharmacokinetic properties from other amphetamines. Specifically, LDX is a prodrug, whereby the core component (*d*-amphetamine) is inactive until the lys-moiety is cleaved by metabolism resulting in in vivo transformation of lisdexamfetamine into *d*-amphetamine (Heal et al. 2013). This mode of delivery reduces the abuse potential of this drug and also promotes longer acting effects on symptoms (up to 13 h, as well as avoiding inter-individual effects in gut metabolism, which can influence the onset and duration of medication effects but are difficult to predict a priori in individual patients (Goodman 2010)).

Nonstimulant medications take longer to reach a clinically therapeutic effect, although peak plasma effects can be just as rapid as stimulant medications. For

instance, ATX reaches peak plasma levels after 1–2 h with a half-life of around 5 h in most people, although this can be up to 20 h in some (Barton 2005). Based on RCTs and open-label design studies, there appear to be sub-groups of non-responders, partial responders and maximal responders, with the latter group showing a response after just 1 week, but the other two groups potentially taking over 12 weeks to reach a therapeutic response (reviewed in: Clemow and Bushe 2015). Indeed, there is evidence that the magnitude of the therapeutic response of ATX increases during RCTs and that the maintenance of response after treatment withdrawal is longer for ATX than for stimulant medications (Buitelaar et al. 2015). This may explain why once-daily dosing is sufficient for this medication, resulting in symptom reduction which persists into the evening (Clemow and Bushe 2015), despite a 5 h half-life for most people. This pattern of effects also raises the interesting question of whether the typical 12-week follow-up period in RTCs is sufficient to gain an accurate measure of the efficacy of ATX.

Immediate-release versions of GXR and CLON are considered unsuitable for treatment of ADHD because, as described by Huss et al. (2016), the rapid ascension to peak plasma levels results in unpleasant sedative effects such as fatigue and somnolence and the short half-life necessitates multiple dosing throughout the day. The extended-release formulations are slower, reaching peak plasma levels around 5 h after oral administration, with a half-life up to 17 h, resulting in a gradual and sustained effect on receptor activation. However, it can take up to 2 weeks before clinically therapeutic effects are seen on ADHD symptoms.

In the next section we present evidence relating to the neural mechanisms proposed to give rise to ADHD and how ADHD medications may target these mechanisms.

4 ADHD Medications and the Cognitive Neuroscience of ADHD

ADHD is associated with atypical function in a range of cognitive domains. These cognitive impairments and the brain systems underpinning them provide important insights into the aetiology of ADHD and further our understanding of the mechanisms of action of ADHD medications. Cognitive functions most frequently affected in ADHD include attention and the executive functions including response inhibition, task-switching, selective and divided attention and working memory (Rommelse et al. 2011). These functions depend upon the PFC and its connectivity with other cortical and sub-cortical brain regions including the basal ganglia, anterior cingulate cortex, cerebellum, thalamus, and the temporal, parietal and occipital association cortices (Duncan and Owen 2000; Miller and Cohen 2001). Atypicalities in these brain regions in ADHD have been reported in many functional and structural MRI studies (for reviews see: Konrad and Eickhoff 2010; Cortese and Castellanos 2012; Rubia 2018). Furthermore, stimulant and nonstimulant medications have been

shown to enhance cognition and normalise activity in the brain networks that support cognitive function (Groom et al. 2010; Liddle et al. 2011; Rubia et al. 2014; Hawk et al. 2018).

Catecholamine signalling is strongly implicated in the cognitive processes commonly found to be impaired in ADHD (Chandler et al. 2014). Both DA and NE show an inverted U-shaped relationship with cognitive performance: too much or too little of either neurotransmitter is associated with poorer performance (Arnsten 2009). Moderate levels of NE stimulate postsynaptic α_{2A} receptors in the PFC and are associated with good performance on tasks of working memory, response inhibition and attention in animal studies, whereas low levels are associated with a drowsy, inattentive state (Aston-Jones and Cohen 2005). High levels, for instance under conditions of stress, stimulate the lower affinity α_{2B} receptors, leading to distractibility and poorer cognitive performance (Arnsten 2009). Dopaminergic effects on cognition are thought to arise from stimulation of D1 receptors such that moderate rates of stimulation lead to optimal performance but higher rates are associated with suppressed firing and are linked to poorer cognitive function (reviewed in: Berridge and Arnsten 2013). This evidence, coupled with evidence of atypical DAT and NET levels in ADHD (Dougherty et al. 1999; Jucaite et al. 2005), suggests that DA and NE transmission is atypical in ADHD and that ADHD medications exert their effects by enhancing catecholamine signalling in cortico-striatal brain regions.

As well as direct effects on PFC function, NE exerts effects on cognition via modulation of arousal states in response to environmental context and task demands (Aston-Jones and Cohen 2005; Berridge and Arnsten 2013). NE signalling in ADHD has not been thoroughly investigated but more broadly, there is evidence implicating arousal dysregulation in ADHD. For instance, autonomic and electrophysiological markers suggest hypoarousal (Geissler et al. 2014; Strauß et al. 2018; Bellato et al. 2020), which may contribute to some of the cognitive deficits commonly reported in ADHD, including difficulties with response conflict/inhibitory processing (Borger and van der Meere 2000; Bellato et al. 2021) and increased response time variability (RTV) (Kuntsi and Klein 2012; Karalunas et al. 2014). Furthermore, both MPH and ATX reduce RTV (Ni et al. 2016), implicating NE and DA-mediated effects on arousal in the mechanisms of action of these medications.

In summary, there is a range of evidence demonstrating a clear role for DA and NE in the cognitive and neural differences that have been described in ADHD. These findings provide further context to the mechanisms of action of the main ADHD medications and suggest that they promote cognition, and alleviate symptoms, partly via their effects on frontally mediated brain circuits that rely on DA and NE signalling. The relatively low level of precision afforded by current neuroimaging brain methods precludes a firmer understanding of the roles of DA and NE in cognition in ADHD but, with the growth in techniques such as MR spectroscopy, the increase in high-field strength MRI capable of imaging small regions such as the LC, and the refinement of functional imaging methods, significant advances in knowledge in this area seem likely in the near future.

5 Efficacy and Tolerability: Comparison Between Medications

The individual treatments included in this chapter are efficacious in reducing ADHD symptoms over the short, medium and longer term, provided treatment is maintained (Cortese et al. 2018). The evidence attesting to their efficacy forms the basis of the clinical guidelines that specify how they should be selected and, in combination with prescribing guidelines in each country, how they should be titrated and monitored. For the sake of brevity, we will not review the efficacy and tolerability of each individual treatment. Instead, in this section, we compare the treatments with one another.

A recent systematic review and network meta-analysis (Cortese et al. 2018) compared the efficacy and tolerability of all the primary current pharmacological treatments for ADHD (MPH, AMP (including LDX), ATX, CLON and GXR, in addition to bupropion and modafinil, which, in some countries, are used 'off-licence' for ADHD). The authors calculated (from published and unpublished double-blind RCTs) the standardised mean difference of each treatment against placebo. They also compared treatments with one another by conducting a network meta-analysis, an approach which adjusts for between-study variability and therefore gives a more robust estimate of the differences in efficacy between treatments. The results were calculated separately for children and adolescents (6–17 years) and adults (18+ years). The primary outcome was ADHD symptom change reported by clinicians and, in children and adolescents, teacher-reported symptoms. Secondary outcomes included tolerability (measured as the proportion of participants who left the trial early). Mean differences from baseline were computed at timepoints closest to 12 weeks, 26 weeks and 52 weeks, where available. Of 133 RCTs, 81 reported data from children and adolescents (aged >5 to <18 years), 51 reported data from adults (aged 18+) and 1 reported data from children, adolescents and adults.

The network meta-analysis showed significant effects at the 12-week time-point for all drugs (compared with placebo) on clinician-rated symptoms in children and adolescents. The effects were more variable for teacher-rated symptom improvement with only MPH and modafinil superior to placebo. The pattern of results was similar in adults, but modafinil was not superior to placebo, and there were no data available for CLON or GXR in accordance with the fact that these medications are not yet licensed for use in adults.

In line with previous meta-analyses (Faraone 2009; Faraone and Buitelaar 2010; Hodgkins et al. 2012; Joseph et al. 2017), AMP was superior to MPH and ATX in all the age groups included in the meta-analysis. In addition, AMP was superior to GXR and MPH was superior to ATX in children and adolescents while, in adults, MPH, ATX and bupropion were superior to modafinil. This is partially in line with a previous meta-analysis showing superiority of short- and long-acting stimulants over nonstimulants in adolescents (Faraone 2009) and evidence favouring LDX over other stimulant and nonstimulant medications in children and adolescents (Joseph

et al. 2017). Further research is needed to provide estimates of efficacy of guanfacine in adults.

Previous RCTs have also measured the effects of medication withdrawal, including the duration of maintenance of treatment effects after withdrawal. ATX has been shown to have a substantially longer maintenance phase (post-medication withdrawal) relative to stimulant medications. Specifically, there are positive effects on ADHD symptoms for up to 6 months after ATX withdrawal (Michelson et al. 2004; Buitelaar et al. 2007), albeit at 50% of the maximum clinical effect, whereas stimulant withdrawal leads to a rapid return of symptoms within 1–2 weeks in children (Coghill et al. 2014) and adults (Brams et al. 2012).

With regard to tolerability, the most commonly reported side effects of stimulant and nonstimulant medications are loss of appetite, dry mouth, insomnia, fatigue, headache, nausea, abdominal pain/discomfort and irritability. These side effects are recorded within RCTs and are used to give insights into the side-effect profile of the medication. Tolerability is also assessed by measuring the numbers of participants who leave a trial early due to side effects. The network meta-analysis of Cortese et al. (2018) reported that, in children and adolescents, GXR and AMP were inferior to placebo in terms of their adverse events profile while, in adults, all medications included in the analysis, namely ATX, MPH, AMP and modafinil, were inferior to placebo. The authors also assessed change in weight and blood pressure during the trial. AMP, MPH, ATX were all associated with a significant decrease in weight compared with placebo in children, adolescents and adults; in addition, modafinil led to decreased weight in children and adolescents. Systolic blood pressure increased in children and adolescents treated with MPH, ATX and AMP and in adults treated with MPH and ATX.

Further analyses were conducted on LDX separately from other amphetamines due to the unique pharmacokinetics of LDX. The authors found that LDX was less well-tolerated than placebo in children and adolescents whereas the other amphetamines were tolerated slightly better than placebo, suggesting that the initial tolerability analysis reported above was influenced by the inclusion of LDX in the amphetamine category. This is an important finding because, as described above, LDX has been shown in some studies to have superior efficacy to other stimulant medications, but this may come at the cost of inferior tolerability in some individuals. The tolerability profile for LDX seems to be dependent on age, however, as tolerability was found to be superior to other amphetamines in adults.

In another meta-analysis focusing exclusively on the α_{2A}-adrenoceptor agonists, Hirota (2014) identified issues with tolerability for GXR and CLON. Although neither compound was associated with greater all-cause discontinuation, or discontinuation due to non-efficacy, than placebo across RCTs, all α_{2A}-adrenoceptor agonists were associated with somnolence and fatigue in addition to reduced systolic and diastolic blood pressure and heart rate (see Sect. 7 for further discussion of these effects). This is consistent with Joseph et al. (2017) who reported tolerability that was higher for ATX than GXR, although both were lower than MPH. The α_{2A}-adrenoceptor agonist medications appear to have a slightly different side-effect profile from stimulants and ATX with a greater incidence of somnolence and

sedation. This is an important consideration because some individuals may be more sensitive to these effects, and it is difficult to predict a priori who will be adversely affected. Careful monitoring in the initial phase of titration is needed.

In summary, evidence supports the use of MPH and AMP as first-line medications for ADHD where pharmacological treatment is warranted, as specified in international guidelines (see Table 1). Importantly, although evidence on efficacy and tolerability is weaker for nonstimulant medications, there is sufficient evidence of efficacy to support their use in patients who do not respond to MPH or ATX or cannot tolerate side effects. Identifying adverse events and minimising their persistence is an essential part of treatment titration during the early initiation phase of medication. If titrated properly, as part of regular monitoring, adverse events are less likely to emerge, and therapeutic effects are higher (Martinez-Raga et al. 2017; Huss et al. 2017). This is a particularly important consideration because treatment discontinuation increases the risk of poor long-term outcomes in individuals with ADHD.

Finally, it is important to note concerns about the quality of some research in this field. In separate published Cochrane reviews of the efficacy of MPH (Immediate-Release formulations) and ATX in adults (Cunill et al. 2013; Epstein et al. 2014), studies were rated as low quality, with some classed as very low, indicating that caution is needed when interpreting findings on efficacy in adults. Large standard deviations were found when assessing efficacy and tolerability of the newer (and therefore less well-researched) compounds, GXR and CLON, in the network meta-analysis of Cortese et al., indicating that further research is needed to establish more reliable estimates of the efficacy and tolerability of these medications.

6 Effects of ADHD Medications on Other Outcomes and Comorbidities

Although symptom reduction is often the primary outcome when assessing treatment response, evidence indicates that this may not always be the most important outcome to those with ADHD. Research has highlighted the importance of other outcomes including quality of life (QoL), social function, academic attainment and risks of accidents and injuries. The effects of medication on psychiatric outcomes, either by exacerbating known comorbidities, or increasing the risk of poor mental health outcomes, are also important areas of research. In this section we will consider research that has assessed the effect of ADHD medications on these other outcomes.

QoL is becoming an important outcome of ADHD treatment in recognition that the impact of ADHD extends beyond the symptoms of the condition to other aspects of the person's life (Adamo et al. 2015). Health-related Quality of Life (HR-QoL) is defined by the World Health Organisation (WHO) as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The World Health Organisation Quality of Life [WHOQOL] 2021). It is typically measured

using standardised rating-scales completed either by proxy (usually parents in studies of children and adolescents with ADHD) or self-report (Adamo et al. 2015).

Adamo et al. (2015) reviewed the current evidence of HRQoL in ADHD and reported that there are reductions in HRQoL ratings in ADHD that are at least as large as those for physical health conditions, such as asthma. These authors highlight the importance of HRQoL as an outcome measure in ADHD, both in clinical practice and when investigating treatment effects in RCTs. Coghill et al. (2017) conducted a meta-analysis of RCTs of pharmacotherapy for ADHD and investigated their efficacy on HRQoL in children, adolescents and adults with ADHD. The data were not subjected to meta-analysis but the authors present the statistical results from each study and effect sizes for the comparison of medication against placebo. Of 12 studies that investigated HRQoL in children and adolescents (all parent-ratings), 10 reported a significant effect of medication on at least one HRQoL domain and of these, 7 were associated with an effect size greater than 0.5 (favouring medication over placebo). The most reliable effects were on measures of achievement, risk-taking behaviour and interpersonal relationships and, on these indices, effect sizes were larger for stimulants (effect size range 0.54–1.28) than nonstimulants (effect size range 0.29–0.87). To facilitate a comparison between effects of medication on symptoms and HRQoL, Coghill et al. provided the effect sizes for symptom ratings on the studies they included in their review. In children and adolescents, the effect sizes for symptom ratings range from 0.8 to 1.8 for stimulants and 0.43 to 1.2 for nonstimulants, compared with the HRQoL effect size ranges provided above, revealing that effect sizes for HRQoL are smaller than for symptoms, and also follow the same pattern of larger effect sizes for stimulants than nonstimulants reported by (Cortese et al. 2018). The effects of medications on HRQoL were smaller overall in adults than children and adolescents, ranging from 0.21 to 0.93 from 7 studies, with only one study identifying an effect size greater than 0.5 on one measure of HRQoL, 'life productivity'.

As the data in this review were not appropriate for meta-analysis, and multiple outcome measures and scales were reported, it is difficult to establish an overall effect of medications on HRQoL. The authors also highlight that there are difficulties with measuring QoL, mostly around whether the instrument is specific to ADHD (measures tended to be centred on ADHD in adult studies but were more likely to be general health QoL measures in children and adolescents) and whether the rating is conducted by proxy or by children and adolescents themselves. It has been found that self-ratings of HRQoL tend to be lower than proxy ratings (Adamo et al. 2015). Considering that the adult studies included in the review used self-reports of HRQoL, whereas the child/adolescent studies were all parent-rated reports, this may contribute to the finding of smaller effects of medication on HRQoL in adults.

More broadly, differences in the instruments used to assess HRQoL, including whether they are rated by self or proxy, may explain the high degree of variability between studies in the effect of medication on QoL and modest correlations with symptom improvements (Adamo et al. 2015). These measurement issues require further research to develop more effective and accurate measures of these important outcomes in ADHD. In particular, it is essential to develop ADHD-specific measures

that are reliable across different raters and that capture aspects of QoL that are deemed important to those with ADHD, preferably by involving those with ADHD, or their advocates, in the design.

Boland et al. (2020) conducted a narrative review and meta-analysis of the effects of ADHD medications on functional outcomes and identified 40 studies that had examined the risk of comorbid mood disorders (depression and bipolar disorder), Substance Use Disorder (SUD), criminality, suicidality, traumatic brain injury, motor vehicle accidents, accidents and injuries, and academic attainment. The narrative synthesis reported that stimulant medications were associated with reduced risk of criminality, motor vehicle accidents, injuries and with enhanced academic outcomes (performance on tests, school attendance and reading). Many of these effects did not reach statistical significance in meta-analysis, but this is likely due to the small number of studies on each outcome and associated heterogeneity. Importantly, where possible, the authors examined the outcomes in relation to within-individual differences in medication adherence and reported that outcomes were better during periods of medication adherence than non-adherence.

Similarly, in a systematic review and meta-analysis of studies adopting a within-individual design, Chang et al. (2019) reported no significant increase in suicidality in relation to ADHD medication use, with some evidence of a protective effect of medication in reducing incidents of self-harm and suicide. Similarly, the review identified a decrease in hospital visits due to depression and decreased rates of SUD and criminality in ADHD patients when on than off ADHD medication. The authors also reviewed evidence on accidents and injuries and reported reduced injury and trauma, reduced driving accidents and enhanced academic achievement during periods of medication adherence. Overall, the general pattern is for ADHD medication to improve these other outcomes, or at least not to exacerbate them.

In a similar vein, Krinzinger et al. (2019) presented an evidence map of research that has measured the long-term outcomes of treatment with MPH for at least 12 months. The findings indicated that MPH is associated with improvements on some neuropsychiatric outcomes, notably depression, SUD and suicidality, and the authors described the evidence on these outcomes as strong. The authors highlighted some evidence of increased tics and psychotic symptoms in their evidence map but also reported evidence that these outcomes are rare and appear to be negated once MPH is withdrawn. In support of this, a recent Cochrane systematic review (Osland et al. 2018) reported no adverse effects of any ADHD medications (including stimulant treatments) on tics in children with comorbid ADHD and tic disorder, and significant improvements in tics following treatment with MPH, GXR and CLON, suggesting that initial concerns over treatment with stimulant medications may not be warranted. As the data reviewed by Krinzinger et al. (2019) were not submitted to a meta-analysis, firm conclusions cannot be drawn, but it is useful to note that the findings of Boland et al. (2020), Chang et al. (2019) and Krinzinger et al. (2019) are broadly congruent and indicate overall potential protective effects ADHD medications on these other outcomes.

As well as studies that have been conducted to examine the effects of ADHD medications on the emergence of mental health difficulties, others have focused on

whether medications exacerbate, or improve, the symptoms of current comorbidities. Common ADHD comorbidities include autism spectrum disorder (ASD), oppositional defiant disorder (ODD), conduct disorder (CD), tic disorders and mood disorders (Jensen and Steinhausen 2015). There has been some concern that stimulants may exacerbate comorbidities, particularly tics, psychosis and ASD, and this led clinicians to favour nonstimulants when treating ADHD in the presence of comorbid symptoms.

Two questions arise from this: (1) do nonstimulants treat ADHD symptoms effectively when there are comorbidities present; and (2) do nonstimulants exacerbate or improve comorbid symptoms? In response to the first question, evidence obtained from recent systematic reviews suggests that the efficacy of ATX in treating ADHD symptoms is not diminished by the presence of comorbidities including anxiety, tics, ASD, mood disorder, and ODD/CD in children (Hutchison et al. 2016) or adults (Clemow et al. 2017). However, in response to the second question, according to these reviews, only anxiety symptoms and ODD/CD improved under treatment with ATX; other comorbidities were neither exacerbated nor ameliorated, indicating that additional treatment targeting the comorbid symptoms is necessary.

The precise role of ADHD medications in improving comorbid symptoms remains to be established: do these medications improve some comorbid symptoms through their effect on ADHD symptoms, or do they have a direct effect on the comorbid symptoms themselves? Further research is needed in this area, particularly as patients with comorbidities have historically tended to be excluded from RCTs; we therefore have limited understanding of the efficacy of ADHD medications in treating ADHD symptoms, and/or comorbidities, in these individuals (Chang et al. 2019). This is a significant limitation considering that in one large population study (Jensen and Steinhausen 2015), 52% of children, adolescents and adults with ADHD had at least one comorbidity, and 26% had more than one. There are also widely reported difficulties with devising effective treatment plans for children with ADHD with comorbidities (see Davis and Kollins 2012; Antshel and Russo 2019), partly because of the paucity of data on the efficacy of ADHD medications in the context of comorbidities.

Remarkably few studies have been conducted to evaluate the effects of ADHD medication on social function, an area of significant impairment in ADHD (Nijmeijer et al. 2008; Davis and Kollins 2012). A small number of studies suggest that medication may decrease the rates of negative peer interactions but without a concomitant increase in pro-social behaviours (McQuade and Hoza 2008). There is a need for further research in this area to compare different types of ADHD mediations on a range of social outcomes in ADHD and to determine whether such impairments (and their potential amelioration by medication) arise from comorbidity with autism spectrum conditions and oppositional defiant/conduct disorder, or whether they reflect a core impairment in ADHD.

7 Factors to Consider When Choosing Treatments

When selecting treatments, clinicians are guided by the evidence and clinical guidelines which advocate stimulant medications (MPH, AMP or LDX) in the first instance, unless there is a clear reason why these medications would not be suitable (see Table 1). This is supported by evidence indicating that MPH and AMP are superior in efficacy to other medications in children, adolescents and adults (Cortese et al. 2018). As outlined in Sect. 3 above, there are a number of medication preparations to choose from, particularly MPH and AMP-based preparations, each with different pharmacokinetic properties These features lead to differences in the onset and duration of response to medication, meaning that some medications are more effective early in the day, while others peak later. Furthermore, these factors interact with age, as described by Coghill et al. (2013) in their systematic review of head-to-head studies of long-acting MPH formulations.

As shown in Table 2, medications are also available in different preparations, including tablets, capsules, oral suspensions and transdermal patch. This flexibility in drug preparation provides greater choice to patients; in particular, younger children may find it difficult to swallow tablets and capsules whole and several of the medications can be crushed or chewed specifically to overcome this problem. Discussions with the patient and their parent/carer are crucial to finding the right balance between the timing of maximum drug effects, with due consideration of the effects of the dosing regime on sleep onset, duration and quality, appetite and functional outcomes during the day (e.g., school or work).

In addition to considerations about the timing and duration of the drug effects, it is important to take a full medical history to establish whether there are any physical health factors, co-occurring neurodevelopmental or mental health diagnoses/symptoms, or other medications, that may influence treatment decisions. Height and weight should be monitored regularly as evidence indicates that MPH is associated with reduced growth (height and weight) in children (Carucci et al. 2021). Although the deviation from normal growth is small and resolves after medication withdrawal, significant changes in these parameters indicate a possible need for adjustments in dosing schedule/level or medication breaks.

Secondly, there is consistent evidence of small but statistically significant changes in systolic and diastolic blood pressure (BP) indices and heart rate (HR) in response to ADHD medications. Specifically, there are increases in HR and BP with stimulants and decreases with α-adrenoceptor agonists (Hirota 2014; Hennissen et al. 2017; Cortese et al. 2018; Fay and Alpert 2019), which may be more pronounced when medication is first started (Martinez-Raga et al. 2017). Despite these changes, the odds of serious cardiovascular events are not significantly increased in those prescribed stimulants or ATX (Liu et al. 2019; Houghton et al. 2020) although it is important to bear in mind that the confidence intervals around the effects reported in some studies do not rule out moderately increased risk on some measures (Liu et al. 2019). Careful monitoring of HR, BP and weight and height are therefore important components of treatment titration and longer term

monitoring, as well as establishing family history of cardiac illness prior to treatment initiation. Furthermore, medications for other mental health conditions should be checked as part of a thorough investigation of medical history prior to initiating ADHD medication (Faraone 2018). In particular, monoamine oxidase inhibitors, prescribed for the treatment of mood disorder may lead to significant risk of hypertension and should not be co-administered with any ADHD medications described in this chapter.

It is also important to ensure that medications prescribed to treat ADHD do not exacerbate comorbidities or increase risk for the emergence of other psychiatric outcomes. As described in Sect. 6, the research conducted so far suggests some caution is needed when prescribing stimulant medication to those with tics or history/risk of psychosis, but in general, the risks of exacerbating (latent or diagnosed) comorbidities seem low overall. Indeed, the NICE (UK) guidelines (National Institute of Health and Care Excellence 2018) recommend offering the same treatment to individuals with ADHD with comorbid conditions as those without comorbid conditions, but to withdraw medication from anyone experiencing a psychotic or manic episode. Treatment of ADHD symptoms seems to be effective when comorbidities are present (see Sect. 6), although there is little evidence that these comorbidities are effectively treated by ADHD medications. A multi-modal treatment approach is therefore likely to be needed in these more complex cases. Cortese (2020) presents clinical recommendations for assessing, monitoring and responding to a range of possible adverse events, including appetite loss (and associated height and weight changes), increased blood pressure or heart rate, sleep disturbance, tics, seizures and psychotic symptoms.

Age is a key consideration when discussing medication choices with the patient and their family/carers primarily because some medications are not yet licensed for adults (GXR, CLON) and some cannot be used in children aged under 5 years. The network meta-analysis of Cortese et al. (2018) revealed that efficacy and tolerability differed between children and adolescents (aged 6–17 years) and adults (aged 18+) for several of the medications included in the review, and GXR and CLON are not yet licensed for use in adults.

In relation to age, it is also important to consider the risk of misuse (taking the medication at higher doses than prescribed) or diversion (selling or giving away) of stimulant medications which is likely to be of particular concern in young men aged 18–25 (Faraone et al. 2020). This is often motivated by a desire to experiment with drugs or to enhance cognitive or academic performance but carries with it the risks of adverse events and side effects described above. In cases where there is significant concern over the potential for misuse or diversion, nonstimulant medications are the preferred option. Changes in weight and height with age also necessitate regular, effective monitoring of treatment effects to ensure the dosing regimen remains optimal.

8 Conclusions

In conclusion, this chapter has provided a review of current pharmacological treatments for ADHD, focusing specifically on those medications that are FDA-approved at the time of writing, and those that are recommended in treatment guidelines published in several countries including the UK, the USA and Canada. The evidence reveals advances in understanding the mechanisms of action of the main treatments for ADHD and increasingly sophisticated drug formulations and drug delivery modes. The range of medications available provides clinicians and patients with choice when selecting the optimum treatment for each individual.

The evidence of efficacy from several studies has informed the development of treatment guidelines and has also found these medications to be generally well-tolerated and safe. Despite these advances, treatment is still reliant on a trial-and-error approach, sometimes lasting several months. In the life of an individual with ADHD this is a significant amount of time and many decide not to continue, choosing other means to manage their symptoms such as exercise, strategies to aid organisation and time management, and practising good sleep hygiene. There is a need for significant investment in research to develop prognostic markers of treatment response that can accurately predict non-response to a given treatment and/or the likelihood of intolerable side effects. This will lead to more rapid improvements in symptoms and other functional outcomes and enhance medication adherence. Further research is also needed to explore the interactions between ADHD medications and common comorbidities with ADHD to determine whether they remain effective in treating ADHD symptoms without exacerbating comorbid conditions.

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The Benefits and Limitations of Stimulants in Treating ADHD

David Coghill

Contents

Abstract This chapter focusses on the benefits and limitations of stimulant medications in the treatment of ADHD. We highlight the key similarities and differences between the different stimulants used to treat ADHD and briefly discuss mechanisms of action, pharmacokinetics, and pharmacodynamics. We will discuss some of the political, ethical, and moral discussions about the use of stimulants including a

D. Coghill (✉)
Financial Markets Foundation Chair of Developmental Mental Health, Departments of Paediatrics and Psychiatry, School of Medicine, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, VIC, Australia

Murdoch Children's Research Institute, Parkville, VIC, Australia
e-mail: david.coghill@unimelb.edu.au

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consideration of the treatment of subsyndromal ADHD and the use of stimulants as cognitive enhancers. We review the comparative efficacy and effectiveness between stimulants and non-pharmacological treatments for ADHD, between stimulant classes and formulations and between stimulant and non-stimulant medications. We discuss the effects on core symptoms, common associated symptoms, cognition, and more distal outcomes including quality of life and functioning and issues related to tolerance, tolerability and adverse effects. Looking at the clinical implications of these findings, we discuss the importance of measurement-based care in the treatment of ADHD. Finally, we will look at the benefits and limitations of stimulants across several different populations and clinical subgroups.

Keywords ADHD · Amphetamines · Lisdexamfetamine · Methylphenidate · Stimulants

Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ADHD	Attention-deficit hyperactivity disorder
D-DTODS	Dundee Difficult Times of Day Scale
DSM	Diagnostic and statistical manual or psychiatric disorders
EAGG	European ADHD Guidelines Group
EMA	European Medicines Agency
ICD	International Classification of Diseases
MTA	Multimodal Treatment of ADHD Study
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
PATS	Preschool ADHD Treatment Study
PET	Positron emission tomography
RMP	Risk management plan
SMD	Standardised mean difference
SNAP	Swanson Nolan and Pelham
SUD	Substance use disorder
VMAT	Vesicle membrane associated transporter

1 Introduction

In this chapter we will explore the benefits and limitations of the stimulants in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). As a psychiatrist who has been treating ADHD for over 30 years, I feel it is essential that we begin by disclosing that I have a clear bias on this topic. I prescribe stimulant medications for

many of my patients and would not do so if I did not believe that the benefits of doing so usually outweigh the limitations. However, I also recognise that these medications are not a panacea for those with ADHD. For some they are not effective, for some they are not well tolerated and, even when they work well, there are very few, if any, individuals with ADHD for whom they are enough, on their own, to optimise outcomes.

We will start by describing the stimulants used in the treatment of ADHD, highlighting some of their similarities and differences and briefly discussing mechanisms of action, pharmacokinetics, and pharmacodynamics. We will discuss some of the political, ethical, and moral discussions about the use of, including a consideration of the treatment of subsyndromal ADHD and the use of stimulants as cognitive enhancers. We will then look at comparative efficacy and effectiveness between stimulants and non-pharmacological treatments for ADHD, between stimulant classes and formulations and between stimulant and non-stimulant medications. We will consider evidence for effects on core symptoms, common associated symptoms, cognition, and more distal outcomes including quality of life and functioning and issues related to tolerance, tolerability, and adverse effects. We will then discuss the importance of measurement-based care in the treatment of ADHD. Finally, we will look at the benefits and limitations of stimulants across several different populations and clinical subgroups.

2 Stimulants Used to Treat ADHD

The two main classes of stimulants licensed for the treatment of ADHD are the amphetamines and methylphenidate. Modafinil is an atypical stimulant which, while not licensed for ADHD, has some evidence to support efficacy. While we will mention modafinil periodically during this discussion, the focus will be on methylphenidate, the amphetamines, and the dexamphetamine prodrug lisdexamfetamine.

Both the amphetamines and methylphenidate have a longer history than many realise. Amphetamines were first discovered in the 1880s although they were not produced as drugs until 1933 when Smith, Kline and French marketed Benzedrine (a racemic mixture of amphetamine) as an over-the-counter decongestant in inhaler form. In 1937 a tablet form of Benzedrine was introduced and prescribed for narcolepsy, depression, and chronic fatigue. In a well-known study in the late 1930s Charles Bradley administered Benzedrine to 30 ‘problem’ children at the Emma Pendleton Bradley Home in Providence, Rhode Island, in an attempt to alleviate headaches. He however observed a ‘spectacular’ improvement in school performance in 15 of the 30 children with behavioural problems shortly after they were administered the medication (Strohl 2011). While amphetamines use increased dramatically during the Second World War, when soldiers used them to help them maintain focus and stay awake, the increases in prescribing amphetamines (and methylphenidate) for ADHD were more gradual.

Several different forms of amphetamine are currently licensed for medical use. Dexamphetamine the 'right-handed', enantiomer of amphetamine, mixed amphetamine salts, a combination of amphetamine salts, composed of equal parts of racemic amphetamine and dextroamphetamine, and lisdexamfetamine, which is an inactive prodrug formed by the condensation of dexamphetamine with the carboxylate group of the essential amino acid *l*-lysine. After ingestion the lysine is cleaved from the lisdexamfetamine molecule releasing dexamphetamine, the active compound that is responsible for the drug's activity.

Methylphenidate was first synthesised in 1944 and marketed as 'Ritalin' in 1954 by the Swiss company CIBA (now Novartis). Although methylphenidate is most strongly associated with the treatment of ADHD, it was initially used for several other indications including chronic fatigue, lethargy, depressive states, disturbed senile behaviour, psychosis associated with depression and narcolepsy. Although amphetamines have traditionally been the preferred treatment for ADHD in the USA, methylphenidate is the most frequently prescribed medication for ADHD across the globe. The profile of use is however changing as the prescription of lisdexamfetamine increases in those countries where it is licensed.

The exact mechanism of action of the stimulants is not known (Solanto 1998). However, methylphenidate and the amphetamines both block the dopamine and norepinephrine transporters preventing reuptake of dopamine and norepinephrine into the terminal increasing the levels of dopamine in the synaptic and peri-synaptic space. Amphetamines are also competitive inhibitors of vesicular monoamine transporter (VMAT), which means they are taken into the terminal and packaged into vesicles with dopamine. This leads to the displacement of dopamine from the vesicle into the terminal, which increases the concentration of dopamine in the terminal reversing the transport of dopamine through the dopamine transporter into the synaptic space. Following the hydrolysis of lisdexamfetamine into lysine and dexamphetamine the mechanism of action is the same as for dexamphetamine. These alterations in availability of dopamine and norepinephrine serve to modulate neurotransmission in the key glutaminergic and GABAergic circuits involved in optimising a range of cognitive functions including attention, inhibition, memory, and decision-making.

The onset and offset of clinical response to stimulants closely follows their pharmacokinetic profile. While the original immediate-release preparations of methylphenidate, dexamphetamine, and mixed amphetamine salts had a quick onset (around 30 min) they also had a relatively short duration of action (around 4 h) which meant that multiple daily doses were usually required. More recently several different extended-release and delayed-release formulations of methylphenidate have been developed that prolong duration of action (between 8 and 12 h) and reduce the need for multiple daily doses. There are currently no extended-release Dexamphetamine preparations but there are extended-release mixed amphetamine salts preparations with extended duration of action.

In addition to the extended-release formulations there are also delayed-release methylphenidate preparations which are taken in the evening but start to work in the morning and a methylphenidate patch. For both methylphenidate and the

amphetamines, a large proportion of the active drug is metabolised during the first pass through the liver. There are also substantial inter-individual differences in pharmacokinetic profiles, which probably reflect genetic differences in metabolism but could to some degree be a consequence of individual differences in gut motility and absorption. This is a major reason why there are considerable inter-individual differences in optimal doses for methylphenidate, dexamphetamine and mixed amphetamine salts (Kimko et al. 1999; Heal et al. 2013).

Following oral administration, inactive lisdexamfetamine is rapidly absorbed as an intact prodrug. It is then hydrolysed to *l*-lysine and pharmacologically active dexamphetamine within the cytosol of red blood cells. This protects the dexamphetamine from metabolism during the first pass through the liver. While the onset of action for lisdexamfetamine is slower than for dexamphetamine (between 1 and 2 h after administration), lisdexamfetamine does have an extended duration of action with effects lasting for around 10–13 h. Interestingly there is considerably less inter-individual variation in the pharmacokinetics of lisdexamfetamine than there is for dexamphetamine meaning that blood levels for different strength doses are much more predictable (Ermer et al. 2010).

3 Political, Ethical, and Moral Issues Relating to the Use of Stimulants for the Treatment of ADHD

Notwithstanding the considerable evidence, summarised in the following sections, that gives strong support for the efficacy, effectiveness, and safety of the stimulants as treatments for ADHD, they continue to be considered controversial by some (Timimi 2015). At a political level, the acceptance of stimulants as treatments for ADHD is handled very differently by governments and regulatory bodies across the world. This means that there are currently considerable between-country differences in approval of stimulants for the treatment of ADHD.

Methylphenidate is approved for use in more countries than the amphetamines but there are still many low- and middle-income countries where methylphenidate is not approved and where people with ADHD do not have access to any ADHD medications. The World Health Organisation recently chose not to add methylphenidate to their essential medications list. This decision, which goes against the recommendations of all available international evidence-based guidelines, is being challenged by international professional organisations and consumer groups and a new application was made in 2020. Amphetamine based medications are approved for use in many countries including North America, several European countries, Australia and New Zealand. At the time of writing, lisdexamfetamine is approved in North America, across Europe, in Australia and Mexico and Brazil. However, amphetamine-based medications are generally not available across much of Asia where many countries have a blanket ban on all amphetamine-based drugs and the

authorities remain concerned about the potential for illicit use. Lisdexamfetamine has however been authorised recently for use in several Asian countries.

It has been noted that the diagnostic concept of ADHD was developed hand-in-hand with, and was influenced by, knowledge about the targets and effects of ADHD medications, primarily stimulants (Taylor 2018). This has led critics of the use of medication as a treatment for ADHD to argue that modern diagnostic formulations, from the 1960s onwards, were too much influenced by the input of pharmaceutical companies. Although it may be true that these companies may have influenced clinical practice with relation to ADHD it is, as pointed out by Taylor (2018), unlikely that these commercial interests influenced these early stages of the development of the ADHD concepts as they were not involved in the funding of the early psychopharmacology trials. Although use has increased more recently, the use of medications to treat ADHD did not take off rapidly. At that time child mental health in the USA was dominated by a psychodynamic vision and, as Eisenberg pronounced, 'brainlessness' ruled (Eisenberg 1969). As a consequence, psychiatry displayed a clear reluctance to accept the value of medications as valid treatments for mental health problems.

On the other hand, paediatricians were increasingly extending their range to offer services for mental disorders and in particular neurodevelopmental disorders like ADHD. For them, as was normal practice in physical medicine, it was natural to include psychotropic drugs in their repertoire (Taylor 2018). This resulted in a polarisation of attitudes that increased tension between the disciplines with impulsiveness and inattention at its heart. There were similar anti-medication attitudes amongst child mental health professionals where the rejection of neurobiological formulations was probably even more persistent than in the USA. For many years this resulted in the rejection of ADHD as a valid construct amongst European clinicians. This situation was complicated by concern about prescribing 'drugs of abuse'. In the UK this resulted in a concordat between physicians that they would refrain from prescribing both barbiturates and amphetamines. Since that time, attitudes have changed considerably and rates of prescription for stimulants have risen considerably. While these increases have been seen across the world, they have been more pronounced in the USA and there continues to be considerable variation globally (Raman et al. 2018). A comparative study of data from 13 countries identified that the prevalence of prescribing in 2010 for children and adolescents aged between 3 and 18 years varied between 0.27% and 6.69% across countries and regions (0.95% in Asia and Australia, 4.48% in North America, 1.95% in northern Europe, and 0.70% in western Europe). While the prevalence of ADHD medication use increased over time in all countries and regions, the absolute increase per year also showed considerable between-country variation ranging from 0.02% to 0.26% (Raman et al. 2018).

Some critics of ADHD and ADHD medications have suggested that this global variation in stimulant drug consumption supports a notion of ADHD as a social rather than medical construct. While this is not necessarily so, it does highlight that a socio-cultural analysis could make an important contribution to identifying and evaluating key environmental factors that shape ADHD diagnosis and stimulant

drug treatment patterns. However, as pointed out by Singh and Rose, in their presentation to the National Institute for Health and Care Excellence (NICE) ADHD Diagnosis Guideline Consensus Conference in 2006 (NICE 2008), it is not yet clear what level of socio-cultural analysis would be most useful to address this issue and whether this should start from a macro-level study of by-nation variation, a micro-level analysis of the beliefs and practices of individual teachers and psychiatrists in local settings or, perhaps more likely, a combination of the two.

At the same NICE consensus conference, Timimi, a critic of the ADHD construct and opponent to the use of medication for the treatment of child mental health disorders, presented a view that the current evidence fails to justify the dominance of a biological basis for ADHD and challenged the 'use of biological remedies as first-line and often only treatment for those diagnosed with ADHD' (NICE 2008). His objections included: an over reliance on short-term studies and an absence of strong long-term effectiveness data; an over reliance on the results of the NIMH sponsored Multimodal Treatment of ADHD Study (MTA) (Group 1999), which he believes had major methodological and interpretive flaws; and that the literature on ADHD medication has exaggerated stimulants' effectiveness and minimised risk. In an earlier article he had argued that a medical model and medication treatments leads us to disengage 'from our social responsibility to raise well-behaved children' and that 'By acting as agents of social control and stifling diversity in children, we are victimising millions of children and their families by putting children on highly addictive drugs that have no proven long-term benefits' (Timimi and Taylor 2004).

Presenting the other side of this debate Taylor presented a more balanced view pointing out that rather than polemicise we should try to better understand the ways that genes and the environment interact to lead to ADHD (Timimi and Taylor 2004). He goes on to highlight one of the key issues surrounding the (increased) use of stimulants. Whether they are prescribed too much, appropriately, or too little. This very much depends where in the world you are looking. In the USA there is some evidence for a patchy mixture of over and under treatment with rates of treatment in some regions higher than the recognised epidemiological prevalence (Visser et al. 2014). In much of the rest of the world, however, the chief evidence is for under treatment as most children with ADHD are still not recognised, diagnosed, or treated (Sayal et al. 2018; Raman et al. 2018).

4 The Treatment of Subsyndromal ADHD and the Use of Stimulants as Cognitive Enhancers

The fact that stimulants are prescribed in some parts of the world at rates higher than the generally accepted epidemiological prevalence rates for ADHD of around 5% (Polanczyk et al. 2007) has contributed to two other important ethical discussions. Should individuals with subsyndromal ADHD be treated with medication? Should stimulants be used more generally as cognitive enhancers?

There is considerable evidence to support the notion of ADHD as a dimensional rather than categorical diagnosis (Coghill and Sonuga-Barke 2012). The boundaries set by the Diagnostic and Statistical Manual for Psychiatric Disorders (DSM) and International Classification of Diseases (ICD) diagnostic systems are essentially arbitrary (Coghill et al. 2018). Put simply there is no empirical evidence to say that those whose symptoms and impairments fall just to one side of the boundary are essentially different to those that fall just to the other side. While adhering to the letter of the diagnostic criteria is clearly important in research, where it is essential to clearly define who has been included in a study as having or not having ADHD, in clinical practice it is important to acknowledge the arbitrary nature of this boundary and take a somewhat more flexible approach.

Recently there has been a discussion and debate about the potential relevance and importance of recognising those individuals with subsyndromal ADHD (i.e., those who have symptoms and impairment but who do not meet diagnostic criteria) and whether these individuals should be offered treatment, including questions about medication. A recent review of the outcomes of subsyndromal ADHD in child clinical samples found that these children had significantly higher rates of family dysfunction, cognitive impairment, executive dysfunction, interpersonal and school deficits, temperament problems, psychiatric comorbidity and juvenile delinquency compared to children with no ADHD symptoms (Kirova et al. 2019).

My research group was sceptical of these findings and suspected that they may, at least in part, reflect a referral bias and be explained by the presence of other psychopathologies. We therefore looked at data from several population-based samples and took care to control for other mental health problems. To our surprise, we found that children with subsyndromal ADHD not only had educational outcomes similar to those with ADHD and worse than those with no ADHD, but also had similar increased prevalence of suicidality even when we controlled for other mental health problems (Mulraney et al. 2021; Zendarski et al. 2020). These findings mean that we need to seriously ask whether we should be treating at least some of those with subsyndromal ADHD and if so, should we be prescribing stimulants? There is no evidence base to work from here. Clinical trials have almost all focussed on individuals who meet diagnostic criteria and while there is evidence to suggest that stimulants do improve cognitive functioning and concentration in typically developing individuals, we are unaware of any trials that describe efficacy and tolerability in those with subsyndromal ADHD. It is, however, likely that this is the group that accounts for the higher rates of prescription in the USA, and it would be interesting if we were able to look at this group more closely. At present, however, we would recommend adhering to evidence-based guidelines and to avoid, in day-to-day clinical practice, the routine prescription of stimulants to those who do not meet diagnostic criteria.

The use of stimulants for cognitive enhancement by healthy people is increasing and it is estimated that around 90% of modafinil use, which unlike the amphetamines and methylphenidate is not a scheduled drug in the UK, USA, Canada, Germany and Australia, by healthy individuals is off label and usually illicit (Sahakian et al. 2015). These medications all reduce tiredness and, in adults at least, have been

demonstrated to improve learning, attention, working memory, inhibitory control and planning (Smith and Farah 2011). Interestingly in healthy participants the greatest improvements were found in those with lower than optimal baseline performance (del Campo et al. 2013). This contrasts with our recent work in ADHD where the effects of methylphenidate on cognition were independent of baseline performance (Idema et al. 2021).

In a recent study exploring the impact of dexamphetamine, methylphenidate, and modafinil on complex decision-making in health adults, we found that while all three medications increased motivation to spend more time on the tasks, this often resulted in decreased overall performance because exploration of the potential solutions became more random (Bowman et al. 2019). This was interesting as while participants would look more engaged in the task, they performed less well. Similar to the previous research, those who performed less well on placebo were the ones most likely to benefit while the opposite was true for those with stronger placebo performance.

While it does seem to be the case that stimulants may indeed improve performance for some healthy individuals in some situations, we know almost nothing about the safety profiles of these medications when used regularly in this context and these require considerably more research. As Sahakian points out there are also ethical concerns (Sahakian et al. 2015). For example, when asked why they use cognitive enhancers, college students in the USA most commonly answered 'to improve intellectual performance' and 'being able to study longer'. This is relevant as an increase of performance in the range of 10% could lead to a very real improvement in key academic outcomes (Sciences 2008). This has been interpreted by Duke University as cheating under the category 'academic dishonesty' in their academic conduct policy (University 2014). There are of course alternative views put forward. These include potential benefits in fields where constant high performance is essential such as in surgeons, shift workers, the military, and air traffic controllers. This is an area where there are more evidence gaps than strong evidence. Clearly much more research is required before we can adequately address the scientific and ethical questions.

5 Comparative Efficacy Between Stimulants and Non-pharmacological Treatments for ADHD

Once a diagnosis of ADHD has been made in a clinical setting it is essential to start making a management plan. This will usually begin with a program, either formal or informal, of psychoeducation and information-giving whereby the clinician will discuss clinical and scientific understanding of ADHD and the available treatments. A key decision at this stage will be whether to recommend pharmacological or non-pharmacological treatment. This decision should be collaborative, and it is the clinician's responsibility to make sure that the patient and their carer has accurate

information on which to base their decisions. Quite understandably many patients and parents would prefer to avoid medication where possible. This was, until recently, also the view taken by many international clinical guidelines and recommendations. While the USA recommendations, including those from the American Academy of Child and Adolescent Psychiatry (AACAP) (Pliszka and Issues 2007) and the American Academy of Pediatrics (AAP) (2000), have always classified medication as a first-line treatment for ADHD symptoms for all patients with ADHD, excepting those still in pre-school, European guidelines were more conservative recommending medication as the initial treatment only for those with the most severe ADHD (NICE 2008; Taylor et al. 2004). In these European guidelines behavioural parent training (i.e., training parents in more efficient approaches to manage their child's behaviours) was recommended as the initial treatment for ADHD symptoms for those with mild to moderate ADHD with medication reserved for those who did not respond to the parent training.

These recommendations are now starting to change. The most recent version of the NICE guidelines supports the use of medication for all patients with ADHD who remain impaired after remediations, and adjustments have been tried to address their difficulties. Why the change? These decisions were, to a large part, based on the findings from a series of systematic reviews conducted by the European ADHD Guidelines Group (EAGG) (Daley et al. 2014, 2017; Sonuga-Barke et al. 2013). In these the EAGG demonstrated that, while behavioural parent training appears to be effective at reducing ADHD symptoms when unblinded ratings are used to assess outcome, these effects were not seen when blinded ratings are used. That is, there is no evidence for efficacy of behavioural parent training when measured by raters who were blind to the treatment. This is not the same as saying that parent training is not helpful to children with ADHD. There were clear positive effects on parenting with increases in positive parenting practices and decreases in negative practices and clear reductions in oppositional behaviours. On this basis, NICE recommended that parent training is reserved for those with ADHD and coexisting oppositional defiant disorder and that medication is considered as a first-line treatment for all children and adults with ADHD. The EAGG have also reviewed the evidence for cognitive training and neurofeedback in ADHD (Cortese et al. 2015, 2016). They have concluded that neither modality is currently supported as an efficacious treatment for ADHD.

It is therefore now the case that almost all of the international evidence-based clinical guidelines for ADHD recommend medication as an initial treatment for ADHD ahead of non-pharmacological treatments for school-aged children, adolescents, and adults (Faraone et al. 2021; Coghill et al. 2021), although the recent German guidelines do still recommend initial treatment with parent training for children with mild ADHD (Banaschewski et al. 2017) and most guidelines support this approach for pre-school children (Coghill et al. 2021).

6 Comparative Efficacy, Effectiveness, and Safety of Pharmacological Treatments for ADHD

Once a decision to start medication for ADHD has been made it is necessary to: (1) choose whether to start with a stimulant or a non-stimulant medication; and (2) if the choice is a stimulant, decide which stimulant to start with. Fortunately, there is considerable evidence on which to base these decisions, at least with regard to short-term treatment.

The most up-to-date and comprehensive review of efficacy and tolerability of ADHD medications in children, adolescents, and adults, at the time of writing, is the network meta-analysis conducted by the EAGG (Cortese et al. 2018). One caveat of these data is that only studies up to 12 weeks were included as there were too few longer studies to complete a meaningful analysis.

6.1 Children and Adolescents

For children and adolescents, 81 eligible randomised controlled trials were identified, which included a total of 10,068 participants. These trials compared amphetamines (including lisdexamfetamine), methylphenidate, modafinil, atomoxetine, bupropion, clonidine, and guanfacine either with each other or placebo. The primary outcomes were efficacy (change in severity of ADHD core symptoms based on teachers' and clinicians' ratings) and tolerability (proportion of patients who dropped out of studies because of side effects).

For efficacy, treating ADHD core symptoms rated by clinicians in children and adolescents, closest to 12 weeks, all the included drugs were superior to placebo. The standardised mean difference (SMD) for the stimulants ranged from −1.02 (95% Confidence Intervals −1.19 to −0.85) for amphetamines, to −0.78 (−0.93 to −0.62) for methylphenidate, to −0.62 (−0.84 to −0.41) for modafinil. Those for the non-stimulants were −0.56 (−0.66 to −0.45) for atomoxetine, − 0.71 (−1.17 to −0.024) for clonidine, −0.67 (−0.85 to −0.50) for guanfacine and −0.96 (−1.69 to −0.22) for bupropion. By contrast, for the comparisons based on teachers' ratings, only methylphenidate (SMD –0.82, 95% CI –1.16 to −0.48) and modafinil (−0.76, −1.15 to −0.37) were more efficacious than placebo (as no data were available for amphetamines and clonidine). In head-to-head comparisons, the only identified differences in efficacy (clinicians' ratings) were found, favouring amphetamines over modafinil, atomoxetine and methylphenidate (SMDs ranged between −0.46 and −0.24).

With respect to tolerability in children and adolescents, amphetamines (odds ratio [OR] 2.30, 95% CI 1.36–3.89) and guanfacine (2.64, 1.20–5.81) were inferior to placebo. With respect to specific adverse effects in children and adolescents, weight was decreased significantly by amphetamines (SMD –0.71, 95% CI –1.15 to −0.27), methylphenidate (−0.77, −1.09 to −0.45), atomoxetine (−0.84, −1.16 to −0.52),

and modafinil (−0.93, −1.59 to −0.26), compared with placebo. Systolic blood pressure was increased with use of amphetamines (SMD 0.09, 95% CI 0.01–0.18) and atomoxetine (0.12, 0.02–0.22) compared with placebo. Use of amphetamines (0.21, 0.12–0.31), atomoxetine (0.28, 0.18–0.37), and methylphenidate (0.24, 0.14–0.33) significantly increased diastolic blood pressure compared with placebo.

6.2 Adults

For adults, 51 eligible randomised controlled trials were identified, which included a total of 8,131 participants. The same medications were eligible to be included although there were no eligible studies for either clonidine or guanfacine. The analyses and outcome measures were (apart from teacher ratings) the same as those reported for the child and adolescent studies. For efficacy treating ADHD core symptoms in adults, as rated by clinicians, amphetamines (SMD –0.79, 95% CI –0.99 to −0.58), methylphenidate (−0.49, −0.64 to −0.35), bupropion (− 0.46, −0.85 to −0.07), and atomoxetine (−0.45, −0.58 to −0.32), but not modafinil (0.16, −0.28 to 0.59), were superior to placebo. In head-to-head comparisons, only differences in efficacy (clinicians' ratings) were found, favouring amphetamines over modafinil, atomoxetine, and methylphenidate (SMD –0.94 to −0.29).

With respect to tolerability, amphetamines (OR 3.26, 1.54–6.92); atomoxetine (2.33, 1.28–4.25), methylphenidate (2.39, 1.40–4.08), and modafinil (4.01, 1.42–11.33) were all less well tolerated than placebo in adults. For specific adverse effects, weight was decreased significantly by amphetamines (SMD –0.60, −1.03 to −0.18) and methylphenidate (−0.74, −1.20 to −0.28). Systolic blood pressure was increased with the use of methylphenidate (0.17, 0.05–0.30) in adults, compared with placebo. Atomoxetine (0.19, 0.08–0.30) and methylphenidate (0.20, 0.08–0.32) significantly increased diastolic blood pressure compared with placebo in adults.

Taking these findings together the EAGG concluded that, even though amphetamines were the most efficacious compounds in children, adolescents, and adults, the variation between the different medications across age groups and outcomes required a more nuanced interpretation. For example, while atomoxetine had the lowest mean effect size in children and adolescents, based on clinicians' ratings, in adults its efficacy on ADHD core symptoms was comparable with that of methylphenidate. The large confidence intervals that were seen for the efficacy and tolerability of bupropion, clonidine, guanfacine, and modafinil indicate that clinicians should be cautious when interpreting these data. With regard to tolerability, safety, and acceptability: in children, only amphetamines and guanfacine were less well tolerated than placebo, whereas in adults, methylphenidate, amphetamines, and atomoxetine were worse than placebo. Amphetamines significantly increased diastolic blood pressure in children and adolescents, but not in adults. In children and adolescents, methylphenidate was the only drug with better acceptability than placebo; in adults, amphetamines were the only drugs with better acceptability than placebo.

6.3 Comparisons Between Different Stimulant Formulations

One of the main changes in the treatment of ADHD over the past 20 years has been the development of different formulations of methylphenidate and, to a lesser degree, amphetamines, with different pharmacokinetic and pharmacodynamic properties. The potential benefits of longer-acting stimulant preparations, in terms of once-a-day dosing with a smoother profile of clinical effects across the day, had been recognised much earlier. However, initial attempts to develop long-acting stimulant preparations using wax matrix technologies were not particularly successful due to the slow initial release of medication, which significantly delayed the onset of action.

However, in 2000 OROS methylphenidate was licensed in the USA and ushered in a new era of medications that combined immediate-release and extended-release stimulants into a single tablet. A series of studies, led by Jim Swanson and his team at University of California Irvine many of which were conducted using a laboratory school protocol developed by Swanson's colleagues, Sharon and Tim Wigal, demonstrated that the pharmacodynamic profile of methylphenidate (the profile of action across the day) could be predicted by the pharmacokinetic profile of a particular formulation (Swanson et al. 2003; Swanson and Volkow 2002). This has led to the development and marketing of a wide range of stimulant preparations with a range of pharmacokinetic profiles, with different immediate-release versus extended-release proportions and durations of action of 8–12 h that can be used to sculpt clinical response across the day, based on the individual patient's needs. If used thoughtfully and sensibly, these can really improve a patient's experience. However, this does require the clinician to really understand the profile of each preparation, in terms of the balance between immediate- and extended-release components, the actual amounts of immediate-release medication available and delivered at each dose and the intended duration of action, in some detail.

More recently the amphetamine prodrug, lisdexamfetamine, has been licensed in several countries. Although not an extended-release preparation, lisdexamfetamine does, due to the way that the prodrug is metabolised into dexamphetamine and lysine, have a relatively quick onset of action and extended duration of action of around 12–13 h. An important caveat to the use of lisdexamfetamine is that, unlike the extended-release methylphenidate preparations, where one can predict the dose equivalence when switching between immediate- and extended-release preparations (see for example Table 2 in Coghill and Sinita 2014) it is not possible to predict the optimal dose of lisdexamfetamine based on the optimised dose of immediate-release dexamphetamine. This is due to differences in the metabolic pathways for the two drugs. Immediate-release dexamphetamine, when ingested orally, undergoes extensive metabolism by cytochrome P-450 2D6 on the first pass through the liver to 4-hydroxyamphetamine which is an active metabolite but one that does not pass through the blood brain barrier well and therefore does not have significant behavioural effects. The 4-hydroxyamphetamine is then conjugated by sulfotransferase or glucoronyltransferase in inactive metabolites. The dexamphetamine in lisdexamfetamine is 'protected' from this first pass metabolism

as the parent prodrug needs to first be metabolised and by the time this has occurred the dexamphetamine is already in the systemic circulation. This is the same mechanism by which the apparent half-life of the dexamphetamine in lisdexamfetamine is extended and results in the longer duration of action (Hutson et al. 2014; Krishnan et al. 2008; Pennick 2010). A full discussion of the pharmacology and profiles of these medications is beyond the scope of this chapter; however, the interested reader can find a fuller discussion in Zuddas et al. (2018).

7 Clinical Implications of These Findings

Taking all the included outcomes into account, the EAGG has recommended that methylphenidate should be the first pharmacological choice for ADHD in children and adolescents, and amphetamines in adults. This is based on amphetamines being not only the most efficacious compounds, as rated by clinicians and by self-report in adults, but also as well tolerated as methylphenidate and the only compounds with better acceptability than placebo. In children and adolescents, they conclude that even though amphetamines were marginally superior to methylphenidate according to clinicians' ratings, methylphenidate was the only compound with better acceptability than placebo and, was not, unlike amphetamines, worse than placebo in terms of tolerability (Coghill et al. 2021; Cortese et al. 2018).

A common question asked both by patients and colleagues is whether we can predict who will respond to which stimulant? The short, and actually very important, answer to this question is 'no we can't'. In general, studies have identified that around 70% of those with ADHD respond well to one class of stimulant and 70% respond well to the other with between 90 and 95% responding well to one or the other [28]. There are currently no reliable indicators of who will respond to what or, indeed, if they do respond what will be their optimal dose. In our clinics we believe it is best practice to discuss this issue in some detail with every patient before writing their first prescription. The reason for doing this is two-fold. Firstly, we want them to understand what we are doing, why it must be trial and error, why it sometimes takes time and why they should not get disenchanted if we don't get things right the first time. Secondly, we want to make sure that they are not coming into treatment with any urban myths that they may have picked up from the internet, friends, family, or quite often clinical colleagues. It is, for example, not uncommon for me to hear from colleagues that they have developed a clear belief that one medication works better than the others in a particular group of patients. Perhaps they are right, even though whenever we have tried to look at this in a structured way through research, we have been unsuccessful. They will, however, then tell their patients that they believe that drug X will be the best for people in their situation. If, however drug X does not work out and we then want to switch to drug Y many patients will have lost a bit of confidence in our skills and knowledge and will be asking themselves, why did I not respond to the 'best' drug and why should I now expect to respond better to one that is not the best? My preference is to say at the outset that we have several different

medications, they are all good and while one is not better than the other, different people respond differently. I will then explain that we unfortunately can't tell which one will be right for any individual person. I will explain that we will usually start with a stimulant as these have the strongest evidence as first-line treatments. We will choose one to start with but with the reassurance that if this does not work out, we will try the other and if neither suits not to worry as we have alternative options that we can try: the non-stimulants.

When thinking about patients who do not respond to the first trial of a stimulant, we do think that it is important to review the case notes and ask yourself several questions before deciding to switch to another medication. Does the patient have no response, an inadequate response, or is it more an issue of tolerability? Have we titrated up to the maximum tolerated or maximum recommended dose? Has there been a partial response? If so, is there a good response at some time-points with the effect wearing off early than expected, or is there a moderate response that continues across the expected time frame?

Where there is no response, despite titration up to the maximum recommended dose, then switching to the other class of stimulant will often result in a clinical response. Where the issue is one of tolerability then, unless the adverse effects were considered dangerous (e.g., cardiac toxicity or psychosis), it is again generally recommended to try a stimulant from the other class, explaining to the patient that, while they may have similar adverse effects with the second class, that is certainly not guaranteed as, similar to clinical effects, adverse effects to one do not necessarily mean that you will experience them with another medication. Where there has been a partial response, without undue adverse effects, it can be effective to increase the dose above the usual recommended maximum dose. For methylphenidate, a maximum of around 100 mg per day is usually quoted, for dexamphetamine around 50 mg per day and for lisdexamfetamine 100 mg. In countries where an extended-release preparation of guanfacine or clonidine is licensed, another increasingly popular option for partial stimulant response is to augment with an α_2-adrenceptor agonist. This has several potential benefits. Most importantly, several of the adverse effects of the α_2 -adrenceptor agonists, such as lowering pulse and blood pressure and sedation, are opposite in direction to those of the stimulants, which improves tolerability for many patients. In contrast to the stimulants which have a maximum duration of effectiveness of 12–13 h the α_2 -adrenceptor agonists have a full 24 h effect on ADHD core symptoms which many patients, particularly adolescents and adults, find particularly helpful.

Alongside trying to optimise symptom reduction from day to day, it is also helpful to focus on attaining a smooth and adequate response across the day. This is where the different stimulant formulations mentioned above come into their own. Optimising treatment response across the day does, however, require the clinician to adjust their clinical questioning to ask not just about overall response but to break this down across the day. We developed The Dundee Difficult Times of Day Scale (D-DTODS, Du et al. 2018; Coghill and Sinita 2014) which can be used to provide a structure around which a discussion about times of the day when a medication is and is not working can be framed and treatment adjusted accordingly.

8 Monitoring Treatment Response and the Potential Benefits of Integrating Measurement-Based Care Approaches into Clinical Practice

Notwithstanding the strong evidence to support the efficacy of stimulants in treating core ADHD symptoms, there is also evidence to suggest that this is not always borne out in routine clinical practice (Group 1999; Langley et al. 2010) where clinical outcomes often appear to fall well short of those that would be expected from the clinical trials. While this is likely to be in part due to the cases admitted into clinical trials being less complex than those seen in clinical practice, this does not seem to be the whole explanation. The 14-month findings from the Multimodal Treatment of ADHD (MTA) study showed that a carefully crafted medication treatment program that included a rigorous titration phase and regular follow-up appointments, which based treatment decisions on feedback from parents and school, resulted in superior outcomes to those seen when medication was used in routine clinical care (MTA Group 1999). Some of these differences were due to the clinical protocols while some probably reflected the fact that those receiving the MTA medication protocol were receiving higher doses (around 10 mg more methylphenidate per day) and were receiving three times a day medication rather than the twice daily dosing that was more typical in the routine clinical care group (Greenhill et al. 1996).

Coghill and Seth adapted the MTA medication protocol for use in a UK publicly funded clinical service with particular focus on the measurement-based care approaches. They measured ADHD symptoms using the clinician rated Swanson Nolan and Pelham (SNAP) rating scale at each appointment and used these scores to support clinical decision-making in an attempt to optimise medication response (Coghill and Seth 2015). Using this approach, they demonstrated a very clear and clinically meaningful improvement in clinical outcomes. For example, the proportion of patients in remission rose from 44% prior to implementation of the new protocols to 67% afterwards. Interestingly, these are almost identical rates to those seen in the MTA study at the end of the 14-month randomised trials (Group 1999). Coghill and Seth also noted that their symptom outcomes were very similar to those seen in randomised controlled trials. Importantly, in view of the controversy over long-term effectiveness of stimulants, both the remission rates and symptom reductions persisted into the long-term and were still present 10 years after treatment was initiated. We believe that these findings together make a strong case for the implementation of measurement-based care approaches in the management of ADHD, and probably more generally, in child and adolescent mental health.

Thus far, the approach to measurement-based care for ADHD has not extended beyond symptoms. There is, however, strong evidence to support a beneficial effect of stimulants on broader outcomes including cognition (Coghill et al. 2014), quality of life (Coghill et al. 2017b), and functional impairment (Coghill et al. 2017c). Adamo et al. (2015) reviewed each of these outcome domains as well as adverse effects and concluded that ideally they all should be routinely monitored as part of a comprehensive ADHD care pathway. A particularly strong argument for doing so is

the observation that, while there is clear evidence that ADHD medications, and in particular stimulant medications, have a positive impact on each of them, the same evidence also suggests that these effects are, to some extent, independent of each other (Coghill et al. 2007, 2017c; Coghill 2014). This means that response in one domain, no matter how strong, does not always imply a similar response in the other aspects of functioning. Even if core ADHD symptoms are normalised by medication there still may be continuing cognitive impairment, and quality of life and functioning may not be normalised. On the other hand, it may be the case that, even if there is little impact on core symptoms, it is possible that there have been important positive impacts on cognition that have also led to improvements in quality of life and functioning. Unfortunately, few studies have investigated these potential relationships in sufficient detail or in large enough samples. We need further studies before we can make evidence-based recommendations on how best to measure these different outcomes and how to use these measurements in evidence-based clinical decision-making.

9 Do Stimulants Work and Are They Safe Over the Long Term?

Despite the very clear evidence for short-term efficacy from well-conducted randomised controlled trials (Cortese et al. 2018) and from the MTA study of continued effectiveness, if prescribed and monitored carefully, for at least 14 months (Group 1999) there is far less evidence to support long-term effectiveness. Long-term effectiveness studies for ADHD medications are complicated to design well, and no single study design will capture the entire picture. Although randomised controlled trials are the highest level of evidence, most authorities agree that, when you have treatments as efficacious as the ADHD medications, it is neither practical nor ethical to conduct long-term placebo-controlled randomised controlled trials.

The MTA study included a 16-year observational follow-up period, although medication use was only measured up to 10 years. The findings at 3 years (just under 2 years after the active interventions ended) showed that the superiority seen for those randomised to the MTA medication protocol over the other groups had dissipated (Jensen et al. 2007). Analyses of the longer term follow-up data also suggest that, as currently used in routine clinical care, ADHD medications do not result in more positive symptom outcomes compared with other clinical approaches (Swanson et al. 2018). The reasons for this are not well defined. While some experts have argued that this suggests a lack of long-term effectiveness for stimulant medication (Swanson 2019), this is not necessarily the case and the data suggest the medications are not being used effectively (Coghill 2019). As argued above, the data from the initial 14-months of the MTA provide some support for this. That the medication protocol was superior to treatment as usual – even when it included medication – suggests that how we use the stimulants is the key to getting the best

results. The previously described Dundee clinical protocol, which itself was derived from the MTA medication protocol, supports this as the clinical benefits described earlier were long-lasting, with an average time in treatment of 4.5 years and a range of 1–10 years, and did not diminish over time. While pragmatic implementation trials of these enhanced approaches into clinical care that can demonstrate transferability and scalability are required, we believe that these data provide strong initial evidence that, when used carefully, stimulant medications are effective in the long term.

Another issue that could result in reduced effectiveness of the stimulants over time is the potential to develop pharmacological tolerance to stimulants. The possibility that some patients may develop tolerance is supported by evidence from a positron emission tomography (PET) study (Wang et al. 2013), even though the extent and frequency of this occurring is not well understood. Where tolerance is suspected a short drug holiday (e.g., during the weekend or for brief periods of time such as over a vacation) could be considered. Indeed, to simply keep on increasing the dose in the face of tolerance as, often occurs, may seem to provide a temporary solution, but after a period of time, tolerance would probably manifest again.

As it is usually recommended that ADHD medications are continued for relatively long periods, a major concern, even if long-term effectiveness is confirmed, is long-term safety. Unfortunately, the quality and quantity of data on long-term safety of stimulants is far from adequate. For many years there were very few data as the regulators were focussed on the short-term. More recently, the European Medicines Agency (EMA) has insisted that companies developing medications for ADHD conduct open label safety studies of at least 1 year with prospective follow-up for a longer period of time as a part of the Risk Management Plan (RMP) post-licensing (http://bit.ly/1O2XRPp) and have directed that these studies focus on growth and puberty, cardiovascular safety, as well as psychiatric and neurological adverse effects. However, the lack of a comparison group in these studies (e.g. Coghill et al. 2017a) makes interpretation of their findings much more complicated. Studies are underway to address some of these failings (Inglis et al. 2016) and these data have been augmented recently by an increasing number of observational studies using large national registries in Scandinavia and Hong-Kong. Several of these have used innovative designs, such as the use of self-controlled case series (e.g., Man et al. 2015) which attempt to mitigate these limitations and reduce the bias due to the lack of randomisation in observational studies. Overall, data from these population studies as well as systematic reviews and meta-analyses, which focussed on the long-term safety of stimulants have been positive in terms of psychiatric and neurological symptoms (Krinzinger et al. 2019; Man et al. 2016, 2017, 2020), cardiovascular safety (Hamilton et al. 2012; Hennissen et al. 2017) and growth (Carucci et al. 2020) although there is probably a relationship between the long-term use of stimulants during childhood and a shorter than expected stature of around 2 cm.

From a clinical perspective, all current evidence-based clinical guidelines recommend the routine measurement of height, weight, blood pressure, and pulse during treatment. It is of course not just important to make the measurements but also to

compare these to the relevant norms and where there is a deviation from the norm to do something about it. This may sound simple and uncontentious, but our audits of our own practice have shown that these important steps are not always followed though.

10 Considerations for Different Clinical Populations

Finally, it is important to consider whether it is necessary to alter our practice when managing particular clinical populations. Almost all the recommendations in this section are based on expert opinion as the evidence base is small and for all of these populations further study is required.

A key group are those pre-schoolers, usually defined as less than 6 years of age, who have been diagnosed with ADHD and who have not responded to behavioural interventions and accommodations. While my own practice in this situation is usually quite conservative there are times when it seems appropriate to consider medication and when we do it is usually a stimulant. The one large trial in this area is the National Institutes of Health (NIH) sponsored Preschool ADHD Treatment Study (PATS). The findings from PATS were clear (Abikoff et al. 2007; Ghuman et al. 2007; Greenhill et al. 2006). Pre-schoolers with ADHD do respond to stimulant medication, but their response is not as strong as that for school-age children; they require lower doses, and they suffer from increased adverse effects and tolerate the stimulants less well than older children.

Interestingly the presence of comorbid disorders was predictive of response in this study. Where there was no, or one, comorbid disorder (primarily oppositional defiant disorder) there was more likely to be a large treatment response at the same level as has been found in school-aged children. Two comorbid disorders predicted moderate treatment response whereas the presence of three or more comorbid disorders predicted no treatment response to MPH (Ghuman et al. 2007).

There is also a lack of high-quality controlled clinical trials of children with intellectual disability or autism spectrum disorder. The best study for these groups is that of Simonoff et al. (2013). In this relatively large 16-week randomised controlled trial 122 drug naïve children with hyperkinetic disorder and IQs between 30 and 69 were randomised to methylphenidate or placebo. Methylphenidate was shown to be superior to placebo with effect-sizes for the parent and teacher Conners ADHD index of 0.39 [95% confidence intervals (CIs) 0.09, 0.70] and 0.52 (95% CIs 0.23, 0.82). Neither IQ nor autistic symptoms affected treatment efficacy. There were relatively high rates of sleep difficulty, loss of appetite, and weight loss in the methylphenidate treated group but there were no significant differences between the effects of methylphenidate and placebo on pulse or blood pressure. While data from smaller trials and observational studies also suggest that stimulants are effective for reducing ADHD symptoms in those with autism, the evidence is generally poor quality. It is however clear that the rates of adverse effects are higher than usual.

It is therefore essential to monitor closely and adhere to the maxim of 'start low go slow' in this group (Cortese et al. 2012).

Stimulants can increase tics in those with a pre-existing tic disorder and occasionally trigger tics in someone who has not experienced them previously, although the evidence is far from clear cut (Cortese et al. 2013). This has led some formularies to suggest that stimulants are contra-indicated in those with tics. However, this exacerbation of tics is only seen in about 20% of those who have pre-existing tics. My personal practice is to discuss the possible outcomes with the patient and, if we are all in agreement, treat the ADHD with stimulants and observe the tics carefully. In this context it is important to remember that tics typically wax and wane, with a periodicity of around 3 months, so it is preferable to observe for an extended period, if possible, to ensure that any increase is not just a natural waxing. Where it becomes clear that stimulants are increasing the frequency or severity of tics, or are not considered acceptable by the patient, then atomoxetine is both safe and may be associated with a reduction in tics, as can the α_2 -adrenoceptor agonists, clonidine and guanfacine, which are often used to treat tics and which can be co prescribed with stimulants.

There are of course concerns about the use of stimulants to treat ADHD in those with either a history of, or active, substance use disorder (SUD). In fact a meta-analysis of studies in youth suggested that there is a reduction of risk of around 1.9 for youths with ADHD who were treated with stimulants compared to those who were not treated (Wilens et al. 2003). The same group found no evidence that stimulant treatment increases or decreases the risk for subsequent SUD in children and adolescents with ADHD in a 10-year prospective follow-up study (Biederman et al. 2008). However prescribed stimulant medications are diverted in school-age children, college students, and adults (Wilens et al. 2008) and there have been some suggestions that this type of diversion is increasing in many communities. Risk factors for ADHD medication misuse include conduct disorder, pre-existing SUD, use of an immediate-release psychostimulant, and being male (Faraone and Wilens 2007). From their review of the literature the European ADHD Guidelines Group conclude (Cortese et al. 2013): (1) there is no evidence that treatment with psychostimulants increases the risk for later SUD; (2) that a subsample of individuals with ADHD and certain non-ADHD individuals may be prone to abuse and misuse of ADHD medication; (3) in patients with ADHD and SUD treatment of the addiction disorder needs to be addressed initially, with ADHD treatment quickly thereafter; (4) in cases of current or previous substance abuse, an extremely close monitoring of a patient's psychostimulant use is important. The choice of stimulant should be an extended-release formulation of methylphenidate or lisdexamfetamine. For high-risk cases or where a non-prescription stimulant, such as methamphetamine, cocaine or MDMA is being abused, atomoxetine or an α_2-adrenoceptor agonist would be sensible alternative to stimulants.

11 Summary and Conclusions

Over the last few years, I have worked to the adage 'ADHD easy to treat, hard to treat well'. Stimulant medications are just so effective that it is pretty simple in most cases to make a positive impact on someone's life just by writing a prescription for either methylphenidate or an amphetamine. Most patients and their families will come to the next appointment full of praise for you and letting you know what a big impact you have had on their lives. However, we have learnt that it is often a mistake to simply accept this plaudits and praise and to say earnestly 'that's great, keep taking the pills and we will see you again in a few months'. First it is important to remember that while the significant changes being described by our patients are, on the one hand, remarkable, it is likely that over the next few weeks or months they will realise that there are still issues. The immediacy of effect with the stimulants is, on the one hand, a real strength, however, it is also to a degree a limitation. In my experience many of my patients, who tell me at that first follow-up appointment that things are going really well, will, when asked, acknowledge that they are still experiencing problems associated with their core symptoms. I generally find that these issues can be better managed if we take time to titrate their medication with an aim of optimising treatment. My personal aim is, therefore, for maximum benefit with the minimum dose and adverse effects. This often requires titrating past the optimal dose and then pulling back. In addition to optimising treatment this also allows us to know that if it appears that the medication is no longer working a few months down the track, that this is more likely to be tolerance rather than under dosing and that increasing the dose is unlikely to be the best solution.

Another limitation of stimulants is summed up by the oft used phrase 'pills don't make skills'. We need to be clear with our patients from the beginning that our medications will help them focus, make them less impulsive and often more able to contain their emotions. They will not, however, make them do better at work, college, or school. These achievements are going to be theirs. Medication can help them get there but they will have to do the work. Is this a benefit or a limitation? Probably a bit of both. We are using medication to support our patients to do better, be it at their work or at play, when out with their friends or family, to pay attention during a therapy session, or to manage a comorbid condition. It is they who will be doing the hard work and, at the same time, learning to succeed and, hopefully, how it feels to be praised.

I was clear at the beginning of this chapter that I am biased and believe that the benefits of ADHD medications in general, and the stimulants in particular, outweigh the limitations. This does not mean that they are the right treatment for everyone with ADHD, but I do believe that when there are both symptoms and impairments and we make a diagnosis of ADHD, then the stimulant medications should almost always be considered as a possible part of the treatment plan.

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New Drugs to Treat ADHD: Opportunities and Challenges in Research and Development

David J. Heal, Jane Gosden, and Sharon L. Smith

Contents

D. J. Heal (✉)
DevelRx Ltd, Nottingham, UK

Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
e-mail: david.heal@develrx.com

J. Gosden and S. L. Smith
DevelRx Ltd, Nottingham, UK
e-mail: jane.gosden@develrx.com; sharon.smith@develrx.com

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Abstract Since the landmark MTA (Multimodal Treatment of ADHD) trial unequivocally demonstrated the efficacy of methylphenidate, catecholaminergic drugs, especially stimulants, have been the therapeutic mainstay in treatment of Attention-Deficit Hyperactivity Disorder (ADHD). We review the new drugs which have entered the ADHD formulary. The lessons learned from drug-candidates that have succeeded in clinical trials together with those that have not have also been considered. What emerges confirms and consolidates the hypothesis that clinically effective ADHD drugs indirectly or directly increase catecholaminergic neurotransmission in the prefrontal cortex (PFC). Attempts to enhance catecholaminergic signalling through modulatory neurotransmitter systems or cognitive-enhancing drugs have all failed. New drugs approved for ADHD are catecholaminergic reuptake inhibitors and releasing agents, or selective noradrenaline reuptake inhibitors. Triple reuptake inhibitors with preferential effects on dopamine have not been successful. The substantial number of failures probably accounts for a continued focus on developing novel catecholaminergic and noradrenergic drugs, and a dearth of drug-candidates with novel mechanisms entering clinical development. However, substantial improvements in ADHD pharmacotherapy have been achieved by the almost exclusive use of once-daily medications and prodrugs, e.g. lisdexamfetamine and Azstarys®, which improve compliance, deliver greater efficacy and reduce risks for diversion and abuse.

Keywords Attention-deficit hyperactivity disorder · ADHD drugs · Treatments

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ADHD RS	ADHD Research Scale
AE	Adverse event
AISRS	Adult ADHD Investigator Symptom Rating Scale
BED	Binge-eating disorder
BIS-11	Barratt Impulsiveness Scale, Version 11
BRIEF	Behaviour Rating Inventory of Executive Function
C-II; CIV	Schedule 2; Schedule 4 controlled drug
CGI-S	Clinical Global Impressions Scale
CNS	Central nervous system
DA	Dopamine
DAT	Dopamine reuptake transporter
DBRCT	Double-blind, randomized clinical trials
EDE-Q7	Eating Disorder Examination Questionnaire Brief Version
ER	Extended release
FDA	Food and Drug Administration
IR	Immediate release
LDX	Lisdexamfetamine

MTA	Multimodal treatment of ADHD
NA	Noradrenaline (norepinephrine)
NET	Norepinephrine reuptake transporter
NICE	National Institute for Health and Care Excellence
NSDUH	National Survey on Drug Use and Health
PERMP	Permanent Product Measure of Performance
PFC/FC	Prefrontal cortex/Frontal cortex
SDX	Serdexmethylphenidate
SERT	Serotonin reuptake transporter
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham scale
YBOCS-BE	Yale-Brown Obsessive Compulsive Scale adapted for Binge Eating
XR	Extended release

1 Introduction

The intervening decade between the publication of our previous review (Heal et al. 2012) and this one has been one of contradictions. Several new drugs to treat Attention-Deficit Hyperactivity Disorder (ADHD) have entered the formularies, but the search for new drugs with novel mechanisms to deliver a better balance between clinical benefit and risk has been unsuccessful. Knowledge about ADHD, its neuropathology and the pharmacological mechanisms of drugs that are effective in treating the disorder has substantially increased. On the other hand, the failure of many drug-candidates, with mechanisms different from indirect or direct potentiation of catecholaminergic neurotransmission, has closed off many research avenues. The outcome has been to focus research on enhancing the therapeutic efficacy of catecholaminergic ADHD drugs and diminish their deficiencies, e.g. duration of action, adverse events and potential for abuse.

In the UK, there has been a major shift by NICE (National Institute of Health and Care Excellence) to recommend stimulants as first-line therapy in ADHD in children ($\geq$5-years) and adults (NICE: Guidance NG87, 2018). This contrasts with its previous opinion there was no clinically significant difference between the efficacy of non-stimulants and stimulants in treating ADHD (NICE: Review of Technical Appraisal 13, 2006); a view that was not shared by the British Association of Psychopharmacology Consensus Group on ADHD (Bolea-Alamañac et al. 2014).

For researchers in the field, it has consolidated the link between the catecholaminergic pharmacology of clinically effective ADHD drugs (and now prodrugs), their relative efficacy and relative potential for adverse events.

In this chapter, we will explore these topics, offer an assessment of the prospects for new drugs to treat ADHD and possible directions for future research.

2 Current Status of Drugs to Treat ADHD

The list of currently approved drugs in the USA and UK/Europe for the management of ADHD is reported in Table 1. The number and variety of drugs available to prescribers in the USA is far more extensive than in UK/Europe. As an example, mixed enantiomers/mixed salts amphetamine (Adderall and Adderall-XR), which was for some considerable period the most widely prescribed ADHD drug in the USA, has never been approved in UK/Europe.

New additions to the formulary since writing the last review are the global introduction of the *d*-amphetamine prodrug, lisdexamfetamine (LDX) and an extended-release formulation of the α_2-adrenoceptor agonist, guanfacine. Other medications approved in the USA are clonidine-XR, viloxazine (a selective norepinephrine reuptake inhibitor with some additional serotonergic properties) and Azstarys® (a fixed-dose combination of d-methylphenidate and serdexmethylphenidate [d-methylphenidate prodrug]).

3 Non-clinical and Clinical Pharmacology of Approved Drugs to Treat ADHD

As shown in Fig. 1, all ADHD drugs exert their therapeutic actions by enhancing the signalling of either norepinephrine and dopamine or norepinephrine alone. They accomplish this action by one of four distinct mechanisms: selective inhibition of the norepinephrine reuptake transporter (NET) (atomoxetine), dual inhibition of NET and the dopamine reuptake transporter (DAT) (methylphenidate), catecholamine release by the NET and DAT transporter substrates (*d*- and *l*-amphetamine) or direct activation of postsynaptic α_{2A}-adrenoceptors (guanfacine and clonidine).

It is important to note that these drugs all potentiate norepinephrine neurotransmission (either alone or in combination with dopamine), but none of them selectively enhances dopaminergic neurotransmission.

One of the common misconceptions is dopamine is the primary mediator of the therapeutic effects of ADHD drugs (Volkow et al. 2012; del Campo et al. 2011, 2013; Sharma and Couture 2014; Aarts et al. 2015). The misconception probably derives from the fact that amphetamine and methylphenidate are powerful dopaminergic stimulants and consequently this mechanism underpins their efficacy in ADHD.

It has been demonstrated in multiple studies that the dopamine neuronal systems in the brains of subjects with ADHD are dysregulated (Ernst et al. 1999; Volkow et al. 2007; del Campo et al. 2013; Aarts et al. 2015) and the dopaminergic reward system in the brain is also underactive (Patros et al. 2016; Marx et al. 2021). However, in our view, linking efficacy in ADHD with drug effects in the striatum (e.g., Volkow et al. 2012; del Campo et al. 2011, 2013; Aarts et al. 2015) is misleading because it places excessive emphasis on a secondary therapeutic

Table 1 List of drugs currently approved to treat ADHD

Generic drug name	Trade names	Generic versions	Mode of action	USA		UK/Europe	
				Children adolescents	Adults	Children adolescents	Adults
d-Amphetamine	Adzenys ER, Adzenys XR-ODT, Dexedrine Spansules, Dyanavel XR Evekeo, Evekeo ODT	Yes	Catecholamine (NA +DA) releasing agent[a]	Yes	Yes	Yes	Yes
Mixed salts/mixed enantiomers amphetamines (3:1 mixture of d- and l-isomers)	Adderall, Adderall-XR	Yes	Catecholamine (NA +DA) releasing agent[b]	Yes	Yes	N/A	N/A
Methamphetamine	Desoxyn	Yes	Catecholamine (NA +DA) releasing agent[c]	Yes	Not approved	N/A	N/A
Lisdexamfetamine (d-Amphetamine prodrug)	Vyvanse	No	D-Amphetamine prodrug Catecholamine (NA +DA) releasing agent	Yes	Yes	Yes	Yes
dl-*threo*-Methylphenidate	Aptensio XR, Concerta, Concerta XL, Cotempla XR-ODT, Daytrana, Delmosart, Equasym XL, Jornay PM ER, Matoride XL, Medikinet XL, Metadate CD, Methylin, Quillichew ER, Quillivant XR, Relexxii, Ritalin, Ritalin SR, Xaggitin XL, Xenidate XL	Yes	Psychostimulant catecholamine (NA+DA) reuptake inhibitor	Yes	Yes	Yes	Yes
d-*threo*-Methylphenidate	Focalin, Focalin-XR	Yes	Psychostimulant catecholamine (NA+DA) reuptake inhibitor[d]	Yes	Yes	N/A	N/A

(continued)

Table 1 (continued)

Generic drug name	Trade names	Generic versions	Mode of action	USA		UK/Europe	
				Children adolescents	Adults	Children adolescents	Adults
Serdexmethylphenidate (d-*threo*-methylphenidate prodrug) + d-*threo*-methylphenidate	Azstarys	No	Psychostimulant catecholamine (NA+DA) reuptake inhibitor[d]	Yes	Yes	N/A	N/A
Atomoxetine	Strattera	Yes	NA-selective reuptake inhibitor	Yes	Yes	Yes	Yes
Viloxazine	Qelbree	No	NA-selective reuptake inhibitor/$5HT_{2C}$ agonist/$5HT_{2B}$ antagonist[e]	Yes	No	N/A	N/A
Guanfacine	Intuniv, Tenex	Yes	α_{2A}-Adrenoceptor agonist	Yes[f]	Yes[f]	Yes	Not approved
Clonidine	Kapvay	Yes	α_{2A}-Adrenoceptor agonist	Yes[f]	Yes[f]	N/A	N/A

N/A Not available, *NA* norepinephrine, *DA* dopamine

[a] Profile in vivo DA $\geq$ NA (Heal et al. 2009)

[b] Profile in vivo DA $\approx$ NA (Heal et al. 2008)

[c] Profile in vivo DA $>$ NA with lower potentiating effect on NA transmission in PFC (Kuczenski et al. 1995; Shoblock et al. 2003, 2004)

[d] Profile in vivo almost identical to dl-*threo*-methylphenidate (Heal and Pierce 2006; Heal et al. 2009).

[e] Yu et al. (2020)

[f] Also approved as adjunctive therapy in combination with stimulants

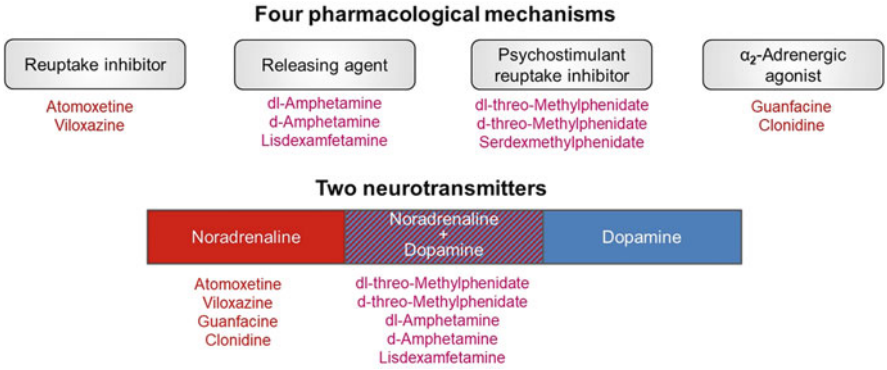

Fig. 1 Mechanism of action of ADHD drugs

mechanism of these drugs. Moreover, it ignores the fact that selective norepinephrine reuptake inhibitors and α_2-adrenoceptor agonists, which are clinically effective in ADHD, do not enhance striatal or limbic dopaminergic signalling (Bymaster et al. 2002; Gresch et al. 1995; Tanda et al. 1996).

It is widely accepted that ADHD drugs reduce its core symptoms by potentiating catecholaminergic signalling in the prefrontal cortex (PFC; Arnsten 2009; Arnsten and Pliszka 2011; Berridge and Devilbiss 2011; Sharma and Couture 2014; Heal and Pierce 2006; Heal et al. 2008, 2009, 2012, 2013a) and the major driver of the effect is through a norepinephrine-based mechanism. The PFC has sparse and diffuse dopaminergic innervation, but it is the low density of DAT sites (Hitri et al. 1991; Sesack et al. 1998) and their inefficient clearance of synaptic dopamine (Cass and Gerhardt 1995; Sesack et al. 1998; Mundorf et al. 2001) that results in a substantial proportion of released dopamine being transported into norepinephrine-releasing neuronal terminals via NET sites (Morón et al. 2002; Stahl 2003). Blockade of PFC NET sites by norepinephrine reuptake inhibitors increases extracellular concentrations of both norepinephrine and dopamine (Gresch et al. 1995; Bymaster et al. 2002; Swanson et al. 2006; Yu et al. 2020). In contrast, selective blockade of DAT sites in the PFC has little impact on synaptic dopamine or norepinephrine concentrations (Tanda et al. 1997). Through their inhibitory and autoreceptor actions, α_2-adrenoceptor agonists actually decrease the exocytotic release of norepinephrine and dopamine in the PFC (Gresch et al. 1995; Tanda et al. 1996) and yet are effective in treating the disorder. Clear evidence that DAT is not a critical effector of efficacy in ADHD is illustrated by the weak efficacy of bupropion in clinical trials (see Heal et al. 2012) and discontinuation of several drug-candidates that preferentially enhance dopaminergic neurotransmission (see Table 2).

If one accepts the premise that enhancing norepinephrine or general catecholaminergic neurotransmission in the PFC is a prerequisite in treating ADHD, it does not preclude an important secondary role for dopaminergic actions. Numerous articles have implicated abnormal reward processing in sub-cortical brain regions including the caudate, putamen, ventral striatum and nucleus accumbens (Teicher et al. 2000; Volkow et al. 2012; Paloyelis et al. 2012; Costa Dias et al. 2013; Aarts

Table 2 New drug-candidates evaluated as potential treatments for ADHD

Drug-candidate	Mode of action	Company	Status in ADHD	References
Centanafadine (EB1020)	Noradrenaline + dopamine reuptake inhibitor	Otsuka/ Neurovance	Phase 3 in children Positive findings in Phase 2 and 3 trials in adults	Wigal et al. (2020b)
Mazindol	Noradrenaline + dopamine reuptake inhibitor	NLS Pharmaceutics	Phase 2/3 Positive findings in Phase 2 trials in adults and children	Konofal et al. (2014) Wigal et al. (2018)
Dasotraline	Noradrenaline + dopamine reuptake inhibitor	Sunovion	Positive findings in Phase 3 trials FDA declines approval Discontinued in 2020	Adler et al. (2021) Findling et al. (2019)
Vortioxetine	Serotonin reuptake inhibitor + $5HT_{1A}$ agonist + $5\text{-}HT_3$ antagonist	Lundbeck	Lack of efficacy in Phase 2 trial Discontinued in ADHD	Biederman et al. (2019)
Edivoxetine (LY22166840)	Noradrenaline reuptake inhibitor	Eli Lilly	Positive findings in Phase 2 trials Discontinued in 2013	Lin et al. (2014) Nery et al. (2017)
GSK372475 (NS2359)	Triple monoamine reuptake inhibitor	GSK/ Neurosearch	Lack of efficacy Discontinued	Wilens et al. (2008)
DOV102677	Triple monoamine reuptake inhibitor	Dov Pharmaceuticals	Discontinued Company wound up	No published data
SPD473	Triple monoamine reuptake inhibitor	Shire Pharmaceuticals	Discontinued Shire acquired by Takeda	No published data
Posanicline (ABT089)	Nicotine α_4/β_2 partial agonist	AbbVie/ NeuroSearch	Lack of efficacy Discontinued Neurosearch wound up	Wilens et al. (2011) Bain et al. (2012) Apostol et al. (2012)
AZD1446 (TC6683)	Nicotine α_4/β_2 partial agonist	AstraZeneca/ Targacept	Lack of efficacy Discontinued Targacept acquired by catalyst	Jucaite et al. (2014)

(continued)

Table 2 (continued)

Drug-candidate	Mode of action	Company	Status in ADHD	References
Sofinicline (ABT894)	Nicotine α_4/β_2 agonist	AbbVie/ NeuroSearch	Minimal efficacy Discontinued Neurosearch wound up	Bain et al. (2013)
AZD3480 (TC1734)	Nicotine α_4/β_2 agonist	AstraZeneca/ Targacept	Minimal efficacy Discontinued Targacept acquired by catalyst	Potter et al. (2014)
Bavisant (JNJ31001074)	Histamine H_3 antagonist	Johnson & Johnson	Lack of efficacy Discontinued	Weisler et al. (2012)
Org26576	AMPA modulator	Merck	Lack of efficacy Discontinued	Adler et al. (2012)

et al. 2015) and dysregulated dopaminergic connectivity with the PFC (Paloyelis et al. 2010; Volkow et al. 2012; Costa Dias et al. 2013; Fabio et al. 2020) in the psychopathology of ADHD. Although there is general consensus on these points, there is also considerable disparity between the findings, which probably reflects the complexity and heterogeneity of the disorder.

Delay-discounting is an accepted measure of intolerance of delayed reward and impulsivity. Individuals with ADHD exhibit steeper rates of delay-discounting than individuals without ADHD (Shiels et al. 2009; Paloyelis et al. 2010; Patros et al. 2018; Castrellon et al. 2019; Fabio et al. 2020). A large meta-analysis exploring possible associations between dopaminergic function and reward discounting in adults revealed minimal influence on discounting in healthy individuals (Castrellon et al. 2019). In contrast, impulsivity and intolerance of delayed reward has been linked to the dopamine transporter gene, DAT1 (Paloyelis et al. 2010, 2012; Aarts et al. 2015; Castrellon et al. 2019), the metabolizing enzyme, catecholamine-*O*-methyltransferase $(COMT)_{val158met}$ (Paloyelis et al. 2012) and $D_{2/3}$ receptor availability (Rosa-Neto et al. 2005; Volkow et al. 2012; Castrellon et al. 2019).

The involvement of striatal dopaminergic systems in the therapeutic effect of stimulant ADHD drugs comes from several sources. Methylphenidate reduces delay-discounting in children with ADHD (Shiels et al. 2009). Rosa-Neto et al. (2005) demonstrated a significant correlation between $D_{2/3}$ receptors in the right striatum and the severity of inattention and impulsivity in ADHD. Furthermore, increased synaptic dopamine concentrations produced by methylphenidate correlated with improvements in impulse control, attention, information processing and consistency of attention or variability. Methylphenidate normalized reward processing in adults with ADHD carrying the 9*R* allele on the DAT1 gene (Aarts et al. 2015). Long-term methylphenidate administration to previously treatment-naïve subjects produced increases in synaptic dopamine concentrations in the ventral striatum, prefrontal and temporal cortices that correlated with objective reductions in ratings of inattention and hyperactivity (Volkow et al. 2012).

The synopsis above summarizes the pivotal role which enhanced catecholaminergic neurotransmission in the PFC and dopaminergic neurotransmission in the ventral striatum and limbic regions play in mediating the therapeutic actions of all ADHD drugs. Moreover, as they are generally compounds with no off-target affinity, it creates the situation where the pharmacological effects responsible for efficacy in ADHD are the same as those which produce their adverse effects (see Heal and Pierce 2006; Heal et al. 2008). Therefore, optimizing benefit/risk when using these drugs to treat ADHD is a fine balance between maximizing efficacy and inducing unacceptable levels of side-effects.

Previously, we described how the use of intracerebral microdialysis can provide insights into the efficacy, side effects and abuse potential of ADHD drugs (Heal and Pierce 2006; Heal et al. 2008, 2009, 2012). In this review, we use the same approach to evaluate the latest generation of ADHD drugs and those in clinical development. We discuss the pharmacology of many of the drugs currently used to treat ADHD and the strong link between their pharmacological properties and efficacy, side effects and abuse liability. To avoid repetition, for a general overview of amphetamine, methylphenidate, atomoxetine, modafinil and bupropion, we refer readers to our earlier reviews (Heal et al. 2009, 2012), for the pharmacology of the isomers of amphetamine (Heal et al. 2008) and for methylphenidate (Heal and Pierce 2006), for an in-depth analysis of the pharmacology of amphetamine (Heal et al. 2013a) and the enigmatic, cocaine-like pharmacology of methylphenidate (Heal et al. 2014). Here, we confine ourselves to an analysis of ADHD drugs that have been approved since the publication of Heal et al. (2012) with a revisit on the pharmacology of the α_{2A}-adrenoceptor agonists, which now appear to be differentiated pharmacologically and clinically from the non-stimulants.

3.1 Lisdexamfetamine

Lisdexamfetamine (LDX) is a *d*-amphetamine prodrug comprising *d*-amphetamine covalently bonded to L-lysine. LDX is highly unusual because it is not catabolized to liberate the active drug in the gut or the liver, as are most other prodrugs; instead, it is metabolized by a rate-limited enzymatic hydrolysis in red blood cells (Pennick 2010; Sharman and Pennick 2014). The catabolic products are *d*-amphetamine (active drug) and the naturally occurring amino acid, L-lysine. *d*-Amphetamine is a close analogue of the catecholamine neurotransmitters, dopamine and norepinephrine, it is a competitive substrate for DAT and NET and the vesicular monoamine transporter-2 (VMAT-2) (see review by Heal et al. 2013a). *d*-Amphetamine is translocated into presynaptic terminals by these ATP-driven carrier systems where it displaces dopamine and norepinephrine from the cytosolic (newly synthesized) and vesicular storage pools. These monoamines are expelled into the synaptic cleft by reversal of DAT and NET's direction of transport ("reverse transport") (Heal et al. 2013a).

The pharmacokinetics due to the rate-limited enzymatic catabolism of LDX profoundly influence its pharmacological actions, resulting in more gradual and

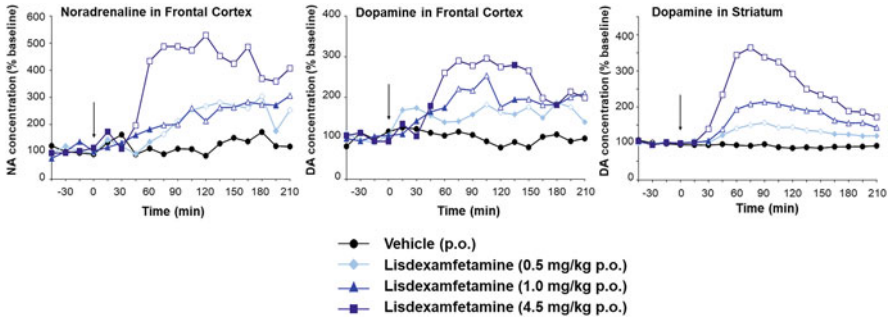

Fig. 2 Profile of LDX on catecholaminergic neurotransmission in the frontal cortex (FC) and striatum. Dual-probe microdialysis experiments in freely-moving rats (Rowley et al. 2014). Results are statistically-adjusted means; $n = 5–8$ rats/group. Doses of LDX are expressed in terms of *d*-amphetamine base. The vertical arrow indicates time of drug administration. Data were analysed by ANCOVA followed by multiple *t*-test (*d*-amphetamine) and Williams' test (lisdexamfetamine). Significant differences are denoted by the open symbols. *NA* norepinephrine [noradrenaline], *DA* dopamine

sustained monoamine increases at the synaptic level with a less stimulant profile than *d*-amphetamine. This point is exemplified when the effects of LDX and immediate-release *d*-amphetamine (IR-*d*-amphetamine) on extracellular dopamine in the striatum and locomotor activity were compared in rats (Rowley et al. 2012). LDX had a much longer duration of action than IR-*d*-amphetamine and, at the same dose, was markedly less stimulant (Fig. 2). LDX also exhibited anticlockwise hysteresis in its pharmacodynamics resulting in reduced activation as extracellular dopamine concentrations increased and longer maintenance of effect when they declined (Rowley et al. 2012). This phenomenon, which is not shared by IR-*d*-amphetamine, may help to explain why LDX has an extended duration of efficacy in the clinic. LDX dose-dependently increased extracellular concentrations of both catecholamines in the PFC and dopamine in the striatum (Rowley et al. 2014). The peak of monoamine efflux occurred ~60 min after LDX was administered and was ~400% of baseline in both brain regions (Fig. 3). Therefore, LDX has the ability to markedly potentiate catecholaminergic neurotransmission in PFC (essential for efficacy) and dopaminergic neurotransmission in the striatal and limbic systems (a secondary driver of efficacy).

The efficacy of LDX in ADHD has been demonstrated in several, large-scale, double-blind, randomized clinical trials (DBRCTs) in children (Biederman et al. 2007; Coghill et al. 2013; Dittmann et al. 2013; Ichikawa et al. 2020a, b) and adults (Adler et al. 2008a; Babcock et al. 2012). LDX is approved to treat ADHD in many countries in North and South America, Europe and Asia, and in 2019, it became the first stimulant drug to be approved for use in ADHD in Japan.

LDX's efficacy in ADHD is rapid in onset with significant separation from placebo as early as Week-1 in children (Biederman et al. 2007; Coghill et al. 2013; Ichikawa et al. 2020a) and adults (Adler et al. 2008a) and it reaches a plateau

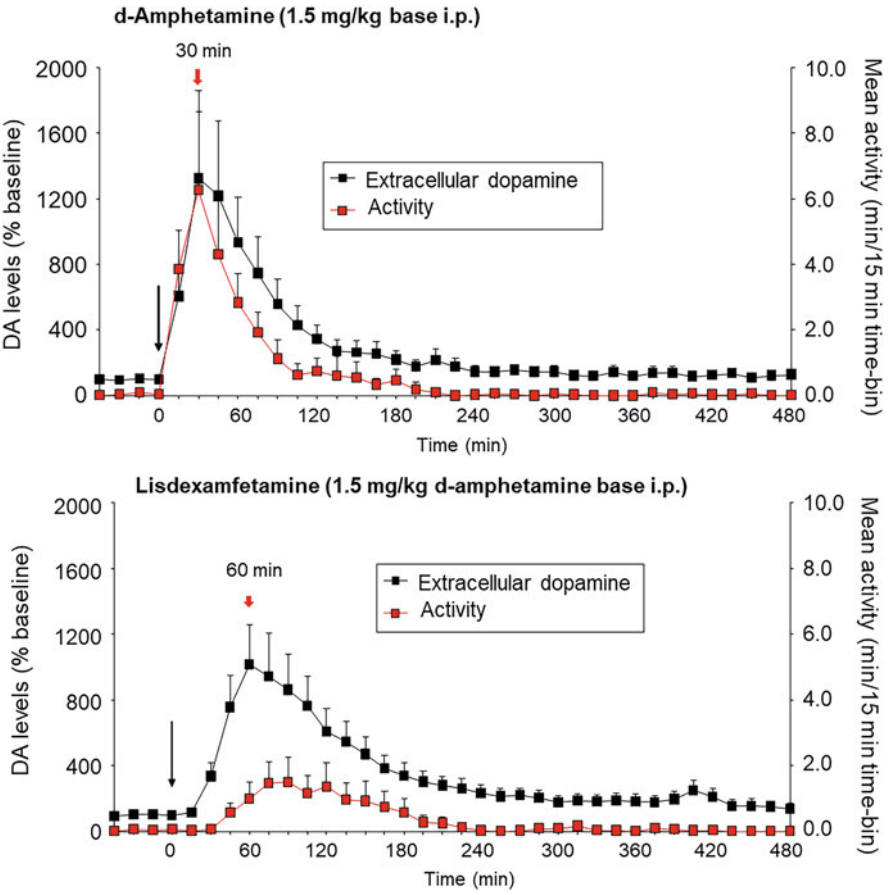

Fig. 3 Comparison by microdialysis of the effects of d-amphetamine and LDX on extracellular dopamine (DA) in the striatum and on locomotor activity of rats. Locomotor activity measured simultaneously with automated microdialysis sampling using the Culex Bambino/Raturn system. The >1000% increase of extracellular DA that occurred very shortly after administration of immediate-release d-amphetamine induced profound locomotor activation, whereas the gradual, >1,000% increase in extracellular dopamine following administration of LDX kept the rats awake and alert with minor effect on locomotor activity. *DA* dopamine

after 5–6 weeks (Dittmann et al. 2013; Adler et al. 2008a; Brams et al. 2012). LDX substantially decreases ADHD symptoms (ADHD-RS-IV Total), including reductions in the inattentive and hyperactivity/impulsiveness sub-scales (Coghill et al. 2013, 2014a; Adler et al. 2008a; Wigal et al. 2011). LDX's efficacy was extremely high and similar across both assessment methods (Wigal et al. 2011; Coghill et al. 2013, 2014a).

LDX's effects are dose-dependent in children and adults, but its magnitude of effect appears to be greater in children than adults across all symptom domains. The

unique rate-limited hydrolysis of LDX gives it a long duration of action with significant improvements for at least 11–14 h (Biederman et al. 2007; Wigal et al. 2011; Martin et al. 2014; Coghill et al. 2014b); however, its onset of action appears somewhat slower than IR-amphetamine (Martin et al. 2014).

No pharmacological tolerance to LDX's therapeutic effect occurs on long-term treatment with efficacy in open-label trials reported at 6 months (Coghill et al. 2014b), 1 year (Mattingly et al. 2013; Ichikawa et al. 2020b) and 2 years (Coghill et al. 2017). Compared with baseline performance, cognitive function in children and adolescents was not impaired after two years on LDX, but it was not generally improved either (Coghill et al. 2018). Interestingly several novel drugs with cognitive-enhancing properties, such as vortioxetine (see Sect. 4.4), have failed in ADHD clinical trials. It exemplifies the point that ADHD is primarily driven by its psychopathology of inattentiveness, impulsivity and hyperactivity and it is reducing these abnormalities not cognitive enhancement which delivers efficacy.

LDX's adverse events (AEs) are typical of powerful catecholaminergic drugs and include decreased appetite, insomnia, abdominal pain, irritability, dizziness, nausea, vomiting, dry mouth and weight loss. The lower efficacy of LDX in treating adults compared with children/adolescents is reflected in the AE profile where frequency increases substantially with dose in children (Biederman et al. 2007) but is relatively stable across doses in adults (Adler et al. 2008a).

The active metabolite of LDX, *d*-amphetamine, is a C-II controlled drug (drugs with a high potential for abuse, but have an accepted medical use) in UK, the USA and many other countries. Microdialysis/behavioural experiments clearly demonstrated due to its rate-limited enzymatic liberation of *d*-amphetamine, LDX was far less stimulant than IR-*d*-amphetamine (Rowley et al. 2012), suggesting poses a lower risk for abuse. This was supported by findings from drug-discrimination and intravenous self-administration studies in rats (Heal et al. 2013b) where LDX failed to generalize to *d*-amphetamine and did not serve as a positive reinforcer. In contrast, methylphenidate generalized to *d*-amphetamine and was self-administered at levels similar to cocaine. Changing the route of administration of methylphenidate or *d*-amphetamine from oral to intraperitoneal increased their potency 2 to 3-fold in the drug-discrimination but had no effect on the potency of LDX. Even when rats were given intravenous access to LDX, the prodrug still did not serve as a reinforcer.

Reduced abuse potential was also observed in human abuse trials where LDX was compared against *d*-amphetamine by both the oral (Jasinski and Krishnan 2009a) and intravenous routes (Jasinski and Krishnan 2009b). When given orally, LDX took 4 h to produce maximum drug-liking compared with 1 h for *d*-amphetamine and, in addition, it was ~50% less potent (Jasinski and Krishnan 2009a). When administered by the intravenous route at the same dose (in terms of *d*-amphetamine base equivalents), *d*-amphetamine produced an unequivocal "drug-liking" signal, but LDX did not differentiate from placebo (Jasinski and Krishnan 2009b).

Another important factor when assessing abuse potential is the feasibility for employing dangerous, non-clinical routes. In this regard, LDX is highly advantaged because its potency is not increased when taken intranasally or intravenously (Heal et al. 2013b; Hutson et al. 2014; Ermer et al. 2016). The US scheduling of LDX in

C-II reflects the vagaries of the Controlled Substances Act whereby prodrugs get placed into the same schedule as their active metabolite. The decision by most other countries to follow this lead does not in our view accurately reflect the lower abuse risk that is posed by LDX, which is a novel chemical entity, compared with *d*-amphetamine.

3.2 Viloxazine

Viloxazine is a weak, selective, norepinephrine reuptake inhibitor that was approved for use as an antidepressant in Europe in the 1970s but is no longer in the formulary. Viloxazine was revived as an extended-release formulation, viloxazine-ER (SPN-812; Qelbree®) to treat ADHD and approved for use in children and adolescents in the USA in April 2021 (Qelbree® FDA Product Label 2021).

Viloxazine has a weak affinity for NET (*K*i=155 nM) with >100-fold selectivity versus the serotonin transporter (SERT: *K*i=17,300 nM) and negligible affinity for DAT (*K*i >100,000 nM) (Yu et al. 2020). In vitro, tritiated monoamine uptake inhibition studies confirmed those transporter affinities (Martin et al. 1978). Yu et al. (2020) have portrayed SPN-812 as having an advantaged pharmacology based on its actions at 5-HT_{2B} and 5-HT_{2C} receptors; since they occur at >10 μM, they are unlikely to be clinically relevant.

In vivo microdialysis experiments showed that SPN-812 increased efflux of norepinephrine and dopamine in the PFC; the effect was reasonably rapid in onset with peaks of ~700% of basal at 60 min (Yu et al. 2020). Unusually for a drug with this pharmacology, SPN-812 increased 5-HT (serotonin) efflux in the PFC by ~500% over basal and significantly enhanced extracellular dopamine, norepinephrine and 5-HT in the nucleus accumbens (Yu et al. 2020). These effects should be viewed with caution because they occurred after intraperitoneal injection at a single dose of 50 mg/kg which is far higher than the pharmacological or clinical dose range (≤400 mg/day; Qelbree® US Product Label).

Viloxazine-ER was evaluated in 4 Phase 3, clinical trials in paediatric patients. Studies 812P301 and 812P303 evaluated viloxazine-ER in children and 812P302 and 812P304 in adolescents. Once-daily doses ranged from 100–400 mg in children and 200–600 mg for adolescents (FDA Qelbree® Integrated Review 2021; Johnson et al. 2020; Nasser et al. 2020, 2021). In study 812P301 (Nasser et al. 2020), children had moderate/severe ADHD. Both viloxazine-ER doses separated from placebo at Week-6, but there was no difference in efficacy between 100 and 200 mg/day. The differences from placebo were statistically significant, but the clinical benefit was moderate. Viloxazine-ER decreased scores on the Inattentive and Hyperactivity/impulsivity sub-scales. Separation from placebo was evident at Week-1 on 100 mg/day, but not the higher dose. Results from the second 6-week trial in children and the two trials in adolescents are reported in detail in the FDA Qelbree® Integrated Review (2021). Results from 812P303 mirrored the first trial in children with 200 and 400 mg/day showing moderate efficacy in ADHD, with a slow onset of

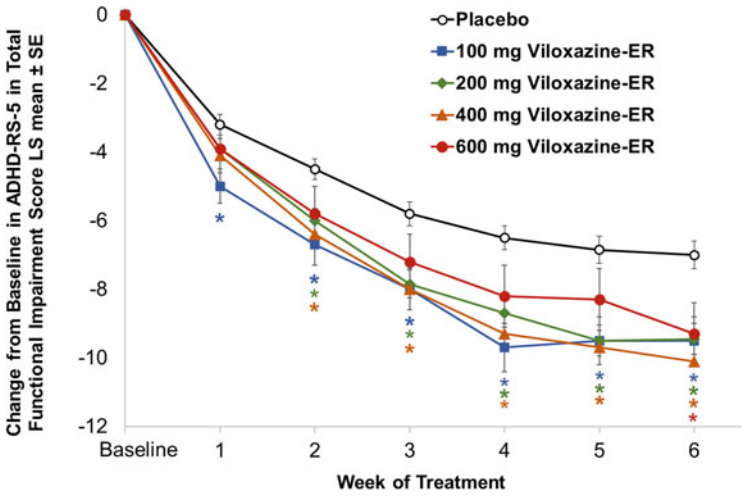

Fig. 4 Efficacy of viloxazine-ER in Phase 3 trials in paediatric ADHD subjects. Results are mean ± SEM change from baseline in the ADHD-RS-5 Total Functional Impairments (ADHD-RS-5 TFI) score by treatment week for 100, 200, 400 and 600 mg/day versus placebo. Significantly different from placebo: $*p < 0.05$. Asterisks colour coded to match each dose of Viloxazine-ER. *P* values obtained from mixed-model, repeated measures change from baseline in ADHD-RS-5 TFI score as function of fixed-effect terms for baseline ADHD-RS-5 Total FI Score, age group, treatment, visit and treatment-by-visit interaction, as fixed independent variables. *TFI* Total Functional Impairment. Data abstracted from Nasser et al. (2021).

action and no difference in efficacy between the two doses. In the two trials in adolescents, the moderate efficacy, slow onset of action and lack of dose-response for viloxazine-ER were confirmed; in fact, neither the 400 or 600 mg/day doses met the primary endpoint in 812P304 (FDA Qelbree® Integrated Review 2021). Nasser et al. (2021) collated the findings from all four trials to produce an overview of the efficacy and tolerability of viloxazine-ER in paediatric subjects. The ADHD-RS-5 results in Fig. 4 illustrate the slow onset of effect, moderate efficacy and lack of a dose-response relationship. Frequently reported AEs associated with viloxazine-ER treatment were somnolence/sedation, headache, fatigue, decreased appetite, abdominal pain, upper respiratory infection, nausea and vomiting (FDA Qelbree® Integrated Review 2021). The FDA noted that somnolence appeared to be dose-related, occurring at rates of 10%, 12%, 14% and 19% at doses of 100, 200, 400 and 600 mg/day, respectively. Sedation, fatigue and nausea also appeared to be dose-dependent.

In summary, viloxazine-ER performs in ADHD like a selective norepinephrine reuptake inhibitor in terms of efficacy, onset of action and AE profile. Based on the clinical evidence, the augmented pharmacology of viloxazine-ER has not differentiated it from atomoxetine.

3.3 Prodrugs for Methylphenidate

The prodrug approach has also been applied to methylphenidate. Dr. Travis Mickle, who discovered LDX, made a prodrug of *d-threo*-methylphenidate (*d*-methylphenidate) (Mickle 2019). Serdexmethylphenidate (SDX) consists of *d*-methylphenidate connected to a nicotinoyl-L-serine molecule via a carboxymethylene linker (Azstarys® FDA Multi-discipline Review 2021). As a prodrug, SDX has no affinity for DAT, NET or SERT and does not bind to any receptor, transporter, modulatory site, ion channel or transporter that mediates the actions of drugs.

The enzymes responsible for catabolizing SDX to liberate *d*-methylphenidate (active moiety) and *d*-ritalinic acid (inactive) are not known. Enzymatic conversion of SDX is believed to take place in the lower gastrointestinal tract (Azstarys® FDA Multi-discipline Review 2021) and, therefore, therapeutic concentrations of *d*-methylphenidate do not appear in patients until several hours after taking the medication. Since the efficacy of drug action correlates with plasma *d*-methylphenidate concentrations (Azstarys® FDA Multi-discipline Review 2021), SDX is unsuitable for treating ADHD as monotherapy. Azstarys® is a combination medication comprising SDX plus *d*-methylphenidate (SDX/d-methylphenidate: 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg). Azstarys has been approved based on biological equivalence to Focalin-XR; it has not been evaluated in Phase 3 trials. Azstarys is as effective as other methylphenidate-based medications and has a ~10 h duration of action. The AE burden of Azstarys compared against other methylphenidate ADHD drugs is not known at this stage.

Commave Therapeutics/KemPharm conducted three trials in drug-experienced human volunteers to evaluate the abuse potential of Azstarys via the oral, intranasal and intravenous routes. When tested orally the FDA concluded that Azstarys (120 and 240 mg) showed less abuse potential than Focalin-XR® (80 mg; C-II) or phentermine (60 mg; an amphetamine-like drug in C-IV), but the study failed to show that the prodrug had no abuse potential when compared with placebo (Azstarys® FDA Multi-discipline Review 2021). Intravenously injected Azstarys (30 mg) demonstrated less abuse potential than *d*-methylphenidate (15 mg, i.v.; C-II) and did not have abuse potential compared with placebo (Azstarys® FDA Multi-discipline Review 2021). Although insufflated Azstarys (80 mg) had less abuse potential than *d*-methylphenidate (40 mg intranasal), it unequivocally showed greater abuse potential than placebo (Azstarys® FDA Multi-discipline Review 2021). Its peak "drug-liking" occurred ~15 min after nasal administration, which was similar to *d*-methylphenidate. Moreover, ~25% subjects reported high "overall liking" of the Azstarys session and 20% strongly wanted to take it again. These data reveal that the most likely route of abuse of Azstarys will be intranasal. FDA has classified SDX in C-IV; however, because *d*-methylphenidate is in C-II, Azstarys is classified as a C-II medication (Azstarys® FDA Product Label 2021).

Since Azstarys has been approved, based on biological equivalence to Focalin-XR, it is reasonable to assume that the drug's efficacy, duration of action and safety will also be similar. Dose-for-dose, the human abuse potential of Azstarys was less

than Focalin-XR, which is an advantage. However, Azstarys is a C-II controlled drug and therefore the hurdles to prescribing it have not been reduced. Overall, we do not believe that Azstarys will be a "game changer" in ADHD pharmacotherapy.

3.4 Comment (Summary/Overview)

The last decade has witnessed a consolidation of the position that catecholaminergic drugs are the only effective pharmacological treatment for ADHD. New drugs have refined and varied the offering with the introduction of prodrugs for *d*-amphetamine and *d*-methylphenidate, and by offering a raft of drug delivery systems to provide once-daily medications with an extended duration of action. No drug with a novel pharmacological mechanism has been approved. In the following section, we will discuss the state of play for new pharmacological approaches.

4 Update on the Progress of R&D in the Search for New Drugs to Treat ADHD

Defining the pharmacological, clinical and tolerability/safety characteristics of the "ideal" drug to treat ADHD is a useful measure against which to evaluate existing drugs and assess the progress of research and development when developing new drugs. We propose the following target product-profile for the ideal ADHD drug.

The "ideal" drug should:

- Reduce impulsivity, distractibility, inattention and hyperactivity symptoms of ADHD
- Improve cognitive control and function
- Deliver high levels of efficacy and remission
- It should be suitable for treating ADHD patients with comorbidities: e.g., depression, anxiety, oppositional/defiant disorder, conduct disorder, substance use disorder, tics
- It should have a benign adverse event profile: no insomnia, no effect on sleep, no effect on appetite/weight, normal growth, no necessity for "drug holidays"
- It should be safe when used long-term
- It should be a once-daily medication

The "ideal" drug should not:

- Produce pharmacological tolerance that would result in dose-escalation
- Cause psychological or physical dependence
- Have potential for human abuse
- Be a Controlled Drug

The drug-candidates under evaluation at the time of writing the previous chapter (Heal et al. 2012), together with those that have entered, and in some cases exited, clinical development in the ensuing period, are reported in Table 2. Every drug-candidate has been discontinued for lack of efficacy, except edivoxetine (Eli Lilly). Development compounds seeking to modulate prefrontal function through nicotinic, histaminergic and AMPA receptor mechanisms failed to demonstrate efficacy in clinical trials. Edivoxetine (a selective norepinephrine reuptake inhibitor) was shown to be effective in ADHD trials (Lin et al. 2014; Nery et al. 2017), whereas the triple uptake inhibitors with relatively powerful dopaminergic actions, GSK372475 (NS2359; GSK/Neurosearch), DOV102677 (Dov Pharmaceuticals) and SPD473 (Shire Pharmaceuticals) proved to be ineffective (Table 2). With the downgrading of atomoxetine (Eli Lilly) to third-line therapy in ADHD, due to its perceived lesser efficacy than the stimulants, it is likely that edivoxetine was discontinued in development in ADHD for strategic and marketing reasons.

Four drug-candidates in Table 2, centanafadine (EB-1020), mazindol, dasotraline and vortioxetine entered development after publication of our previous review.

4.1 Centanafadine

Centanafadine (EB-1020), developed by Otsuka, is a monoamine reuptake inhibitor with IC_{50} potencies for norepinephrine, dopamine and 5-HT of 6 nM, 38 nM and 83 nM, respectively (Bymaster et al. 2012). Irrespective of whether the compound is viewed as a catecholamine or triple reuptake inhibitor, its pharmacological profile includes potent norepinephrine reuptake inhibition properties. In microdialysis experiments, centanafadine increased extracellular dopamine and norepinephrine in the PFC with peak increases of 300–400% occurring 40–60 min after intraperitoneal administration of 10 or 20 mg/kg (Bymaster et al. 2012). Centanafadine also produced similar increases of dopamine in the striatum (Bymaster et al. 2012). The compound was effective in preventing hyperactivity in the neonatal 6-hydroxydopamine brain lesion model of ADHD (Bymaster et al. 2012).

Wigal et al. (2020b) published the findings from two Phase 2 clinical trials of centanafadine in adults with ADHD. In the Phase 2A, flexible-dose study, 41 subjects received escalating doses of centanafadine $\leq$500 mg/day. ADHD severity was high at baseline but was significantly reduced by centanafadine at Week-4. All doses (200–300, 400 and 500 mg/day) produced significant improvements in total Adult ADHD Investigator Symptom Rating Scale (AISRS) scores, and inattention and hyperactivity/impulsive sub-scales. The Phase 2B study employed a 2 $\times$ 3-week crossover design with a 1-week washout in between. Of 85 patients, 42 were randomized to a centanafadine-SR/placebo sequence and 43 *vice versa*. Although 400 mg/day formed the largest treatment arm, higher 600 and 800 mg/day doses were also investigated. All doses showed significant efficacy on the primary outcome, but the two higher ones were not well tolerated. Centanafadine 400 mg/day significantly decreased AISRS total, inattention and hyperactivity/impulsive scores

at Week-3. It was efficacious from as early as Week-1. The most common AEs (placebo-subtracted results) were decreased appetite (16%), nausea (13%), insomnia (11%), fatigue (9%) and dry mouth (7%). Discontinuations for AEs were the same as for placebo.

In June 2020, Otsuka posted a press release announcing positive results from two, 6-week, Phase 3 clinical trials to evaluate the efficacy, safety and tolerability of oral centanafadine in adults with ADHD (Otsuka Press Release 2020). In both trials, centanafadine (200 mg and 400 mg/day) produced statistically significant improvement over placebo on the primary efficacy endpoint, which was change from baseline to Day-42 on the AISRS total score. Centanafadine also significantly improved Clinical Global Impressions Scale (CGI-S), the key secondary efficacy outcome measure. The company stated that trials to study the efficacy and safety of centanafadine in paediatric patients with ADHD were underway.

When the non-clinical findings (Bymaster et al. 2012 and below) and clinical results are viewed overall, they indicate centanafadine is not a stimulant like methylphenidate, but its ability to enhance striatal dopaminergic neurotransmission also differentiates it from the noradrenergic ADHD drugs, atomoxetine and viloxazine. Centanafadine's effect places it between these two drug classes. The safety profile in clinical trials showed no AE signals to indicate that centanafadine has stimulant effects; on the contrary, fatigue was a commonly reported AE.

We have explored the abuse potential of centanafadine in animals in comparison with methylphenidate and bupropion. Centanafadine generalized to *d*-amphetamine in drug-discrimination testing in rats, but only at the high oral dose of 10 mg/kg (Heal et al. 2020). Methylphenidate and bupropion also dose-dependently generalized to *d*-amphetamine. In an earlier study, we showed that atomoxetine does not generalize to *d*-amphetamine (Gosden et al. 2018). In intravenous self-administration in cocaine-trained rats, methylphenidate and bupropion served as strong reinforcers maintaining self-administration at the same level as cocaine. However, centanafadine served as a reinforcer at only two of four tested doses and maintained self-administration at a significantly lower level than cocaine (Heal et al. 2020). If the non-clinical findings translate to humans, they indicate that centanafadine's potential for human abuse will be low.

4.2 Mazindol

Mazindol is a highly potent norepinephrine reuptake inhibitor: *K*i = 0.65 nM to 0.9 nM (Hyttel 1982; Cheetham et al. 1996). It is also a moderately potent reuptake inhibitor of dopamine (*K*i = 18 nM; Hyttel 1982) and 5-HT (*K*i = 30 nM; Hyttel 1982). Mazindol's potency as a NET inhibitor is similar to atomoxetine (*K*i = 0.7 nM). Recently, there have been claims that mazindol has a unique pharmacological profile based on its affinity for 5-HT_{1A}, 5-HT_7, H_1, μ-opioid and orexin-2 receptors (Wigal et al. 2018). Given that these actions were observed at a screening concentration of 10 μM, their relevance to the actions of mazindol can be discounted.

Mazindol (Mazanor®, Sanorex®) is an old drug that was originally developed in the 1960s as a short-term appetite suppressant for weight loss in obesity. Mazindol is no longer marketed in the USA as an appetite suppressant and its sale in Europe was banned by European Medicines Agency in 2003.

There are no published microdialysis data on the effects of mazindol on extracellular catecholamines in the PFC. In rat striatum, mazindol produced rapid, dose-related increases in dopamine efflux with peak effects at 60 min of ~400% and ~750% of basal concentrations at doses of 10 mg/kg and 25 mg/kg, respectively (Ng et al. 1992). Mazindol's effect on dopamine was sustained for several hours. Nakachi et al. (1995) similarly reported that mazindol (28.5 mg/kg) produced a rapid increase in striatal dopamine efflux with a peak of ~500% of basal at 60 min. The drug produced low level activation and stereotypy as well as some odd behavioural effects, e.g. shaking and skin jerks. Mazindol's activating effects were lower than those produced by nomifensine or GBR12909 (Nakachi et al. 1995).

Although the pharmacological characterization of mazindol is incomplete, it is reasonably safe to assume that, given its potency as a NET inhibitor, it will substantially enhance norepinephrine and dopamine neurotransmission in the PFC in addition to dopaminergic signalling in the striatum. Therefore, the pharmacological properties of mazindol are consistent with those of a clinically effective ADHD drug. The effect of mazindol on brain dopamine signalling has been studied by positron emission tomography (PET) imaging in human subjects (Sakayori et al. 2014). Mazindol 0.5 and 1.5 mg dose-relatedly increased synaptic dopamine concentrations as revealed by the displacement of [^{11}C]-raclopride in the striatum, caudate and putamen. Comparing mazindol's dopamine increase against other CNS-active drugs, Sakayori et al. (2014) concluded that its magnitude of effect was similar to *d*-amphetamine and nicotine.

The efficacy and safety of mazindol in ADHD has been evaluated in children (Konofal et al. 2014) and adults (Wigal et al. 2018). A 1-week, open-label, pilot study was carried out in 24 children who were low responders to methylphenidate (Konofal et al. 2014). Mazindol 1 mg/day produced an impressive decrease from baseline in the children's ADHD-RS-IV score at Week-1, with a highly significant improvement in the CGI-S score. AEs were moderate in 34.8% of subjects and severe in 19.6%. They included decreased appetite (37.0%), drowsiness (17.4%), intestinal distension (8.7%) and upper abdominal pain (6.5%). Mean weight loss was 0.5 kg compared with baseline and 0.8 kg compared with the follow-up.

A controlled-release formulation of mazindol was evaluated in a 6-week, DBRCT in 85 adults (mazindol-CR = 43; placebo = 42). Mazindol-CR (up to 3 mg/day) significantly decreased ADHD-RS-V scores starting at Week-1 with maximum effect occurring at Week-4. The effect size suggested that the efficacy of mazindol-CR was on a par with the stimulants, but this conclusion should be tempered because of the use of a forced-titration design, which favours efficacy over tolerability. Frequently reported AEs (placebo-subtracted) were gastrointestinal disorders (15.4%), dry mouth (8.6%), nausea (8.6%), constipation (5.6%), decreased appetite (4.6%) and fatigue (5.9%). Weight-loss was 1.7 kg overall and probably more in the maximum 3 mg/day mazindol-CR group. Heart rate was increased by

11 bpm, diastolic blood pressure and systolic blood pressure by 5.3 and 5.4 mmHg, respectively. Based on these limited clinical findings, mazindol is unequivocally effective as an ADHD treatment; however, the onerous level of AEs observed with the high dose producing the greatest efficacy indicates that, if the drug is approved, its effectiveness may be reduced by limitations placed on the maximum daily dose.

The controlled drug scheduling of mazindol has already been determined; it is a C-IV drug in the USA and C-III in the UK, setting its risk for human abuse at a lower level than the C-II stimulants. In drug-discrimination studies, mazindol dose-dependently generalized to cocaine (Witkin et al. 1991; Mansbach and Balster 1993; Baker et al. 1993) and *d*-amphetamine (Gosden et al. 1996). Mazindol was more potent than cocaine but less potent than *d*-amphetamine (Witkin et al. 1991; Baker et al. 1993; Gosden et al. 1996). Mazindol has been reported to serve as a positive reinforcer in intravenous self-administration experiments in monkeys (Bergman et al. 1989; Spealman et al. 1989) and dogs (Risner and Silcox 1981), and in conditioned place preference in rats (Kankaanpää et al. 2002). The results from human abuse studies tell a rather different story with mazindol producing dysphoric and aversive effects in normal human volunteers (Holmstrand and Jonsson 1975; Chait et al. 1984) and no positive signals of drug-liking in amphetamine-dependent subjects (Götestam and Gunne 1972) or experienced cocaine users (Preston et al. 1993).

Based on the non-clinical and clinical findings and many years of post-marketing experience as an appetite suppressant, the evidence shows that mazindol has the powerful catecholaminergic properties to make it an effective ADHD treatment. It has greater potency on NET than DAT, which is consistent with the former being the main driver of efficacy. Mazindol is clearly stimulant, but nonetheless poses a relatively low risk for human abuse. The effect size of mazindol at 3 mg/day is impressive, but in our opinion, this efficacy comes with an unacceptably high level of AEs, especially those relating to increases in blood pressure and heart rate, and decreases in appetite and body weight.

4.3 Dasotraline

Dasotraline [(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetra-hydronaphthalen-1-amine] is a potent catecholamine reuptake inhibitor (DAT: $IC_{50} = 3$ nM and NET: $IC_{50} = 4$ nM) with weaker effects on 5 HT (SERT: $IC_{50} = 15$ nM) (Koblan et al. 2016). Dasotraline is slowly absorbed after oral administration in humans with a t_{max} of 10–12 h and a long $t_{1/2}$ (terminal elimination half-life) of 47–77 h (Chen et al. 2016; Hopkins et al. 2016; Koblan et al. 2015). It takes 2 weeks of daily dosing to reach steady-state plasma concentrations (Chen et al. 2016; Koblan et al. 2015).

Microdialysis measurements of nucleus accumbens dopamine efflux were consistent with human pharmacokinetics: small, dose-dependent increases that were slow in onset and sustained for many hours (Fig. 5; Heal et al. 2017; Rowley et al. 2017). Dasotraline is clearly different from the stimulants, *d*-amphetamine and

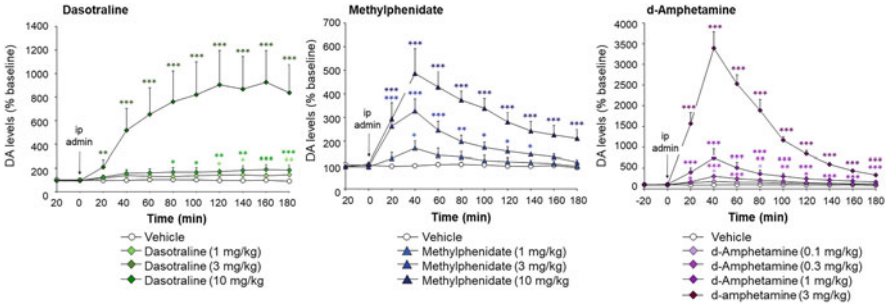

Fig. 5 Comparison of dasotraline, d-amphetamine and methylphenidate on extracellular dopamine concentrations in rat nucleus accumbens. Single probe microdialysis experiments were performed in freely-moving rats with microdialysate dopamine concentrations quantified by HPLC-ECD. Results were back-transformed, adjusted means ± SEM (n = 6–9 rats/dose group). Drug doses are reported as free base and the time of administration is indicated by the vertical arrow. Data were log-transformed and analysed by ANCOVA with log(baseline) as covariate followed by Williams' test. Significant differences versus the vehicle group are denoted by: $*p<0.05$, $**p<0.01$, $***p<0.001$. DA dopamine. N.B. The graphs for dasotraline, methylphenidate and d-amphetamine are plotted using different scales for levels of dopamine efflux

methylphenidate, which produce rapid, large short-lasting increases in dopamine efflux (Fig. 5). One key difference between the mechanisms of releasing agents and reuptake inhibitors is the former are transporter substrates which expel neuronal monoamines by firing-independent reverse transport, while the latter are transport blockers which potentiate and prolong synaptic monoamines after firing-dependent exocytosis (Heal et al. 2013a). Tetrodotoxin blocked neuronal firing and abolished dasotraline's ability to increase synaptic monoamines, showing its actions are exclusively mediated by reuptake inhibition (Heal et al. 2017).

Dasotraline was evaluated in a DBRCT proof-of-concept trial in adults (Koblan et al. 2015). Three hundred and forty-one subjects were randomized in a 1:1:1 ratio to receive 4 weeks of treatment with dasotraline at a fixed dose of 4 or 8 mg/day or placebo (337 received ≥1 treatment). The primary outcome measure was the ADHD RS-IV with CGI-S as one of the secondary measures. Subjects were moderately to severely ill at baseline. At Week-4, the reduction from baseline in ADHD RS-IV score was significant for the higher dose of dasotraline, but not the lower dose. The placebo-subtracted efficacy of dasotraline was relatively modest, and there was no significant effect of the 8 mg/day dose until Week-3. The computerized cognitive assessment battery showed no significant effects for dasotraline on measures of attention, working memory, or episodic memory.

Drop-out rates for AEs on dasotraline were high compared with placebo (4 mg/day = 10.3%; 8 mg/day = 27.8%: placebo = 1.8%). Reasons for discontinuation from dasotraline included insomnia, anxiety, panic attack and a psychotic disorder. Placebo-subtracted AEs included insomnia, decreased appetite, dry mouth, anxiety, nausea, palpitations, weight decrease and panic attack. Heart rate and blood pressure were also dose-dependently increased.

Adler et al. (2021) reported data from a second DBRCT of dasotraline in adults with ADHD. Subjects received 8 weeks of double-blind, once-daily, fixed-dose treatment with dasotraline 4 mg/day, 6 mg/day, or placebo. Neither dose of dasotraline reduced the ADHD RS-IV score from baseline to Week-8 to a significantly greater level than placebo. On the lower hurdle of using uncorrected data, the higher, but not the lower, dose of dasotraline significantly reduced ADHD-RS-IV total score and CGI-S relative to placebo.

The efficacy and safety of dasotraline was also investigated in two studies in children with ADHD (Findling et al. 2019; Wigal et al. 2020a). Findling et al. (2019) conducted a 6-week DBRCT at fixed daily dose of 2 and 4 mg in 336 children. Only the higher dose of dasotraline met the primary endpoint (change from baseline in the ADHD RS-IV total score) and it was also significantly superior to placebo on the inattentive and hyperactive/impulsive sub-scales.

Frequent AEs in the dasotraline (4 mg) group (placebo-subtracted) were insomnia (17.4%), decreased appetite (16.5%), weight decreased (8.7%), affect lability (3.5%), anxiety (3.5%), tachycardia (3.4%) and nausea (3.4%). Seven patients (6.3%) discontinued due to AEs in the 2 mg/day group for insomnia, phobia, decreased appetite, aggression, syncope and EEG changes and 14 patients discontinued in the 4 mg/day group due to insomnia, irritability, abnormal behaviour, ADHD, emotional poverty, visual, mixed or hypnopompic hallucinations, chest pain, costochondritis and pruritus. Psychosis-related symptoms (e.g., hallucinations, illusions) were reported as AEs by seven subjects treated with dasotraline. Although the authors claimed that this incidence was similar to those reported for other ADHD drugs, this conclusion was strongly disputed by Mosholder et al. (2019).

Dasotraline 4 and 6 mg/day has also been investigated in a DBRCT in a 14-day laboratory classroom setting in children (Wigal et al. 2020a). Eligibility for enrolment was established responsiveness to methylphenidate and a $\geq$30% worsening in ADHD during the methylphenidate washout period. Although the protocol was designed to evaluate fixed doses of 4 and 6 mg/day, the 6 mg/day arm was terminated early because of the appearance of unacceptable neuropsychiatric AEs. Thus, a total of 112 subjects were randomized equally to dasotraline 4 mg/day or placebo and comprised both the intention to treat (ITT) and safety populations. Compared with placebo, dasotraline 4 mg/day produced a significantly greater improvement from baseline to Day 15 in the primary SKAMP-combined score (Swanson, Kotkin, Agler, M-Flynn and Pelham) and SKAMP-deportment sub-scale scores. The onset of effect was rapid. Dasotraline also produced significant improvements in the Permanent Product Measure of Performance (PERMP) scores (a skill-adjusted maths test).

The most frequent AEs (placebo-subtracted) in the dasotraline 4 mg/day group were insomnia (16%), decreased appetite (7.1%), perceptual disturbances (5.4%) and orthostatic tachycardia (5.4%). Discontinuation rates were 5.4% (all due to AEs) compared with 10.7% in the placebo group (1.8% for AEs). AEs leading to withdrawal in the dasotraline 4 mg/day group were insomnia, hallucination and rash. In

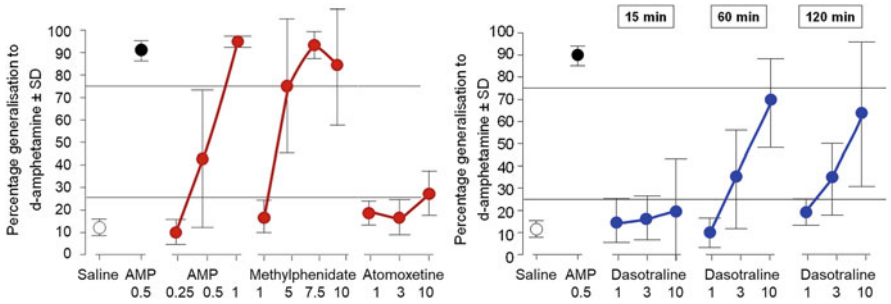

Fig. 6 Comparison of dasotraline and various reference ADHD drugs in d-amphetamine-cued drug-discrimination testing. Freely-fed, female, Lister hooded rats were trained to discriminate between d-amphetamine [AMP] (0.5 mg/kg i.p.) and saline (1 ml/kg i.p.) using a sweetened milk reward in a 2-choice lever-pressing model on a fixed ratio-5 (FR-5) schedule of reinforcement. Test compounds including d-amphetamine for study validation purposes were administered by the oral route. Test sessions were 10 min duration. Rats were not rewarded for operant responses made during the first 2.5 min of the test session. In the remaining 7.5 min, rats were rewarded for presses on either lever on an FR-5 schedule. Results from the non-rewarded 2.5 min part of the 10 min test sessions were used. Results are mean percentage generalization to d-amphetamine ± SD. Total cohort: $N = 26$. Individual drug doses: $N \geq 6$

addition, three patients in this group reported hallucinations (tactile, auditory, visual).

We investigated the abuse potential of dasotraline in *d*-amphetamine-cued drug-discrimination in rats (Gosden et al. 2018). The C-II stimulants, methylphenidate and *d*-amphetamine, both dose-dependently generalized to the *d*-amphetamine training cue, whereas the selective norepinephrine reuptake inhibitor, atomoxetine, generalized to saline. None of the doses of dasotraline generalized to *d*-amphetamine; the greatest effect was ~70% generalization with a dose-test interval of 60 min (Fig. 6).

In stimulant-using, human volunteers, the abuse potential of dasotraline (8, 16 and 36 mg) was compared against methylphenidate (40 and 80 mg) or placebo in a crossover DBRCT (Koblan et al. 2016). Both doses of methylphenidate produced significantly increased "drug-liking" (primary endpoint), "overall drug-liking" and "take drug again" scores relative to placebo. Dasotraline did not separate from placebo on the first two scales but, at the highest dose, marginally did so on the third. Dasotraline (36 mg) produced statistically significant but clinically marginal effects on several other abuse scales and also produced significant negative effects on the "bad drug" and "LSD (dysphoria)" scales. Overall, the non-clinical and clinical evidence demonstrate that dasotraline was clearly differentiated from the C-II stimulant ADHD drugs and posed a minimal risk for human abuse.

Viewing the data overall, dasotraline is a potent DAT and NET inhibitor, but its pharmacological effects are profoundly influenced by its slow rate of brain penetration and extremely persistent inhibition of NET and DAT. There are no published microdialysis data to reveal the magnitude dasotraline's action on extracellular norepinephrine and dopamine in the PFC, and therefore, estimates must be made

based on data from microdialysis experiments in the nucleus accumbens (Fig. 5). These results suggest that dasotraline is likely to produce relatively small, but persistent, increases in norepinephrine and dopamine efflux which would accord with the moderate efficacy of dasotraline in ADHD clinical trials.

The pharmacodynamics of dasotraline on synaptic dopamine concentrations in the nucleus accumbens predict minimal potential for abuse as a stimulant and that prediction has been confirmed by findings in drug-discrimination and human abuse studies. On the other hand, dasotraline's sustained potentiation of mesolimbic dopaminergic transmission accounts for the emergence of psychotic adverse events which limited the tolerable dose range for clinical use. A New Drug Application for the use of dasotraline to treat ADHD was declined by the FDA in August 2018 (Sunovion Press Release 2018). The FDA stated that additional clinical data were needed to further evaluate the efficacy and tolerability of dasotraline. Sunovion continued clinical development of dasotraline for binge-eating disorder (BED) in adults, but in 2020 the company discontinued development of dasotraline in both indications (Sunovion Press Release 2020).

4.4 Vortioxetine

Vortioxetine (Trintellix®) is approved for treatment of major depressive disorder in adults. It has agonist actions at 5-HT_{1A} receptors, partial agonist actions at 5-HT_{1B} and antagonist actions at 5-HT_{3A} and 5-HT_7 receptors (Mørk et al. 2012). Vortioxetine is a potent 5-HT reuptake inhibitor ($IC_{50} = 5.3$ nM) with 26-fold and 170-fold selectivity versus norepinephrine and dopamine reuptake, respectively (Bang-Andersen et al. 2011). Consistent with a reuptake inhibition profile that is potent on 5-HT and weak on norepinephrine, in microdialysis experiments in rats, vortioxetine substantially increased the extracellular concentration of 5-HT in the PFC with marginal increases in dopamine and norepinephrine (Mørk et al. 2012). Vortioxetine showed cognitive-enhancing effects in various animal models including novel object recognition, Y-maze spontaneous alternation and reversal of phencyclidine-induced deficits in attentional set-shifting (Sanchez et al. 2015).

Vortioxetine was evaluated in a DBRCT, proof-of-concept study in 227 adults (Biederman et al. 2019). The study employed an enrichment strategy by including a second stage in which non-responders to placebo were re-randomized to active treatment or placebo. The objective was to minimize the impact of high placebo response rates, thereby increasing the statistical power of the study. Subjects were initially randomized 1:1:3 to vortioxetine, 10 mg/day or 20 mg/day, or to placebo for 6 weeks (Stage 1). Non-responders on placebo were then randomized 1:1:1 to vortioxetine, 10 mg/day or 20 mg/day, or placebo for the following 6 weeks (Stage 2). The subjects were composed of the hyperactive/impulsive (79%) and inattentive (21%) ADHD presentations. In Stage 1, Stage 2 and the pooled analysis set, neither dose of vortioxetine separated from placebo on the primary AISRS scale nor on any of the secondary outcome measures except the Sheehan Disability Scale.

On the specific scales included to measure the effect of vortioxetine on cognitive function (Behaviour Rating Inventory of Executive Function [BRIEF]; BRIEF-A and BRIEF-B), the drug showed no beneficial effects. This large and well-powered clinical trial unequivocally demonstrated vortioxetine's lack of efficacy in ADHD. From a pharmacological perspective, it provides yet another incidence of a serotonergic drug being ineffective in ADHD. We have previously hypothesized that all clinically effective ADHD drugs, with the exception the α_{2A}-adrenoceptor agonists, produce substantial increases in extracellular norepinephrine and dopamine in the PFC (Heal and Pierce 2006; Heal et al. 2008, 2009, 2012, 2013a), the minimal effect of vortioxetine (Mørk et al. 2012) provides further confirmation of the validity of the hypothesis. The final implication of the evidence is that enhancing cognitive function *per se* is of no therapeutic benefit in ADHD unless it is accompanied by a drug-induced reduction of inattentiveness, distractibility, impulsivity and hyperactivity.

4.5 Droxidopa

Droxidopa is a CNS-penetrant norepinephrine prodrug that is metabolized by DOPA decarboxylase to liberate noradrenaline (Goldstein 2006). Droxidopa (Northera®) is approved for adults with symptomatic neurogenic orthostatic hypotension. Adler and Gorny (2019) reported based on an ADHD trial in 20 adult subjects (open-label phase) and 11 subjects (double-blind phase to assess the effect of adjunctive carbidopa) that Droxidopa (3× daily at doses of 200–600 mg for 3 weeks) produced a moderate decrease in the ADHD-RS-Total score. Efficacy was not substantially greater after 6 weeks of treatment. Co-administration of carbidopa did not augment the therapeutic effect of droxidopa. Adverse events appear burdensome with 25% occurrence of headache and somnolence, 20% depressed mood, 15% suicidal ideation, myalgia, hyperhidrosis, and 10% insomnia, musculoskeletal stiffness, nausea, sedation, abnormal dreams and cough (Adler and Gorny 2019).

The effect of droxidopa is exclusively mediated via increased extracellular concentrations of norepinephrine in the brain, and therefore, its efficacy would be predicted to be similar to the α_{2A}-adrenoceptor agonists. Without concomitant norepinephrine reuptake inhibition and/or monoamine oxidase inhibition, inactivation due to neuronal uptake and catabolism would be very rapid making once-daily dosing difficult to achieve. The observation that droxidopa is efficacious in ADHD is interesting from a clinical and mechanistic perspective, but the probability of droxidopa becoming an addition to the ADHD treatment formulary is probably remote.

4.6 Baicalin

Baicalin (or baicalein) is a flavonoid extracted from the plant *Scutellaria baicalensis Georgi* that is used in Chinese traditional medicine. This compound appears to interact with DAT because it is protective against a number of neurotoxins which employ this transporter system (Gao et al. 2015; Hung et al. 2016). Zhou et al. (2019) proposed baicalin as an interesting compound for the treatment for ADHD based on the observations that it decreased hyperactivity in the spontaneously hypertensive rat model and increased markers of striatal dopamine function. This proposal was based on the erroneous hypothesis by Zhou et al. (2019) that ADHD is a dopamine deficit disorder and ADHD drugs produce efficacy by increasing striatal dopaminergic transmission. Whether baicalin will be efficacious in ADHD will only be answered in clinical trials.

4.7 Summary

A search of the literature revealed relatively few novel pharmacological approaches or compounds being proposed for the treatment of ADHD. Kim et al. (2018) proposed H_3-receptor antagonists as potential ADHD treatments based on the effects of three commercially available compounds in their neonatal habenula lesioned, rat model of ADHD. No drug-candidates with this mechanism are currently in development. An earlier attempt by the company, Johnson and Johnson, to develop the H_3-receptor antagonist, bavisant (JNJ31001074), in ADHD was discontinued due to a lack of efficacy in clinical trials (Weisler et al. 2012).

This overview of new approaches to treat ADHD has confirmed and consolidated the hypothesis that clinically effective ADHD drugs indirectly or directly increase catecholaminergic neurotransmission in the PFC. Attempts to enhance catecholaminergic signalling through modulatory neurotransmitter systems have all been discontinued; most for lack of efficacy. Treatment of ADHD with cognitive-enhancing drugs has similarly failed. New drugs that have been approved for ADHD are either catecholamine or selective norepinephrine reuptake inhibitors. Triple reuptake inhibitors with preferential effects on dopamine reuptake have not been a success. The substantial number of failures in the last decade probably accounts for the focus on developing novel catecholaminergic and noradrenergic (norepinephrine) drugs and the dearth of drug-candidates entering clinical development.

5 Progress in the Pharmacological Management of ADHD

In the previous section, we outlined the profile of the ideal drug to treat ADHD. In this section we will review progress in achieving those objectives.

5.1 Efficacy in ADHD

Results from clinical trials (e.g., Wigal et al. 2005; Wang et al. 2007; Newcorn et al. 2006, 2017; Dittmann et al. 2013; Martin et al. 2014; Soutullo et al. 2013; Nagy et al. 2016) and meta-analyses (e.g., Faraone et al. 2002; Cunill et al. 2016; Bushe et al. 2016; Cortese et al. 2017; Stuhec et al. 2019; Elliott et al. 2020) clearly demonstrate that the effect levels in children, adolescents and adults with ADHD and the proportion of patients that are effectively treated by the current portfolio of drugs are very high. It is often assumed that evidence from these sources also supports the hypothesis that stimulant drugs are more effective than non-stimulants (Dittmann et al. 2013; Cunill et al. 2016; Liu et al. 2017; Riera et al. 2017; Cortese et al. 2018) which has resulted in drugs like atomoxetine being relegated from first-line therapy in the UK (NICE: Guidance NG87 2018). However, the situation is rather more complex. For example, although OROS-methylphenidate (Concerta®) has been reported to be superior to atomoxetine in efficacy in some ADHD trials (Kemner et al. 2005; Starr and Kemner. 2005), it showed no substantial advantage over atomoxetine in others (Kratochvil et al. 2002; Wang et al. 2007). Hanwella et al. (2011) and Rezaei et al. (2016) conducted meta-analyses which revealed that OROS-methylphenidate, which has highly predictable pharmacokinetics, was more clinically effective than atomoxetine, whereas IR-methylphenidate which is less consistently efficacious because it has to be taken 3× daily was not superior. Clinical trial design may also distort the outcomes. Many trials are of short duration, e.g. 6 or 8 weeks, which favours drugs with a rapid trajectory of efficacy. A significant proportion of patients prescribed atomoxetine show a gradual improvement (Sobanski et al. 2015) and meta-analyses of clinical trials of at least 12-week duration showed no efficacy advantage of OROS-methylphenidate over atomoxetine (Bushe et al. 2016; Elliott et al. 2020). Forced-titration protocols are another potential source of bias because they maximize efficacy at the expense of increased AEs. LDX was significantly more efficacious than OROS-methylphenidate in a forced upward-titration trial, but not in a flexible-dose regimen, which balances efficacy against tolerability (Newcorn et al. 2017).

With these caveats in mind, the balance of evidence from clinical trials (Faraone et al. 2002; Soutullo et al. 2013; Martin et al. 2014; Coghill et al. 2013, 2014a; Nagy et al. 2016) or meta-analyses (Faraone and Buitelaar 2010; Stuhec et al. 2015; Cortese et al. 2018) supports the view that LDX and other amphetamine-based medications are the most effective in treating ADHD.

The pharmacology of effective ADHD drugs is highly restricted, which begs the question what happens when patients are unresponsive to their prescribed medication. Hodgkins et al. (2012) analysed data from crossover trials with methylphenidate and amphetamine and observed that 41% of subjects responded well to either medication, but 28% of the group preferentially responded to amphetamine and 16% preferentially to methylphenidate. There is also evidence to demonstrate that switching not only between stimulants, but also to non-stimulant drugs can improve outcomes in poor responders (e.g., Quintana et al. 2007; Newcorn et al. 2008; Jain et al. 2013). The use of guanfacine as an adjunctive treatment is an emerging strategy which is being employed for patients with comorbid disorders (e.g., Findling et al. 2014) and in patients who have troubling residual disability when maintained on stimulants (Wilens et al. 2012; Cutler et al. 2014; Butterfield et al. 2016; McCracken et al. 2016).

Since all effective ADHD drugs have catecholaminergic mechanisms, a logical question is what benefit derives from medication switches or combination therapy? ADHD results from dysregulation in norepinephrine and dopamine signalling; the system is not broken, merely out of balance. The probable explanation is the appropriate balance between norepinephrine and dopamine neurotransmission is needed to optimize drug effect, which is why even subtle changes in medication can have a profound clinical impact.

It is important to appreciate that relative efficacy estimates from head-to-head trials or meta-analyses are based on population data. However, for the prescriber and the ADHD patient, benefit is measured by the clinical outcome for the individual. It all comes down to which drug best meets the patient's needs.

5.2 Once-Daily Medication

All pharmacotherapies for ADHD are available as once-daily medications (see Table 1) including the new introductions, LDX, viloxazine-ER, Azstarys and clonidine-XR. Once-daily pharmacotherapy in ADHD is now regarded as essential. For a disorder that is characterized by inattention and distractibility, expecting a child or adult to self-medicate several times a day is inappropriate and inevitably produces gaps in therapeutic effect. Moreover, all medications with the exception of the α_2-adrenoceptor agonists are C-II controlled drugs. Patients taking them into schools creates opportunities for diversion and places a burden on school authorities. This point has now been accepted in clinical practice guidance documents where once-daily drugs, rather than cheaper immediate-release, are now recommended (Bolea-Alamañac et al. 2014; NICE 2018 Guidance).

Some children are resistant to swallowing pills or capsules and another compliance advantage offered by several drugs is the ability to break the capsule and mix the medication with food or drinks or provide it as a liquid formulation.

5.3 Relapse on Withdrawal

ADHD is now accepted to be a disorder that spans childhood and, for a substantial number of individuals, persists into adulthood. Although clinical trials have shown the efficacy of ADHD medications in all of the relevant age cohorts, most pivotal trials in ADHD are relatively short duration: e.g., 6–12 weeks. The question of whether drugs are effective when taken long-term (>12 weeks) has been answered adequately for the stimulants (Buitelaar et al. 2012; Mattingly et al. 2013; Coghill et al. 2018; Matthijssen et al. 2019) and non-stimulants (Kratochvil et al. 2006; Wilens et al. 2006; Adler et al. 2008b; Fuentes et al. 2013), but perhaps less satisfactorily for the sedative α_2-adrenoceptor agonists (Sallee et al. 2009; Newcorn et al. 2016). If the premise that long-term treatment of ADHD is beneficial, one of the major challenges is to maintain medication compliance. Discontinuation rates in open-label extension trials can exceed 50% (e.g., Sallee et al. 2009; Newcorn et al. 2016). Ahmed and Aslani (2013) indicated non-adherence rates to ADHD medication ranging from 15 to 87%. In the landmark Multimodal Treatment of ADHD (MTA) study, ~25% were found to be non-compliant with drug treatment in ≥50% saliva assays with only 54% of subjects drug-adherent at every time-point (Pappadopulos et al. 2009). There is agreement that although compliance is reasonably good early in treatment during childhood, it declines quite substantially after about a year (Efron et al. 2020) and as the patients enter late adolescence (Ahmed and Aslani. 2013; Efron et al. 2020; Rao et al. 2021), with a particular problem occurring in the transition from home to college (Schaefer et al. 2017). Discontinuation of treatment often results in a regression of the disorder (e.g., Coghill et al. 2014b; Matthijssen et al. 2019) with serious adverse outcomes for a significant proportion of individuals with ADHD (Rao et al. 2021).

As medication compliance is far from ideal, it raises the question of the consequences of discontinuation. Discontinuing amphetamine- or methylphenidate-based stimulants leads to a rapid deterioration of symptoms and rapid relapse to pre-medication status (e.g., Coghill et al. 2014a, b; Brams et al. 2012; Arnold et al. 2004; Matthijssen et al. 2019). Relatively rapid relapse has also been reported after discontinuation of guanfacine-XR (Newcorn et al. 2016). In contrast, efficacy after discontinuing atomoxetine is maintained at high levels for many weeks or months (Michelson et al. 2004; Upadhyaya et al. 2013; Buitelaar et al. 2015; Tanaka et al. 2017). Following 6 months open-label treatment, adults randomized to placebo showed >90% maintenance of efficacy for the following 6 months (Upadhyaya et al. 2013).

This is an interesting and potentially important finding. As discussed earlier in this review, atomoxetine has a relatively slow onset of action compared with the stimulants and often takes 2–3 months to produce its maximum effect. In this respect, the therapeutic effect of atomoxetine resembles the time-course of effect of monoamine reuptake inhibitors in treating depression. This contrasts with the almost instantaneous efficacy produced by the stimulants, and it is well established their effects are directly driven by the concentration of drug in plasma and brain.

Clearly, there are two very different therapeutic mechanisms at work. The intriguing possibility is that atomoxetine may be effecting a more permanent resetting of catecholaminergic function in the brain, leading to remission in patients for substantial periods. The stimulants merely provide daily symptom relief that rapidly dissipates when treatment is discontinued.

5.4 Drug-Induced Side Effects

This topic has been extensively discussed in previous reviews (Heal and Pierce 2006, Heal et al. 2009, 2012, 2013a, b). ADHD drugs are generally selective monoamine transporter ligands that are devoid of off-target actions. Viloxazine-ER might be an exception because it is also proposed to interact with various other drug targets (Yu et al. 2020). Overall, recent drug introductions and the failure of all drug-candidates with non-catecholaminergic mechanisms have consolidated the earlier position. Identical pharmacology mediates the therapeutic effect and side-effects of these drugs and, therefore, optimizing treatment will be a balance between maximizing efficacy whilst maintaining side-effects at tolerated levels. This point is clearly illustrated by the head-to-head comparison trial between LDX and OROS-methylphenidate (Newcorn et al. 2017). LDX was significantly more efficacious than OROS-methylphenidate in a forced upward-titration [a design which maximizes efficacy] but not in a flexible-dose regimen [a design which balances efficacy against tolerability] (Newcorn et al. 2017). The advice to prescribers is to avoid over-medicating patients; each incremental dose of the chosen ADHD medication should be given sufficient time to deliver efficacy and for AEs to ameliorate before increasing the dose if the response is inadequate.

As described in earlier sections of this review, many, but not all, AEs are common across all catecholaminergic ADHD drugs. ADHD drugs are usually referred to as "stimulants" and "non-stimulants". Based on pharmacology, therapeutic and AE profile, we propose that the α_2-adrenoceptor agonists should be classified as "sedative" ADHD drugs.

5.5 Abuse Liability

Abuse liability is a major issue for ADHD drugs. Expert opinion and clinical guidance now agree that the stimulants should be first-line treatment in paediatric and adult ADHD (Bolea-Alamañac et al. 2014; [NICE 2018 Guidance]). The current stimulants are all in C-II, which is the most restrictive category for controlled drugs. It creates administrative and logistical challenges for prescribers and remains a barrier to treatment for many parents and some prescribers. Discovering a novel ADHD drug with efficacy equal to *d*-amphetamine or methylphenidate combined with a reduced potential for abuse is a long-standing aspiration in the pharmaceutical

industry and one that has not yet been fully realized. Whilst not downplaying the seriousness of stimulant abuse, the situation for ADHD drugs has improved substantially over the years, but much of the progress does not receive the recognition it deserves because of the rigidity of controlled drug legislation.

Once-daily formulations and prodrugs administered in the home give parents control over drug compliance and removes the need for controlled drugs to be carried by children and adolescents creating risks of theft, diversion and abuse.

Many of these once-daily medications have abuse-deterrent and/or tamper-resistant properties, which makes extracting and abusing the active ingredient extremely difficult. Examples are the Eudragit® polymer beads in Adderall-XR which expand to form a sticky gel if attempts are made to liquid extract amphetamine, rendering the product unusable for insufflation or injection. LDX is a prodrug that is virtually impossible to cleave to yield *d*-amphetamine even under extreme chemical conditions (Alda et al. 2014).

Prodrugs like LDX and Azstarys also reduce the risk of abuse because: (1) they are by definition pharmacologically inactive; (2) they have a delayed onset of effect eliminating the immediate "high" sought by stimulant abusers; (3) at pharmacologically equivalent doses, they produce less drug-liking than the active moiety when taken orally; and (4) their potency is not enhanced when taken by insufflation or intravenous injection (Heal et al. 2013b; Hutson et al. 2014; Ermer et al. 2016; Azstarys FDA Multi-discipline Review 2021).

The greatly reduced risk of abuse compared with illicit cocaine and methamphetamine is reflected in the results from the National Survey on Drug Use and Health (NSDUH) in an annual, household-based national survey on the use of illicit drugs, alcohol and tobacco by Americans aged 12+ years (National Survey on Drug Use and Health [NSDUH], 2015–2019). However, with the exception of the classification of SDX as a C-IV controlled drug, none of these risk-reduction measures is reflected either by the abuse warnings in the product labels or less restrictive scheduling.

6 The Link Between ADHD and Binge-Eating Disorder

There are now established links between ADHD and binge-eating disorder (BED). Many of the mental health problems prevalent and commonly comorbid with ADHD including conduct problems, negative affect, anxiety and impulse control and substance abuse disorders (De Alwis et al. 2014; Eme 2012; Ishii et al. 2003; Pliszka 1998) are also risk factors for the development of BED (Hilbert et al. 2011, 2014; Hudson et al. 2007; Kessler et al. 2013; McCuen-Wurst et al. 2018). ADHD is also associated with higher rates of eating disorders and behavioural addictions (gambling, compulsive buying disorder and internet addiction) (Romo et al. 2018), and anxiety and depression are frequently comorbid with ADHD (Chen et al. 2018; Polyzoi et al. 2018). Impulsivity and intolerance of delayed reward are core

symptoms of BED. McElroy et al. (2016b) reported that subjects with BED exhibited deficits in motor and non-planning impulsiveness, but not attentional impulsiveness.

Mole et al. (2015) studied delay-discounting in obese subjects with/without BED and showed both groups exhibited greater delay-discounting: i.e., increased cognitive impulsivity, compared with normal, healthy volunteers. Increased delay-discounting as an indicator of impulsive choice in binge-eating disorder sufferers has been observed by other investigators (Davis et al. 2010; Stojek et al. 2014). The overlap between the psychopathology of BED and ADHD led to the hypothesis that binge-eating is also an impulse control disorder (Heal and Smith 2021; Kessler et al. 2016; Reinblatt 2015; Ural et al. 2017). This conclusion is further supported by the observation that two catecholaminergic medications, LDX and dasotraline, have proven efficacy in treating BED (Citrome et al. 2019; McElroy et al. 2015; McElroy et al. 2016a; Navia et al. 2017). Beneficial effects of LDX included significant decreases on the obsessional and compulsive scores of the Yale-Brown Obsessive Compulsive Scale adapted for Binge Eating (YBOCS-BE) and the Barratt Impulsiveness Scale, version 11 (BIS-11) self-reported questionnaire scores for non-planning and motor impulsivity (McElroy et al. 2016b). Dasotraline also significantly reduced scores on the YBOCS-BE obsession and compulsion scales (Navia et al. 2018) and although impulsivity scores were not reported, dasotraline-treated subjects showed a marked and significant increase in the dietary restraint score on the Eating Disorder Examination Questionnaire Brief Version (EDE-Q7) scale (Navia et al. 2018). LDX is the only medication that has been approved to treat binge-eating disorder. Dasotraline was recently discontinued in the USA as a treatment for BED (Sunovion Press Release 2020).

7 Concluding Remarks

The intervening decade since we wrote our last review on the pharmacotherapy of ADHD has produced no evidence to question the hypothesis that ADHD is a catecholaminergic disorder which responds to drugs that potentiate noradrenergic and/or dopaminergic signalling in the brain.

Attempts to treat this disorder successfully through neurotransmitter systems that modulate catecholaminergic function or with cognitive enhancers all failed in clinical trials. All of the recently approved drugs and those currently in late-stage clinical development broadly remain within the same pharmacological confines as existing medications. Nonetheless, considerable progress in ADHD therapy has been achieved, particularly in the areas of once-daily treatment, greater levels of efficacy and reduced risks of diversion and abuse.

In our view, the current stratification of ADHD medications as non-stimulants and stimulants does not adequately reflect either their pharmacological or clinical profiles. As illustrated in Fig. 7, we recommend that a third classification of "sedative ADHD drugs" should be added to non-stimulants and stimulants. α_2-Adrenoceptor

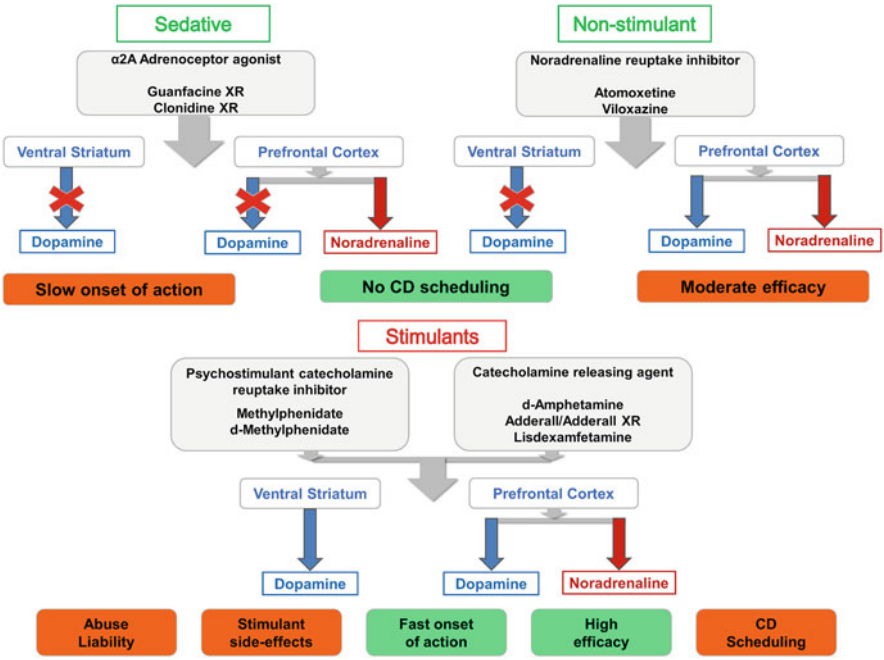

Fig. 7 Revised classification of ADHD drugs. Previous knowledge on the pharmacology of ADHD drugs supplemented by the successes and failures in clinical development of various new drug-candidates supports classification of ADHD drugs into three broad categories based on their actions on catecholaminergic neurotransmission in the PFC, striatum and mesolimbic system. Guanfacine and clonidine which make up the "Sedative" ADHD drugs enhance noradrenergic transmission via α_{2A}-adrenoceptor receptors. These drugs decrease noradrenergic signalling via other adrenoceptor subtypes and either attenuate or are inactive on dopaminergic neurotransmission. The selective noradrenaline reuptake inhibitors comprise the "Non-stimulant" ADHD drugs. They increase noradrenergic and dopaminergic neurotransmission in the PFC, but do not potentiate dopaminergic signalling in the striatum and accumbens. The amphetamines and methylphenidate make up the "Stimulant" ADHD drugs. Although the former are releasing agents and the latter are cocaine-like stimulants, both types of stimulant simultaneously increase noradrenergic and dopaminergic neurotransmission in the PFC and dopaminergic signalling in the striatum and nucleus accumbens. The strengths (in the green boxes) and weakness (in the amber boxes) are shown for the Sedatives, Non-stimulants and Stimulants. The absence of a secondary action on striatal and limbic dopamine function is in our view the main reason why these drugs are less efficacious than the Stimulants and have a slower onset of action. On the other hand, they pose no risk for abuse and they are not Controlled Drugs

agonists, which comprise the sedative category, have an exclusively norepinephrine- and PFC-based therapeutic mechanism which delivers moderate efficacy with a gradual onset of action. With no dopaminergic component to their pharmacology, they pose no risk for human abuse and are not controlled drugs. The non-stimulants comprising the selective norepinephrine reuptake inhibitors deliver noradrenergic and dopaminergic therapeutic effects in the PFC but have no secondary action

dopaminergic neurotransmission in the ventral striatum. The non-stimulants have moderate efficacy with a gradual onset of action and are not abused or controlled drugs. The amphetamine- and methylphenidate-based drugs comprise the stimulant ADHD medications. These powerful drugs markedly increase catecholaminergic neurotransmission in the PFC and dopaminergic neurotransmission in the ventral striatum and carry a significant abuse risk. Although this risk has been considerably reduced through formulation, tamper-resistance and prodrug strategies, they still remain as C-II controlled drugs.

There are few new compounds in early or late-stage development in ADHD. This situation may reflect the failure of drug-candidates with novel pharmacological mechanisms in clinical trials, the high bar for efficacy that has been set by the current generation of ADHD medications, or a belief that when all of these drugs lose patent protection the marketing opportunities for new entries will be relatively modest. Our view is pharmacotherapy for ADHD would be greatly improved by the introduction of new drugs that will offer the efficacy equivalent to the stimulants with a significantly reduced risk of abuse; the latter resulting in less restrictive controlled drug scheduling. Given the experience of LDX and dasotraline, such novel ADHD drugs could also be of considerable benefit in treating binge-eating disorder.

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Effects of Methylphenidate on the Dopamine Transporter and Beyond

Tyra S. C. Zetterström, Emmanuel Quansah, and Martin Grootveld

Contents

Abstract The dopamine transporter (DAT) is the main target of methylphenidate (MPH), which remains the number one drug prescribed worldwide for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). In addition, abnormalities of the DAT have been widely associated with ADHD. Based on clinical and preclinical studies, the direction of DAT abnormalities in ADHD are, however, still unclear. Moreover, chronic treatment of MPH has been shown to increase brain DAT expression in both animals and ADHD patients, suggesting that findings of overexpressed levels of DAT in ADHD patients are possibly attributable to the effects of long-term MPH treatment rather than the pathology of the condition itself. In this chapter, we will discuss some of the effects exerted by MPH, which are

T. S. C. Zetterström (✉), E. Quansah, and M. Grootveld
Pharmacology and Neuroscience Research Group, Leicester School of Pharmacy, Faculty of Health and Life Sciences, De Montfort University, Leicester, UK
e-mail: tyra.zetterstrom@dmu.ac.uk

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related to its actions on catecholamine protein targets and brain metabolites, together with genes and proteins mediating neuronal plasticity. For this purpose, we present data from biochemical, proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) and gene/protein expression studies. Overall, results of the studies discussed in this chapter show that MPH has a complex biological/pharmacological action well beyond the DAT.

Keywords ^{1}H-nuclear magnetic resonance (spectroscopy: ^{1}H-NMR) · ADHD · Arc · Dopamine · Dopamine transporter (DAT) · Gamma-aminobutyric acid (GABA) · Methylphenidate · Neuronal plasticity · Noradrenaline (norepinephrine) transporter (NET) · Tyrosine

Abbreviations

^{1}H-MRS	Proton magnetic resonance spectroscopy
^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy
AAAs	Aromatic amino acids
ADHD	Attention-deficit hyperactivity disorder
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Arc	Activity-regulated cytoskeleton-associated gene
Arp2	Actin-related protein 2
ATP	Adenosine triphosphate
BAIAP2	Brain specific angiogenesis inhibitor 1 associated protein 2 (see also: IRSp53/58)
BBB	Blood brain barrier
BCAA	Branched-chain amino acid
cAMP	Cyclic adenosine monophosphate
Cdc42	Cell division control protein 42
DAT/SLC6A3	Dopamine transporter
GABA	γ-Aminobutyric acid
IRSp53/58	Insulin receptor substrate protein 53/58 (see also: BAIAP2)
LAT-1	Large neutral amino acid transporter
LNAA	Large neutral amino acids
LTP	Long-term potentiation
MPH	Methylphenidate
MRS	Magnetic resonance spectroscopy
NET/SLC6A2	Noradrenaline transporter
NMDA	N-methyl-D-aspartate
PCA	Principal component analysis
PCD	Postsynaptic density
PLS-DA	Orthogonal projection to latent structure discriminant analysis
PLS-DA	Partial least squares discriminant analysis
PND	Post-natal day

RT-PCR	Real time polymerase chain reaction
SHR	Spontaneously hypertensive rat
TH	Tyrosine hydroxylase
VMAT2	Vesicular monoamine transporter 2

1 Introduction

Despite decades of clinical, biochemical, genetic and neuroimaging research, the neuro-biological mechanisms underlying Attention-Deficit Hyperactivity Disorder (ADHD) and its psychostimulant drug treatment remain not fully understood. The 'monoamine hypothesis' of ADHD is currently the leading theory of the condition. Based on clinical, animal and pharmacological studies, it proposes that hypofunction of the frontostriatal monoamine circuit gives rise to key symptoms associated with the condition including inattention, hyperactivity and impulsivity (Del Campo et al. 2011). In support of the 'monoamine hypothesis' of ADHD, methylphenidate (MPH) the first-line drug for ADHD (Vles et al. 2003; Fusar-Poli et al. 2012) blocks neuronal reuptake of dopamine and norepinephrine (Del Campo et al. 2011), a mechanism which increases the extracellular concentration of dopamine and norepinephrine in both rodents and humans (Moghaddam et al. 1993; Kuczenski and Segal 1997; Volkow et al. 2001; Berridge et al. 2006). Whilst meta-analytic studies support the safety and efficacy of MPH for ADHD treatment in adults and children, not all ADHD patients experience sufficient reductions of symptoms and functional improvement and hence a clinically satisfactory response (Castells et al. 2011; Catala-Lopez et al. 2017; Cortese et al. 2018). In this respect dopamine transporter (DAT) polymorphism(s) can affect the efficacy of MPH (Pitzianti et al. 2020), calling for an improved understanding of the molecular mechanism of action by MPH in the brain.

Apart from the action of MPH on the neuronal transporters for dopamine and norepinephrine, interactions of MPH with other proteins and neurotransmission systems have also been suggested to be involved in its pharmacological action. These include: dopamine, norepinephrine and AMPA (glutamate) receptors (Arnsten and Dudley 2005; Gamo et al. 2010; Rozas et al. 2015), as well as modulation of signalling for serotonin, glutamate and GABA (Daniali et al. 2013; Miller et al. 2019; Solleveld et al. 2017). In addition, other pathways such as those mediating neuronal plasticity, energy metabolism, cell differentiation, oxidative stress, cellular respiration and metabolic processes have also been shown to be affected by MPH (da Silva et al. 2019).

Overall, this evidence indicates that MPH has a complex biological/pharmacological action well beyond the neuronal catecholamine transporters. In this chapter we will discuss some of the effects exerted by MPH, which are related to its actions on catecholamine protein targets and brain metabolites, together with genes and proteins mediating neuronal plasticity.

2 Methylphenidate and the Central Catecholamine Systems

2.1 Methylphenidate and the Catecholamine Transporters

The hypo-functional dopamine hypothesis of ADHD emerged from initial molecular imaging studies that focused on the role of the DAT and found an increased DAT density in the basal ganglia, including the striatum, of ADHD patients (Dougherty et al. 1999; Cheon et al. 2003; Spencer et al. 2005). An overexpressed DAT predicts that extracellular dopamine is quickly taken up by the transporter into the presynaptic neuron, a process limiting the synaptic availability and neurotransmission by this monoamine (Del Campo et al. 2011). Indeed, DAT is the main target of MPH and abnormalities of this transporter have been widely associated with ADHD (Dougherty et al. 1999; Volkow et al. 2007; Del Campo et al. 2011).

However, the direction of DAT abnormality in ADHD is still unclear, and hence is currently a subject of intense debate. Some studies suggest increased striatal DAT expression in individuals diagnosed with ADHD, compared with healthy controls (Dougherty et al. 1999; Cheon et al. 2003), while other reports indicate a decrease (Volkow et al. 2007, 2009; Hesse et al. 2009) or no difference (van Dyck et al. 2002; Jucaite et al. 2005). Interestingly, a similar confusion exists in studies using animal models of ADHD. Specifically, those using the spontaneously hypertensive rat (SHR), a validated model for some of the signs of ADHD (Sagvolden and Johansen 2012), have shown increased striatal DAT gene and protein expression, along with diminished DAT expression in cortical and striatal areas when compared to those of normal rats (Roessner et al. 2010; Simchon et al. 2010; Somkuwar et al. 2013). It is, however, possible that the selection of different reference strains used as control animals could explain these differences (Sagvolden et al. 2009).

Given the inconsistency of DAT expression using animal models of ADHD, and the lack of a defined pathogenesis and reliable biomarkers for ADHD (Faraone et al. 2014), a recent study used normal (i.e. genetically unmodified) rats to investigate the action of MPH on protein markers for dopamine and norepinephrine function. Specifically, this study found that, when using adolescent normal rats, MPH increased striatal DAT expression, an effect that was more pronounced in chronically-treated rats than that observed after a single administration (Quansah and Zetterstrom 2019). This preclinical finding of MPH-induced DAT expression is consistent with a clinical study, which demonstrated that chronic exposure to this drug increased ventral striatal DAT density in ADHD patients (Wang et al. 2013). Taken together, this suggests that findings showing overexpressed levels of DAT in ADHD patients are possibly ascribable to the effects of long-term MPH treatment rather than the pathology of the condition itself.

In this respect MPH is known to increase the extracellular concentration of dopamine (Kuczenski and Segal 2002; Berridge et al. 2006) in rodents, and presynaptic DAT density has, in turn, been shown to be regulated by extracellular dopamine, i.e., DAT density declines when extracellular dopamine levels are lower than normal and increases when it is higher than normal (Zahniser and Sorkin 2004).

Thus, it is possible that the increased DAT density observed in both humans and animals, following chronic MPH injections reflects an adaptive response to prolonged MPH treatment. Indeed, several studies have previously shown that both acute and chronic MPH treatment increase extracellular dopamine concentration in a number of forebrain areas of rodents, including ventral and dorsal striatum, as well as in areas of the cortex and the midbrain (Volkow et al. 2001; Kuczenski and Segal 2002; Berridge et al. 2006; Wagner et al. 2009; Koda et al. 2010; Calipari et al. 2014; Calipari and Jones 2014).

A sustained MPH-induced elevation of extracellular dopamine, despite an upregulation of DAT, the main target of the drug, could be explained, at least partially, by a recent finding that chronic MPH administration to normal adolescent rats causes a partial down-regulation of dopamine D2 auto-receptor function in the ventral tegmental area (Di Miceli et al. 2018). Given the evidence that MPH blocks the norepinephrine transporter (NET) and increases extracellular levels of norepinephrine (Koda et al. 2010), chronic MPH has also been shown to increase NET density in the ventral striatum (Quansah and Zetterstrom 2019). Hence it is conceivable that, similar to the striatal DAT, the levels of NET could also vary as a function of its substrate norepinephrine. In addition, it is possible that the reported MPH-induced upregulations of DAT and NET following MPH treatment contribute to the occasional requirement for larger doses of the drug during long-term treatment in order to attain sufficient therapeutic efficacy (Hazell 2011; Wang et al. 2013).

Some clinical reports show right hemisphere abnormalities in ADHD: more specifically in the right frontostriatal circuitry, with ADHD individuals not showing the expected pattern of greater right caudate volume as compared to the left side (Heilman and Van Den Abell 1980; Heilman et al. 1986; Castellanos et al. 1996; Vance et al. 2007). In support of this, children with developmental right hemisphere deficits are more likely to show attention problems than children with left hemisphere damage (Wasserstein and Stefanatos 2000). Furthermore, some studies have described under-development of various white matter regions, especially the corpus callosum, in people diagnosed with ADHD (Paule et al. 2000). In this respect, the right hemisphere is made up of relatively more white matter as compared to the left hemisphere, hence white matter changes may especially affect right hemisphere function (Gur et al. 1980). Given the suggested involvement of a preferentially dysfunctional right hemisphere in ADHD, the action of MPH-induced alterations of DAT in the two hemispheres is of clinical interest. In this respect, chronic treatment with MPH indeed showed a hemispheric effect on DAT expression in the adolescent rat brain. However, in contrast to the lateralisation of abnormalities in the human brain, this effect was more pronounced on the left side of the dorsal rat striatum (Quansah and Zetterstrom 2019). In support of our preclinical study, a clinical investigation has also demonstrated more pronounced left hemisphere (i.e., left cortical and left striatal) effects of MPH on several brain neurochemicals in ADHD children (Benamor 2014).

2.2 *Methylphenidate and Other Catecholamine Protein Targets*

Apart from the DAT and NET, altered expression of some additional key proteins for dopamine and norepinephrine neurotransmission has also been suggested as candidate for signs of ADHD. These include: tyrosine hydroxylase (TH), which is the rate-limiting step in the synthesis of dopamine and norepinephrine; the vesicular monoamine transporter protein 2 (VMAT2); and some dopamine receptors (Volkow et al. 2007, 2009; Calipari et al. 2014). In particular, the D_1 dopamine receptor, an abundant brain dopamine receptor with a prominent action on cortical cognitive function, has been implicated in the signs of ADHD and its treatment (Del Campo et al. 2011; Calipari et al. 2014; Narendran et al. 2015).

Although there are a few inconsistences in the literature regarding the preclinical effects of MPH on TH activity in the brain, some of these studies highlight the importance of the brain region examined, the neurodevelopmental stage of the animals, and the duration of treatment on the effect of the drug. Some studies have, for example, failed to show MPH- induced effects in areas of the frontal cortex and the striatum, which are often highlighted as brain areas that are pivotal for the key symptoms of ADHD (Castellanos et al. 1996; Semrud-Clikeman et al. 2000; Ashtari et al. 2005; Bush 2011). Moreover, functional and structural neuroimaging studies in ADHD individuals have identified abnormalities of the brain regions comprising: cingulate, frontal, and parietal cortex (Bush 2011). In this context, a recent study using adolescent rats (PND 25) found that MPH preferentially enhanced TH density in the parietal cortex following 2 weeks of treatment, while there was no effect in the frontal cortex and dorsal striatum (Quansah and Zetterstrom 2019).

Similar to the study reported by Quansah and Zetterstrom (2019), another investigation using normal adolescent rats also failed to show MPH-induced changes in TH expression in the frontal cortex (Pardey et al. 2012). In contrast, another study, that used normal rats, but beginning the chronic MPH treatment at an earlier stage of development (PND 7) and with a longer duration (4 weeks), detected increases in TH-immunoreactive fibre density in the frontal cortex (Gray et al. 2007). The discrepancies between the above studies specifically highlight the influence of the developmental stage on the action of MPH. Indeed, some studies have shown that MPH-induced effects on gene expression, in addition to firing of prefrontal cortex neurons, are also age-dependent (Banerjee et al. 2009; Gronier et al. 2010).

Conceivably related to the effect of MPH on TH expression, some studies have shown that MPH influences the cellular distribution and expression of VMAT2. Thus, MPH increases vesicular [^{3}H]DA-uptake and binding to the VMAT2, as well as promoting protein expression and cellular redistribution of VMAT2 from the plasmalemmal membrane fraction (i.e., membrane-bound vesicles) to the vesicular subcellular fraction (Sandoval et al. 2002; Quansah and Zetterstrom 2019).

Taken together, the published results on MPH-induced effects on TH and VMAT2 activities suggest that MPH treatment increases synthesis and vesicular storage of dopamine and norepinephrine in both striatal and cortical areas. In this

respect, it is interesting to note that it has been shown that a single MPH injection to adolescent rats increases the concentration of the catecholamine precursor, tyrosine, in tissue samples of the cerebrum (Quansah et al. 2017a). Given that MPH-induced increase of extracellular catecholamines is sustained following chronic administration (Kuczenski and Segal 2002; Koda et al. 2010), simultaneous increases of TH, VMAT2 and tyrosine could compensate for the continuous blockade of DAT and NET and thereby help to sustain high concentrations of the two catecholamines within the synaptic cleft.

As already pointed out psychostimulant-induced activation of the dopamine D_1 receptor is associated with the reduction of ADHD symptoms, including hyperactivity and cognitive defects (Gamo et al. 2010; Napolitano et al. 2010; Wu et al. 2012). In this respect, it has been shown that chronic MPH increases D_1 receptor density in the parietal cortex and ventral striatum suggesting that MPH treatment increases D_1 receptor-mediated dopamine signalling in these brain areas (Quansah and Zetterstrom 2019).

The combination of functional magnetic resonance imaging (fMRI) with a specialised cognitive task, the Multi-Source Interference Task (MSIT), which has shown to activate the cingulo-frontal-parietal cognitive/attention network, indicates that a dysfunction of cingulate, frontal and parietal cortical regions is implicated in the pathophysiology and symptoms of ADHD including impairment of cognitive performance (Bush and Shin 2006). In this context, the recorded enhancement of D_1 receptor expression in the parietal cortex could contribute to a sustained therapeutic action following long-term MPH treatment (Mehta et al. 2000). The potential beneficial action of enhanced D_1 function in the ventral striatum is however questionable, since D_1 receptor activation in this region of the brain is known to stimulate reward-related behaviour following psychostimulant administration and hence could influence/promote drug-seeking behaviour (Self 2014).

2.3 Summary: Methylphenidate and the Catecholamine Systems

The DAT is the main target of MPH and abnormalities of this transporter have been widely associated with ADHD. Based on clinical and preclinical studies, the direction of DAT abnormalities in ADHD is, however, still unclear. Chronic treatment with MPH increases DAT protein expression in both animals and ADHD patients, suggesting that findings of overexpression of DAT in ADHD patients are possibly attributable to the effects of long-term MPH treatment rather than the pathology of the condition itself. The effect of chronic MPH to enhance protein density of DAT, NET and VMAT2 suggests that the drug might, in a long-term context, lose some of its acute action to increase extracellular levels of dopamine and norepinphrine. Future studies are needed to assess if these preclinical findings are related to clinical

practice where long-term higher doses of MPH are often required to attain its optimal clinical efficacy.

3 Metabolomic Studies and Methylphenidate

Metabolomics refers to the comprehensive profiling of multiple metabolite concentrations and their changes in response to drugs, genetic modulations, environment, or diet, for example, in order to help identify the beneficial or adverse effects of such interactions (Beckonert et al. 2007). Such studies are typically performed using highly reproducible and specialised multicomponent analytical techniques. In humans, metabolomics-type studies employing in vivo proton (^{1}H) magnetic resonance spectroscopy (^{1}H-MRS) are increasingly used for the direct study of psychiatric disorders and the effects of their treatments. Thus, conditions such as schizophrenia (Marsman et al. 2014) and bipolar disorders (Brambilla et al. 2005), as well as ADHD have been studied using this type of approach (Perlov et al. 2007).

By comparison, ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectroscopic analysis of pre-collected biofluids and tissues, although related to ^{1}H-MRS, offers higher spectral resolution, in addition to more accurate quantification and greater selectivity and sensitivity, allowing the detection of less abundant metabolites, including the neurotransmitter GABA, one of the possible downstream targets for MPH (Du et al. 2015). Indeed, ^{1}H-NMR spectroscopy has already been successfully applied to study alterations in human metabolite content in post-mortem tissue and cerebrospinal fluid collected from patients diagnosed with various psychiatric and neurological disorders (Prabakaran et al. 2004; Holmes et al. 2006; Lan et al. 2009). However, only a few studies have explored drug-inducible metabolic changes in human or animal brain tissue using high-resolution ^{1}H-NMR analysis. Drugs already investigated using this ^{1}H-NMR-linked metabolomics strategy include the mood stabiliser lithium, antipsychotic drugs, methamphetamine (McLoughlin et al. 2009; Bu et al. 2013) and, more recently, MPH to simultaneously explore effects on a wide range of brain metabolites in the adolescent rat (Quansah et al. 2017a, 2018).

3.1 Application of ^{1}H-NMR-Based Metabolomics Provides New Insights Into the Mechanism of Action of Methylphenidate

High-resolution ^{1}H-NMR is a quantitative technique that provides a high level of detailed molecular information on the magnetic properties of NMR-active nuclei such as ^{1}H, ^{13}C, ^{31}P and ^{19}F, etc., of solution-state molecules (Beckonert et al. 2007). In a typical NMR experiment, a solution of a biological sample (e.g., an aqueous brain tissue extract) is placed into a 5.0 mm diameter NMR tube, which is then

placed between the poles of a powerful external superconducting magnet with an operating frequency of typically 300–700 MHz. Briefly, the emitted radio-wave frequency resonances can then be analysed computationally and transformed to produce a typical multicomponent NMR spectrum. Commonly, ^{1}H is used as the nucleus of interest in metabolomics investigations in view of its powerful magnetic properties and high natural abundance. For the purpose of investigating drug-induced effects on individual brain metabolite concentrations, ^{1}H-NMR spectra of appropriate aqueous extracts of brain samples from saline- and drug-treated rats can then be analysed using available statistical packages.

Representative, mean ^{1}H-NMR spectra acquired on an aqueous cerebral extract derived from saline-treated controls and MPH-treated rats spanning the spectral regions (A) 0.80–4.50 and (B) 5.6–8.9 ppm are shown in Fig. 1 (Quansah et al. 2017a). On the basis of literature values and information available in the *Human Metabolome Database*, and via a consideration of chemical shift values, coupling patterns and coupling constants, these spectra contained a large number of prominent resonances. These were assignable to a wide range of low-molecular-mass metabolites, including amino acids (e.g., alanine, aspartate, GABA, lysine, tyrosine and phenylalanine), organic acid anions (acetate, formate, lactate, etc.), creatine, phosphocreatine and *myo*-inositol, together with purines and pyrimidines and their nucleoside adducts (hypoxanthine, inosine, etc.). The top 22 discriminatory metabolites identified by multivariate analysis technique using *MetaboAnalyst 3.0* (Xia et al. 2015) and their fold-changes and raw *p* significance values are listed in Table 1 (Quansah et al. 2017a).

3.2 *Methylphenidate Increases Brain Tissue Amino-Acid Neurotransmitter Content*

Compared to the high number of clinical and preclinical studies addressing the involvement of monoamines (in particular dopamine) in the manifestations and treatment of ADHD, studies of amino acid neurotransmitters, including GABA and glutamate in ADHD, are limited and inconsistent. Such detected inconsistencies between different studies are possibly due to a number of factors including age differences, brain area investigated as well as symptom severity of participating ADHD subjects. For example, a study using magnetic resonance spectroscopy (MRS) reported diminished concentrations of the inhibitory neurotransmitter GABA in sensorimotor cortex in children diagnosed with ADHD (Edden et al. 2012). In comparison, an additional study demonstrated age-dependent modifications of GABA concentrations in a subcortical region (i.e. basal ganglia). Thus, while adults diagnosed with ADHD, showed symptom scores which were correlated with increased GABA concentration, no significant correlations were notable in children (Bollmann et al. 2015).

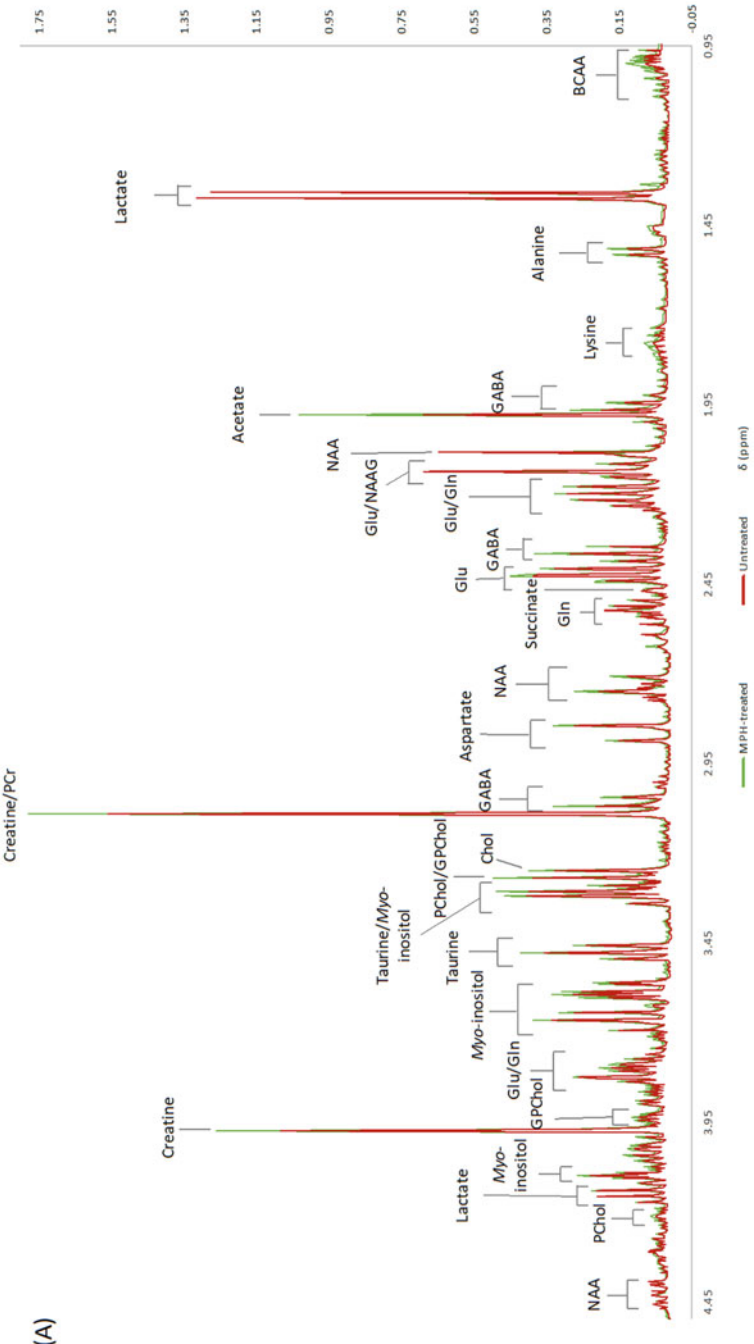

Fig. 1 Representative 400 MHz ^{1}H NMR spectra of the cerebral extracts obtained from the saline-treated controls and the MPH-treated rats, (**a**) 0.85 to 4.45 ppm spectral region (**b**) 5.15 to 9.65 ppm spectral region [resonance intensity amplitude enhanced 20-fold of that of (**a**)]. *BCAA* branched-chain amino acids (valine, isoleucine, leucine); *GABA* γ-aminobutyric acid; *NAA N*-acetylaspartate; *NAAG N*-acetylaspartylglutamate; *Glu* glutamate; *Gln* glutamine; *Chol* choline; *PChol* phosphocholine; *GPChol* glycerol-phosphocholine; *NAD* nicotinamide adenine dinucleotide (from Quansah et al. 2017a, Neurochemistry International 108 (2017) 109–120

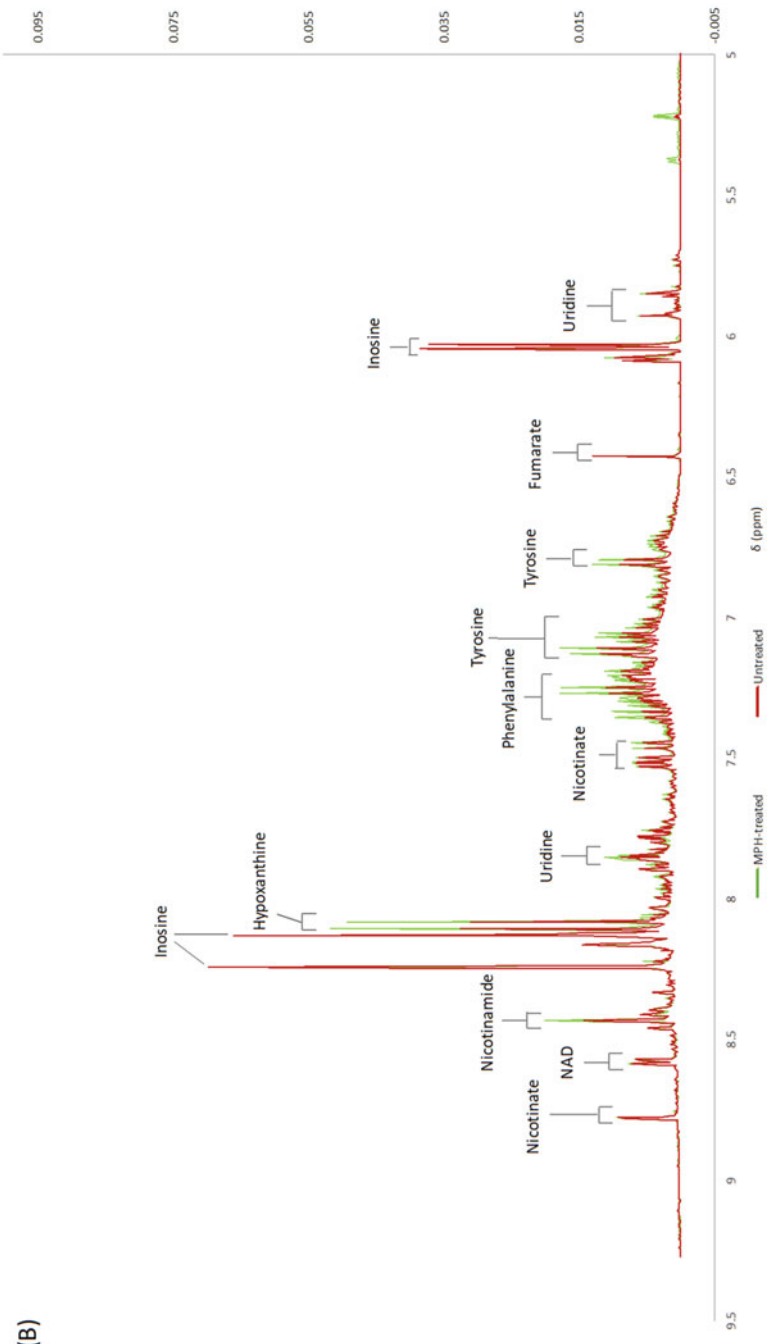

Fig. 1 (continued)

Table 1 Top 22 discriminatory ISB variables for the MPH-treated and control cerebral extracts selected by PLS-DA based on their VIP scores. A positive fold-change indicates that the variable mean value for the MPH-treated group was higher than that of the saline control one

Variable ranking	ISB (ppm)	Assignment	Multiplicity (*J*, Hz)	Raw ANOVA *p*-values for 'between treatment status' factor	Fold-change
1	1.85–1.95	GABA-C3-CH_2	*q* (7.47, 7.48)	4.53×10^{-4}	+1.49
2	2.99–3.03	GABA-C2-CH_2	*d* (2.95)	6.06×10^{-4}	+1.45
3	2.25–2.33	GABA-C4-CH_2	*t* (7.31)	9.25×10^{-4}	+1.39
4	0.91–1.00	Valine-C4-CH_3	*m* (3.85, 4.25)	1.42×10^{-3}	+1.51
5	3.51–3.58	*Myo*-inositol-C3-CH_2	*dd* (2.96, 2.81)	3.21×10^{-3}	+1.29
6	1.45–1.53	Alanine-C3-CH_3	*d* (7.39)	2.44×10^{-3}	+1.43
7	1.66–1.75	Lysine-C5-CH_2	*m* (1.66, 1.57)	4.07×10^{-3}	+1.43
8	1.00–1.08	Valine-C4'-CH_3	*d* (7.24)	3.57×10^{-3}	+1.53
9	8.21–8.23	Hypoxanthine-C7-CH	*s*	7.64×10^{-6}	+1.76
10	8.17–8.21	Hypoxanthine-C2-CH	*s*	1.16×10^{-5}	+1.68
11	3.58–3.66	*Myo*-inositol-C4-CH	*t* (3.70)	6.75×10^{-3}	+1.26
12	3.21–3.25	Phosphocholine/ Glycerol-phosphocholine-N$(CH_3)_3$	*s*	5.22×10^{-3}	+1.29
13	2.73–2.81	Aspartate-C3-CH_{2a}	*d* (4.58)	8.56×10^{-3}	+1.31
14	3.08–3.13	Phenylalanine-β-CH_2	*dd* (4.88, 6.51)	2.96×10^{-3}	+1.48
15	7.40–7.48	Phenylalanine-C2-CH	*m* (7.38, 6.89)	3.51×10^{-4}	+1.85
16	3.39–3.48	Taurine-C1-CH_2	*t* (3.39)	8.86×10^{-3}	+1.26
17	3.25–3.33	*Myo*-inositol-C5-CH	*t* (6.36)	1.53×10^{-2}	+1.23
18	4.03–4.08	*Myo*-inositol-C2-CH	*t* (4.06)	7.83×10^{-3}	+1.26
19	2.33–2.39	Glutamate-C4-CH_2	*m* (6.90, 7.14)	4.07×10^{-2}	+1.20
20	7.16–7.23	Tyrosine-C6-CH	*m* (7.87, 6.89)	4.66×10^{-3}	+1.41
21	2.81–2.88	Aspartate-C3-CH_{2b}	*d* (4.44)	6.29×10^{-3}	+1.34
22	3.94–3.96	Phosphocreatine-C2-CH_2	*s*	2.94×10^{-3}	+1.44

From Quansah et al. (2017a), Neurochemistry International 108 (2017) 109–120

To the best of our knowledge, only two studies have measured brain tissue concentrations of GABA in adolescent rats following MPH treatment using ^{1}H-NMR-based metabolomics strategies (Quansah et al. 2017b, 2018). Both studies,

which analysed samples collected from different parts of the brain (i.e., cerebrum and the cerebellum) showed MPH induced enhancements of GABA levels (data from cerebrum is shown in Table 1). Given that an electrophysiological type study demonstrated that MPH increases GABAergic neurotransmission in the sensory thalamic nuclei of rat cerebrum (Goitia et al. 2013), it is possible that the MPH-induced increase of GABA tissue concentrations in both the cerebellum and the cerebrum indicates that the drug induces an overall enhancement of brain inhibitory neurotransmission.

Additional support for the involvement of GABA in the molecular actions of MPH has been provided by a study that performed a pharmacogenomic analysis of human plasma samples from adult ADHD patients undergoing MPH treatment. This investigation revealed a nominal association for gene-sets related to GABA transmission (da Silva et al. 2019). While MPH's ability to block monoamine transporters (i.e., DAT and NET) is well established and a process shown to result in increased content of extracellular dopamine and norepinephrine (Volkow et al. 2001; Kuczenski and Segal 2002; Berridge et al. 2006; Wagner et al. 2009; Koda et al. 2010; Calipari et al. 2014), the mechanistic link between this effect and increased whole tissue levels of GABA remains, however, somewhat unclear. The upregulated GABA levels are not unique to MPH, since previous animal studies using high-resolution ^{1}H-NMR analysis have detected similar effects following both single and repeated injections of the anti-manic drugs lithium and carbamazepine (McLoughlin et al. 2009; Lan et al. 2009).

Abnormalities of the excitatory amino acid neurotransmitter, glutamate, have also been implicated in the pathophysiology of ADHD. Human studies using proton magnetic resonance spectroscopy (^{1}H-MRS) have shown that children with ADHD have significantly higher concentrations of glutamate compared to controls. (Moore et al. 2006). Furthermore, anti-ADHD drugs, such as MPH, modulate glutamate neurotransmission in animal models, including glutamate NMDA receptor function, long-term potentiation (LTP) and cognition (Chen et al. 2015; Di Miceli and Gronier 2015; Schmitz et al. 2016; Rozas et al. 2015). In this context, the application of ^{1}H-NMR-based metabolomics detected enhanced levels of glutamate in brain samples of the cerebrum from MPH-treated rats when compared to those of the saline-treated control group (Quansah et al. 2017b), as noted in Table 1. ^{1}H-NMR analysis of brain samples from the cerebellum, which demonstrated an MPH-induced decrease of metabolites associated with excitatory amino acid neurotransmission: i.e., glutamate and its precursor glutamine, further complicated the actions of MPH on brain biomolecules (Quansah et al. 2018).

These contrasting findings regarding MPH-induced effects on glutamate levels in the cerebellum versus the cerebrum are in line with some previous findings from both human and rodent studies. These have, for example, shown that MPH gives rise to differential metabolic effects in these two parts of the brain (e.g., those involving glucose) (Volkow et al. 1997; Michaelides et al. 2010). Interestingly, these reports indicate that such changes, at least in part, could be attributed to differences in dopamine D_2-like receptor levels as well as differences in their localisation in the cerebellum versus the cerebrum (Volkow et al. 1997; Michaelides et al. 2010).

However, given that glutamate is stored in both neuronal and glial cells, it is unclear if the MPH-induced enhancement and reduction of tissue glutamate levels within the cerebrum and the cerebellum, respectively, are indeed related to a change in excitatory neuronal transmission.

The non-essential amino acid aspartate, like glutamate, is stored in both glia cells and neurons. Indeed, some studies have suggested vesicular co-storage of glutamate and aspartate (Patneau and Mayer 1990; Morland et al. 2013). Furthermore, ^{1}H-NMR analysis of cerebral samples detected an MPH-induced elevation of aspartate and taurine content (Quansah et al. 2017a) (Table 1). Based on the fact that aspartate acts as a full agonist on the glutamatergic N-methyl-D-aspartate (NMDA) receptors, it has been proposed that aspartate also acts as a co-transmitter with glutamate in excitatory synapses (Patneau and Mayer 1990; Morland et al. 2013). Given that recordings from adult mice CA1 pyramidal neurons have shown that glutamate alone fully accounts for neurotransmission at excitatory synapses in the hippocampus, such a role for aspartate has been contested in this part of the brain (Herring et al. 2015).

The enhancement of taurine content in brain samples of rats treated with MPH could also be of neurochemical importance (Table 1). Indeed, taurine is one of the most abundant amino acids in the brain and is involved in a variety of brain functions, including cytoprotection and brain development (Ripps and Shen 2012). The chemical structure of taurine is similar to GABA and it acts as an agonist on $GABA_B$ receptors (Kontro and Oja 1990), as well as on the glycine site of the NMDA receptor (Chan et al. 2014). MPH is known to enhance monoamine function and this effect is implicated in the drug's promotion of long-term potentiation (LTP): Jenson et al. 2015). In this regard, it is interesting to note that previous studies have found that taurine affects dopamine release and, together with D_1 receptor activation, it promotes LTP, an NMDA receptor-dependent mechanism (Salimaki et al. 2003; Suarez et al. 2014). Hence, it is possible that the MPH-induced upregulation of brain tissue levels of both taurine and aspartate is involved in MPH-induced long-term potentiation (Jenson et al. 2015).

3.2.1 Methylphenidate Increases Brain Content of Large Neutral Amino Acids

Dysfunctional neurotransmission of the dopamine and norepinephrine systems are implicated in the signs of ADHD and these catecholamines play important roles in the control of motor activity and executive brain function (Del Campo et al. 2011). In addition, both animal and clinical studies demonstrate that MPH increases extracellular levels of these catecholamines (for details see Sect. 2.1 of this chapter).

Moreover, it has been demonstrated that MPH increases levels of the aromatic amino acids (AAA), tyrosine and its precursor phenylalanine, in addition to the branched-chain amino acid (BCAA), valine, in the brain of MPH-treated adolescent rats compared with saline-treated controls (Quansah et al. 2017a) (Table 1). Importantly, tyrosine functions as a precursor for both dopamine and norepinephrine

biosynthesis in the brain. Specifically, L-tyrosine hydroxylation generates L-3,4-dihydroxyphenylalanine (L-DOPA) via the rate-limiting enzyme, tyrosine hydroxylase (TH). It has further been suggested that under normal conditions TH is close to saturation (>75%) and hence the rate of tyrosine hydroxylation is mainly dependent by TH activity rather than the supply of tyrosine (Fitzpatrick 1999). Such assumptions are based on animal experiments measuring DOPA levels in brain tissue ex vivo after systemic administration of tyrosine together with an aromatic-L-amino-acid decarboxylase inhibitor (e.g. NSD-1015) (Carlsson et al. 1972; Carlsson and Lindqvist 1978; Badawy and Williams 1982). Typically, such experiments failed to increase L-DOPA levels following concentrations of tyrosine up to 600 μm, well above the estimated intracellular concentration of tyrosine (110–150 μm) (Kaufman 1995). However, given the instability and low baseline levels of L-DOPA, in vivo confirmation of the apparent high saturation rate of TH under normal conditions has been difficult to confirm (Westerink et al. 1982).

A more recent in vivo microdialysis study indicates that local application of NSD-1015 together with concentrations of tyrosine by reverse dialysis indeed increases extracellular L-DOPA levels in striatum and medial prefrontal cortex. These findings suggest that under basal in vivo conditions, brain TH may not be fully saturated with tyrosine. However, it remains unclear if the measured increase of L-DOPA content represented a net increase of tyrosine hydroxylation or simply a 'heteroexchange' of tyrosine for intracellular L-DOPA (Brodnik et al. 2012).

A more direct effect of tyrosine on dopamine function was shown by another microdialysis study where systemic injections of tyrosine increased dopamine concentrations in dialysates collected from both striatum and nucleus accumbens of adult rats (During et al. 1988). Consequently, it is feasible that ex vivo factors such as diet, exercise and systemic MPH (Table 1) that enhance the brain pool of tyrosine could also increase the rate of conversion to newly synthesised dopamine and norepinephrine in their respective nerve terminals, ultimately elevating their synaptic concentrations (Fernstrom and Fernstrom 2007). In this context, a recent study in humans showed support for the idea that tyrosine indeed increases dopamine availability, thus a significant association between tyrosine intake and cognitive performance related to dopamine function was demonstrated (Kuhn et al. 2019). In contrast, when tyrosine transport into the brain is suppressed by the dietary administration of a tyrosine/phenylalanine-free large neutral amino acids (LNAA) mixture, the physiological- and amphetamine-evoked release of dopamine in animal models is impaired (McTavish et al. 2001; Le Masurier et al. 2014). Similarly, in humans, dietary tyrosine/phenylalanine depletion has been shown to attenuate some reward-related behaviour, which can be driven by dopamine (Bjork et al. 2014).

LNAAs, including tyrosine and phenylalanine, are all polar compounds that cannot pass across the blood-brain barrier (BBB) freely. In order to enter the brain from blood plasma, they utilise an active transport system, the large neutral amino acid transporter LAT-1 (Fernstrom 2013). Different types of LNAAs compete with each other for transport from the plasma to the brain via the LAT-1 system. Hence MPH may indeed modify the physiological balance of LNAAs in the plasma, a process that may favour the entry of some of these LNAAs into the brain over others

(Fernstrom and Fernstrom 2007). Moderate doses of MPH (2.0–5.0 mg/kg) to rats give rise to pronounced behavioural activation, including increased locomotion, sniffing and rearing (Appenrodt and Schwarzberg 2003; Kuczenski and Segal 2005; Claussen et al. 2015). Given that rats exposed to treadmill-running show increased brain levels of tyrosine (Acworth et al. 1986), it may be speculated that MPH-induced increase in motor activity enhances the plasma to brain transport of selected LNAAs, including tyrosine and its precursor phenylalanine. In addition, another psychostimulant, *d*-amphetamine, which is used to treat ADHD induces increased locomotion in rats and also increases rat brain levels of LNAAs, including tyrosine (Fernando and Curzon 1978).

The MPH-induced increase in brain tyrosine levels may indeed be relevant to a neuropsychological study reporting that tyrosine-free amino acid mixtures disrupt performance in a range of behavioural and cognitive tasks that are dependent on dopamine and norepinephrine (Coull et al. 2012). Therefore, it is possible that MPH alleviates ADHD symptoms by two key mechanisms: (1) via blockade of DAT and NET, and (2) by enhancing the brain pools of tyrosine and phenylalanine.

In addition, the study by Quansah et al. (2017a) detected that brain levels of the non-essential amino acid, alanine, were higher in brain samples from MPH-treated rats than in those of the corresponding control group. Alanine can be manufactured in the body from the branched-chain amino acid (BCAA), valine, which was also demonstrated to be upregulated by MPH (Table 1). In addition, alanine undergoes transamination to pyruvate, which is used for gluconeogenesis in the liver (Felig 1973). Although the brain is normally not associated with glycogenesis, some previous data suggest that this might indeed be the case; however, it may be at a significantly lowered efficacy in the brain than that occurring hepatically (Bhattacharya and Datta 1993). Moreover, brain levels of the essential amino acid, lysine, were also significantly elevated in MPH-treated rats. Although the direct functional impact of this effect is not yet clear, lysine has been reported to block serotonin receptors, and a reduced lysine intake is associated with anxiety, a symptom occasionally comorbid with ADHD (Smriga et al. 2002; Mulraney et al. 2018).

3.3 Methylphenidate Alters Energy Metabolism and Membrane-Related Metabolites

Studies have suggested that MPH alters brain energy metabolism. Specifically, MPH has been shown to alter cerebral glucose utilisation and uptake in the brain of young and adult rats (Porrino and Lucignani 1987; Reus et al. 2015). Creatine kinase catalyses the transfer of a phosphoryl group from adenosine triphosphate (ATP) to creatine, producing phosphocreatine and adenosine diphosphate. Interestingly, MPH has been shown to increase creatine kinase activity in several regions of rat cerebrum, including the prefrontal cortex, hippocampus and striatum, all of which are

implicated in the mechanisms of action of MPH (Scaini et al. 2008). Presumably related to this action, Quansah et al. (2017a) detected a MPH-induced upregulation of phosphocreatine levels in the cerebrum (Table 1).

Taken together, the MPH-induced upregulation of creatine kinase and phosphocreatine levels indicates that MPH causes an imbalance in the transfer of a phosphoryl group from ATP to creatine. This reaction is, of course, reversible, and hence creatine kinase may play an important role in the rapid regeneration of ATP in high energy-consuming tissues such as the cerebrum. Furthermore, MPH elevates neuronal activity, as is evident from its ability to increase the transcription of several activity-dependent genes, together with their corresponding proteins (Yano and Steiner 2007; Banerjee et al. 2009; Gronier et al. 2010), and it is likely that this effect is dependent on a localised elevated ATP metabolism level. Although it is not possible to establish the precise mechanism behind the MPH-induced elevation of phosphocreatine levels, it is likely that this effect is related to the known blockade of DAT by MPH, which increases synaptic dopamine levels and hence stimulation of dopamine receptors. In support of this, antipsychotic drugs known to block D_2 receptors reduce creatine kinase activity and creatine levels in the brains of rats and humans, respectively (Assis et al. 2007; Sarramea Crespo et al. 2008).

In addition to the creatine/phosphocreatine cycle, purine metabolism is also closely linked to ATP production and utilisation and the purine derivative hypoxanthine has been shown to be significantly enhanced in the cerebrum of the MPH-treated rats compared to that of controls (Quansah et al. 2017a, Table 1).

Myo-inositol is abundant in both neurons and glial cells and is known to be a marker of membrane turnover as well as glial cell integrity (Brand et al. 1993); brain levels of *myo*-inositol have been shown to be increased following MPH administration (Quansah et al. 2017a, Table 1). In contrast, some other psychoactive drugs, including some antipsychotic drugs as well as the mood stabilising drugs, lithium and valproate, have been found to reduce brain levels of *myo*-inositol in both animal and human studies (Lan et al. 2009; McLoughlin et al. 2009).

Finally, phosphocholine is a known precursor of various membrane phospholipids in both glial cells and neurons (Paoletti et al. 2011); increased concentrations of this metabolite were also observed in the MPH-treated brain samples (Table 1). The enhancement of phosphocholine and *myo*-inositol by MPH could indicate that the drug alters the dynamics of brain cell membranes.

3.4 Summary: Metabolomic Studies and Methylphenidate

While findings in metabolomic studies of MPH do not undermine the possibility that the key therapeutic mechanism underlying the action of this psychostimulant in treatment of ADHD is an enhancement of dopamine and norepinephrine transmission, they offer important new insights into the molecular action of the drug beyond the catecholamine transporters (i.e., DAT and NET). Thus, metabolomic studies show that MPH treatment increases several rat cerebral metabolites, including amino

acid neurotransmitters (such as GABA and glutamate), as well as LNAAs (such as tyrosine and its phenylalanine precursor). Metabolomic studies also indicate that MPH alters membrane and energy metabolism in brain cells. As such, further applications of metabolomics will be important for future studies into the mechanism of action by MPH and its long-term effect on the still developing and mature brain. In conclusion, some of the preclinical findings regarding MPH-induced increases of LNAAs offer opportunities for clinical research into additional non-drug treatments for ADHD. In particular the potential role of diet and regular exercise in ADHD treatment deserves more research.

4 Methylphenidate and Neuroplasticity

The increased usage of MPH for the treatment of ADHD in young children has stimulated research into the long-term effects of MPH on gene expression for key proteins with important neuronal and synaptic function (Swanson and Volkow 2008). These include genes encoding proteins of the postsynaptic density (PSD), which is a complex network of cytoskeletal scaffolding and signalling proteins that are critical for normal transmission (Kaizuka and Takumi 2018; da Silva et al. 2019). Specifically, prolonged exposure to MPH induces changes in neuroplasticity-related genes (Adriani et al. 2006; Yano and Steiner 2007). This includes genes that modulate neuronal characteristics such as dendritic elongation and the number of dendritic spines (Adriani et al. 2006; Chase et al. 2007; Banerjee et al. 2009; Kim et al. 2009; Allen et al. 2010; Quansah et al. 2017b).

Importantly, some of these neuronal alterations are associated with synaptic activity such as LTP (Alvarez and Sabatini 2007; Soria Fregozo and Perez Vega 2012) and underlie memory and drug-related behaviours including drug-seeking and relapse after abstinence (Vanderschuren and Kalivas 2000; Tzschentke and Schmidt 2003; Kalivas and O'Brien 2008).

4.1 Methylphenidate and the Regulation of Genes and Proteins Mediating Neuroplasticity

Chronic exposure to psychostimulants including MPH, amphetamine and cocaine increases dendritic branching and dendritic spine density in some parts of the brain including the hippocampus and nucleus accumbens (Robinson and Kolb 1997; Lee et al. 2006; Kim et al. 2009). To better understand the molecular mechanisms behind these effects recent studies have investigated the actions of chronic MPH on genes and proteins that could be candidates for driving these morphological changes. For example, alterations of dendritic spine density are closely related to the expression pattern of actin-associated genes (Sarowar and Grabrucker 2016), which are

involved in the production of filaments of actin forming dendritic spines from spine precursors (filopodia). Given that MPH increases extracellular levels of dopamine in areas of the brain connected to the symptoms of ADHD, including ventral and dorsal striatum, the spines covering the dendrites of the striatal GABAergic medium spiny neurons represent major contact sites for dopaminergic nerve terminals and hence could be of major importance for the mechanism of action by MPH (Soria Fregozo and Perez Vega 2012).

The activity regulated cytoskeleton-associated protein (Arc) is of high relevance for neuronal plasticity and regulates dendritic spines through actin remodelling, such that mice lacking the *Arc* gene have decreased dendritic spine density (Peebles et al. 2010). The Arc protein also increases the proportion of the so-called learning spines (thin spines) that are more plastic, while it decreases the proportion of the more stable stubby spines (Peebles et al. 2010).

Given that one of the mechanisms that triggers Arc gene expression is D_1 receptor-induced increase of cAMP levels and that MPH increases extracellular levels of dopamine, via DAT blockade, a number of studies have investigated the drug's effect on *Arc* gene expression in dopamine rich brain areas. Indeed, MPH induces stark upregulation of *Arc* mRNA in striatal and cortical regions of the juvenile and adult rat following both acute and chronic administration (Chase et al. 2007; Banerjee et al. 2009; Gronier et al. 2010). The gene expression of *Arc* is also triggered by an influx of Ca^{2+} through NMDA receptors and voltage-gated Ca^{2+} channels (Korb and Finkbeiner 2011). Possibly related to this effect of MPH, a recent metabolomic study has shown that a single injection of MPH increases levels of glutamate and its precursor glutamine in the cerebrum of adolescent rats (Quansah et al. 2017b).

Methods such as in situ hybridisation and RT-PCR have been extensively used over the last two decades for the measurement of psychostimulant-induced gene expression in the brain. Albeit not covered in this chapter, the recent application of epigenetics has further enhanced our understanding of psychostimulant-induced gene network regulation (Schmidt et al. 2013; Hamza et al. 2019; Pitzianti et al. 2020).

MPH has been studied widely for its action on gene expression following both acute and chronic administrations (Adriani et al. 2006; Chase et al. 2007; Yano and Steiner 2007; Banerjee et al. 2009). While the effects of acute MPH administration on gene expression mainly probe changes of neuronal activity, to clarify the site of action by the drug within the brain, the effects on gene expression (e.g., *Arc*) following chronic treatment with this psychostimulant are more likely to signal a neuroadaptive action of the drug (Chase et al. 2003, 2007; Yano and Steiner 2007; Quansah et al. 2017b).

Further, it has become clear that drug-induced changes of the density of gene expression often do not fully reflect the expression of the corresponding protein. For example, we have shown that, following chronic administration of MPH to young rats, the Arc protein was upregulated in the nucleus accumbens, dorsal striatum and the hippocampus, but the *Arc* mRNA levels were increased only in the dorsal striatum (Quansah et al. 2017b). This lack of correspondence between the

MPH-induced change of Arc protein and gene expression is likely to be due to different turnover-rates of proteins and mRNA levels (Greenbaum et al. 2003; Vogel and Marcotte 2012).

The cerebellum is an area of the brain that plays a role in a number of neuropsychiatric and behavioural disorders including ADHD (Ivanov et al. 2014). Interestingly, this part of the brain reacts to MPH-induced *Arc* gene expression in a different way compared to regions of the cerebrum. Thus, while MPH failed to alter cerebellar *Arc* gene expression, this drug decreased levels of the corresponding protein (Quansah et al. 2017b). Given that an increase of Arc protein enhances spine density in vitro and a disruption of Arc formation decreases spine density in vivo (Peebles et al. 2010), MPH-induced increase of Arc protein in the hippocampus, following chronic treatment, may improve learning. In comparison, MPH-induced increase of *Arc* gene expression in the nucleus accumbens could signal MPH induced behavioural sensitisation (Moore et al. 2006; Chase et al. 2007; Bramham et al. 2010; Koob and Volkow 2010; Korb and Finkbeiner 2011) and hence addictive properties of MPH (Everitt and Wolf 2002; Kim et al. 2009). There is, however, little evidence that MPH induces dependence when used clinically (Mannuzza et al. 2008).

Apart from the role of Arc on neuronal plasticity, recent studies have increased our understanding of other proteins that control the formation of dendritic spines. These include the filament nucleating Arp2/3 complex and its Rho family of GTPase regulators, one of which, namely the cell division control protein 42 (Cdc42), promotes the formation of filopodia (Soria Fregozo and Perez Vega 2012). In addition, Cdc42 serves as one of the main signalling proteins that promote branching of dendritic spine heads (Kang et al. 2016).

A major actin regulator that has attracted a great deal of attention recently is the insulin receptor tyrosine kinase substrate protein 53 (IRSp53), which is also known as brain specific angiogenesis inhibitor 1 associated protein 2 (BAIAP2), (Yeh et al. 1996). IRSp53 is a multi-domain adaptor protein that regulates membrane and actin dynamics at actin-rich structures, such as filopodia (Govind et al. 2001; Krugmann et al. 2001; Yamagishi et al. 2004). This is supported by evidence that IRSp53 localises to the tips of filopodia (Nakagawa et al. 2003). Although the functions of IRSp53 were initially mainly studied in non-neural cells, recent evidence supports a neuronal function, particularly in the regulation of actin dynamics at excitatory synapses (e.g., glutamatergic). Further, IRSp53 has been implicated in several brain disorders including ADHD (Ribases et al. 2009; Liu et al. 2013).

In this respect, studies on the behavioural phenotypes of mice lacking IRSp53 show social and cognitive deficits, as well as hyperactivity (Kim et al. 2009; Sawallisch et al. 2009; Chung et al. 2015). Evidence that IRSp53 knockout animals show some of the core symptoms of ADHD supports the usage of these behavioural phenotypes as animal models of ADHD (Kim et al. 2020). Of importance for the long-term effect of MPH in the developing brain, it has been shown that chronic treatment with MPH to adolescent rats increases the expression of IRSp53, as well as Cdc42 and Arp2, in the striatum and nucleus accumbens, respectively. Conversely, chronic treatment with MPH decreased both Arc and IRSp53 expression in the

cerebellum, which provides additional evidence for differential effects of the drug in cerebral areas relative to the cerebellum (Quansah et al. 2018).

4.2 Summary: Methylphenidate and Neuroplasticity

The increasing prescription rate of MPH for the treatment of ADHD symptoms in young children during the last couple of decades has led to increased research efforts into the drug's long-term effects. Specifically, research into MPH-induced changes of gene and protein expression of biomolecules with important neuronal and synaptic functions has intensified over the last 20 years. In this respect, studies show that chronic exposure to MPH increases dendritic branching and spine density in parts of the brain associated with some of the symptoms of ADHD. In addition, gene and protein studies show that long-term MPH treatment increases expression of mRNAs (and their corresponding proteins), which are associated with dendritic spine formation and neuronal plasticity in target areas of the cerebrum. In contrast, long-term MPH treatment decreased expression levels of some of these proteins in the cerebellum adding further evidence for a different action of MPH in cerebral areas and the cerebellum. Some of the effects discussed here in adolescent rats are of relevance for a better understanding of the molecular action by MPH and possibly in the treatment of ADHD. Furthermore, these findings may be useful in the future research efforts into new pharmacological targets that could lead to the development of better tolerated medications for the treatment of ADHD.

5 Conclusions

Overall, results of the studies discussed in this chapter show that MPH has complex biological/pharmacological actions, well beyond the neuronal catecholamine transporters DAT and NET. While DAT remains the main target of MPH, and a vast literature has discussed changes of this transporter in connection with ADHD, the direction of the DAT abnormality in the condition remains unclear. Interestingly, long-term treatment with MPH has been shown to increase DAT levels in both animals and ADHD patients, suggesting that overexpression of DAT in individuals diagnosed with ADHD is due to the treatment rather than the condition itself. The idea of a neuroadaptive increase of DAT as well as NET and VMAT2 following chronic treatment with MPH is consistent with studies demonstrating that MPH may be effective in the short-term but that its long-term clinical effectiveness may be limited, as larger doses may be required to ensure clinical effectiveness.

Applications of ^{1}H-NMR-based metabolomics have provided new insights into the mechanism of action of MPH. This technique has revealed that a single dose of MPH causes an appreciable increase in up to 22 metabolites in cerebral extracts from adolescent rats, compared to the corresponding samples from saline-treated animals.

Some of these MPH-induced changes, detected by ^{1}H-NMR-based metabolomics and supported by electrophysiological studies, include an overall elevation of brain inhibitory neurotransmission. Importantly, this MPH-induced upregulation of GABA content does not appear to be a general effect recorded with all brain-active amphiphilic drugs. Abnormalities of glutamate transmission have also been implicated in the pathophysiology of ADHD and metabolomic studies show that MPH increases levels of glutamate in brain samples of the cerebrum from MPH-treated rats. In contrast the same treatment decreased glutamate levels in the cerebellum highlighting the differential action of the drug in these two main parts of the brain.

Possibly of future clinical relevance, metabolomic studies in animals show that MPH increases brain levels of tyrosine and its precursor phenylalanine. Thus, it cannot be excluded that MPH modifies the physiological balance of LNAAs between plasma and brain, a process that may favour the entry of tyrosine and phenylalanine into the brain over some other LNAAs. In addition, the application of ^{1}H-NMR-based metabolomics demonstrates MPH-induced elevations of phosphocholine and *myo*-inositol suggesting that the drug could alter the dynamics of brain cell membranes.

Frequently, MPH-induced changes of brain biomolecules depend on the duration of treatment and thus indicate that the drug induces neuroplasticity. For example, chronic exposure to MPH increases dendritic branching, dendritic spine density as well as the expression of proteins promoting such morphological changes. In contrast, long-term MPH treatment decreased expression levels of some of these proteins in the cerebellum adding further evidence of differential action of MPH in cerebral areas relative to the cerebellum.

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Comorbidity of Attention-Deficit Hyperactivity Disorder and Autism Spectrum Disorders: Current Status and Promising Directions

Chandan J. Vaidya and Christoph Klein

Contents

Abstract High rates of co-occurring Attention-Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD) suggest common causal pathways,

C. J. Vaidya (✉)
Department of Psychology, Georgetown University, Washington, DC, USA

Children's Research Institute, Children's National Health System, Washington, DC, USA

C. Klein
Clinic for Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Department of Child and Adolescent Psychiatry, Medical Faculty, University of Cologne, Cologne, Germany

Psychiatry Department, National and Kapodistrian University of Athens, Medical School, University General Hospital "ATTIKON", Athens, Greece

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which await elucidation. What is well-established, however, is the negative impact of comorbid ADHD and ASD on outcomes for everyday living, particularly in social interaction and communication and on broader psychopathology. Neurocognitive approaches suggest correlates of comorbidity are rooted in functional connectivity networks associated with executive control. There is support for familial origins, with molecular-genetic studies suggesting a causal role of pleiotropic genes. Further investigation is needed to elucidate fully how genetic risk for ADHD and ASD affects neurodevelopment and to identify structural and functional neural correlates and their behavioral sequelae. Identification of intermediate phenotypes is necessary to advance understanding, which requires studies that include the full spectrum of ASD and ADHD symptom severity, use longitudinal designs and multivariate methods to probe broad constructs, such as executive and social function, and consider other sources of heterogeneity, such as age, sex, and other psychopathology. Randomized efficacy trials targeting comorbid symptomatology are needed to mitigate negative developmental outcomes.

Keywords Brain imaging · Executive control · Functional connectivity · Genetic

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ADI-R	Autism diagnostic interview
ASD	Autism spectrum disorder
CD	Conduct disorder
CNV	Copy number variant
DCC	Deleted in colorectal cancer
DZ	Dizygotic (twins)
MD	Major depression
MZ	Monozygotic (twins)
ODD	Oppositional defiant disorder
SCQ	Social communication questionnaire
SRS	Social responsiveness scale

1 Introduction

Comorbidity, defined as meeting criteria for two or more disorders at the same time, is increasingly being recognized in psychiatry, prompting changes to diagnostic classification systems and research agendas. Among neurodevelopmental disorders, comorbidity of Attention-Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) has gained sufficient recognition to force substantive changes in psychiatric classification and clinical practice (Young et al. 2020; Simmons et al.

2019). As official recognition of their comorbidity, the two diagnoses are no longer considered mutually exclusive in the latest revisions of the Diagnostic and Statistical Manual (American Psychiatric Association 2013) and the International Statistical Classification of Diseases to be adopted in January 2022 (World Health Organization 2019). Research designs of studies are increasingly including assessment of ADHD symptoms and autistic traits as continuous measures, in acknowledgement of their complex and dynamic contributions to comorbidity. While great advances have been made in the understanding of psychological, genetic, and neurobiological characteristics of ADHD and ASD, their co-occurrence remains to be fully elucidated.

Clinical phenotypes of ADHD and ASD are appreciably different. ASD is characterized by qualitative impairments in social communication and interaction as well as overt behavioral manifestations like restricted, repetitive and stereotypic behaviors. Interests and activities, with impaired social interaction and rigidity being the "essence" of the clinical phenotype (Van Engeland and Buitelaar 2008). ADHD, by contrast, is characterized by the symptom trio of attention deficits, impulsivity, and/or hyperactivity, with the last two symptom groups often clustered together. Also, while autism onsets early and persists lifelong, ADHD onsets some years later and shows significant improvements at least in some symptom domains (hyperactivity in particular) (Cherkasova et al. 2013; Van Engeland and Buitelaar 2008). Furthermore, while there is currently no pharmacological treatment targeting the *core* symptoms of autism, methylphenidate or amphetamine are established as successful pharmacological treatments for ADHD.

A large literature has accumulated that evaluates shared and unique genetic, phenotypic, and endophenotypic characteristics of ADHD and ASD [for excellent reviews, see Rommelse et al. (2011); Antshel and Russo (2019); Mikami et al. (2019); Hartman et al. (2016); Waye and Cheng (2018)]. This chapter presents the current status of understanding of ADHD-ASD comorbidity, featuring some notable studies, rather than a comprehensive review, and offers directions for future research.

2 Prevalence of Comorbidity

We are aware of more than 40 studies reporting prevalence rates of ASD in participants with ADHD (space limitations prohibit their presentation in full) covering age groups as young as 3 years to 30 years on average and sample sizes between 16 and 3,066 participants. Likewise, we have identified more than 20 studies reporting increased ASD symptoms in participants with ADHD. Overall, the likelihood of increased ADHD symptoms in those with ASD is greater than the likelihood of ASD symptoms in those with ADHD (Grzadzinski et al. 2016; Antshel et al. 2016). Like the pure disorders themselves, these samples are dominated by male participants, with the vast majority of studies including 75% or more males.

Most of the samples are clinical samples, but comorbidity prevalence rates in school or community samples have also been reported. Informants are mainly parents but, in some studies, symptomatology was assessed by teachers or clinicians. Depending on the study, comorbidity judgments are based on the full ADHD syndrome, components of it, or symptoms. Many studies provide a break-down of comorbidity according to ADHD presentation, with the largely consistent result that ASD comorbidity rates are highest in those with ADHD presentations that show impaired attention, rather than just hyperactivity, corresponding to the relative ADHD presentation frequency itself.

It has been shown that symptoms of autism in children with ADHD exceed those of the general population (Hattori et al. 2006; Reiersen et al. 2007) and significant correlations between symptoms of ADHD and symptoms of ASD have been shown in the general population (Ronald et al. 2010). The greatest ASD symptoms expressions, measured with the Social Responsiveness Scale (SRS) scores, were reported for the inattentive and the combined ADHD subtypes in the study by Reiersen et al. (2007). Likewise, various studies have reported increased levels of ADHD symptoms in participants with ASD (Arnold et al. 2003; Gadow et al. 2006; Goldstein and Schwebach 2004; Hattori et al. 2006; Lee and Ousley 2006; Yoshida and Uchiyama 2004). Furthermore, the persistence of ADHD symptoms tends to be accompanied by persistence of ASD symptoms, possibly indicating that the stability of social and communication difficulties may contribute to greater stability of ADHD symptoms over time (St Pourcain et al. 2011).

The high degree of comorbidity of ASD and ADHD is considered to reflect possibly the presence of a strong general psychopathology factor indicating severity and chronicity of problems (Hartman et al. 2016) and etiological overlap at the genetic level (Rommelse et al. 2010). This conclusion is in line with findings showing that those with the comorbid ADHD+ASD diagnoses, as compared to those with the "pure" ADHD diagnosis, are more likely of the combined subtype (67% vs 43%) and less likely of the inattentive (21% vs 43%) subtype and thus more severely disordered (Grzadzinski et al. 2011).

2.1 Role of Development

In neurodevelopmental disorders like ASD or ADHD that show some, or even substantial, developmental changes in symptomatology, the potential modulation of comorbidity by age is an issue. Overall, it seems that the comorbidity of ASD and ADHD symptoms is not entirely stable across development, being less likely in young children and in older ages (Sokolova et al. 2017) and more likely in adolescence (Hartman et al. 2016). In a large study of child referrals to a university hospital developmental disabilities speciality clinic and a child psychiatry outpatient service, Gadow et al. (2006) compared the presence of parent-rated ADHD comorbidity in samples of ASD patients in $N = 169$ young children aged 3–5 years versus $N = 280$ children aged 6–12 years that had (3–5 years: $N = 70$; 6–12 years: $N = 170$) or had

not (3–5 years: $N = 99$; 6–12 years: $N = 110$) had ADHD. While comorbidity of any subtype of ADHD was 44% in the young children group, this figure rose to 61% in the children group. This pattern held for the combined subtype (13% → 20%) and the inattentive subtype (21% → 36%), but not for the hyperactive subtype (10% → 5%). This pattern corresponds to the well-known relative developmental changes in attentive versus hyperactive symptoms in ADHD.

2.2 Sex Differences

As all neurodevelopmental disorders are more prevalent in males rather than females, it is a relevant question whether diagnostic comorbidity or trait correlations differ according to sex. Regarding the number or severity of symptoms, results are not entirely consistent. In a community sample, boys rather than girls with ADHD had higher ASD symptom expressions, particularly stereotyped behaviors rather than social symptoms (Green et al. 2015). Similarly, Gargaro et al. reported more ADHD symptoms for boys with ASD than for girls with ASD (Gargaro et al. 2014). Mulligan et al. also reported higher ASD symptom levels (SCQ) in male, as compared to female ADHD children, and even more so in their siblings (Mulligan et al. 2009). This study also found greater proband-sibling correlations of autistic and ADHD symptoms in males (0.63) than females (0.49), suggesting greater familiality of autistic symptoms in male, compared to female ADHD probands, thus pointing to potential sex differences in the etiology of the ASD/ADHD co-occurrence. Reiersen et al. (2007), however, reported that 75% of girls with ADHD of the combined-type had ASD scores in the clinical range (SRS $\geq$ 74) whereas only 32% of combined-type ADHD boys surpassed the male-specific threshold (SRS $\geq$ 91).

3 Impact of Comorbidity on Adaptive Outcomes

Overall, comorbidity is associated with poorer adaptive outcomes, elevated symptoms of the primary diagnosis, and selective effects on the type of associated psychopathology and domain of everyday life.

3.1 Psychopathology

Comorbidity is associated with higher maladaptive behavior, such as elevated symptomatology of the primary diagnosis and other psychiatric and developmental disorders. Comorbid ASD in ADHD samples was associated with higher inattention and impulsivity, such that autistic trait severity predicted higher inattention and

impulsivity as early as 18–37 months ($N = 1{,}206$) (Tureck et al. 2015). This was also the case in a large sample of older children diagnosed with ADHD ($N = 711$), after adjusting for age, sex, IQ and family income (Cooper et al. 2014). Furthermore, this study also reported that higher autistic traits predicted higher externalizing (Oppositional Defiant Disorder – ODD; Conduct Disorder – CD) and internalizing (anxiety, depression) symptoms. ASD core symptoms appear to affect distinct domains in children with ADHD such that repetitive behaviors were associated with emotional and conduct problems, and social symptoms with peer problems (Stephens et al. 2021). Negative effects extend beyond emotional and social domains as in a large multi-site sample ($N = 821$) of children with ADHD, those with the highest autistic traits also met criteria for language, reading, and motor disorders in addition to ODD and CD (Mulligan et al. 2009).

Comorbid ADHD in ASD samples was associated with greater social disability and presence of externalizing symptoms. Relative to ASD alone, children with both ASD and ADHD diagnoses had higher autistic traits measured by the Social Responsiveness Scale (SRS) and the social interaction scale of the Autism Diagnostic interview (ADI-R) but not the symptom observation measures (Autism Diagnostic Observation Schedule) (Yerys et al. 2009; Sprenger et al. 2013); similar findings were reported with other parent reported social problems measures (Luteijn et al. 2000). As the SRS measures social functioning broadly, rather than autistic symptoms specifically, these findings suggest that comorbid ADHD in ASD may exacerbate social disability associated with ASD. Further, these studies also reported higher externalizing problems, attention problems, and hyperactivity in the comorbid group relative to the ASD group, whereas the groups did not differ on internalizing symptoms.

3.2 Adaptive Behavior

Comorbidity is associated with poor adaptive outcomes, including higher impairment in independent functioning in real life, particularly in socialization (e.g., interaction with peers) and communication (e.g., understanding verbal and nonverbal language). Activities of daily living (e.g., dressing themselves) are also implicated in some studies. Adaptive behavioral difficulties in ASD are well-established (Kanne et al. 2011) and they predict worse adult outcomes (e.g., residential and work status, quality and quantity of friendships) beyond those predicted by intellectual functioning alone (Farley et al. 2009). Similarly, ADHD is also associated with worse social, communication, and daily-living skills than that predicted by intellectual function (Stein et al. 1995). Children with diagnosis of ADHD and ASD had worse adaptive functioning than those with either diagnosis alone and poorer socialization and communication abilities than that predicted by intellectual functioning (Ashwood et al. 2015). Further, ASD but not ADHD symptoms accounted for variance in socialization, communication, and daily-living skills, suggesting that the presence of autism was driving the negative outcomes. In addition to

psychosocial health, negative effects of autistic symptoms in children with ADHD extend to quality of sleep (Green et al. 2016b) and physical health (Thomas et al. 2018). Additionally, parents' emotional functioning and time, and family activities are affected (Green et al. 2016a), indicating that the negative impact of ASD comorbidity in ADHD extends beyond the child to the family's quality of life.

Studies of ADHD comorbidity in ASD reveal similar negative effects. A large sample of children with ASD ($N = 3{,}066$) spanning early and late childhood and adolescence showed that those with co-occurring ADHD had poor quality of life in psychosocial, physical, and emotional domains (Sikora et al. 2012). Severity of inattentive but not hyperactivity symptoms predicted adaptive functioning over and above intellectual functioning and ASD symptoms (Avni et al. 2018). Others have found that even when ADHD symptoms do not reach diagnostic cutoffs, they predict worse adaptive outcomes after controlling for age, sex, intellectual function, and ASD symptom severity (Yerys et al. 2019b).

4 Causal Pathways

In addressing the question of *why* comorbidity between two distinct clinical phenotypes may occur, two broad approaches have been fruitful: attempts to glean functional domains that are commonly implicated in comorbidity and identify their neural underpinnings (Rommelse et al. 2011); and attempts to identify etiological roots of comorbidity (Rommelse et al. 2010).

4.1 Functional Domains

Developmental studies point to early origins of comorbidity and suggest symptoms or traits that may be of particular importance in elucidating comorbidity. While a reliable diagnosis of ASD can be established by 2 years of age (Charman and Baird 2002) analyses of the age of diagnosis in large national datasets reveal that ADHD symptoms are noted prior to those of ASD. In the 2011–2012 US National Survey of Children's Health ($N = 1{,}496$; 2–17 years), in children with a current ASD diagnosis, 20% had received an ADHD diagnosis approximately 3 years before the ASD diagnosis (Miodovnik et al. 2015). An average lag of 1.8 years between an initial ADHD diagnosis and subsequent ASD diagnosis was reported in another large sample of children and adults with ASD from the Netherlands ($N = 2{,}212$), which also found that 59.5% of the sample maintained that first ADHD diagnosis (Kentrou et al. 2019).

These results could be interpreted in multiple ways, namely ADHD symptoms might mask symptoms of ASD, or they might manifest earlier than those of ASD, or more importantly, early manifestations of both disorders are similar and thus, difficult to discern. Indeed, as early as 18–37 months of age, severity of ASD and

ADHD symptoms is highly correlated ($N = 2{,}300$); (Tureck et al. 2015) and, specifically, restricted and repetitive behaviors at that early age predicted severity of inattention and hyperactivity later in adolescence (Zachor and Ben-Itzchak 2019). Even earlier, at 14 months, the ability to sustain and shift attention and to recover from distress, termed *regulatory function*, predicted ASD traits measured by the SRS and symptoms of inattention (but not hyperactivity) at 7 years (Bedford et al. 2019). These results converge with studies of temperamental traits, which single out problems with attentional control as a shared risk for both disorders (Visser et al. 2016).

Examination of patterns of co-occurrence of symptoms of ADHD and ASD, later in development, reveals divergence in how inattention/impulsivity and hyperactivity may relate to ASD symptoms. Factor analysis applied to ASD and ADHD symptoms in a large combined sample of children without intellectual disability, who had a primary diagnosis of ASD ($N = 303$) or ADHD ($N = 319$), revealed four factors consistent with the classic diagnosis-specific domains; importantly, inattention/impulsivity and hyperactivity did not distinguish between ASD and ADHD, whereas social problems and restricted and repetitive behaviors were higher in those with ASD than ADHD (Krakowski et al. 2020). The same approach, when applied to a large ADHD sample ($N = 821$) that included intellectual disability, revealed a common factor combining hyperactivity and restricted and repetitive behavior, in addition to the diagnosis-specific factors (Martin et al. 2014). Thus, level of intellectual functioning moderates associations between ASD and ADHD symptoms.

Associations between these symptoms were analyzed with exploratory causal modeling (e.g., Bayesian Constrain-based Causal Discovery algorithm in a structural equation model) applied to a large sample of $N = 1{,}393$ participants, aged 4–20 years, including 417 children with ASD and/or ADHD, 562 affected and unaffected siblings, and 414 controls (Sokolova et al. 2017). ADHD symptom assessments were based on combined parent and teacher ratings, but ASD symptoms on parent ratings only. These analyses replicated some known effects (males have higher symptoms scores than females, hyperactivity decreases with age, ASD and/or ADHD are associated with lower IQ) and revealed strong correlations between ASD and ADHD symptoms altogether. More specifically, they suggested that autistic social "ineptness" was causally associated with inattention and impulsivity, whereas stereotyped, repetitive behavior was causally associated with hyperactivity. Furthermore, verbal IQ provided a relay between inattention and social ineptness. Together, this work suggests that the level of intellectual functioning must be considered in any account of comorbidity and that the domains of inattention and impulsivity are central to identifying intermediate phenotypes of comorbidity.

Inattention, impulsivity, and hyperactivity, as well as temperamental traits of regulatory functioning are manifestations of the capacity to exert self-control in goal-directed behavior. Collectively, processes of self-control are subsumed under the term "executive function" and its measurement includes assessment of core processes of inhibitory control, flexible switching of attention, and updating in working memory (Miyake et al. 2000), with additional inclusion of fluency and planning in some models (Pennington and Ozonoff 1996). A large literature has documented

impairments in all executive function processes in both ASD and ADHD with some studies showing higher response inhibition deficits associated with ADHD and higher flexibility and planning difficulties associated with ASD (Craig et al. 2016); the comorbid groups showed both inhibition and flexibility deficits. No clear diagnosis-specific or comorbidity-specific profile of executive function has been observed, primarily because both disorders are marked by significant heterogeneity (Nigg et al. 2005; Kenworthy et al. 2008).

With increasing recognition of the multivariate composition of executive function, data-driven methods have recently been applied to parse heterogeneity for discovering subgroups identified by unique functional profiles or dimensions that cut across ASD and ADHD diagnoses. In one such study, using parent report measures ($N = 1{,}012$), three transdiagnostic subgroups were distinguished by profiles that were marked by primary weakness in either flexibility and emotion regulation, or inhibitory control, or working memory and organization and planning (Vaidya et al. 2020). Interestingly, the tripartite structure also described the typically developing sample, which suggests that variability in executive dysfunction is nested within normal variability.

In another study that used both parent report and performance measures, distinct profiles of executive function processes predicted subgroups distinguished by low and high inattention and hyperactivity/impulsivity (Cordova et al. 2020). Both studies used machine learning to test for predictive validity so that new cases can be reliably subtyped and, thus, hold promise in targeting personalized treatment efforts. They also reveal the multivariate structure that underpins individual variation, which points to challenges for identifying single dimensions that could serve as intermediate phenotypes.

4.2 Brain Correlates

Functional and structural brain imaging approaches have been increasingly utilized in the search for neural correlates that may shed light on comorbidity (Uddin et al. 2017; Hong et al. 2020). A large brain imaging literature has accumulated showing that ADHD is associated with thinner prefrontal cortices and smaller striatal volumes, structurally. Functionally, weaker prefrontal-parietal mediated control processes and associated functional connectivity have been observed together with hyper-responsive sensory regions and associated functional connectivity (Pereira-Sanchez and Castellanos 2021). In contrast, ASD is largely associated with larger cortices and atypical engagement and functional connectivity of ventromedial prefrontal, temporo-limbic regions comprising the default mode network, which is associated with social functioning (Li et al. 2021). However, studies have noted substantial individual differences in each disorder. Empirical (Boedhoe et al. 2020) and meta-analytic (Lukito et al. 2020) findings from group comparisons between ASD and ADHD samples support structural and functional differences, rather than shared correlates.

Some recent studies with large samples comprising both ASD and ADHD children suggest some shared correlates, including white matter microstructure of the corpus callosum (Aoki et al. 2017), which implicates interhemispheric connectivity. There is also a smaller volume of the post-central gyrus (Mizuno et al. 2019) that implicates somatosensory function and impaired functional connectivity of the precuneus (Di Martino et al. 2013), which is implicated in perceptual, mnemonic, and affective integration. The precuneus is located in the medial parietal lobe and anchors the posterior end of the default mode network, which is important for social function and has been found to be atypical in ASD (Harikumar et al. 2021).

Other studies have examined correlates of ADHD symptoms or parent report of executive functioning in ASD samples and find weaker functional connectivity of fronto-parietal and operculo-insular regions comprising salience/ventral attention networks (Lynch et al. 2017; Yerys et al. 2019c). These correlates are borne out in transdiagnostic studies examining differences in subgroups characterized by executive function dimensions. For example, patterns of network connectivity distinguished subgroups associated with executive function profiles predicting inattention and hyperactivity (Cordova et al. 2020). Vaidya et al. (2020) found that the right inferior parietal cortex, known to play a central role in visual attention, was selectively associated in ASD and ADHD children with flexibility and emotion regulation difficulties. Thus, while structural brain imaging has not been insightful in shedding light on comorbidity as yet, recent functional connectivity findings suggest brain networks involved in executive function and social function as important loci for understanding comorbidity.

4.3 Genetics

The frequent comorbidity of ASD and ADHD may suggest that both are associated with a third factor, or share etiological factors (Rommelse et al. 2010). Given that both disorders are highly heritable, a third factor or shared etiological factors are likely to be genetic in nature. The assumption of shared etiological factors, favored by Rommelse and her colleagues, has indeed been supported with various approaches, including family studies (Holtmann et al. 2007), twin studies (Ronald et al. 2010), and molecular-genetic studies (Smoller et al. 2019).

In a first large-scale family study with 1,871 participants aged 7–17 years, Mulligan et al. (2009) showed that about 56% of the phenotypic correlation between symptoms of autism and ADHD could be explained by common *familial* influences. The assumption of shared causal influences, paving the way for the comorbid occurrence of the two disorders, has been further supported by various twin studies (e.g., (Constantino and Todd 2003); (Reiersen et al. 2008); (Ronald et al. 2008), specifying that the aforementioned familial influences in fact may be *genetic* in nature.

Such studies compare the similarity of monozygotic (MZ) and dizygotic twins (DZ) and infer (additive) genetic effects if the MZ correlation is at least twice as large

as the DZ correlation (Robinson et al. 2012). The resulting heritability estimates (h^2) quantify the proportion of phenotypic (inter-individual differences) variance that can be explained by such genotypic variance. Indeed, if one dyad of a pair of twins has ASD, it is much more likely than could be expected from general epidemiological data that the other dyad has ADHD, and vice versa (Ghirardi et al. 2018). Furthermore, monozygotic twins with ASD or ADHD are more similar in their ASD- or ADHD-related symptomatology than dizygotic twins (Ronald et al. 2008). Twin studies have revealed also that about 76%, 90%, or 50–70% of the phenotypic variance in ADHD, Childhood Autism, or ASD, respectively, can be explained by genetic factors (Faraone et al. 2005; Freitag 2007; Reiersen et al. 2008; Ronald et al. 2008). Overall, the heritability of ASD and ADHD traits, as well as their association, increases across development due to increasing genetic effects or new relevant genes going "on-line" (Ronald et al. 2010).

The high heritability of ASD and ADHD and their comorbid occurrence naturally leads to the search for the genes that constitute the pathway to the disorders and their comorbid occurrence. In a large-scale re-analysis of genome-wide studies on Anorexia Nervosa, ADHD, ASD, Bipolar Disorder, Major Depression (MD), Schizophrenia and Tourette Syndrome which included more than 700,000 participants (cases and controls combined), there were 23 loci with pleiotropic effects on at least four disorders and 109 loci associated with at least two of them (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019). The term "Pleiotropy" refers to the fact that one and the same gene may code for more than one phenotype, such as ASD and ADHD. Employing exploratory factor analysis and hierarchical clustering, the authors identified three disorder groups with shared genomics, one of those being ASD and ADHD (and MD) as well as a higher-order genetic structure pointing to more general genetic risks for psychopathology.

While most of the identified loci were pleiotropic (affecting more than one of the eight disorders) the most pleiotropic of these (associated with all eight disorders) was related to a protein coding gene, *netrin* 1 receptor DCC (Deleted in Colorectal Cancer) gene, which is involved in early development of white matter connections. Other loci also showed the association between pleiotropic and neurodevelopmental effects and could be distinguished in this aspect from disorder-specific (non-pleiotropic) loci. Overall, such pleiotropic effects seem to manifest in neurogenesis, regulation of central nervous system development and neuronal differentiation; they begin their expression in the second trimester of fetal development and continue throughout adulthood. Furthermore, the so-called Copy Number Variations (CNVs), albeit being extremely rare, contribute strongly to the etiology of neurodevelopmental disorders (Greaton et al. 2012).

5 Future Directions

Overall, the current evidence does not support the view that children with concurrent diagnosis of ASD and ADHD represent a separate clinical phenotype. Rather, it supports a moderating influence of the comorbid symptomatology, which serves to exacerbate inattention and impulsivity in ASD and social disability in ADHD. Those with concurrent diagnosis have worse adaptive outcomes and so early detection and targeted treatment of both ASD and ADHD symptoms is warranted. To that end, focus on brain connectivity and the domain of executive functioning shows promise, particularly with the use of data-driven approaches aimed at characterizing individual variability.

5.1 Design Characteristics

Future studies must control for two important confounds. First, current estimates of prevalence of comorbidity or inclusion criteria of most studies depend primarily upon parent report of symptoms. A systematic instrument bias, i.e., correlation between ratings because they were reported by the same informant, may elevate incidence of ASD-ADHD comorbidity. This factor is not usually controlled in most studies, but should be, because addition of a parent factor led to the association between ASD and ADHD becoming non-significant in a structural equation model exploring the role of theory of mind and executive function in comorbidity (Lukito et al. 2017). Therefore, studies ought to use symptom reports from multiple informants, or clinician reports, and/or observation measures (De Los and Kazdin 2005).

Secondly, some common environmental and biological factors increase risk for both ASD and ADHD, including parental age, maternal medications (such as valproic acid), maternal infections, and preterm birth (Taurines et al. 2012). The mechanistic role of these factors in neurodevelopment is not understood and careful birth histories of participants are often not accessible. At least, birth weight could be considered as an inclusion criterion as it is associated with multiple pre/perinatal negative developmental outcomes.

5.2 Sources of Heterogeneity

The next phase of investigation of ADHD-ASD comorbidity would benefit from considering the moderating influences of some important sources of heterogeneity.

Inclusion of typically developing children along with children with ASD and ADHD diagnosis is important to understand the full continuum of function and symptom expression. Both autistic traits and ADHD symptoms vary along continua and clinical cutoffs are useful for identifying those most in need of treatment, but not

for understanding the full interplay of symptom expression. Further, as discussed above, age and sex moderate symptom expression. Symptom co-occurrence varied over the lifespan such that it was highest in adolescence and lowest in early childhood and old age (Hartman et al. 2016). Emerging data suggest that autistic women and girls without intellectual disability may "camouflage" symptoms, a term used to describe active hiding or compensation of social communication difficulties (Lai et al. 2017; Wood-Downie et al. 2021). Such behavior biases against accurate diagnosis in women and girls and places a high burden on effortful control; indeed, executive functioning skills predicted camouflaging in adolescents with ASD (Hull et al. 2021).

It is important to consider ADHD-ASD comorbidity in the context of broader psychopathology as other comorbid symptoms contribute to heterogeneity. In a large population-based birth-cohort study, childhood ADHD had a four-fold risk of association with an internalizing disorder (e.g., mood disorders, anxiety disorders, somatoform disorders; odds ratio = 4.1) and a ten-fold risk of association with an externalizing disorder (e.g., Oppositional Defiant Disorder, Conduct Disorder, impulse-control disorders, substance-use disorders; odds ratio = 10.0) or combined externalizing and internalizing disorder (odds ratio = 10.6) (Yoshimasu et al. 2012). In particular, anxiety and aggression explained significant variance in the association between ASD and ADHD in a path analysis (Lawson et al. 2015).

Finally, motor-coordination problems have been reported in both ADHD and ASD children, and children with motor delays are at risk of both disorders (Rodriguez et al. 2019). Thus, examination of motor characteristics may provide insight into alternate causal pathways not currently considered to be central to comorbidity. In sum, elucidation of causal pathways of ASD-ADHD comorbidity requires parsing multiple sources of heterogeneity.

5.3 Treatment

A key gap in current knowledge about comorbidity is information about evidence-based treatments, including efficacy, moderators, and adverse events. While stimulant medication is commonly prescribed for ADHD, a wide variety of medications are prescribed for ASD, with 70% over 8 years receiving at least one psychoactive medication (Oswald and Sonenklar 2007). Data from the U.S. Department of Education's National Longitudinal Transition Study showed that among 13–16 year-olds receiving special education services, highest rate of psychotropic medication use was in children with both ASD and ADHD diagnosis (58.2%), followed by those with ADHD alone (49.0%) and lowest in ASD alone (34.3%) (Frazier et al. 2011). Further, the comorbid group had higher usage for all classes of medication, including antipsychotics, antidepressants, antianxiety, mood stabilizers, and stimulants, with stimulant usage being higher (33%) than others. While few randomized controlled studies have focused on the comorbid group, a meta-analysis of four trials for treating ADHD symptoms in pervasive developmental disorders

found high efficacy of the stimulant, methylphenidate (effect size = 0.66) but also higher side effects such as social withdrawal and irritability that are not commonly reported for ADHD (Reichow et al. 2013). Whether these are unique to the comorbid group or stem from diagnostic difficulties is an important future direction, in addition, to the need for more efficacy trials targeting comorbid symptomatology. In addition, there is need to explore non-pharmacological alternatives and initial promising evidence comes from combining antipsychotics with parent training for behavior management (Aman et al. 2009), computerized training for flexibility, an executive function (Yerys et al. 2019a), and a scripts-based behavioral executive functioning intervention implemented in both home and school contexts (Kenworthy et al. 2014). Future work along these multiple lines is needed to make headway in finding ways to mitigate the negative outcomes of ASD-ADHD comorbidity.

6 Concluding Remarks

Ultimately, two research domains that had developed independently of each other in the past – research on ASD and research on ADHD – should be systematically merged to investigate ASD, ADHD, and their co-occurrence in direct head-to-head comparisons. Such comparisons may employ broad constructs of overarching relevance in neuropsychiatric research, such as "executive functions," including sub-constructs, like inhibition and flexibility, that have proven useful in a fine-grained differentiation of ASD- versus ADHD-related cognitive deficits.

Alternately or in addition, head-to-head comparisons could use constructs and measures that may be causally linked to at least one of the two disorders as intermediate phenotype showing high familiality and/or heritability. Furthermore, developmental studies including longitudinal components (for instance, proper longitudinal or cross-sequential designs) may help disentangle "causes and effects" in the development of ASD-ADHD comorbidity at different ages. Given the genetic contributions to the etiology of neurodevelopmental disorders and their manifestation in disordered brain function or brain structure, the aforementioned approaches should include assessments at the molecular-genetic, neural and behavioral levels using measures with high and similar psychometric properties (reliability). Finally, adopting the dimensional view on neuropsychiatric disorders, such studies would benefit from independent assessments of the core symptom domains of ASD and ADHD.

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Adult Attention-Deficit Hyperactivity Disorder/Substance Use Disorder Dual Disorder Patients: A Dual Disorder Unit Point of View

Icro Maremmani, Vincenza Spera, Marco Maiello, Angelo G. I. Maremmani, and Giulio Perugi

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I. Maremmani (✉)
Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS), Pietrasanta, Lucca, Italy

V.P. Dole Research Group, G. De Lisio Institute of Behavioral Sciences, Pisa, Italy

Saint Camillus International University of Health and Medical Sciences – UniCamillus, Rome, Italy

V. Spera
Psychiatric Clinic, Sociopsychiatric Organization, Mendrisio, Switzerland

M. Maiello
Drug Addiction Unit, Northern-West Tuscany Region Local Health Unit, Apuan Zone, Massa, Italy

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Abstract Substance Use Disorders (SUDs) are often associated with Attention-Deficit Hyperactivity Disorder (ADHD) in adult populations due to multiple neurobiological, genetic, and psychosocial risk factors. This chapter provides a picture of the clinical aspects of adults with both ADHD and SUDs at treatment entry into a Dual Disorder Unit introducing the concept of different types of craving that may lead to substance use and abuse. At treatment entry, the presence of different comorbid SUD clusters, characterized by either stimulants/alcohol or by the use of cannabinoids, has not been shown to influence ADHD-specific symptomatology or severity, despite being crucial for the identification of a specific type of craving. We identified four clinical presentations of adult ADHD: Emotional Dysregulation, Substance Use, Core-ADHD Symptoms, and Positive Emotionality variants, that offer a practical guide in diagnosing and managing adult ADHD patients. Although the evidence of an effective medical treatment for Cocaine Use Disorder is insufficient, in our experience, toxicomanic behavior during stimulant treatment is sharply reduced in ADHD patients with cocaine addiction. Moreover, caffeinated compounds in military soldiers with ADHD may help reduce ADHD symptoms, making caffeine a potential pharmacological tool worth further investigation. Finally, substance use comorbidity does not influence treatment retention rate.

Keywords Adult ADHD · ADHD Clinical presentations · Caffeine · Cocaine Use Disorder · Substance Use Disorder

Abbreviations

A-ADHD	Adult ADHD (patients)
ADHD	Attention-deficit hyperactivity disorder
ATM	Atomoxetine
BIS-11	Barratt impulsiveness scale (short version)
BPRS	Brief psychiatric rating scale
CAARS-O: S	Conner's adult ADHD rating scales–observer
Co-ADHD	Core-ADHD symptoms
CUD	Cocaine use disorder
DD	Dual disorder

A. G. I. Maremmani
Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS), Pietrasanta, Lucca, Italy

V.P. Dole Research Group, G. De Lisio Institute of Behavioral Sciences, Pisa, Italy

Department of Psychiatry, North-Western Tuscany Local Health Unit, Tuscany NHS, Versilia Zone, Viareggio, Italy

G. Perugi
Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa, Pisa, Italy

DERS	Difficulties in emotion regulation scale
DIVA (2.0)	Structured clinical interview for axis I and II disorders
DSM-5	Diagnostic and statistical manual of mental disorders (edition 5)
ED	Emotional dysregulation
HCL-32	Hypomania checklist
ICASA	International collaboration on ADHD and substance abuse
MEQ	Morningness-eveningness questionnaire
MPH	Methylphenidate
NDD	Non-dual disorder
PE	Positive emotionality
PFC	Prefrontal cortex
RIPoST-40	Reactivity intensity polarity stability questionnaire
SCID	Structured clinical interview for Axis I and II disorders
SU(D)	Substance use (disorder)
TEMPS-M	Temperament evaluation of Memphis, Pisa, Paris and San Diego
WHODAS	World Health Organization disability assessment schedule

1 Neurobiological Mechanisms of Attention-Deficit Hyperactivity Disorder (ADHD) and Substance Use Disorders (SUDs)

1.1 Emotional Dysregulation and Core Symptomatology

Attention-Deficit Hyperactivity Disorder (ADHD), once identified solely as a neuropsychiatric childhood illness, is now known to persist into adulthood in about two-thirds of patients, with adult prevalence rates estimated to be between 3 and 5% (De Graaf et al. 2008; Kessler et al. 2006). The Diagnostic and Statistical Manual of Mental Disorders (edition 5; DSM-5) defines ADHD as a "persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development" and further describes three ADHD presentations, which are based on the most prevalent core symptomatology (e.g., primarily inattentive, primarily impulsive/hyperactive or a combination of both). It is becoming increasingly clear that the DSM-5 criteria are limited in characterizing ADHD in adults, mainly because they were initially designed to diagnose ADHD in childhood.

About half of children and adolescents with ADHD experience a reduction of observable hyperactivity on reaching adulthood (Hinshaw et al. 2006). However, many adults continue to experience intrapsychic hyperactivity, including difficulty relaxing accompanied by constant internal tension (Adler and Cohen 2004). Prevalence studies have shown that inattentiveness tends to persist more into adulthood, together with impulsivity (Adler and Cohen 2004; Wilens et al. 2009). In clinical practice, adult ADHD patients (A-ADHD) show various internalizing and externalizing psychiatric syndromes, which led to ignoring and misdiagnosing ADHD.

In addition, the DSM-5 criteria for ADHD do not include a variety of affective symptoms displayed by most of the adult ADHD population, such as affective lability, hot temper, short-lived explosive outbursts, and emotional over-reactivity that, perceived together, characterize the construct of "emotional dysregulation" (ED) (Wender 1998). It has been estimated that as many as 34–70% of adults with ADHD display a deficit in emotional regulation, compared with the 25–45% observed in children (Shaw et al. 2014). ED alone is responsible for the impairment observed in various life domains (e.g., familial, social, and work-related) (Barkley and Murphy 2010; Skirrow and Asherson 2013; Stringaris et al. 2009; Stringaris and Goodman 2009; Surman et al. 2013). A deficit in these domains is more severe in ADHD patients presenting with ED than those with preserved self-regulatory skills (Wehmeier et al. 2010), even when considering comorbidities such as conduct disorder (Biederman et al. 2012). Although there is no formal definition of ED, its characteristics are widely accepted. They include a deficiency in inhibitory control, the presence of strong emotionality and the inability to carry out self-regulatory measures. Some hypothesize that the lack of control over emotion-motivation regulation could be the root of inattention, hyperactivity, and impulsivity (Barkley 2015).

Three models have been proposed to explain the link between ADHD and ED. The first of these hypothesizes that ED is a core symptom of ADHD, with a common neurocognitive substrate (Barkley and Fischer 2010; Schmitt et al. 2012; Shaw et al. 2014). The second model suggests that ADHD and ED are distinct nosological entities. The comorbid condition of ADHD and ED is therefore made recognizable by its independent etiology and clinical course (Biederman et al. 2012; Surman et al. 2011). The third model postulates that ADHD and ED may be related while representing different dimensions with overlapping neurocognitive features, such as reducing ADHD symptoms following a lower level of ED (Surman et al. 2013).

The presence of ED and, consequently, the lack of emotional control and self-regulation seems to be of primary importance in leading to various psychiatric disorders by adding the feature of greater severity in overall dysfunctionality (Biederman et al. 2009; Riley et al. 2006; Wehmeier et al. 2010). In particular, the comorbidity between ADHD and Substance Use Disorder (SUD) is frequent and widely documented, often being recognized in research studies, since the two disorders share the same genetic underpinnings, neurobiological substrates, and risk factors. A meta-analysis of 29 studies showed an adult ADHD prevalence of 23.1%, ranging from 10% to 54.1% among SUD single populations, depending on the used substances, the setting and assessment instruments. Data from the International Collaboration on ADHD and Substance Abuse (ICASA) studies indicate that approximately one out of 6 adults who request SUD treatment also has ADHD. Similarly, about 15% of young adults with ADHD have a comorbid SUD (Kessler et al. 2006).

The predisposition to addictive behaviors and SUD often found in ADHD patients could result from several mechanisms. The "core" symptoms of ADHD, such as difficulties postponing rewards, the search for immediate gratification,

impulsiveness, and sensation seeking, have all been considered possible predictors of subsequent drug use and engagement in risk-taking behaviors related to addiction (De Alwis et al. 2014). Likewise, the executive functioning difficulties experienced by adults with ADHD may increase the likelihood of trying substances more quickly, enhancing vulnerability to addiction to a greater degree than their non-ADHD peers (Ortal et al. 2015). Executive functions, which include a set of cognitive processes (e.g., inhibition, interference control, working memory, emotion regulation, and fluency) necessary for goal-directed behavior, are known to be disrupted in both individuals with ADHD and individuals abusing substances as a result of alterations in neural circuits involving the prefrontal cortex (PFC), limbic system (including the hippocampus and amygdala), basal ganglia (ventral and dorsal striatum), and the thalamus (Bush 2011; Everitt and Robbins 2005).

Moreover, individuals with ADHD frequently report difficulties that delay or modulate reward responses, activating a strong tendency to develop addictive behaviors. Individuals with ADHD and SUDs tend to prefer "smaller sooner" over "larger later" rewards within this framework. Biologically, tonic dopaminergic signaling in both the PFC and the striatum is thought to be responsible for the ability to delay gratification. On the other hand, immediate processes are likely guided by phasic dopamine release. There is evidence that dopamine signaling is impaired in individuals with ADHD. Therefore, drugs, such as cocaine, methamphetamine, and amphetamine, all of which lead to an increase in dopaminergic transmission, especially within the nucleus accumbens, may be used as a simple route to self-treatment by a subgroup of patients (Mariani et al. 2014). The proportional reduction of cocaine use and ADHD symptomatology in addicted adult ADHD patients, observed during treatment with methylphenidate (MPH), supports this self-medication hypothesis. Similarly, it has been reported that substances such as alcohol, heroin, and cannabinoids all seem to relieve some of the psychopathological symptoms of ADHD in the adolescent population (Gudjonsson et al. 2012; Holtmann et al. 2011).

In summary, untreated ADHD has been associated with a large number of psychosocial risk factors, including educational challenges, adverse peer-group influences, and interpersonal difficulties, all of which culminate in an earlier exposure to addictive drugs that may be initiated to cope with these deficits (Molina and Pelham 2014). Conversely, ADHD complicates the clinical picture of patients with SUD. These two conditions lead to a higher risk of suicide attempts, more frequent hospitalizations, a greater propensity to relapses, and lower treatment compliance (Perugi et al. 2019).

Although treatment with MPH and the catecholamine reuptake inhibitor, atomoxetine, should improve cognitive control over substance use while reducing addictive behaviors, some authors highlight the lower efficacy of these treatments when SUD is present. A possible explanation is the lower compliance with the treatment regimens of ADHD-SUD patients, as shown by a retrospective study, indicating SUD as a negative predictor of treatment retention, and also RCTs pointing to the high number of dropouts in this cohort of patients (Carpentier and Levin 2017). A few studies have reported a beneficial effect of treatment with stimulants on treatment retention (Medscape 2020) that could be explained by the

increased compliance of ADHD-SUD patients (Konstenius et al. 2014) therefore reducing the rate of dropouts.

1.2 Reward Craving and Relief Craving

Recent advances in neurobiological, pathophysiological, and clinical knowledge have brought essential changes to the framing of drug addiction, including the concept of "craving" as a diagnostic criterion for SUDs in DSM-5 (Verheul et al. 1999). The term "craving" is used to identify the unfolding desire for a psychoactive substance, or any other gratifying object-behavior, and it is the primary driver responsible for addictive behavior (Maremmani and Pacini 2003). Craving is a clinical entity distinguished by neurovegetative somatic symptoms, an active search for the drug or the desired situation, and the inability to interrupt this behavior despite its negative physical and social consequences.

Three types of craving have been described: reward, relief, and obsessive. From a neurobiological point of view, "reward craving," or desire for the stimulating or enhancing properties of used substances, seems to be linked to both opioidergic/dopaminergic dysregulation and temperamental traits characterized by novelty sensation-seeking and impulsivity. Used substances stimulate the brain's reward systems, eliciting feelings of pleasure. The search for this sensation is so powerful that it motivates the constant wish to pursue these substances.

The first step in the natural history of addiction takes the form of contact with the substance in the form of a voluntary, motivated action to pursue gratification or reward. By repeating the assumptions, the substance, through the gratification evoked by activation of the mesolimbic dopaminergic system, exercises a reinforcing action triggered by easily recognizable search behaviors. Over time, the conduct of drug use changes from an initial voluntary and motivated action to a primary, instinctive drive that manifests itself as an unstoppable and uninhibited pattern of behavior. During this first stage of addiction, known as "the honeymoon stage," the substance is seen as a means to achieve gratification and the subject keeps control over its use.

Over time, the honeymoon gradually fades away, leaving the stage to a new picture where feelings of deprivation are central. At this point, the substance is used to seek pleasure and avoid the uneasiness related to the withdrawal symptoms (anxiety, agitation, demotivation). The aim of relieving craving pushes the individual to intake a substance (or cross-reactive) to avoid an expected or "in progress" withdrawal symptomatology. The trait most frequently associated with relief craving is high-stress sensitivity or harm avoidance.

The third typology of craving, the obsessive one, is characterized by a lack of control over the intrusive thought of the substance. The neuroendocrine dysfunction associated with this third condition seems to be a deficiency in the serotonin system, correlated with a personality type that has to face impulse control difficulties (Maremmani et al. 2020; Verheul et al. 1999).

Thus, craving is a psychopathological entity marked out by an egosyntonic nature that plays a central role in substance use relapses and is experienced by the patient with SUD as a push to act, based on a constant and unchangeable thought that is directed at obtaining the substance itself.

2 Clinical Aspects of ADHD/SUD Patients Recruited in a Dual Disorder Unit

2.1 Four Dimensions of ADHD Patients

According to the DSM-5, ADHD features inattention and/or hyperactivity-impulsivity symptoms that first emerged during childhood, hence presupposing a two-dimensional model. This structure has been criticized (Epstein and Loren 2013). It has been argued that a two-dimensional model overlooks other fundamental factors for the diagnosis and clinical management of A-ADHD patients, such as affective lability, hot temper, short-lived explosive outbursts, and emotional over-reactivity that best define a large part of the adult population (Reimherr et al. 2020). Indeed, different variants of A-ADHD have been described, among which one of the best represented is the presence of emotional dysregulation. This trait seems to be an essential component of ADHD (Franke et al. 2018; Skirrow and Asherson 2013), is associated with various psychiatric comorbidities such as SUDs, bipolar disorder, and personality disorders, and thus to more impairment in overall functioning (Biederman et al. 2009; Riley et al. 2006; Wehmeier et al. 2010).

Although many publications have explored the symptomatological variants of ADHD in children and adolescents, few studies have assessed the clinical characteristics of A-ADHD. Epidemiological studies estimate a 2.5–4% prevalence of adult ADHD (De Graaf et al. 2008; Kessler et al. 2006). As regards sex differences, males display predominant externalizing behaviors, with a more precise presentation of hyperactive/impulsive traits. In females, internalizing disorders are more evident and have more inattentiveness symptomatology (Rucklidge 2010).

To detect the presence of various clinical patterns of A-ADHD, we conducted a multicentric, cross-sectional, observational study recruiting 164 A-ADHD outpatients (Pallucchini et al. 2021). Clinical evaluation was performed using the following scales: the Structured Clinical Interview for Axis I and II Disorders (SCID), Diagnostic Interview for ADHD in adults (DIVA 2.0), Conner's Adult ADHD Rating Scales-Observer (CAARS-O:S): Short Version, the Barratt Impulsiveness Scale (BIS-11), the brief Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-M) for affective temperaments, the Brief Psychiatric Rating Scale (BPRS), the Difficulties in Emotion Regulation Scale (DERS), the Reactivity Intensity Polarity Stability Questionnaire (RIPoSt-40), the Hypomania checklist (HCL-32), and the World Health Organization Disability Assessment Schedule (WHODAS 2.0). Using an exploratory factor analysis, the main finding of the

study has been the identification of four clinical variants of A-ADHD: the first was marked out by Emotional Dysregulation (ED), the second by Substance Use (SU), the third by Core-ADHD Symptoms (Co-ADHD), and the fourth by Positive Emotionality (PE).

In the ED factor, the severity of emotional dysregulation and the associated affective temperaments (depressive and cyclothymic), which can be seen as an indirect measure of ED, were clustered and independent of DSM-5 core-ADHD symptoms. This subgroup was characterized by earlier treatment with antidepressants due to depressive symptoms in the family history. It was frequently associated with a diagnosis of borderline personality disorder, for which symptoms feature a high level of emotional instability. Consistent with prior research, ED severity was associated with a worse overall functionality. In contrast, A-ADHD patients grouped in the PE factor were distinguished by hyperthymic temperament (personality traits characterized by extroversion and high energy level), more hypomanic symptoms and a higher level of functionality. This factor was independent of ED, suggesting a subtype of ADHD devoid of emotional instability, with a consequently better adaptation to social and working environments. The SU factor groups the A-ADHD patients with the lifetime use of substances. Unlike current literature on the subject, which found a positive correlation between used substances and ADHD severity (Ercan et al. 2003; Wilens et al. 1998), this study showed evidence of SUD features and core-ADHD symptoms being independent.

Moreover, substance use was not associated with more severe ADHD symptomatology. SUD features were not correlated with severe emotional dysregulation or externalizing symptoms, although it was associated with a worse psychopathological clinical picture at the BPRS evaluation. The clinical variants offer practical implications for diagnosing and managing A-ADHD patients in various psychiatric conditions.

2.2 Two-Dimensional ADHD/SUDs

Alcohol, nicotine, cannabinoids, and stimulants (amphetamines and cocaine) are examples of substances that may be misused in the context of ADHD. Overall, comorbidity between SUD and ADHD is associated with an earlier age at the onset of substance use, more hospitalizations, higher rates of polysubstance use and weaker treatment response, configuring a worse clinical picture with a more rapid and severe SUD progression (Perugi et al. 2019). Many authors have studied the influence of ADHD symptomatology on the course of addiction in individuals experiencing substance use. However, these have focused on a single substance rather than on comparisons between different use patterns in most cases. Similarly, there is a shortage of data on the various used substances being taken within A-ADHD clinical symptomatology.

To fill this gap, two observational, cross-sectional, non-interventional studies have been conducted by our research group; these have assessed substance use

patterns among adults with ADHD by comparing the demographic, clinical, and functional features occurring in the different patterns of substance use. In the first preliminary study (Spera et al. 2020), 72 outpatients (in the 18–65 age range) with concomitant ADHD and SUD (Dual Disorder) were evaluated by the following instruments: the DIVA 2.0, the CAARS-O:S, the Structured Clinical Interview for Axis I and II Disorders (SCID-I), the BIS-11, the BPRS, the RIPoSt-40, the WHODAS 2.0, and the Morningness-Eveningness Questionnaire (MEQ). An exploratory factor analysis was conducted to group patients by clusters in different typologies of substance use.

Two distinct patterns of use were found; the first (Type 1), prevalent in 44 patients (61.1%), was characterized by the use of both stimulants and alcohol, whereas the second (Type 2), prevalent in 28 patients (38.9%), showed the use of cannabinoids. Consistent with the literature on the topic (Anker et al. 2020), ADHD patients mainly used stimulants, alcohol, and cannabinoids and fewer opiates and benzodiazepines. Type 1 users were significantly younger and displayed more criminal issues. Surprisingly, few differences were found when comparing the two patterns of substance use. Using the MEQ questionnaire, patients were assessed regarding their individual preference in sleep-wake cycles (morningness-eveningness preference), which showed overall no significant differences. However, those who mainly used cannabinoids went to bed earlier, suggesting a potentially significant role of cannabinoids in sleep induction.

Overall, current research on cannabinoid use and sleep has produced controversial results in the general population, with several publications supporting a role for the endocannabinoid system in regulating the circadian sleep rhythm (Sanford et al. 2008; Vaughn et al. 2010). ADHD patients with sleep disturbances may be using cannabinoids to recognize their short-term benefits on sleep while aiming at a therapeutic function (Chait 1990). Over time, however, long-term cannabinoid use may cause dependence to its effects on sleep, so creating a higher risk of addiction and more severe sleep disturbances if the drug is stopped (Barratt et al. 1974). Specifically, when we talk about "dependence," we usually refer to a physical dependence on the substance with tolerance and withdrawal symptoms. However, long-lasting substance use could lead to an "addiction" mainly characterized by an inability to stop using a substance despite the harmful consequences (combination of physical, mental, and behavioral symptoms).

No other differences were found regarding psychiatric comorbidities, impulsivity, emotional dysregulation, general psychopathology, hypomanic symptoms, or global functioning by comparing the two patterns of substance use. The main finding from the study was that the two patterns were similar in terms of ADHD-specific symptomatology and severity, suggesting that differences in the clusters of substances used did not affect the clinical manifestation of A-ADHD at treatment entry. Subsequently, a more comprehensive sample was enrolled. It was assessed by utilizing the same instruments to compare demographic, clinical, and symptomatological features among Dual Disorder A-ADHD (DD/A-ADHD) patients, according to the substance use typologies found previously, and A-ADHD patients without substance use (NDD/A-ADHD) (Spera et al. 2021). Of the 166 A-ADHD patients

who entered the study, 41 (24.7%) belonged to Type 1 (cocaine and alcohol as substances of choice), 40 (24.0%) to Type 2 (cannabinoids), and 85 (51.2%) to A-ADHD without SUD (NDD/A-ADHD). In this case, subjects abusing stimulants and/or alcohol reported more criminal issues. In the literature, high rates of ADHD have been found among adult inmates; similarly, the risk for criminal behavior among individuals with ADHD is increased when there is psychiatric comorbidity, specifically conduct disorder and substance use disorder. Overall previous studies showed a high frequency of violent behaviors and antisocial and illicit forms of conduct among people with SUD and ADHD (Sebastian et al. 2019). ADHD patients without SUD were more frequently diagnosed as inattentive ADHD presentation. They showed less severe symptoms of hyperactivity/impulsivity compared to Type 1 DD/A-ADHD patients, but not to Type 2 DD/ADHD. Among the substances, cannabinoid users showed more severe symptomatology with more activation, hostility, suspiciousness, and thought disturbances; this profile is in line with studies in the literature that associated THC use with psychosis, paranoia, and aggressiveness in chronic and heavy users (Parrott 2018). Few data are available in the literature dedicated to A-ADHD regarding the effects of the various substances, especially those most used (stimulants and cannabinoids) on the "core" symptomatology. These data raise the hypothesis of a different drive in substance use patients with ADHD.

Overall, both samples of Dual Disorder (Types 1 and 2) patients showed more impulsivity than NDD. Regardless of the used substance, illicit drugs seem to harm the behavior of ADHD patients by enhancing impulsive behavior. At the same time, high impulsivity traits in people with ADHD could increase their vulnerability to substance use disorders. According to Khantzian's "self-medication" hypothesis, a significant proportion of adults with ADHD may use stimulants as a way of managing symptoms of inattentiveness and restlessness, with a "calming" effect. The latter arises from an increased dopaminergic transmission, which is deficient in ADHD. Therefore, stimulants may be driven by a relief of craving, which is activated to reduce the burden of executive and behavioral dysfunctions that are typical of ADHD. While both Type 1 and Type 2 patients displayed the same high levels of impulsiveness, only the use of stimulants may have masked inattentive symptomatology in this population. On the other hand, it has been hypothesized that cannabinoids might be used because a reward craving might drive those taking them. Indeed, their use has been associated with a higher psychopathological burden but without apparent effects on the inattentive symptomatology.

3 Pharmacotherapeutic Strategies for the Treatment of Attention-Deficit Hyperactivity (ADHD) Disorder with Comorbid Substance Use Disorder (SUD)

3.1 From Intense to Occasional Use of Cocaine in Dual Disorder (Adult Attention-Deficit Hyperactivity Disorder/Cocaine Use Disorder) Patients Treated with Medication for ADHD

Cocaine Use Disorder (CUD) must be considered a global health burden involving about 18.2 million users worldwide (United Nations Office on Drugs and Crime 2016), mainly spread over the Americas and Europe. A recent systematic review and meta-analysis, assessing the lifetime prevalence of cocaine use and CUD among adult patients with ADHD, have found prevalence rates of 26.0% and 10.0%, respectively, meaning that about 1 in 4 of ADHD patients uses cocaine (Oliva et al. 2020). Deficient dopamine transmission in the mesolimbic reward circuit has been widely documented in ADHD, which could partly explain the increased risk of substance use in adults with ADHD as an attempt to compensate for this deficit. In particular, when stimulants are used, the dopaminergic transmission in the reward system (nucleus accumbens) could, paradoxically, act to lower emotional distress and counteract inner restlessness, hyperactivity, and inattention, improving the executive dysfunctions (Levin et al. 2018; Rubio Morell and Hernández Expósito 2019). The pathophysiological model proposed is that CUD/ADHD patients might use cocaine as a self-therapy to soothe ADHD symptomatology, at least in the early stages. Afterwards, the later dysphoric and addictive effects of cocaine may aggravate the psychopathological picture, adding to the patient's total burden. In contrast, stimulant medications have no dysphoric impact, are effective in relieving hyperactivity and inattention, so reducing the symptoms that lead to cocaine use in the first place.

Stimulant medications are considered the gold standard treatment worldwide for ADHD core symptoms, most likely due to their action in increasing the synaptic dopamine concentrations in the basal ganglia and anterior cingulate gyrus (Arnsten 2009; Volkow et al. 2012). Increasing evidence also supports the protective role of ADHD medications during childhood in reducing the subsequent development of SUD during adulthood (Faraone and Wilens 2003; Wilens et al. 2003). A recent review examined the pharmacotherapeutic strategies for the treatment of ADHD plus SUD: the results of the treatment trials were mixed because the efficacy of stimulant and non-stimulant medications on SUD symptomatology seems to be inadequate (Perugi et al. 2019). However, both stimulants and non-stimulants have been shown to minimize ADHD symptomatology in patients with concomitant SUD (Abel et al. 2014; Wilens et al. 2010). A few authors have demonstrated improvements in ADHD and CUD after treatment with stimulating medications, suggesting a

possible role for these specific treatments even when the medical condition in question is SUD (Levin et al. 2015, 2018).

The use of stimulants and/or non-stimulants in SUD patients is still controversial and has led to contrasting results. One Swedish trial found that ADHD patients with amphetamine dependence who were given MPH had a reduced incidence of positive urine tests and better treatment retention (Konstenius et al. 2014). Similarly, Levin et al. (2015) observed a reduction of cocaine use in cocaine-dependent ADHD patients after a treatment with extended-release mixed amphetamines (Levin et al. 2015). Another study carried out on ADHD methadone-maintained patients did not detect any reduction in the use of cocaine after a treatment with MPH, bupropion, or placebo (Levin et al. 2006). Similarly, other randomized controlled trials found no reduction of SUD symptoms in patients treated with standard doses of MPH (Levin et al. 2006; Riggs et al. 2011; Schubiner et al. 2002).

Given the lack of conclusive data on the efficacy of stimulant treatments in Dual Disorder patients, our research group retrospectively assessed a sample of 20 patients (age range: 18–65 years) with both A-ADHD and CUD, under treatment with methylphenidate (MPH) or atomoxetine (ATM), to explore the effects of adult ADHD treatment on cocaine use (Manni et al. 2019). Patients were followed for a mean period of 7 months with standardized questionnaires. Our preliminary findings showed that both MPH and ATM exerted similar positive influences on cocaine addiction in terms of severity and long-term outcomes. Indeed, cocaine use reduction was directly correlated with improved patients' A-ADHD, which was attributable to better control of inattentive/emotional symptoms and improved cognitive performance. The clinical implication of these findings is that the initial reduction of CUD symptoms in patients with concomitant ADHD might be due to the specific relief craving investigated in these subjects. Moreover, this differs from those usually reported by non-ADHD cocaine users who seek the euphoria and excitement induced by stimulants.

3.2 Exploring the Controversial Role of Caffeine in Adult ADHD Symptom Severity of US Army Soldiers

Among the wide variety of substances now being used, a growing literature has shown increased use of energy drinks and caffeinated beverages among children and young ADHD subjects (Bae et al. 2019; Jang and Kim 2012). As reported by many patients and highlighted in the previous paragraph, the use of stimulants may be an attempt to alleviate ADHD symptoms and distress according to the Self-Medication Hypothesis, so bringing some kind of relief from ADHD loss of functionality. Few studies have been conducted on the use of substances like energy drinks and caffeinated compounds in A-ADHD populations or their impact on the ADHD clinical picture. These energy drinks usually contain a high concentration of caffeine, besides additional stimulants like taurine, guarana, and ginseng. Additionally,

the copresence of compounds such as guarana and cocoa may increase the bioavailability of caffeine (Hinshaw 2002; Ishak et al. 2012). Previous studies had already linked the excessive use of soft drinks to hyperactivity and inattention symptoms in ADHD children (Kohlboeck et al. 2013; Michels et al. 2012). The use of these beverages was more remarkable in these children than in their peers and was directly proportional to the severity of ADHD symptomatology (Farsad-Naeimi et al. 2020). Other studies (Lien et al. 2006; Schwartz et al. 2015) have postulated that sweet drinks themselves may increase the odds of developing inattention/hyperactivity by 14% in children and highlighted a greater risk of hyperactive and inattentive symptoms in students who consume energy drinks, compared with their peers.

To better understand this phenomenon, we explored the use of caffeine and its derivatives and the use of alcohol among a sample of US soldiers with A-ADHD by analyzing their effects on ADHD clinical features and their severity (Cipollone et al. 2020). The hypothesis was that adults with ADHD could experience a more robust drive toward using stimulant compounds, including caffeine, and then take action to satisfy a relief of craving. As expected, soldiers diagnosed with A-ADHD had a higher prevalence of SUD diagnosis than their peers without psychiatric comorbidity. They also tended to use more alcohol, caffeine pills, energy drinks, and other caffeinated drinks. Alcohol use was correlated with higher A-ADHD symptoms, except for fast driving, because a weaker tendency toward dangerous driving was found both in alcohol and caffeine users. This fact could be explained by a "relief from relief" effect because alcohol's sedative properties might offset the excessive norepinephrinergic activation exerted by caffeine compounds.

Conversely, energy drinks, caffeine pills, and other caffeinated drinks showed negative correlations with some aspects of A-ADHD symptomatology. For instance, an inverse correlation was found among stimulating compounds (e.g., caffeine) and ADHD symptoms' enduring severity. These findings suggest that caffeinated compounds may help reduce A-ADHD symptoms while also improving cognitive performance. It has been shown that military personnel usually consume large amounts of energy drinks and caffeine, which enhance reaction time, vigilance, physical performance, and higher-order cognitive functions during extended periods of sleep restriction to help sustain workplace productivity and safety (Kamimori et al. 2015). Since military populations often turn out to be heavy caffeine drinkers, mainly because of the need to counteract periods of prolonged wakefulness and cope with a demanding environment and stressful work conditions, those with ADHD might require even greater doses of caffeine, given their already increased vulnerability to stress and cognitive dysfunctions connected with their disease.

Some authors suggest using low doses of caffeine in ADHD children, together with prescribed stimulants, to strengthen their therapeutic effects by taking advantage of caffeine's positive influence on working memory, arousal, and cognitive performance (Leon 2000). Besides taking care to minimize the risks correlated with higher doses of caffeine intake or peak effects, such as the development of irritability, dysphoria, insomnia, and excessive sympathetic activation, it might make good sense to assess the efficacy of low/moderate caffeine doses or modified-release caffeine tablets on A-ADHD clinical outcomes. Even if further studies are now

needed to confirm this hypothesis in the general population, our evidence may highlight the potential benefits to be derived from the use of caffeine in ADHD clinical practice by focusing on the identification of possible and safe therapeutic dosages.

3.3 Influence of Substance Use Disorder on Retention in Treatment of A-ADHD Patients

An overall survey of the literature highlights the fact that the co-occurrence of ADHD and SUD configures a worse clinical picture distinguished by an earlier onset of SUD, higher rates of substance polyuse, a higher probability of suicide attempts, more hospitalizations, a lower likelihood of achieving abstinence, and a lower likelihood of treatment compliance (Anker et al. 2020; Wilens et al. 2009). Many authors have reported the benefits of ADHD medications predominantly on ADHD symptoms themselves, while the effect on SUD in Dual Disorder patients is still being hotly debated. A majority of the randomized clinical trials (lasting: 4–24 weeks) on the treatment of ADHD plus SUD patients has shown low retention rates, with no more than 30–91% of patients completing the treatment. The studies conducted have been few and heterogeneous due to patients' characteristics, the various types of SUD, treatment setting, type of medication used, and outcome measures.

A controlled trial by Riggs et al. (2011) examined 303 ADHD adolescents with SUD treated with osmotic-release methylphenidate (plus CBT) or placebo (plus CBT). Even if methylphenidate did not show greater efficacy in coping with ADHD or reducing substance use than placebo, it was associated with good tolerability, no use or diversion of the medication, and an abundance of negative urine drug screens. Another study by Levin et al. (Levin et al. 2015) found a significant reduction of ADHD symptoms. It improved SUD outcomes with upgraded abstinence achieved by raising doses of sustained-release mixed amphetamine salts.

Given the sharply conflicting results reported in the literature, a recent sequel to our study explored the treatment retention rates in a sample of 118 adult ADHD patients with and without a concomitant SUD. In this sequel to our original analysis, lifetime, past and current forms of substance use in A-ADHD patients were correlated with their outcome (retention rate) during a 5-year follow-up of patients treated with stimulant and non-stimulant medications. After 5 years of observation, the cumulative treatment retention rates observed were 49.0%, 64.3%, and 41.8% for A-ADHD patients without lifetime SUD (NSUD/A-ADHD), A-ADHD with past SUD (PSUD/A-ADHD), and A-ADHD with current SUD (CSUD/A-ADHD), respectively. The main finding was that A-ADHD subjects with concomitant SUD did not display a worse clinical outcome (retention in treatment) with respect to subjects with only A-ADHD. The lack of significant differences was confirmed by a Cox regression demonstrating that the ADHD diagnosis according to DIVA, sex,

education, civil status, presence of psychiatric comorbidity, psychiatric and ADHD familiarity, severity of symptomatological scales as evaluated by WHODAS, BPRS, BIS-11 DERS, HSRS, ASRS did not influence treatment dropout.

In contrast to other studies, our A-ADHD-SUD patients have the same treatment retention rate as A-ADHD patients without SUD, so it seems that substance use comorbidity does not influence this clinical parameter. Apart from some limitations regarding the entity of the sample and the self-assessment bias, the strength of our study has been that our sample included patients treated in a dual disorder unit – a very different way of compounding skills from locations where psychiatric units and addiction units work independently, resulting in poor communication between the two. This kind of collaboration should be encouraged, and the treatment of both aspects of patient psychopathology should be more widely addressed in non-dual disorder settings.

In conclusion, in our Dual Disorder Unit, A-ADHD-SUD patients have the same treatment retention rate as A-ADHD patients without SUD, so substance use comorbidity seems to exert no influence on this clinical parameter at least when patients are treated in a dual disorder therapeutic setting.

4 Conclusions

The advances recently achieved in neurobiological, pathophysiological, and clinical knowledge have brought with them the concept of "craving" as a diagnostic criterion for substance use disorders. Three types of craving have been described – a reward, a relief, and an obsessive kind of craving. Both reward and relief craving affect the clinical expression of Dual Disorder characterized by A-ADHD and may also affect the response to treatment, especially regarding substance use. In our clinical experience with patients treated in a dual disorder unit, we have found that:

- In patients with A-ADHD arriving for treatment to a Dual Disorder Unit, our empirically based description of four clinical A-ADHD variants shows several aspects beyond the definition given by the DSM-5 diagnostic criteria. In particular, we found "Emotional Dysregulation," "Substance Use," "Core-ADHD Symptoms," and "Positive Emotionality" variants.
- In patients with A-ADHD, two patterns of substance use can be identified. Type 1 is characterized by stimulants/alcohol, and type 2 is distinguished by using cannabinoids. The two patterns were similar in terms of ADHD-specific symptomatology and its severity. At treatment entry, the presence of different comorbid SUD clusters does not affect ADHD-specific symptomatology or severity.
- Type 1 and type 2 Dual Disorder A-ADHD patients differ from those without DD. In particular, patients without substance use more frequently met the criteria for ADHD inattentive presentation compared with A-ADHD patients using stimulants/alcohol, but not with respect to A-ADHD ones using cannabinoids. This fact suggests that both types 1 and 2 of substance use differ in their effects on

A-ADHD patients. This outcome brings a variety of likely implications in dealing with the diagnostic and therapeutic processes.

- Our A-ADHD-SUD patients have the same treatment retention rate as A-ADHD patients without SUD, so it seems that substance use comorbidity does not influence this clinical parameter, at least when patients are treated in a dual disorder therapeutic setting.

We can infer that patients treated in a dual disorder unit show clinical characteristics that are very different from those highlighted in locations in which psychiatric units and addiction units work independently, resulting in poor communication between the two. Full collaboration should be encouraged, and both aspects of patient psychopathology should be addressed even in non-dual disorder settings. To conclude this line of thinking, a spread of specific teams trained in the cutting-edge treatment of addiction and A-ADHD has become increasingly desirable.

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Sleep in Individuals with ADHD: Prevalence, Impacts, Causes, and Treatments

Emma Sciberras

Contents

Abstract Sleep problems are common in children and adolescents with ADHD. This chapter covers the basics of sleep and the prevalence and types of sleep problems experienced by children and adolescents with ADHD. The impacts of sleep problems on the day-to-day lives of children with ADHD and their families are covered including impacts on child daily functioning and cognition, as well as family well-being. There is no one cause of sleep problems in children with ADHD with both biological and environmental factors implicated. There are a small number of randomized controlled trials that support the efficacy of treating sleep problems in children with ADHD using behavioral strategies. A small number of studies also have found improvements in sleep onset delay in children with ADHD following treatment with melatonin. Little is known about how to best

E. Sciberras (✉)
Centre for Social and Early Emotional Development, School of Psychology, Deakin University, Geelong, VIC, Australia

Health Services, Murdoch Children's Research Institute, Parkville, VIC, Australia

Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia
e-mail: emma.sciberras@deakin.edu.au

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support adolescents and adults with ADHD with sleep, although a small emerging literature largely in adults with ADHD suggests that bright light therapies could potentially be helpful given the extent of circadian involvement in the sleep problems experienced by individuals with ADHD. This chapter ends with consideration of future research directions largely related to approaches to supporting individuals with ADHD and sleep difficulties.

Keywords ADHD · Comorbidity · Efficacy · Functional outcomes · Melatonin · Methylphenidate · Prevalence · Sex differences · Sleep · Treatment

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CBT-I	Cognitive behavioral therapy for Insomnia
CD	Conduct disorder
DLMO	Dim light melatonin onset
EEG	Electroencephalogram
ENIGMA	Enhancing neuroimaging genetics through meta-analysis
GWAS	Genome wide association studies
ICSD	International classification for sleep disorders
MEQ	Morning-eveningness questionnaire
NREM	Non-rapid eye movement sleep
ODD	Oppositional defiant disorder
PSG	Polysomnography
RCT	Randomized controlled trial
REM	Rapid eye movement
TSMR	Two-sample Mendelian randomization

1 Introduction

The past decade has seen a substantial increase in the recognition of the high rates of sleep problems in individuals with Attention-Deficit Hyperactivity Disorder (ADHD) with over 10,000 articles published on the topic (Becker 2020). The connection between sleep problems and ADHD is especially intriguing given the similarity in the symptoms of ADHD and the behavioral manifestations of sleep deprivation (Hobson et al. 2019), as well as the interconnecting biological systems linking arousal, sleep, and attention (Owens 2005). A recent study found that similar areas of the brain responsible for cognitive control and attention were implicated in both the association between ADHD symptoms and gray matter volume, and both sleep problems and grey matter volume (Chen et al. 2019). It is plausible that the

symptoms of ADHD may make it more challenging to follow consistent sleep-wake schedules and that disrupted sleep may then exacerbate ADHD symptoms. This chapter aims to provide an overview of the prevalence, causes, and impacts of sleep problems in individuals with ADHD, as well as what is known about how to support individuals with ADHD in the area of sleep. This chapter will focus largely on what is known about sleep in children and adolescents with ADHD but will include a discussion of sleep problems in adults.

2 Overview of Sleep

Sleep is essential to survival and considered one of the three pillars of good health, along with good nutrition and regular exercise. Sleep has important functions in helping the body to rest and recover, build immunity and increasingly, is recognized to have an important role in brain development and in optimizing well-being and mental health (Quach 2019). Sleep begins in utero and newborns spend most of the 24-h period engaged in sleep, with sleep duration decreasing throughout the lifespan (Peirano et al. 2003).

Two key processes regulate our sleep: homeostatic regulation (Process S) and circadian rhythm (Process C) (Borbely et al. 2016). Homeostatic regulation refers to the increased need for sleep over time after waking. This operates in a similar way to appetite; the longer the time since last eating, the hungrier one becomes. Process S can also be influenced by the duration and quality of sleep that an individual had on the preceding night (Quach 2019). Process C or our circadian rhythm also plays an important role in sleep. Circadian factors include those environmental cues which help our body to differentiate day and night.

Our circadian system is governed by the suprachiasmatic nucleus located in the hypothalamus. The circadian rhythm has an endogenous component, which functions without external cues (Imeraj et al. 2012). However, it can also be influenced by exogenous or external cues and rhythms to our day (Imeraj et al. 2012). One of the most important stimuli for regulating the circadian rhythm is light, but there are other important environmental factors, including meal times (Korman et al. 2020). In the evening, in dark environments, our brain releases a hormone called melatonin from the pineal gland that promotes sleepiness, but this process may be inhibited if drive for sleep is not elevated, e.g. if one has had a late nap.

Individuals cycle through two rhythms of sleep throughout the night including Non-Rapid Eye Movement sleep (NREM) and Rapid Eye Movement (REM) sleep. NREM and REM sleep can be identified very early in development toward the end of gestation (Mirmiran et al. 2003). NREM and REM sleep can be distinguished from one another physiologically and also in terms of brain activity (Quach 2019). For example, body movement occurs during NREM but not during REM sleep and brain activity is higher in REM compared to NREM sleep. Non-REM sleep comprises four stages commencing with the transition between sleep and wakefulness (Stage 1), sleep onset (Stage 2) and deeper sleep or slow wave sleep (Stages 3 and 4) (Quach

2019). REM sleep periods follow Stage 4 sleep and increase in length as sleep progresses.

During REM sleep dreaming occurs and there is rapid, irregular respiration (compared to slow rhythmic respiration during NREM) and movement is paralyzed (movement preserved during NREM sleep) (Quach 2019). The duration of REM sleep is the highest in infancy and reduces in duration throughout development. After a period of REM sleep, individuals then transition back into Stage 2 of NREM sleep, before progressing through Stage 3 and 4 sleep and back into REM sleep. Individuals cycle between NREM and REM sleep throughout the night with the time in REM sleep increasing as sleep progresses through the night. Sleep cycles are generally up to 50 min in infants and increase to about 90 min in adulthood (Quach 2019).

All individuals vary in their sleep needs throughout development. Some people naturally feel good and refreshed from less sleep than others, while some require greater amounts of sleep to feel refreshed. For example, one study by Price and colleagues examined variation in sleep duration in two large nationally representative cohorts of children in Australia (N ~ 5,000 in each cohort spanning children aged 0–9 years) (Price et al. 2014). In this study the highest mean sleep duration was 14 h at age 4–6 months, while this decreased to 10 h at age 9 years (Price et al. 2014). This study found considerable variation in sleep duration, sleep onset, and wake times across all age groups (Price et al. 2014). However, sleep duration is only one element of sleep that can affect next day functioning. It is also important to consider the quality of sleep, the variability of sleep from night to night and the timing of sleep. Disruptions to sleep can occur at both sleep onset and overnight and can also manifest in the form of early morning waking and excessive daytime sleepiness.

3 Prevalence and Type of Sleep Problems in Children and Adolescents with ADHD

It is now well-recognized that sleep problems are elevated in children and adolescents with ADHD (Sung et al. 2008; Cortese et al. 2013; Becker 2020). There is substantial variability in the types of sleep problems experienced by children with ADHD with difficulties occurring both at sleep onset (dyssomnias) and overnight (parasomnias), and generally the highest rates of sleep problems are obtained when using parent-reported measures of sleep, as is discussed in Sect. 4, below. Research has also pointed to circadian rhythm disruptions being important to consider in the context of ADHD (Bondopadhyay et al. 2022) and increased night to night variability in sleep has been reported in children (Gruber et al. 2000) and adolescents with ADHD (Langberg et al. 2019). Children and adolescents with ADHD have been reported to experience a range of sleep problems including difficulty falling asleep, nocturnal awakenings, more restless sleep, difficulty waking up in the morning, and daytime sleepiness (Sung et al. 2008).

Prevalence rates for sleep problems in the general population vary across the world. In Australia, nationally representative data suggests that 12.5% of 4- to 5-year-old children have a moderate to severe sleep problem by parent report but that this declines to between 5 and 7% between the ages of 6 to 13 years of age (Williamson et al. 2021). A large meta-analysis of over 60 studies examining adolescents from mainland China found that 26% of the general adolescent population experienced sleep problems (Liang et al. 2021). One study examining the prevalence of parent-reported sleep problems in over 200 children and adolescents with ADHD, using the same measure as Williamson et al. (2021), found that 73% of those with ADHD experienced sleep problems ranging in severity from mild to severe, while 45% were reported to have moderate-severe sleep problems (Sung et al. 2008). Overall, it is clear that the rates of sleep problems experienced by children and adolescents with ADHD are much higher than prevalence rates in the general population.

In terms of diagnostic classification of sleep problems, the third edition of the International Classification for Sleep Disorders (ICSD) outlines over 83 sleep-related conditions over 7 categories (American Academy of Sleep Medicine 2014; Sateia 2014). Rarely do studies of children with ADHD use diagnostic nosology such as ICSD to classify the presence or absence of a sleep condition or diagnosis. Rather, most studies have focused on the presence or absence of sleep problem symptoms (Wiggs 2019).

Insomnia refers to impairing difficulties initiating and maintaining sleep or poor sleep quality despite opportunity and conditions being available for sleep (American Academy of Sleep Medicine 2014). Approximately 20–30% of adolescents with ADHD appear to experience insomnia. For example, one study found that 20% of adolescents with combined ADHD presentation had insomnia, compared to 14% of adolescents with ADHD Inattentive presentation and 7% of controls (Chiang et al. 2010). A large population-linkage study found that 29% of adolescents with ADHD compared to 17% of adolescents with no mental health service contact, had insomnia (Hysing et al. 2020). In previous versions of the ICSD, insomnia in children was differentiated into two subtypes including Sleep Onset Association Disorder and Limit Setting Sleep Disorder. Sleep Onset Association Disorder refers to needing to have a person or object present to initiate sleep (e.g., needing to have a parent present), while Limit Setting Sleep Disorder refers to parents finding it difficult to set rules and limits around bedtime (Mindell and Owens 2015; Wiggs 2019). Between 20 and 31% of children and adolescents with ADHD have been reported to have bedtime resistance difficulties (Wiggs 2019), while the specific rates of sleep onset association difficulties are unclear.

Children can also present with anxiety-related insomnia, which may be a cause or a consequence of sleep (Mindell and Owens 2015; Wiggs 2019), and again is more common in individuals with ADHD compared to those without ADHD (Bondopadhyay et al. 2022). Anxiety may relate to specific worries about not being able to fall asleep at night after previous experiences of sleep difficulties, may be broad and relate to worries about school, families, friends, or other areas of their life, and/or may be specific nighttime fears such as fear of the dark (Mindell and

Owens 2015; Wiggs 2019). In contrast, parasomnias refer to physical events that occur during sleep and can occur during both REM and NREM sleep including disorders of arousal (sleep-walking and sleep terrors) and nightmares. Again, these sleep difficulties are more common in children and adolescents with ADHD compared to those without ADHD (Gau and Chiang 2009; Hvolby et al. 2009; Bondopadhyay et al. 2022).

Much of what has been covered in this subsection is focused on what is known about the prevalence and types of sleep problems experienced by children and adolescents with ADHD based on subjective report (parent and/or child/adolescent report) because the vast majority of research in the area of ADHD and sleep has subjectively measured sleep in this way (Bondopadhyay et al. 2022), likely due to feasibility factors. However, there are several medical sleep problems that are more prevalent in children and adolescents with ADHD such as disorders of hypersomnolence (e.g., idiopathic hypersomnolence, narcolepsy), sleep breathing disorders (e.g., obstructive sleep apnea), restless legs syndrome, and periodic limb movement disorder (Sciberras et al. 2019), for which objective measures provide invaluable information.

The appropriate identification and treatment of these conditions in the context of ADHD is essential. For example, research has found substantial improvements in ADHD symptoms following adenotonsillectomy for children with ADHD and obstructive sleep apnea, with greater improvements in ADHD symptoms for those who received adenotonsillectomy relative to children who received methylphenidate treatment (Huang et al. 2007). For a review of the prevalence and treatment of these sleep conditions in the context of ADHD, see Sciberras et al. 2019; Nixon 2019, respectively. The latter sections of this chapter will largely focus on insomnia and circadian rhythm disruptions in individuals with ADHD.

4 How Can Sleep Problems Be Measured?

There are a number of subjective measures of sleep problems, which can include brief questions to assess sleep such as “During the past 4 weeks, has your child’s sleep been a problem?” (Sung et al. 2008; Lycett et al. 2015), and lengthier parent-completed rating-scales such as the Children’s Sleep Habits Questionnaire (Owens et al. 2000) and the Sleep Disturbance Scale for Children (Bruni et al. 1996). Several recent review articles cover the breadth of subjective reported sleep measures available for use in children and adolescents (Lewandowski et al. 2011; Ji and Liu 2016; Van Meter and Anderson 2020; Baddamd et al. 2021). Sleep diaries can also be used to examine sleep patterns such as sleep and wake times, and nocturnal awakenings. Lycett et al. 2016 found good correspondence between a single parent-reported item assessing sleep (as described above) and sleep duration as measured using a sleep diary. However, this study did not include an objective measure of sleep such as actigraphy or polysomnography (PSG).

Objective measures of sleep may provide a more reliable estimate of sleep in children and adolescents with ADHD and are particularly important when considering more biologically-based sleep problems. Actigraphy is one such objective measure, which is a wrist worn device using movement algorithms to determine sleep and wakefulness. Many studies use actigraphy to measure sleep in children with ADHD, but this is more resource intensive as devices can be expensive and need to be worn for at least seven nights alongside the completion of a sleep diary to obtain reliable estimates of sleep. Actigraphy can generate many useful sleep parameters including sleep duration, nocturnal awakenings, sleep onset latency, and sleep efficiency, as well as intra-individual variability in sleep parameters. For the measurement of more biologically-based sleep problems, PSG is the gold standard. This involves an overnight sleep study with electroencephalogram (EEG) recordings and breathing measurement. PSG can provide valuable information about sleep architecture including sleep stages, as well as time spent in NREM and REM sleep. Clinically, PSG assessments occur as part of an overnight sleep study in a medical setting. However, there are a growing opportunities for home-based PSG assessment.

Research using objective sleep measures tends to show fewer differences in sleep parameters between children and adolescents with and without ADHD relative to studies using subjective measures (Cortese et al. 2009). However, a seminal meta-analysis conducted in 2019 still found evidence of differences in objectively assessed sleep between children and adolescents with and without ADHD, including sleep onset latency and sleep efficiency as assessed via actigraphy. Also, while using PSG there were elevations in the apnea-hypopnea index, and, again, lower sleep efficiency (Cortese et al. 2009). Additionally, children and adolescents with ADHD demonstrated higher likelihood of falling asleep than controls when assessed using a Multiple Sleep Latency Test (Cortese et al. 2009).

A subsequent systematic review and meta-analysis found that children with ADHD spent more time in Stage 1 sleep (assessed via PSG) compared to children without ADHD (Diaz-Roman et al. 2016). A more recent systematic review again found that the research examining differences between children with and without ADHD in sleep using objective measures produced mixed findings (Bondopadhyay et al. 2022). For example, some studies found that children with ADHD had shorter sleep duration, longer sleep onset latency, poorer sleep efficiency, and greater sleep fragmentation using objective measures (Bondopadhyay et al. 2022). Using PSG specifically, some studies found evidence of differences in sleep architecture between children with and without ADHD including less REM sleep, faster transition into REM, and lowered eye movements during REM. However, these differences were not uniform across all studies (Bondopadhyay et al. 2022). On balance, the evidence suggests that there are disruptions across multiple aspects of sleep for individuals with ADHD and, as described in the following section, these are connected with poorer functioning across multiple areas.

5 What Is the Impact of Sleep Problems in Children and Adolescents with ADHD?

There is now a growing body of research suggesting that sleep problems independently contribute to poorer functioning in children with ADHD such as poorer quality of life, and poorer cognitive functioning (Bondopadhyay et al. 2022). One of the first studies to demonstrate this was a study of over 200 Australian children and adolescents with ADHD (Sung et al. 2008). In this study, children and adolescents with both ADHD and moderate to severe sleep problems by parent report had poorer quality of life and poorer daily functioning compared to children with ADHD without moderate to severe sleep problems (Sung et al. 2008). In addition, children and adolescents with ADHD and moderate to severe sleep problems were more likely to be late for, or miss, school (Sung et al. 2008).

A number of subsequent studies report the negative impact of sleep problems in children and adolescents with ADHD (Bondopadhyay et al. 2022). Craig and colleagues found that sleep problems in children with ADHD were correlated with both poorer quality of life and poorer social functioning (Craig et al. 2020). A recent study from our research group extended this research to adolescents with ADHD and demonstrated that sleep problems were associated with poorer functioning across multiple areas. When sleep problems of adolescents were assessed using parent report, these included ADHD symptom severity, sluggish cognitive tempo symptoms (e.g., day dreaming, lethargic, etc.), irritability symptoms, and homework problems (Loram et al. 2021). In contrast, there was less robust evidence of associations between sleep and functioning when sleep was assessed using self-reported measures (Loram et al. 2021). However, even using self-report, sleep problems were connected to adolescent-reported irritability and parent-reported sluggish cognitive tempo symptoms (Loram et al. 2021). In terms of cognitive functioning, some research has found associations between sleep problems and poorer cognitive functioning in terms of executive functioning, delay aversion, and working memory in children and adolescents with ADHD (Sciberras et al. 2015; Lambek et al. 2021).

Beyond the effects of poor sleep on the individual, sleep problems in children with ADHD are associated with strain on the family. A systematic review by Martin and colleagues found that sleep problems in children with ADHD were associated with poorer parent mental health (Martin et al. 2019), and a subsequent study verified this finding in parents of over 300 children with ADHD (Martin et al. 2021). However, the review noted an absence of research examining the association between sleep problems in children with ADHD and other domains of parent functioning, such as parenting stress (Martin et al. 2019). Additionally Sung et al. (2008) found that the parents of children with ADHD and moderate to severe sleep problems were more likely to miss, or be late to work, compared to children with ADHD and no moderate to severe sleep problems.

Most of the studies examining sleep in children with ADHD are cross-sectional with few longitudinal studies examining the persistence and impact of sleep problems in children with ADHD (Bondopadhyay et al. 2022). One study found that

parent-reported sleep problems fluctuated over a 12-month period, with 41% of children with ADHD characterized as having no sleep problems, 49% as having transient sleep problems, and 10% experiencing persistent sleep problems (Lycett et al. 2014a). Persistent and transient sleep problems were associated with greater emotional and behavioral difficulties 1 year later (Lycett et al. 2016). The strongest baseline predictors of persistent sleep problems were co-occurring internalizing and externalizing difficulties and higher initial ADHD symptom severity (Lycett et al. 2014a). In a birth cohort study, persistent sleep problems were found to be associated with increased odds of meeting criteria for ADHD in early adolescence (Carpena et al. 2022), suggesting that in some cases sleep problems may precede ADHD.

There are emerging experimental studies examining the cause and effect relationship between poor sleep and functioning in children with ADHD. These studies use a sleep restriction design where participants' functioning is measured during normal sleep conditions and then in conditions where their sleep time is extended or restricted to better capture causal associations between sleep and functioning. Using this design, Becker et al. (2019, 2020b) found that sleep restriction in adolescents with ADHD was associated with higher inattention, more oppositional symptoms, increased daytime sleepiness, and increased emotional dysregulation (Becker et al. 2019, 2020b). These studies provide some of the most robust evidence to date of the impact of reduced sleep duration on the functioning of adolescents with ADHD.

6 What Is the Etiology of Sleep Problems in Children and Adolescents with ADHD?

There are likely many factors contributing the development of sleep problems in children and adolescents with ADHD, many of which are also risk factors for poor sleep in the general population. Engaging in unhealthy sleep practices such as increased caffeine use, screen-time before bed, and the absence of bedtime routines are associated with sleep problems in both children and adolescents with ADHD (Sciberras et al. 2017; Cusick et al. 2020; Martin et al. 2020). A study by Becker and colleagues found that adolescents with ADHD used social media for an average of 5.31 h after 9 pm (Becker and Lienesch 2018). Increased media use was associated with lower sleep duration, more sleep problems, and increased daytime sleepiness even when accounting for severity of ADHD and medication use (Becker and Lienesch 2018).

It is well established that children and adolescents with ADHD have elevated rates of co-occurring externalizing onditions such as oppositional defiant disorder (ODD) or conduct disorder (CD), as well as elevated co-occurring internalizing conditions such as depression or anxiety (Faraone et al. 2015). These co-occurring conditions may confer risk for sleep problems above and beyond ADHD itself. One large study found that having co-occurring internalizing and externalizing difficulties was strongly associated with the presence of moderate to severe sleep problems

in 392 children with ADHD, above and beyond ADHD symptom severity, ADHD medication use, and socio-economic factors (Lycett et al. 2014b). However, this study was cross-sectional in nature and therefore it is possible that sleep problems may be conferring a risk for the development of internalizing and externalizing difficulties rather than vice versa. Supporting this notion, one study found that sleep problems in children with ADHD were associated with the development of oppositional and depressive symptoms 12 months later even after accounting for baseline ADHD symptoms and co-occurring conditions (Becker et al. 2015).

Studies have also found that children with ADHD Combined presentation appear to be at higher risk of sleep problems or have more severe sleep problems compared to other presentations (Bondopadhyay et al. 2022; Miniksar and Ozdemir 2021). However, findings are mixed in this area; this may be due to the tendency of existing studies not have a main focus on understanding the role of ADHD presentation in sleep problems. As a consequence, they have an uneven proportion of individuals with different ADHD presentations (Baddamd et al. 2021).

Other clinical factors such as medication use in individuals with ADHD may be connected with sleep problems. A systematic review examining the impact of methylphenidate in young people with ADHD found robust evidence of an association between methylphenidate use and insomnia and sleep disorders (Faraone et al. 2019). However, studies of children with ADHD who are not taking medication have also reported elevated sleep problems (Corkum et al. 2001). Parenting factors may also be associated with sleep problems. Our research has found that higher levels of consistent parenting practices were associated with lower levels of sleep problems (Sciberras et al. 2017).

Circadian factors appear to be implicated in the manifestation of sleep problems for children and adolescents with ADHD (Bondopadhyay et al. 2022; Imeraj et al. 2012). For example, research has shown that adolescents with ADHD have an evening circadian preference, meaning that they prefer to sleep later and wake later in the morning, have greater self and parent-reported sleep problems even when accounting for sleep duration (Becker et al. 2020a). Similarly, evening circadian tendency has been associated with a delay in sleep onset in children with ADHD (Gruber et al. 2012). In one study comparing children with ADHD with and without sleep onset insomnia, children with sleep onset insomnia were found to have later dim light melatonin onset (DLMO) and a later wake time compared to children with ADHD without sleep onset insomnia (Van der Heijden et al. 2005).

Genetic factors may also play a role in connecting circadian rhythm disruptions to ADHD. Several circadian genes play an important role in generating circadian rhythms including CLOCK or circadian-locomotor output-cycle kaput genes (Korman et al. 2020). The recent review by Korman and colleagues reported that circadian gene single nucleotide polymorphisms were associated with ADHD symptoms, evening preference, and sleep difficulties (Korman et al. 2020). In a recent genome-wide association study (GWAS), there was a genetic correlation between ADHD and several sleep traits such as insomnia, daytime sleepiness, and sleep duration (both shorter and longer) (Carpena et al. 2021). There were also shared genes between ADHD and aspects of sleep such as insomnia, daytime sleepiness,

snoring, short sleep duration, long sleep duration, and napping (Carpena et al. 2021). This study used two-sample Mendelian randomization (TSMR) to understand the causal relationship between ADHD and sleep traits and found evidence that insomnia, daytime napping, and short sleep duration had a causal association with ADHD (Carpena et al. 2021). In contrast, using TSMR, there was evidence that ADHD had a causal association with longer sleep duration and chronotype (Carpena et al. 2021). Further research is needed incorporating genetic, environmental, and other clinical factors (such as co-occurring conditions and medication use), to understand the etiology of sleep problems in individuals with ADHD.

7 Sex Differences in Sleep Problems

Few studies have examined whether sleep problems have similar prevalence in males and females with ADHD. Lycett et al. (2014a) did not find that sex was a predictor of sleep problem trajectories in children with ADHD and similarly, another study found no sex differences in sleep problems between adolescent males and females with ADHD (Gau and Chiang 2009). However, two more recent studies point to sleep problems potentially being more severe in females with ADHD compared to males (Becker et al. 2018; Hvolby et al. 2021).

One study of 181 primary school children with ADHD found that females with ADHD had poorer sleep compared to males with ADHD. These included total sleep problems and specific sleep domains, such as bedtime resistance, sleep-related anxiety, sleep duration, nocturnal awakenings, parasomnias, and daytime sleepiness (Becker et al. 2018). A large population-based study in Denmark found that development of sleep problems was more common in females with ADHD (33.7%, 95% CI, 32.1–35.4%) compared to males with ADHD (27.1%, 95% CI, 26.1–28.2%) (Hvolby et al. 2021). Overall, very little research has examined sex differences in sleep problems for children and adolescents with ADHD, and future research would benefit from better understanding the kinds of sleep problems experienced by girls with ADHD given the high proportion of males with ADHD in existing studies.

8 Supporting Children and Adolescents with ADHD and sleep problems

8.1 Non-pharmacological Approaches

There is a growing number of studies examining the treatment of sleep problems in children with ADHD using behavioral strategies. Such behavioral strategies involve promoting healthy sleep habits such as having consistent sleep-wake schedules, reducing caffeine use, and reducing screen-time before bed. The largest randomized

controlled trial (RCT) to date in children with ADHD and sleep problems examined the efficacy of a brief, 2–3 session behavioral sleep intervention in 244 children with ADHD (Hiscock et al. 2015). The intervention focused on the development of healthy sleep habits and tailored sleep strategies depending on the type of sleep problem the child was experiencing. For example, for children presenting with Delayed Sleep Phase Disorder the focus was on temporarily setting the bedtime at the time the child was naturally falling asleep and then slowly bringing this forward by 15 min every 2–3 days. This was coupled with set wake times each morning and early morning light exposure. At 3 and 6 months post-randomization, children with ADHD in the intervention group had improved sleep and broader functioning (e.g., ADHD symptom severity, quality of life, and daily functioning) compared to the usual care treatment (Hiscock et al. 2015). The treatment group also had better objectively assessed working memory 6 months later relative to the usual care group (Hiscock et al. 2015). Benefits were observed up to 12 months later (Sciberras et al. 2020) and have been translated into real-life clinical practice (Hiscock et al. 2019). Similarly, other RCTs examining the potential benefits of improving sleep in children with ADHD have also found improvements in sleep and broader functioning (Keshavarzi et al. 2014; Corkum et al. 2016). To date, no RCTs have examined the benefits of treating sleep problems in adolescents with ADHD. However, a recent pilot study points to the potential benefits of treating sleep problems in adolescents with ADHD using a transdiagnostic sleep treatment approach (Becker et al. 2021).

Mindfulness-based interventions may be helpful in improving sleep in children with ADHD. A small pilot study found that, in 18 children with ADHD, a 4-week Headspace digital mindfulness program was associated with improvements in sleep. However, this was an uncontrolled study (Fried et al. 2021). Another study found that children who underwent a Mindfulness-Oriented Meditation program three times per week for eight weeks ($n = 15$) had improvements in sleep compared to children in an active control group ($n = 10$) (Zaccari et al. 2021). Again, this study was small and uncontrolled. Overall, the examination of mindfulness-based approaches in improving sleep in children with ADHD are potentially promising but need to be examined in powered RCT designs. Head-to-head comparisons of different treatment approaches with health economics evaluation would be helpful in determining the relative efficacy and value of different treatments.

Few studies have examined whether there are certain characteristics associated with better outcomes in sleep treatment studies. One study found little evidence that factors such as co-occurring conditions moderated sleep treatment outcomes, which suggests that sleep interventions should be suitable for most children with ADHD (Sciberras et al. 2020). However, benefits in terms of sleep were not as sustained for children of parents with clinical levels of depression and benefits were not as strong for those not taking stimulant medication (Sciberras et al. 2020). Additional treatment or booster sessions may be required for these subgroups of children to optimize outcomes. A recent study also found that increased parent use of sleep strategies at home was associated with better sleep treatment outcomes for children with ADHD (Sciberras et al. 2022).

Given the implication of circadian factors in the etiology of sleep problems in children and adolescents with ADHD, there is increasing interest in the role of treatments that specifically target circadian misalignment through use of bright light therapies (Korman et al. 2020). Some small pilot studies have examined the use of bright light in adults with ADHD (see Sect. 9 below) but few studies have examined this treatment in children and adolescents with ADHD. A small study of adolescents with ADHD found that bright light therapy was associated with improvements in inattention and hyperactivity symptoms (Niederhofer 2013), however, further research is needed to better understand the role of bright light therapies in the treatment of sleep problems in children and adolescents with ADHD.

8.2 Pharmacological Approaches

There are a number of pharmacological approaches to managing sleep problems in children with ADHD. This section will largely focus on melatonin given that this is commonly used to improve sleep. However, see Angriman and Cortese 2019 for a review of other medications that may be used in the context of ADHD and sleep problems. In a study of 257 Australian children with ADHD, 14% were reported to be taking melatonin (Efron et al. 2014); however, it is suspected that this proportion is higher now, nearly a decade since this study was completed.

One influential double blind RCT in the field examined the efficacy of melatonin in 105 children with ADHD and sleep onset insomnia and found improvements across all sleep domains assessed (both objective and subjective including sleep onset time, sleep latency, total sleep time, sleep efficiency, and sleep difficulties) for those randomized to melatonin treatment (Van Der Heijden et al. 2007). However, other aspects of sleep were not reported such as day time sleepiness and morning wake time. A subsequent trial examining the efficacy of melatonin in a diverse group of children with neurodevelopmental disorders found similar benefits of melatonin, but in addition, found melatonin use was associated with improved daytime sleepiness (Gringras et al. 2012). In contrast, this study did not find differences between those randomized to melatonin versus placebo in terms of sleep efficiency, and children taking melatonin woke earlier in the morning than those taking placebo (Gringras et al. 2012).

A relatively long-term study of children with ADHD taking melatonin (follow-up: 3.7 years) found no adverse effects (Hoebert et al. 2009). In this study, long-term melatonin was associated with reductions in sleep problems in 88% of children, while discontinued use was associated with a return of delayed sleep onset difficulties (Hoebert et al. 2009). In contrast to trials examining non-pharmacological treatment, there is less evidence that melatonin improves other aspects of functioning such as quality of life (Van Der Heijden et al. 2007; Gringras et al. 2012).

9 Sleep in Adults with ADHD

Much of the research has focused on sleep in children with ADHD with a growing body of research focused on adolescents with ADHD. In contrast, there is relatively little research examining sleep in adults with ADHD. The research in adults suggests that similar to children and adolescents, adults with ADHD are at much greater risk of sleep problems compared to adults without ADHD (Surman and Walsh 2021). A systematic review and meta-analysis including 13 studies examining sleep in adults with ADHD found strong evidence of elevated sleep problems across most domains using subjective report, whereas differences based on objective measurements were less striking (Diaz-Roman et al. 2018). For example, using actigraphy, adults with ADHD had elevated sleep onset latency and poorer sleep efficiency (no differences in other sleep domains were identified), while there were no differences between adults with and without ADHD on any of the PSG measurements (Diaz-Roman et al. 2018).

A more recent systematic review comprehensively examined the nature of sleep problems in adults with ADHD (Lugo et al. 2020) and found similar results to the earlier review by Diaz-Roman and Collegues (2018). Based on subjective reports, a broad range of sleep problems were reported for adults with ADHD including poorer sleep efficiency, longer sleep onset latency, more nocturnal awakenings, and daytime sleepiness (Lugo et al. 2020). Using actigraphy, but not PSG, adults with ADHD had longer sleep onset latency and poorer sleep efficiency compared to adults without ADHD (Lugo et al. 2020). The difference in actigraphy versus PSG findings may reflect actigraphy being able to better capture the day-to-day difficulties in sleep, while PSG may not capture the sleep patterns that naturally occur at home (Lugo et al. 2020). However, based on PSG findings, adults with ADHD were identified to have higher levels of periodic limb movements compared to adults without ADHD (Lugo et al. 2020). Other studies have also reported elevated levels of sleep disordered breathing in adults with ADHD (Surman and Walsh 2021).

Similar etiological factors, as described in children and adolescents with ADHD, have been associated with sleep problems in adults with ADHD. Circadian factors again are crucial in understanding the sleep of adults with ADHD. Adults with ADHD display more of an evening chronotype (Baird et al. 2012; Bumb et al. 2016; Coogan et al. 2019; Lugo et al. 2020; Surman and Walsh 2021), with preference for later sleep and wake times also seen in adults with ADHD not taking medication (Surman and Walsh 2021). DLMO has been found to be delayed in adults with ADHD supporting the notion of the disruption to the circadian system (Van Veen et al. 2010). Furthermore, CLOCK genes have also been implicated in adult ADHD (Baird et al. 2012). A study examining 13 adults with ADHD and 19 age- and gender-matched controls collected survey measures, actigraphy data for a minimum of 7 days, and additionally, took buccal swabs and saliva samples every 4 h over a 24-h period to examine CLOCK genes and melatonin and cortisol levels, respectively (Baird et al. 2012). In the control group, *BMAL1* and *PER2* were rhythmically expressed but this was not the case in the ADHD group (Baird et al. 2012). The

melatonin rhythm in adults with ADHD was lower in amplitude and although cortisol was rhythmic in both groups, it was phase delayed by approximately 2 h in the ADHD group (Baird et al. 2012).

Coogan et al. examined the role of both ADHD and the medication used to treat ADHD in understanding circadian disruption in adults with ADHD (Coogan et al. 2019). In this study, sleep was assessed using actigraphy and circadian gene expression was assessed using human-derived fibroblast cultures (Coogan et al. 2019). Individuals with ADHD who were taking medication had lowered *CLOCK* expression at ZT0 (ZT represents the time of culture synchronization) compared to those with ADHD not taking medication and controls, and higher *CLOCK* expression at ZT24 compared with controls (Coogan et al. 2019). Relative to the individuals with ADHD taking medication and controls, those with ADHD who were not taking medication had altered expression of the *PER2* and *CRY1* circadian genes (Coogan et al. 2019). *PER2* expression was higher in the ADHD and no medication group at ZT0, while *CRY1* peak expression was delayed (Coogan et al. 2019). There was also evidence that both ADHD and medication impacted *BMAL1* phase expression. This was a small study and clearly requires replication but represents an interesting direction for future research.

Less research has examined the neurobiological correlates of sleep problems in individuals with ADHD. One study reported that pineal gland volume is lower in adults with ADHD, compared to controls. Circadian preference was assessed using the Morning-Eveningness Questionnaire (MEQ) with higher scores (indicative morningness) associated with higher pineal volume (Bumb et al. 2016). In contrast, there was no association between MEQ scores and pineal volume. There is considerable scope for further research to understand potential neurobiological underpinnings of sleep problems in individuals with ADHD, in particular, studies using data pooling and meta-analytic approaches.

There is an emerging literature on how to best treat sleep problems in adults with ADHD. A recent review article identified six articles examining different treatment approaches including pharmacological approaches (e.g., melatonin, or the non-specific melatonin receptor agonist, ramelteon) and bright light therapy, Cognitive Behavioral Therapy for Insomnia (CBT-I), and weighted blankets (Surman and Walsh 2021). A recent three-armed RCT found that sleep education, in addition to both melatonin and melatonin plus bright light, advanced DLMO in 51 adults with ADHD and Delayed Sleep Phase Disorder with DLMO advancement especially in the melatonin plus bright light group (1 h 58 min) followed by the melatonin group (1 h 28 min); no effect on DLMO was found for the placebo group (van Andel et al. 2021). There were also promising benefits for sleep in small open pilot studies examining bright light therapy and CBT-I (Surman and Walsh 2021). A relatively large RCT found large improvements in insomnia severity for those randomized to the group using weighted blankets containing metal chains, compared to a light blanket, in adults with psychiatric disorders including ADHD (Ekholm et al. 2020). The potential therapeutic benefit is thought to be related to the pressure applied on different pressure points in the body and parasympathetic activation (Ekholm et al. 2020). Although ramelteon was associated with advancement in mid-sleep time by

45 min in adult patients with ADHD, it was also associated with greater sleep fragmentation and increased daytime sleepiness relative to placebo (Fargason et al. 2011).

10 Future Research and Clinical Directions

Over the past decade, we have learnt a great deal about the nature of sleep problems in children and adolescents with ADHD. A key area for future research is to promote the translation of the implications of poor sleep in individuals with ADHD into real-life clinical practice. It is currently unknown how commonly sleep problems are assessed in children with ADHD presenting to clinical practice. A study completed over a decade ago in Australia found that only half of those with ADHD attending clinical services were asked about their sleep by their clinician, and of those that were asked, only half were offered any supports (Sung et al. 2008). Given the surge in research in the area of ADHD and sleep over the past decade, it is suspected that this number may be higher now, however, there is a lack of empirical data to support this suspicion. Overall, the reviewed studies point to the importance of incorporating at least a brief assessment of sleep into the initial diagnostic assessment of ADHD, as well as follow-up appointments, given that sleep problems can emerge over time. More in-depth sleep assessments should be conducted if initial assessment suggests this is warranted.

Given the high prevalence and impact of sleep problems in children and adolescents with ADHD, it is surprising that only a handful of powered RCTs have examined the efficacy of treatment approaches. There is clearly a lack of RCTs examining ways to assist adolescents and adults with ADHD with sleep; this is a priority for future research. Furthermore, the evaluation of different treatment approaches would be helpful in both pediatric and adult populations. One of our recent papers demonstrated that parents of children with ADHD found some sleep strategies harder to implement at home (e.g., bedtime fading approaches) than others (e.g., reducing caffeine) (Sciberras et al. 2022). It would be beneficial to understand how we can better support parents with the implementation of these strategies at home, as increased frequency of sleep strategy use is associated with improved sleep treatment outcomes (Sciberras et al. 2022). It is anticipated that similar difficulties with consistent implementation of sleep strategies will be encountered by adolescents and adults with ADHD.

Better understanding the role of circadian disruption in the sleep of individuals with ADHD is crucial. In the adult literature, there is emerging evidence that bright light therapies may improve sleep. However, bright light exposure has yet to be thoroughly examined in children and adolescents with ADHD. Furthermore, given the high heritability of ADHD, many children and adolescents with ADHD are likely to have parents and/or siblings who also have ADHD. Family based approaches to improving sleep in all members of the household is likely to yield the most benefit, however, such protocols have yet to be evaluated. Moving forward considering the

role of sleep in promoting improved functioning in children and adolescents with ADHD alongside other lifestyle factors such as nutrition and physical activity would be of interest given the strong relationship between ADHD and a range of medical conditions (Faraone et al. 2021). A recent study found that both diet and physical activity mediated the impact of ADHD on sleep, pointing the importance of considering both diet and physical activity alongside sleep (Hong et al. 2021).

In terms of the epidemiology of sleep problems in individuals with ADHD, most studies tend to report on sleep problem symptoms rather than the proportions meeting criteria for specific sleep problems. A better understanding of the prevalence of sleep problems will enable better development and tailoring of intervention approaches to assisting with sleep. Furthermore, more robust studies using both symptom-based and diagnostic approaches to measuring sleep, utilizing both subjective and objective measures, may help to further shed light on the etiology of sleep problems in individuals with ADHD. To date, prospective studies are yet to track sleep problems in individuals with ADHD from childhood, into adolescence and adulthood. With the newly formed Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) sleep group, the next decade will likely to see growth in our knowledge of the biological underpinning of sleep problems in children, adolescents, and adults with ADHD (Tahmasian et al. 2021).

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Obesity and Attention-Deficit Hyperactivity Disorder

Autumn Lanoye, Elizabeth Adams, and Bernard F. Fuemmeler

Contents

Abstract An association between ADHD and obesity has been established throughout the past 20 years via animal model experiments and both correlational and longitudinal studies in humans. However, much remains to be determined regarding causality, developmental course, and effective treatments targeting both conditions. This chapter provides an overview and update on the current state of the science on the relationship between obesity and ADHD; expands the scope of the connection between obesity and ADHD to include behavioral components important to weight

A. Lanoye and B. F. Fuemmeler (✉)
Department of Health Behavior and Policy, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Massey Cancer Center, Virginia Commonwealth University, Richmond, VA, USA
e-mail: Bernard.fuemmeler@vcuhealth.org

E. Adams
Department of Exercise Science, University of South Carolina, Columbia, SC, USA

Research Center for Child Well-Being, University of South Carolina, Columbia, SC, USA

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regulation – i.e., physical activity, eating behaviors, and sleep; and presents applications of these findings to treatment approaches and future directions.

Keywords Attention-deficit hyperactivity disorder (ADHD) · Executive functions · Obesity · Weight status

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CRP	C-reactive protein
GWAS	Genome-wide association study
IL-6	Interleukin-6
MC4R	Melanocortin-4 receptor
SNP	Single nucleotide polymorphism
TNF-α	Tumor necrosis factor-α

1 Introduction

Key features of Attention-Deficit Hyperactivity Disorder (ADHD) include symptoms of inattention in addition to hyperactive and impulsive behaviors (American Psychiatric Association 2013a). At its core, ADHD is a neurodevelopmental disorder involving deficits in executive functions that are critical for goal-planning, cognitive flexibility, and other higher-order cognitive processes (Sergeant et al. 2002). Difficulty inhibiting behavioral responses in service of goal-directed actions is also a feature of ADHD which manifests as impulsive behaviors. Clinically, ADHD is diagnosed by trained professionals (e.g., psychologists, psychiatrists) via a semi-structured interview, standardized self-report, and/or informant-report measures – and in some cases, supplementary information can be gathered through the administration of objective neuropsychological tasks. In research settings, the measurement of ADHD varies and can include structured clinical interviews, parent-report measures, or self-report measures for older children and adults. The epidemiological prevalence of ADHD among children in the USA varies from 3.7 to 9.4%, with diagnostic clinical interviews resulting in lower estimates than self/parent-report measures (Danielson et al. 2018; Chung et al. 2019).

Obesity is defined in adults in terms of body mass index [BMI; $weight\ (kg) \div height\ (m)^2$], with a BMI $\geq$30 considered obese. In children, obesity is defined as a BMI $\geq$95th percentile for age and sex (Defining Childhood Obesity 2018; Defining Adult Overweight and Obesity 2020; Obesity 2021). Among children and adolescents in the USA, the prevalence of obesity is 19.3%, with rates

reaching nearly one-quarter among Hispanic/Latino and Black children (Fryar et al. 2018). Prevalence rates among US adults are much higher and have risen significantly over the past two decades, with a recent nationwide survey placing the estimate at 42.4% (Hales et al. 2020).

The role of higher-order cognitive processes such as task inhibition and self-regulation was a topic of interest in early theories of obesity, which posited that individuals with obesity may be less capable of inhibiting eating in response to internal satiety cues and external food cues (Stunkard 1959; Schachter 1968). However, over the past 20 years, scientific interest in comorbid obesity and ADHD has grown considerably. In this period of time, investigations have advanced from reporting on the prevalence of ADHD in clinical samples of individuals with obesity (Altfas 2002) to identifying shared genetic and neurobiological underpinnings of these conditions (Do et al. 2019; Martins-Silva et al. 2020; Barker et al. 2021). In fact, so much evidence has been amassed demonstrating the link between obesity and ADHD that several excellent reviews of this literature have already been published (Cortese et al. 2016; Nigg et al. 2016; Cortese and Tessari 2017; Hanć and Cortese 2018; Cortese 2019) including in the previous edition of this book (Cortese and Vincenzi 2012). The consensus across this literature, and specifically from two meta-analyses published in 2016 (Cortese et al. 2016; Nigg et al. 2016), supports an association between obesity and ADHD; however, there is some divergence in respect of for whom the association holds (Cortese et al. 2016; Nigg et al. 2016). In the most stringent analysis (i.e., controlling for confounding factors and limiting both measurement of obesity to objective height/weight and measurement of ADHD to interview-based diagnosis) an association between obesity and ADHD was found for both children and adults (Cortese et al. 2016).

The aims of this chapter are to: (1) provide an overview and update on the current state of the science on the relationship between obesity and ADHD; (2) expand the scope of the connection between obesity and ADHD to include behavioral components important to weight regulation – i.e., physical activity, eating behaviors, and sleep; and (3) present applications of these findings to treatment approaches and future directions.

2 Obesity and ADHD

The meta-analyses published in 2016 by Cortese and colleagues included 42 studies spanning a total of 728,136 participants (6.6% with ADHD; 93.3% control subjects). Findings reflected that individuals with ADHD had greater odds of also having obesity for both children (odds ratio = 1.20; 95% confidence interval = 1.05–1.37) and adults (odds ratio = 1.55, 95% confidence interval = 1.32–1.81). The meta-analyses by Nigg and colleagues published in the same year yielded similar results, with an odds ratio of 1.20 (95% confidence interval = 1.08–1.30) pooled across all ages (Nigg et al. 2016). However, subgroup analyses differed between these meta-analyses with respect to the findings regarding the role of sex and stimulant

medication: Cortese and colleagues reported no significant effect of sex on the association between ADHD and obesity, whereas Nigg and colleagues found the association between ADHD and obesity to be stable only among women. In addition, Cortese and colleagues reported a significant association between unmedicated ADHD and obesity as compared to medicated ADHD and obesity, whereas Nigg and colleagues found no significant moderator effect for ADHD medication status. These divergent findings may be due in part to differences in weight status consideration between the two analyses (i.e., categorical weight status versus continuous BMI). Thus, while it seems clear that the basic association between ADHD and obesity is robust, much remains to be known about the nature of this shared relationship.

2.1 Causality

A critical question that naturally follows from this documented association is whether ADHD predisposes individuals to less effectively manage diet and physical activity, resulting in obesity, or whether obesity causes disruptions in executive functioning resulting in ADHD. Alternatively, a third possibility is that an ongoing reciprocal relationship between these phenotypes explains these coexisting conditions.

In support of the notion that ADHD may precede obesity, longitudinal studies demonstrate that childhood ADHD is prospectively associated with eating disorders occurring in adolescence (Biederman et al. 2010; Mikami et al. 2010; Yoshimasu et al. 2012). Further, ADHD symptoms in childhood have been associated with loss-of-control eating later in adulthood (Egbert et al. 2018). Large longitudinal cohort studies have also found similar prospective relationships between ADHD symptoms, assessed at baseline during childhood, and future obesity-related eating behavior in later childhood and adolescence (Sonneville et al. 2015; Bjørklund et al. 2018).

In a recent study by our group, we examined bidirectional associations between ADHD symptoms and obesity-related eating behaviors as measured by a parent-report measure, the Children's Eating Behavior Questionnaire (Fuemmeler et al. 2020). We found that ADHD symptoms in early childhood (i.e., age 4) predicted greater changes in obesity-related behaviors and greater increases in BMI later in childhood, but the reverse was not observed (Fuemmeler et al. 2020). Similarly, the Generation R cohort study examined bidirectional developmental pathways between obesity and ADHD and found that clinically significant ADHD symptoms predicted greater gains in fat mass over the next 3 years, but early adiposity was not related to emergent ADHD or worsening of ADHD symptoms (Bowling et al. 2018).

However, there is also some evidence to support the possibility that obesity precedes ADHD. Using Mendelian randomization analysis, which enables statistical estimation of causality in observational studies while controlling for reverse causation and residual confounding (Burgess et al. 2013), Martins-Silva and colleagues found a causal effect of BMI on ADHD risk (Martins-Silva et al. 2019). Importantly,

the reverse relationship (ADHD causing greater BMI) was not supported in their analyses. Their study utilized data from genome-wide association studies (GWAS) representing hundreds of thousands of individuals worldwide, ranging from children to adults. Despite these findings, a second Mendelian randomization analysis of the ADHD-obesity relationship by Liu and colleagues found support for bidirectional causal effects between these two conditions (Liu et al. 2020). Specifically, the authors found significant effects when modeling ADHD as the independent variable predicting BMI, but also found significant effects when modeling BMI as the independent variable predicting ADHD. Interestingly, the authors also performed polygenic score analysis in a sample of dizygotic twins and found that the genetic factors associated with BMI had a stronger effect on the development of ADHD in childhood, compared to adolescence, whereas genetic factors associated with ADHD had a stronger influence on the development of BMI in adolescence, compared to childhood. This finding suggests that the directional association between ADHD and obesity may change throughout development.

Regardless of the direction of causality, there is considerable opportunity for a reciprocal relationship between ADHD and obesity, particularly since these conditions are not static, but are dynamically changing over development. Obesity has been found to contribute to deficits in executive functioning implicated in ADHD (Favieri et al. 2019). Thus, the ADHD phenotype contributes to obesity, but obesity may also exacerbate ADHD symptoms, thereby creating a positive feedback loop.

Obesity can be conceptualized as a chronic inflammatory state associated with the overexpression of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) (Hotamisligil 2006; Ellulu et al. 2017). These same cytokines influence cognitive processes at the molecular level by way of decreased neurogenesis, synaptoplasticity, and nerve growth factor (McAfoose and Baune 2009). Inflammatory markers have also been connected specifically to both the pathogenesis of ADHD (Anand et al. 2017) and the severity of ADHD symptoms (Oades et al. 2010; Cortese et al. 2019). Thus, as has been speculated, a transdiagnostic treatment approach targeting reduction of chronic inflammation may ameliorate both obesity and ADHD. While this type of approach has yet to be tested, it represents an interesting avenue for future research.

2.2 Shared Genetic and Neurobiological Underpinnings

The role of genetic contributions in determining weight status has long been a topic of scientific interest (Sørensen 1989; Maes et al. 1997). While environmental influences play a major role in the development of obesity, genetics set the stage for this multi-factorial disease. Monogenetic manifestations of obesity are rare, with the MC4R gene being the most commonly implicated (Vaisse et al. 1998). Inherited phenotypes of obesity most often involve multiple genes: i.e., they are polygenic. Investigations of shared genetic factors between ADHD and obesity are nascent, but available evidence suggests that these two conditions may share genetic

predispositions. In an analysis of siblings/twins enrolled in the Add Health study, our group found that genetic influences on ADHD symptoms in childhood were partially shared with those influencing BMI; however, this pattern was significant only among females (Do et al. 2019). Another study examined the association between *FTO* (a gene consistently associated with predisposition to obesity (Frayling et al. 2007)) and ADHD, with exploratory results suggestive of a link between the two (Choudhry et al. 2013). GWAS have identified overlap in genetic predisposition between ADHD and obesity; however, the mechanisms of action have yet to be discovered and associations to date are minimal. For example, in an examination of 32 obesity risk single nucleotide polymorphisms (SNPs), only five were associated with ADHD or clinical characteristics thereof (Albayrak et al. 2013).

One hypothesis for the shared genetic overlap between ADHD and obesity is that they may share common deficits in dopamine regulation (Cortese and Vincenzi 2012). The role of dopamine in ADHD is complex, with some studies implicating reduced dopamine function and others implicating excessive dopamine function (Sharma and Couture 2014). Despite this, a lack of dopamine receptors in a key area, the nucleus accumbens (which is the target region of the dopaminergic pathway projecting from the ventral tegmental nucleus and is strongly implicated in "reward" responses) has consistently been associated with inattentive symptoms of ADHD (Volkow et al. 2009). Similarly, decreased striatal dopamine receptor availability, proportional to increasing BMI, has been found in individuals with obesity (Wang et al. 2001), providing support for the idea of a "reward deficiency syndrome" at play wherein individuals must overeat to experience the same degree of reward as those with higher levels of dopamine transmission. However, a recent meta-analysis of 33 studies did not find that striatal dopamine deficiency, as measured by Taq1A, a polymorphism associated with lower density of dopamine receptors, was a robust predictor of BMI (Benton and Young 2016).

The prefrontal cortex is another brain region implicated in both ADHD and obesity. In ADHD, functional differences in the prefrontal cortex are associated with impaired performance on behavioral tasks compared to controls. For example, children with ADHD demonstrated longer time to response inhibition and attentional shift compared to children without ADHD; task time was inversely associated with gray matter volume in the anterior cingulate in addition to the striatum and cerebellum (McAlonan et al. 2009). In another study, young adults with ADHD were found to have decreased gray matter volume in the right interior frontal gyrus and poorer behavioral performance on tasks of response inhibition, sustained attention, and processing speed compared to young adults without ADHD (Depue et al. 2010). Several studies (Pannacciulli et al. 2006; Herrmann et al. 2019; Chen et al. 2020) have noted decreased gray matter density in the prefrontal cortex of individuals with obesity; however, a causal link cannot be inferred. In animal models, diet-induced obesity results in decreased activity (i.e., reduced cerebral blood flow) in the prefrontal cortex (Val-Laillet et al. 2011), which suggests that eating behavior may affect brain morphology. On the other hand, there is longitudinal research demonstrating that decreased prefrontal gray matter predicts one-year weight gain (Yokum et al. 2012; Adise et al. 2021). Once again, these reports highlight the need for

additional research in order to establish causal pathways and investigate the possibility of a bidirectional pathway between brain structure and BMI.

3 Associations Between Behavioral Components of Obesity and ADHD

3.1 Eating Behavior

3.1.1 Loss-of-Control and Binge Eating

A sense of lack of control during eating episodes is a defining feature of binge eating (American Psychiatric Association 2013b) and is associated with weight gain and overweight/obesity in both pediatric and adult populations (McGuire et al. 1999; Darby et al. 2007; Sonneville et al. 2013; Byrne et al. 2019; Tanofsky-Kraff et al. 2020). One study reported that children ages 8–14 years with ADHD were 12 times more likely than their non-ADHD counterparts to experience significant loss-of-control eating (Sonneville et al. 2013). Further, this study reported that children with both overweight/obesity and loss-of-control eating were seven times more likely than children with overweight/obesity and no loss-of-control eating to have an ADHD diagnosis (Sonneville et al. 2013); thus, loss-of-control eating appears to be an important component in the relationship between ADHD and obesity. Higher rates of ADHD are seen in conjunction with eating disorders involving binging (i.e., binge-eating disorder; bulimia nervosa) compared to those involving food restriction (i.e., anorexia nervosa); in this study, individuals with ADHD and binging disorders demonstrated deficits in effortful control, or the ability to self-regulate attention (Fernández-Aranda et al. 2013). Further, the rate of binge eating among individuals with ADHD is greater than that found in the general population (Cortese et al. 2007a).

In particular, it appears as though impulsivity is a critical feature of ADHD associated with loss-of-control and binge eating. Among children in residential treatment for obesity, those with a history of eating binges demonstrated greater impulsivity than those without a history of binges; further, greater impulsivity predicted poorer weight loss outcomes (Nederkoorn et al. 2006). In a review of adults with disordered eating, impulsivity was found to differentiate between those with eating disorders involving binge eating and those involving food restriction (Waxman 2009). However, the attentional component of ADHD is also associated with these eating patterns. It has been suggested that binge eating among those with ADHD may serve as a mechanism to cope with the frustration associated with inattention and distractibility (Schweickert et al. 1997). In addition, in a sample of adolescents with obesity, researchers found that binge eating was associated with measures of impulsivity and inattention, but not hyperactivity (Cortese et al. 2007b).

Loss-of-control eating is not the only cognitive-behavioral pathway at play in the association between ADHD and overweight/obesity. In fact, in a laboratory

assessment of snack intake consisting of children with ADHD, children with loss-of-control eating, and children with neither, the children with ADHD consumed significantly more calories than children in either of the other two groups (Hartmann et al. 2012). Thus, it seems clear that other eating-related neurobehavioral processes are implicated in this association.

3.1.2 Eating in the Absence of Hunger

Consuming food for reasons other than physiological need (e.g., hedonic eating, emotional eating) has been linked to overeating and weight gain (Feig et al. 2018). Among children, in particular, eating in the absence of hunger is associated with overweight/obesity (Kral et al. 2012) and longitudinally predicts continued eating in the absence of hunger and the onset of binge eating (Balantekin et al. 2017). An association between ADHD and emotional eating has been documented in children (Tong et al. 2017), which is a particularly important consideration given psychological concerns comorbid with ADHD, such as mood disorder (Gau et al. 2010) and low self-esteem (Harpin et al. 2016).

Although limited prospective longitudinal data exist, a recent study demonstrated that ADHD symptoms preceded emotional overeating, thus suggesting that ADHD may be a risk factor for the development of future obesogenic eating behaviors (Fuemmeler et al. 2020). Impulsivity has been implicated in the tendency to eat in the absence of hunger and there appears to be an interaction with food choice that would promote weight gain and obesity. When presented with high, medium, or low energy-dense foods, children high in impulsivity were more likely than their non-impulsive counterparts to choose high energy-dense foods. However, no differences were found with respect to medium or low energy-dense foods (Nederkoorn et al. 2015).

3.1.3 Ultra-Processed Food Consumption

Ultra-processed foods are those created primarily to increase profits by using low-cost ingredients and ensuring a long shelf-life. These products undergo chemical modifications, include non-nutritive additives, and are typically packaged in synthetic materials. Ultra-processed foods typically contain combinations of sugar, oil, fat, and salts; examples include packaged snacks, pre-prepared frozen meals, and sweets such as cookies, pastries, and ice cream (Monteiro et al. 2019). In an inpatient randomized trial testing the effects of unprocessed versus ultra-processed diets, participants were provided meals matched on calories, sugar, fat, sodium, fiber, and macronutrients, and instructed to eat as much as they desired. Participants in the ultra-processed condition consumed more calories and consequently gained more weight over the course of 14 days (Hall et al. 2019).

In a free-living longitudinal study, researchers found that in a group of individuals of normal weight, those from the highest quartile of ultra-processed food

consumption at baseline were at higher risk of developing overweight/obesity 9 years later compared to those in the lowest quartile at baseline (de Mendonça et al. 2016). A systematic review concluded that a similar pattern is present among children and adolescents as well, with greater consumption of ultra-processed foods linked to higher body fat percentage (Costa et al. 2018).

Ultra-processed food consumption has also been found to be associated with ADHD: in a meta-analysis, children who frequently consumed junk foods were 1.83 times more likely to have ADHD compared to those who consumed a "healthy" diet consisting of whole foods (Shareghfarid et al. 2020). This may be due in part to color additives (Nigg et al. 2012), the negative impact of fat and sugar on brain-derived neurotrophic factor (BDNF) and learning processes (Molteni et al. 2002), BDNF disruption being correlated with ADHD (Liu et al. 2015), and/or the association of high glycemic foods with poor memory, inattention, and frustration in children (Benton et al. 2007). It is certainly possible that ADHD contributes to the decision to consume ultra-processed foods as well; however, a study comparing individuals with ADHD to those without found no difference with respect to appeal-level of processed foods (Hershko et al. 2020). The connections between ultra-processed foods, ADHD and obesity deserve further study given that these foods have been associated with both conditions.

3.2 Physical Activity

Despite increased potential for hyperactivity associated with ADHD, research suggests that children with ADHD are unlikely to achieve physical activity guidelines (Cook et al. 2015; Tandon et al. 2019). In a national analysis, children with ADHD who had more severe symptoms, children of low socio-economic status, and children who had obesity were even less likely to engage in physical activity (Tandon et al. 2019). The prevalence of motor deficits (e.g., difficulty with handwriting) in ADHD is higher than in the general population (Mokobane et al. 2019), which may contribute to children with ADHD opting out of sports and other forms of exercise. In addition, low levels of physical activity among children with ADHD may be explained in part by the role of executive functioning in planning, organization, and execution of action (Cook et al. 2015).

3.3 Sleep

Cortese has proposed a novel line of research related to sleep disruption as a factor common to both ADHD and obesity (Hanć and Cortese 2018). Circadian rhythm disturbances observed in ADHD may lead to systemic metabolic disruption resulting in weight gain, cardiometabolic disease, and insulin resistance (Pickel and Sung 2020). Alternatively, or in combination, high rates of comorbid sleep disorders

among children with ADHD may result in hormonal imbalances in leptin and ghrelin, which regulate appetite. Initial evidence is mixed, but does provide preliminary support for this link. In a study by Türkoğlu and Çetin (2019), morning chronotype was preferred among 86.8% of children with normal weight and ADHD, while evening chronotype was preferred among 61.9% of children with obesity and ADHD. A biological preference for evening is not compatible with a society that operates on a daytime schedule, and may result in metabolic disruption (Wong et al. 2015).

In addition, a study by Vogel et al. (2015) found that short sleep and routine disruption in eating schedules (i.e., skipping breakfast, eating late at night) was associated with increased BMI among individuals with ADHD symptoms. Thus, it appears as though sleep operates via both behavioral and physiological mechanisms to influence the relationship between weight and ADHD symptoms. The incorporation of sleep training into an early childhood obesity, as a preventative intervention, was found to bestow a protective effect against the development of obesity (Taylor et al. 2017). An examination of ADHD symptom development during this type of intervention would provide rich data to further explore the link(s) between sleep, obesity, and ADHD. Sleep treatment programs are discussed further in chapter "Sleep in Individuals with ADHD: Prevalence, Impacts, Causes and Treatments".

4 Treatment Implications

The first examination of the association between ADHD and obesity in a sample of bariatric patients noted not only the high comorbidity of these conditions, but also the difference in weight loss trajectories between those with and without ADHD (Altfas 2002). This study found that despite significantly more clinic visits, individuals with ADHD were less successful with weight loss (Altfas 2002). This same pattern was found in a 4-month behavioral weight-loss trial: those with ADHD reported greater short-lived weight-loss attempts in the past year (10 versus 2 attempts) and greater perceived difficulty in weight-loss skills and strategies, compared to those without ADHD (Pagoto et al. 2010). These findings suggest the importance of cognitive processes in behavioral weight loss. They further suggest that those with impaired executive functions may be at a disadvantage unless ADHD symptoms are addressed prior to weight-loss attempts, or unless there is a dual focus on both improving ADHD symptoms and promoting weight loss (Cortese and Castellanos 2014). However, emerging evidence suggests that participation in multicomponent behavioral weight-loss interventions is associated with improved executive function in both adolescents (Delgado-Rico et al. 2012) and adults (Witbracht et al. 2012).

Recognition of the ADHD-obesity phenotype has enormous implications for the treatment of both of these conditions, with the possibility that one comprehensive or integrated approach may improve functioning in both domains. We are on the precipice of an abundance of literature reporting outcomes of integrating executive

function or other cognitive targets into treatment for overweight/obesity (Eichen et al. 2017). Recent work by Boutelle and colleagues highlights the moderating role of food and satiety responsiveness in the association between executive function and weight status (Boutelle et al. 2020; Rhee et al. 2021). This work paves the way for approaching combined ADHD/obesity interventions from a precision medicine framework: determining for whom, and under what circumstances, targeting executive functions might bolster treatment response.

4.1 Interventions Targeting Executive Functions

4.1.1 Digital Therapeutics

Training protocols targeting executive functions, such as working memory, inhibitory control and attention, have been found to improve these skills (Tucha et al. 2011; Melby-Lervåg and Hulme 2013; Meyer et al. 2020). A recent example of this was a randomized trial of a digital therapeutic tool called AKL-T01, designed to target attention and cognitive control through a video game interface (Kollins et al. 2020). Children of 8–12 years of age with ADHD were randomized to either AKL-T01 or control (computerized word game) and instructed to engage with the program for 25 min each day (divided across 5 daily sessions) over a period of 28 days. Significant improvements in selective attention, sustained attention, and attentional consistency were observed in the intervention compared to the control group at post-treatment follow-up.

The translation of such training to diet change and weight loss has produced mixed findings. A meta-analysis concluded that inhibitory control training for dietary control is effective in short-term experimental paradigms, but there is insufficient data to assess the results of long-term studies in real-world settings (Jones et al. 2016). In a randomized pilot trial, participants who received computerized attention training with personalized food images demonstrated reduced desire for high-calorie foods and greater reduction in body fat at 4 weeks compared to controls (Stice et al. 2017). However, these results were not sustained at 6 months (Stice et al. 2017), again highlighting the need to develop methods for utilizing such interventions in a way that will support long-term change. The use of AKL-T01, in particular, among individuals with obesity and ADHD-like symptoms may provide a novel approach to address weight loss among these individuals.

4.1.2 Episodic Future Thinking

Episodic future thinking targets the cognitive process of delay-discounting, the decline in reward value arising from a delay in receipt of the reward, which is implicated in obesity and long-term weight loss maintenance (Tang et al. 2019). This intervention asks individuals to visualize a future event for which a weight-loss goal

is important, thereby enhancing the salience of this future reward in service of rejecting immediate rewards, such as snack foods (Atance and O'Neill 2001). In both children (Daniel et al. 2015) and adults (Daniel et al. 2013), the practice of episodic future thinking is associated with decreased energy intake in those with overweight/obesity. However, long-term interventions utilizing episodic future thinking are ongoing (Leahey et al. 2020); thus, the extent to which this exercise impacts weight loss remains unknown. Further, studies to date have not specifically targeted or analyzed individuals with poor delay-discounting, executive function deficits, or ADHD.

4.2 Interventions Targeting Physical Activity

Physical activity represents a particularly promising avenue for the treatment of comorbid ADHD and obesity, as there is evidence to support its role in treating both conditions. A systematic review analyzing the effects of habitual physical activity found that aerobic exercise was associated with improvements in a wide variety of cognitive processes as measured by objective testing (Den Heijer et al. 2017). The intensity and duration of exercise required to produce a reduction in ADHD symptoms remains to be settled; however, these parameters are important when considering physical activity as a treatment for both ADHD and obesity, given that clear recommendations have been established for weight loss.

Physical activity is critical for success during the maintenance phase of weight loss, compared to the active phase (Wing and Phelan 2005; Ma et al. 2017; Ostendorf et al. 2019); however, early promotion of exercise in the context of behavioral weight loss programs may contribute to both habit formation and improved cognitive function, thereby allowing for better engagement in weight loss behaviors and strategies. This approach could be particularly beneficial for individuals with ADHD or ADHD-like symptoms.

4.3 Medication

The meta-analysis conducted by Cortese and colleagues found a significant association between ADHD and obesity for individuals who were not medicated for ADHD; however, this association was not present for medicated individuals ($k = 12$) (Cortese et al. 2016). In a longitudinal study among adults with long-term obesity and newly-diagnosed ADHD, psychostimulant pharmacotherapy resulted in significant weight loss more than 1 year after medication start (mean = 12.4% of initial body weight lost) (Levy et al. 2009). Of interest, the authors note that weight loss was largely attributable to the appetite-suppressant effects of the medication during the first 2 months of treatment, but weight loss thereafter was due to improved ability to carry out weight-loss behavior change.

Though not formally assessed, participants reported improvements in working memory, impulsivity, and capacity for persistent goal pursuit.

5 Summary and Future Directions

The material presented in this chapter provides an update on the current scientific evidence for the link between obesity and ADHD, with a particular emphasis on the role of genetics, neurobiology, and weight regulation behaviors. While the present literature supports a consistent association between obesity and ADHD, significant gaps remain in our understanding as to: (1) for whom this relationship exists; (2) the causality of this association; and (3) which weight regulation behaviors, or combination of behaviors, (e.g., eating behaviors, physical activity, screen time, sleep) appear most salient for the development of this shared relationship. Additionally, the observed connection between ADHD and ADHD-like symptoms offers opportunities to expand and improve obesity treatments.

In regard to the question of whether obesity leads to ADHD, or vice versa, the evidence presented here demonstrates scientific support for both directions. Future research is needed to disentangle the directionality of this association and explore the potential for reciprocal relationships in which shared behavioral, genetic, and neurobiological risk factors influence one another. In recent years, investigations have begun to examine the shared genetic underpinnings for both obesity and ADHD and they are finding common genetic and neurobiological predispositions for these conditions. Preliminary evidence suggests the important role of dopamine dysregulation and the underdevelopment of the prefrontal cortex. Yet many questions remain unanswered in this area of work, which precludes our ability to fully understand the directionality and mechanistic pathways that explain these underpinnings. Further examination into these shared genetic and neurobiological pathways is a clear need for future research.

Among children and adolescents, there are important commonalities between weight-regulating behaviors and the development of obesity and ADHD. Eating behaviors influenced by impulsivity, including loss of control eating, binge eating, and eating in the absence of hunger, may be a coping strategy in response to ADHD symptoms that also lead to the development of obesogenic eating patterns. While hyperactivity in children with ADHD is high, their physical activity remains below the recommended guidelines, which may be explained by motor deficits and/or executive functioning. Evidence on children's screen time and sleep behaviors have also found bidirectional links between ADHD and behavioral patterns (e.g., excess screen time, circadian disturbances) that can lead to weight gain. Yet, future research is needed to disentangle the unique and combined influence of obesogenic behaviors and ADHD risk.

In regard to treatment for these conditions, there is great potential for future interventions to comprehensively improve both weight and ADHD outcomes. An integrated approach to improving both weight-related behaviors and executive

functioning may be the key to simultaneously improving multiple health-related outcomes. Strategies such as digital therapeutics, inhibitory control training, episodic future thinking, and the promotion of physical activity have each shown promise in short-term interventions; yet, the long-term success of these approaches for treating comorbid ADHD and obesity remains unknown. Further, the associations between sleep, ADHD, and BMI warrant investigations of the mediating effects of sleep-improvement interventions on ADHD symptoms and weight.

In summary, the evidence around comorbid obesity and ADHD has grown tremendously over the past two decades. The overwhelming evidence suggests a connection between obesity and ADHD or ADHD-like symptoms and behaviors. This recognition has the potential to enhance obesity prevention and treatments in both children and adults. Most notably, recognizing for whom, and under what conditions, obesity treatments may work best can advance the effectiveness of obesity treatments. Additionally, advances in treatments to improve cognitive functions that are impaired in individuals with ADHD (e.g., attention, inhibitory control, etc.) can be leveraged to inform obesity prevention efforts. The scientific advances in this area will undoubtedly forge novel and innovative approaches for addressing both ADHD and obesity.

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Genetics of Attention-Deficit Hyperactivity Disorder

Kate Langley, Joanna Martin, and Anita Thapar

Contents

Abstract Attention-Deficit Hyperactivity Disorder (ADHD) has long been recognized as being a highly heritable condition and our understanding of the genetic contributions to ADHD has grown over the past few decades. This chapter will discuss the studies that have examined its heritability and the efforts to identify specific genetic risk-variants at the molecular genetic level. We outline the various techniques that have been used to characterize genetic contributions to ADHD,

K. Langley (✉)
School of Psychology, Cardiff University, Cardiff, UK

MRC Centre for Psychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
e-mail: LangleyK@cardiff.ac.uk

J. Martin and A. Thapar
MRC Centre for Psychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

Division of Psychological Medicine, School of Medicine, Cardiff University, Cardiff, UK

Wolfson Centre for Young People's Mental Health, Cardiff University, Cardiff, UK

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describing what we have learnt so far, what there is still to learn and the methodologies that can be used to further our knowledge. In doing so we will discuss research into rare and common genetic variants, polygenic risk scores, and gene–environment interplay, while also describing what genetic studies have revealed about the biological processes involved in ADHD and what they have taught us about the overlap between ADHD and other psychiatric and somatic disorders. Finally, we will discuss the strengths and limitations of the current methodologies and clinical implications of genetic research to date.

Keywords ADHD · Copy number variant · Genome-wide association study · Heritability · Polygenic risk score

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CNV	Copy number variant
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and statistical manual of psychiatric disorders – fifth edition
EAGLE	EArly genetics and life course epidemiology (consortium)
EWAS	Epigenome-wide association studies
GWAS	Genome-wide association studies
GWEIS	Genome-wide environmental investigation studies
GxE	Gene–environment interactions
ICD	International classification of diseases
ID	Intellectual disability
iPSYCH	Lundbeck Foundation Initiative for Integrative Psychiatric Research
MR	Mendelian randomization
mRNA	Messenger ribonucleic acid
PGC	Psychiatric genomics consortium
PRS	Polygenic risk score
rGE	Gene environment correlations
SNP	Single nucleotide polymorphism
VCFS	Velo-cardio-facial syndrome

1 Overview

Like many other psychiatric disorders, Attention-Deficit Hyperactivity Disorder (ADHD) is heterogeneous and multifactorial in origin with multiple genetic and environmental factors contributing to the disorder. This chapter will review the contribution of genetic risks to ADHD, including both what we already know and

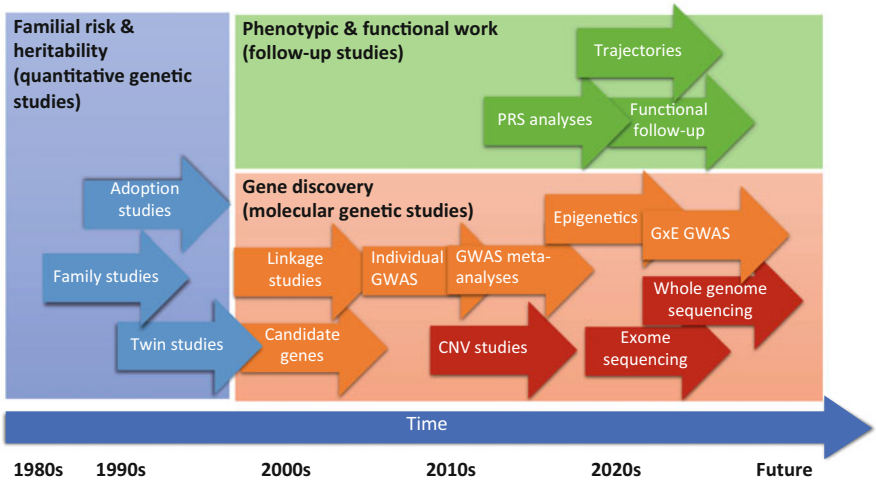

Fig. 1 A representation of an approximate timeline of genetic studies of ADHD. The left side of the arrows indicate the approximate time of the first studies that investigated ADHD genetics using the stated methods. The arrows indicate that these study types have continued to be used, or could return to use in future (e.g., candidate gene studies of specific identified genome-wide significant risk loci could be valuable in future). *GWAS* genome-wide association study, *CNV* copy number variant, *GxE* gene-by-environment interactions

the ways in which research is moving forward to identify additional genetic risks. We will briefly describe some of the different methodologies that are currently utilized to study the genetics of ADHD and highlight how these methods have helped our understanding of its etiology, as well as what our understanding of the genetics of ADHD indicates about the biological processes relevant to the disorder. Figure 1 describes the chronology of the different methodological techniques used in these investigations.

As has been highlighted throughout this book, ADHD is phenotypically heterogenous and this heterogeneity is also relevant to the genetics of ADHD. Thus, we will discuss not only our understanding of the genetics of ADHD, in general, but also how this may differ when looking across development into adulthood, the overlap with other psychiatric and somatic disorders as well as factors such as sex differences. Further, we shall briefly consider the interplay between genetic and environmental risks for ADHD and how these need to be considered together for a fuller understanding, before discussing the implications of our current knowledge of ADHD for clinical practice.

2 Conceptualizing ADHD as a Trait

For clinical purposes, it is helpful to view ADHD as a dichotomous yes/no diagnosis because clinical decisions, such as whether or not to initiate medication, are categorical. However, genetic findings converge with epidemiological evidence in suggesting that ADHD diagnosis lies at the extreme end of a population continuum or trait. Twin-studies show that there is no discontinuity in heritability along the ADHD continuum: i.e., heritability in those with high ADHD symptom scores appears to be the same as across the continuum of ADHD as a trait in the general population (Levy et al. 1997). However, one twin-study suggested that there may be discontinuity for those with extremely low ADHD scores (Greven et al. 2016), although further work is needed to confirm these results. Molecular genetic findings also support the idea that ADHD diagnosis lies at the extreme of a population continuum (Thapar 2018). ADHD polygenic risk-scores derived from ADHD case/control genome-wide association studies (GWAS; methods detailed later) are associated with ADHD trait scores in the general population (Taylor et al. 2019). The most recent, largest ADHD GWAS to date estimated the genetic correlation (r_g) between ADHD diagnosis and a meta-analysis of ADHD trait scores in the general population as 0.94 (Demontis et al. 2019), indicating that common genetic variants strongly overlap across these definitions of ADHD.

3 Heritability of ADHD

For a number of decades there has been strong evidence from quantitative genetic studies, which study similarities between related individuals to infer genetic contributions, rather than directly assessing DNA at a molecular level, that ADHD is a highly familial and heritable disorder. As can be seen in Fig. 1, such insights were first observed using family studies, which compared the rates of ADHD between first-degree relatives of those with the disorder and unrelated controls. Family studies have demonstrated familial aggregation (running in families, possibly due to genetic factors, possibly due to shared environment) of ADHD with relative risks between 4.0 and 5.4% among first-degree relatives of those affected (Thapar et al. 2007). Adoption studies have shown that this familial transmission is explained predominantly by genetic factors, as adopted children are more similar to their biological parents, to whom they are genetically related but do not share a rearing environment, compared to their adoptive parents with whom they share an environment, but not genetics (Cantwell 1975; Cunningham et al. 1975; Sprich et al. 2000). Numerous twin-studies, which quantify the proportion of phenotypic variance attributable to genetic, shared, and non-shared environmental factors, have also confirmed a significant contribution of genetic factors to ADHD. Meta-analyses estimate heritability between 70 and 80% (Nikolas and Burt 2010), with the remaining variance explained mainly by non-shared environmental effects

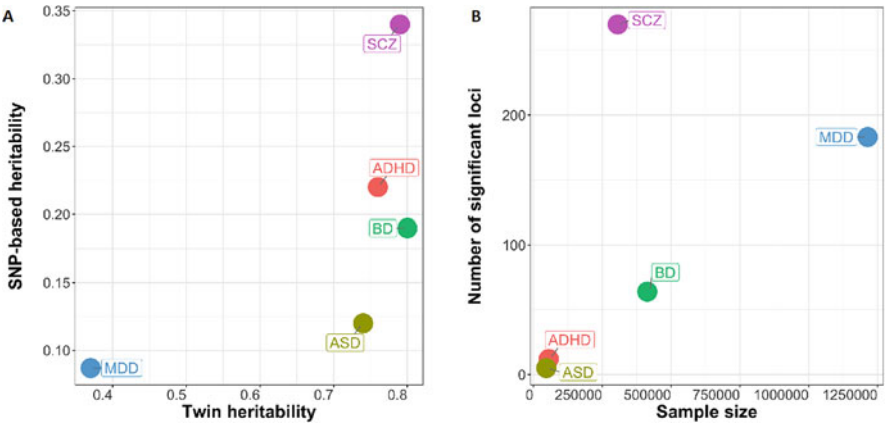

Fig. 2 A comparison of: (**a**) heritability estimates based on twin studies and genome-wide association studies (GWAS), as well as (**b**) the number of significant loci identified by GWAS, given available sample sizes, for ADHD, schizophrenia (SCZ), bipolar disorder (BD), major depressive disorder (MDD), and autism spectrum disorder (ASD). The twin heritability estimates are obtained from meta-analyses (references: Sullivan et al. 2000; Lee et al. 2019; McGuffin et al. 2003; Nikolas and Burt 2010; Tick et al. 2016; Hilker et al. 2018). The estimates of single nucleotide polymorphism (SNP)-based heritability and number of risk loci are obtained from the largest available GWAS for each study (references: Grove et al. 2019; Demontis et al. 2019; Levey et al. 2020; Mullins et al. 2020; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2020)

(environmental factors that make twins more dissimilar, stochastic effects and error variance) and only a small proportion of the variance due to shared environmental factors (Nikolas and Burt 2010).

As illustrated in Fig. 2a, this demonstrates that ADHD has high heritability similar to other neurodevelopmental and psychiatric disorders, such as autism spectrum disorder (ASD), schizophrenia, and bipolar disorder, while being significantly more heritable than other more common mental health disorders, such as major depressive disorder. While these quantitative genetic methods are extremely useful for helping to understand the contribution of genetics at the population level and, as can be seen throughout this chapter, to help elucidate the genetic architecture around the phenotypic presentation of ADHD and its overlap with other disorders, they infer genetic (and environmental) contributions as a whole, rather than identifying specific risk-factors at the individual level. For such investigation, researchers have moved to using molecular genetic techniques. As can be seen in Fig. 1, such research has addressed two broad categories of genetic variants: rare variants (represented in red in Fig. 1) that have a frequency of $<1\%$ in the population and more common frequency variants (represented in orange). We will first discuss research which has looked at rare variants.

4 Rare Variants

There are numerous developmental syndromes that are caused by rare chromosomal mutations, such as aneuploidies and microdeletions. These are characterized by increased risk for a variety of health problems, in terms of neurodevelopment (e.g., intellectual disability (ID)), as well as general mental and physical health (e.g., congenital malformations and cardiac problems). Some of these rare chromosomal mutations are also associated with risk of ADHD and include, for example: Fragile X syndrome, Tuberous Sclerosis complex, Smith-Magenis syndrome, Velocardio-facial syndrome (VCFS), Prader-Willi syndrome, Turner syndrome, Klinefelter syndrome, and Williams-Beuren syndrome (Lo-Castro et al. 2011; Scerif and Baker 2015). In addition to these well-known rare syndromes, newer syndromes are being characterized (e.g., 16p11.2 duplication/deletion syndromes) and have also been linked to ADHD risk (Niarchou et al. 2019).

Beyond these specific syndromes, large rare deletions and duplications of segments of DNA, known as copy number variants (CNVs), have been found to be associated with risk of ADHD across many studies (Williams et al. 2010, 2012). In particular, CNVs spanning genomic regions that have previously been implicated in other neurodevelopmental and psychiatric disorders are associated with ADHD risk (Gudmundsson et al. 2019). Large, rare CNVs in other regions of the genome (i.e., those not robustly linked to neurodevelopmental disorders) are also associated with more broadly-defined, undiagnosed ADHD and other neurodevelopmental problems that are assessed using parental ratings (Martin et al. 2018a). Rare CNVs can be inherited from biological parents or occur de novo in the germline; the latter are on average more deleterious (Lionel et al. 2011; Martin et al. 2020).

Given the large sizes of CNV loci, which are often greater than 100,000 or even 500,000 base-pairs in length, these duplications or deletions can span dozens or even hundreds of genes, follow-up work is needed to identify the causal genes and understand the underlying biology. Several studies have conducted pathway or gene set analyses and determined that CNVs implicated in ADHD impact on biological pathways, including those related to ion channels, cholesterol metabolism, glutamate receptors, and central nervous system development (Elia et al. 2012; Thapar et al. 2016). Also, CNVs implicated in ADHD affect some of the same gene sets that have been implicated in ASD, as well as genes that have been implicated in schizophrenia (Martin et al. 2014a; Thapar et al. 2016).

CNVs that have been studied in relation to ADHD are generally very large (e.g. $>$500,000 or $>$1 million base pairs in length) structural variants. However, rare single-point mutations in protein coding regions of the genome, such as protein-truncating variants or damaging missense mutations, have also been implicated in ADHD, based on recent large exome sequencing studies (Ganna et al. 2018; Satterstrom et al. 2019). Because such exonic mutations are extremely rare, identifying specific genes that are robustly associated with ADHD is challenging, as larger sample sizes are needed to have sufficient statistical power. Collectively, the rare gene variants that have been implicated in ADHD are more common than in control

individuals and also overlap substantially with variants that have been implicated in ASD (Satterstrom et al. 2019). Although the costs of exome sequencing have decreased dramatically in recent years, there are currently few such large studies and no large whole genome sequencing studies (all the genome, not just the exome) of ADHD to date.

It is important to note that the etiology of ADHD is complex and that individuals with rare genetic syndromes, CNVs, or single-point mutations will not always manifest ADHD. Rare aneuploidies and CNVs have incomplete penetrance for a variety of phenotypes (Kirov et al. 2013). Evidently, other genetic or non-genetic factors also contribute to increasing or decreasing the risk of ADHD, in individuals with these rare mutations. To use psychosis as an example, although the 22q11 deletion of VCFS is a strong risk-factor for psychosis, a recent study of individuals with this deletion found that common genetic risk-factors linked to schizophrenia are also associated with increased risk of psychosis in the context of having this rare mutation (Davies et al. 2020). Thus, work integrating rare and common variant genetic risks will be needed to fully understand the impact of rare variants on individual risk of ADHD and heterogeneity in clinical phenotype.

5 Common Variants

Following early studies using candidate gene and linkage analysis approaches (see Fig. 1), hypothesis-free case-control GWAS have become the default genetic study design for assessing the contribution of genetic variants that occur commonly in the general population (typically defined as >1% minor allele frequency), known as single nucleotide polymorphisms (SNPs). Early GWAS analyses of ADHD (Lasky-Su et al. 2008; Neale et al. 2010; Stergiakouli et al. 2012; Yang et al. 2013) consisted of relatively small numbers of individuals with ADHD. These studies were underpowered to identify risk variants at conventional levels of genome-wide significance ($p < 5 \times 10^{-8}$) because they involve testing such a large number of SNPs but yielded important insights, which established that ADHD is characterized by a highly polygenic genetic architecture.

Through an international collaborative effort led by the Psychiatric Genomics Consortium (PGC) and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), the first robustly associated SNPs increasing risk of ADHD have now been identified (Demontis et al. 2019). This largest GWAS to-date consisted of 20,183 individuals with ADHD and 35,191 comparison individuals and identified 12 genomic regions reaching statistical significance, with a total contribution from common risk-alleles to variance in ADHD (i.e., the SNP-based heritability or SNP-h^2) estimated at 21.6% (SE = 0.014) (see Fig. 2b for an illustration). Although the genome-wide significant loci may be individually important in providing clues to the location of the causal genetic risk variants and understanding the underlying biology of ADHD, it is clear that there is a large polygenic component to ADHD, with likely thousands of genes implicated in its

etiology, that are yet to be discovered. This is highlighted in Fig. 2: the currently identified genome-wide significant SNPs account for a small proportion of the heritability identified in twin-studies, something that is similar across disorders (see Fig. 2a), while the number of SNPs identified is small in comparison with discoveries for other psychiatric disorders, likely in part due to much smaller sample sizes (see Fig. 2b).

Secondary analyses based on the GWAS data investigating the functional (biological) role of implicated variants have further revealed that the polygenic signal of ADHD is enriched for regulatory elements that are specific to the central nervous system and also evolutionarily-constrained genomic regions (i.e., regions of particular importance to key biological functions in humans) (Demontis et al. 2019). The analyses also revealed little support for the most widely-studied candidate genes (e.g., dopaminergic genes), which had previously been defined in a hypothesis-driven way. As mentioned earlier (see Sect. 2), another key finding from this ADHD GWAS was the remarkably high genetic correlation between diagnosed ADHD and childhood population traits of ADHD, which was close to a correlation of one, replicating previous work by the EArly Genetics and Life course Epidemiology (EAGLE) consortium (Middeldorp et al. 2016). However, genetic correlation was lower with another definition of ADHD, one of self-reported diagnosis in individuals taking part in genetic testing by the personal genomics company 23andMe, with an estimated correlation of 0.65 (SE = 0.11). This is likely due to the heterogeneity of the ADHD phenotype self-reported by 23andMe participants, as well as ascertainment differences; for example, this is demonstrated by the dissimilar genetic correlation estimates between ADHD and educational attainment using the different definitions of ADHD (Demontis et al. 2019).

Further GWAS analyses using the primary ADHD sample have been performed to stratify the sample based on age and sex, yielding additional insights, which will be discussed later in this chapter. The high genetic correlations of different GWAS justify the prevalent approach of genomic discovery studies in terms of combining as many individuals as possible with a variety of definitions of ADHD, in order to maximize statistical power to facilitate identification of risk-variants (which is clearly necessary to identify genome-wide significant variants, see Fig. 2b). However, such an approach is a trade-off between the number of discovered risk-loci and specificity of those loci to a highly heterogeneous phenotype. Secondary analyses are then necessary to further characterize the impact of discovered genetic risks on specific clinical constructs.

6 Polygenic Risk Scores and Further Insights into Genetic Architecture

One highly versatile method, which can be used to follow up gene discovery studies (see Fig. 1) that has rapidly gained in popularity and has been applied widely in the context of ADHD, is polygenic risk-score (PRS) analysis. This method involves using the SNP effect-sizes obtained from an ADHD GWAS to calculate a genetic risk-score in an independent set of individuals. A variety of methods have been developed to determine how SNPs are selected and weighted to derive PRS (Wray et al. 2020). These scores can then be used to test hypotheses regarding shared genetic risks between ADHD and other phenotypes, compare polygenic burden in different groups, and also in more sophisticated ways (e.g., using mediation analyses, testing gene-by-environment interactions, or examining transmitted and non-transmitted risks across generations).

One of the main limitations of this method is that while the estimated SNP-h^2 of ADHD is 21.6%, PRS only capture a smaller proportion (~5.5%) of the phenotypic variance of ADHD diagnosis status (Demontis et al. 2019), so effect-sizes in secondary analyses tend to be relatively small. Another limitation is that PRS are sensitive to population ancestry and, given the predominantly European ancestry bias of the majority of GWAS analyses, PRS are not as powerful an analytic tool in individuals of non-European ancestries (Martin et al. 2019). These issues limit the current clinical applicability of PRS. However, with these caveats in mind, PRS have been successfully used to test numerous hypotheses, which can help to inform our understanding of ADHD nosology, heterogeneity, and developmental trajectories.

In line with twin-study findings and genetic correlation analyses from GWAS, PRS approaches have consistently demonstrated shared genetic effects between ADHD diagnosis and continuously distributed population traits of ADHD in a variety of samples, using various assessment tools, different informants (parent- and self-rated) and across many ages, including young adults (Groen-Blokhuis et al. 2014; Martin et al. 2014b; Brikell et al. 2018b; Burton et al. 2019; Riglin et al. 2020b). Shared genetic effects with a variety of phenotypes beyond ADHD have also been identified and will be discussed further in the next section.

PRS analyses can also be performed to examine other clinical features in the context of ADHD. Studies examining comorbid mental health problems have determined that a higher ADHD polygenic burden is associated with conduct disorder (Hamshere et al. 2013; Demontis et al. 2021), substance use disorders (such as cannabis and alcohol use: Wimberley et al. 2020), as well as irritability and emotional dysregulation (Riglin et al. 2017; Nigg et al. 2020). Several studies of cognition have also suggested that higher ADHD PRS are associated with more executive function difficulties, particularly in terms of inhibitory control and working memory (Nigg et al. 2018; Chang et al. 2020). On the whole, higher ADHD PRS are not just associated with risk of ADHD, but also appear to be associated with a greater mental health burden and poorer cognitive abilities in the context of having a diagnosis of ADHD.

PRS is a versatile analytic tool and can be used to address more complex hypotheses beyond group differences and univariate association. For example, it is possible to split the set of variants used to derive PRS into those that were transmitted from parents to children versus those that were not transmitted and to derive separate PRS for these sets of variants. Using this approach it appears that polygenic liability for ADHD that is transmitted from parents to children is associated with children's ADHD symptoms, but this is not true of non-transmitted PRS (de Zeeuw et al. 2020). Others have tested mediation models to determine whether ADHD PRS act on ADHD phenotypes via other measured phenotypes, such as working memory or neuroimaging measures (Nigg et al. 2018; Alemany et al. 2019). As the size and diversity of the discovery GWAS for ADHD and other phenotypes grow, PRS analyses will become more robust and better powered to test further hypotheses related to ADHD.

7 Genetic Discoveries and Insights into the Nature of ADHD

7.1 Developmental Change and Adult ADHD

ADHD symptom severity, especially hyperactivity-impulsivity, typically declines across adolescence and into adult life. However, most individuals with ADHD continue to show symptoms and impairment in adult life and a substantial proportion continue to meet full diagnostic criteria for ADHD (see Chapter "ADHD in Children and Adults: Diagnosis and Prognosis"). Longitudinal twin-studies have observed that genetic factors contribute to ADHD symptom persistence from childhood across adolescence (Pingault et al. 2015). More recent investigations have utilized ADHD PRS to examine developmental changes in ADHD symptom scores.

A UK population-based longitudinal study of ADHD symptoms (Riglin et al. 2016) found that ADHD PRS were associated with a persistent ADHD trajectory. Those in the persistent ADHD symptom trajectory class showed a higher burden of ADHD PRS than the low symptom group. ADHD PRS also distinguished the group with persistent ADHD symptoms from those whose symptoms had remitted by adolescence. This finding has now been replicated in another UK population-based study (Agnew-Blais et al. 2021). However, larger studies are needed to confirm these results and further understand the genetic factors linked to age-of-onset, persistence of ADHD in clinical populations, and the developmental trajectory of ADHD.

Despite growing interest in adult neurodevelopmental disorders, there have been far fewer genetic studies of ADHD in adulthood than among children. Early family studies suggested a higher familial loading for adult ADHD than for childhood ADHD (Faraone 2004). A more recent Swedish registry study (Chen et al. 2017) investigated the risk of ADHD in siblings of those with ADHD. This study observed a much higher risk of ADHD diagnosis in siblings of those who had a recorded

diagnosis of ADHD at age 18 or older (hazard ratio 11.49) (considered to be persistent ADHD) than in siblings of those with ADHD recorded only before age 18 years (hazard ratio 4.68). It was puzzling that early twin-studies of adult ADHD showed much lower heritability estimates than those observed for childhood ADHD. However, this is likely explained by the change of informant from parent to self-reported ADHD. More recent studies suggest that when informants are combined, the heritability of adult ADHD is similar to that observed in childhood. The largest twin-study of adult ADHD (Larsson et al. 2014) utilized Swedish registry data where ADHD was defined using an ICD-10 diagnosis or prescribed medication. This study observed substantial heritability for ADHD across the life-span, with a heritability estimate of 72% in adulthood.

To date there has been no well-powered GWAS of adult ADHD. The largest study to date (6,532 adult ADHD cases and 15,874 controls) yielded no genome-wide significant loci (Rovira et al. 2020). However, the authors did show a substantial genetic correlation ($r_g = 0.81$, 95% CI: 0.64–0.97) between ADHD assessed in adults and children. As noted previously, a UK study examined ADHD PRS generated from childhood ADHD GWAS data in a population-based cohort where ADHD symptoms at age 25 years were rated by parent and self (Riglin et al. 2020b). ADHD PRS were associated with both parent and self-rated ADHD symptom scores at age 25, again suggesting that, for common variants, adult and childhood ADHD share an underlying genetic liability.

7.2 Sex Differences

It is well established that ADHD, like other neurodevelopmental disorders, shows sex differences, although it remains unknown why males are more commonly affected and the magnitude of this difference is greater in clinical than epidemiological samples. To date, genetic studies have not elucidated a clear-cut reason for this male bias. Twin-studies of ADHD have not demonstrated sex differences in genetic loading. However, some sibling studies of ADHD have observed that the siblings of females with ADHD may be at higher risk of ADHD than the siblings of affected males (Martin et al. 2018c; Taylor et al. 2019). This suggests that females with ADHD may require a higher burden of familial liability to manifest ADHD than males (also known as the female protective effect); this could help explain the sex difference in prevalence. However, molecular genetic studies have not shown the same sex difference. An investigation of sex differences using the largest ADHD GWAS to date observed a genetic correlation close to 1 between males and females (Martin et al. 2018c). Also, that same study found no sex differences in ADHD PRS (Martin et al. 2018c), contrary to earlier findings of a higher burden of ADHD PRS observed in females with ADHD (Hamshere et al. 2013) in a much smaller study. The findings thus far suggest that the sex difference in ADHD prevalence is not explained by differential effects of common genetic variants, although large-scale

ADHD genetic studies have yet to explore this issue through analyses of sex chromosomes and rare variants.

PRS-by-sex interaction analyses or direct comparison of genetic burden in males and females can also be used to test for sex differences in the context of another psychiatric disorder. For example, it has been observed that the association between ADHD, PRS, and substance misuse disorders in individuals with ADHD is higher in females compared to males (Wimberley et al. 2020). Also, in children with a diagnosis of anxiety and/or depression, ADHD PRS are higher in females compared to males (Martin et al. 2018b), although no sex differences in anxiety or depression PRS have been reported in children with ADHD (Martin et al. 2021). Given the male bias in prevalence of ADHD and sex differences in comorbidity patterns in children with ADHD, further PRS studies examining sex differences will yield additional insights. For example, Martin et al. (2021) found some preliminary evidence for stronger associations between anxiety PRS and anxiety symptoms in males with ADHD compared to females, but this finding requires further investigation.

7.3 Relationship and Genetic Overlap with Other Neurodevelopmental Disorders

The Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5: American Psychiatric Association 2013) now groups ADHD with other childhood-onset neurodevelopmental disorders, including ASD, ID, communication and motor difficulties, as well as tic disorders. These disorders have some common features: typically they onset early in development, show a steady clinical course over time, rather than relapses and remissions, and more commonly affect males (Thapar et al. 2017).

As discussed previously, twin-studies have shown that ADHD and other neurodevelopmental disorders, whether defined as traits or disorder, have a shared genetic etiology. The findings on overlap of ADHD and ASD are especially interesting given that it is only since the publication of DSM-5 and ICD-11 (the most recent editions), that ADHD can be co-diagnosed with ASD. The largest study based on Swedish registry data (Ghirardi et al. 2017) showed that monozygotic co-twins of individuals with ASD had much higher rates of ADHD (odds ratio = 17.77) than dizygotic co-twins of those with ASD (odds ratio = 4.33). Swedish registry data were also used to examine the overlap of ADHD and ID in another study (Faraone et al. 2017). The authors observed that most of the correlation between ADHD and ID was explained by genetic factors (91%) except for those with profound ID. Although ADHD shows substantial phenotypic and genetic overlaps with other neurodevelopmental disorders, ADHD with comorbidities including ASD or ID or Tourette syndrome have historically been excluded from GWAS. This means that affected individuals will not be represented in these studies.

Molecular genetic studies have supported the genetic overlap between ADHD and other neurodevelopmental disorders (Thapar 2018). The largest ADHD GWAS to date observed a significant genetic correlation of 0.36 between ADHD and ASD (Grove et al. 2017). The relationship between ADHD and other disorders has also been examined in a recent GWAS meta-analysis of eight psychiatric/neurodevelopmental disorders that investigated the relationships across different disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019). The authors found three factors that explained the relationship between different disorders, where the "neurodevelopmental" factor encompassed ADHD, ASD, and Tourette syndrome. Surprisingly, depression was also captured by this factor. These findings highlight again that while diagnostic categories may be useful for some clinical purposes they ought not to be reified.

As noted previously, rare genetic variant studies also highlight the overlap between ADHD and other neurodevelopmental disorders. Recent investigations of CNVs associated with ADHD show that these CNVs also contribute to other neurodevelopmental and psychiatric disorders including ASD and schizophrenia (Williams et al. 2010; Lionel et al. 2011; Gudmundsson et al. 2019). A large exome sequencing study of ADHD found that the genes implicated by rare protein-truncating variants were the same as those found in ASD (Satterstrom et al. 2018). Overall, family and twin-studies, as well as common and rare variant genetic studies, all converge on the conclusion that there is a significant degree of shared genetic risks contributing to a broad range of neurodevelopmental disorders, not ADHD alone.

7.4 Relationship and Genetic Overlap with Other Psychiatric and Somatic Disorders

It has become increasingly clear that ADHD shares genetic liability with a range of other phenotypes, including psychiatric and somatic health conditions that typically onset later in life, as well as other complex human traits measured in the general population. PRS studies that have examined shared genetic liability with ADHD are too numerous to summarize comprehensively and we refer readers to a recent systematic review on the topic (Ronald et al. 2021). Here we summarize several important emerging findings.

A systematic review of twin and family genetic correlations between ADHD and other psychiatric phenotypes estimated a moderate pooled genetic correlation ($r_g = 0.50$) across childhood and adulthood neurodevelopmental, internalizing phenotypes such as anxiety or depression and externalizing phenotypes such as disruptive behavior problems (Andersson et al. 2020). In GWAS, the genetic correlation with major depressive disorder ($r_g = 0.44$, SE = 0.03) is the strongest, with significant but smaller correlations seen for anxiety disorders, schizophrenia, and bipolar disorder, as well as a small negative genetic correlation observed for

anorexia nervosa, which implies that some of the underlying risk loci are the same, but acting in opposite directions (Lee et al. 2019; Demontis et al. 2019; Purves et al. 2019). Genetic correlations have also been observed with substance misuse disorders, including alcohol dependence, smoking, and cannabis use (Walters et al. 2018; Demontis et al. 2019; Johnson et al. 2020).

Given the vast shared risks across psychiatric phenotypes, it has been proposed that there is a large major component of shared liability, referred to as a general psychopathology factor, or the "p" factor. Twin-studies support this theory of a shared genetic factor underlying ADHD and other psychiatric phenotypes (Pettersson et al. 2013, 2015), with especially strong genetic correlations with neurodevelopmental disorders (Du Rietz et al. 2020). PRS studies find that part of the shared common variant risk across disorders can be attributed to such a general factor, but that there are also specific genetic effects for ADHD not captured by the general factor (Brikell et al. 2018b; Riglin et al. 2019).

ADHD also shares genetic liability with phenotypes beyond neurodevelopmental and psychiatric disorders, including somatic health conditions and other non-medical traits. Twin studies support shared liability with obesity, asthma, epilepsy, coronary artery disease, and lung cancer (Brikell et al. 2018a; Chen et al. 2019; Holmberg et al. 2015; Demontis et al. 2019). Common variant positive genetic correlations have been reported for phenotypes such as insomnia, neuroticism, obesity, body mass index, number of children born, and rheumatoid arthritis, with negative genetic correlations including educational attainment and cognition, subjective wellbeing, and age at birth of first child (Demontis et al. 2019).

Thus, there are vast shared genetic risks across ADHD and numerous health- and behavior-related phenotypes. This shared liability may help to explain the comorbidity between ADHD and mental health as well as somatic health conditions. The results are largely consistent across different methods, ages and samples, although there are also gaps in the evidence; larger studies are needed to obtain more precise estimates regarding the degree of shared genetic risks. Further work is then needed to understand the specific underlying genetic risks that are shared across ADHD and any given phenotype. Mendelian Randomization studies suggest that some of this genetic overlap could represent causal effects of ADHD on physical health conditions including coronary artery disease and obesity as well as depression (Leppert et al. 2020b; Riglin et al. 2020a, b).

8 Biological Insights

A major motivation for conducting genetic studies is to gain novel insights into the pathophysiology of ADHD and to pave the way for novel treatments. However, a major challenge is that any association between a genetic variant and ADHD represents only the first step because the associated variant is not necessarily causal. Further work is needed to identify which specific genes are indexed by the associated variant and then to assess what these genes do and to characterize the underlying

mechanisms. As genes are expressed as messenger ribonucleic acid (mRNA) in different tissues that subsequently lead to the assembly of amino acids to form different proteins (for further details, see State and Thapar 2015), understanding the biological pathways by which genes influence disorder is important. For disorders such as schizophrenia and autism (Giegling et al. 2017; Thapar and Rutter 2020), multiple genes that have achieved genome-wide significance have been implicated; here, researchers have now focused on investigating whether the different implicated genetic variants converge on the same gene expression and protein networks (depicted as functional follow-up studies in Fig. 1).

These approaches are being used in relation to ADHD genetic discoveries and will become more relevant as high confidence genes are identified. A growing number of bioinformatic resources enable scientists to infer indirectly the biological plausibility and function of an associated genetic variant. For example, it is possible to examine how genetic variants impact on diverse brain cell types, in different places across the brain and at different developmental periods, including prenatally. This is less costly and time-intensive than examining the function of genetic variants, one at a time, in model organisms and cellular models.

GWAS of common variants highlight that, individually, these each have a small effect-size and that tens of thousands of such variants likely contribute to ADHD risk. Typically, GWAS identify only regions of the genome that harbor potential risk-genes and, to date, ADHD GWAS have yet to provide definitive robust biological insights.

Rare variants are especially interesting from the perspective of offering insights into biology because they have larger effect-sizes than common variants. That is because damaging, larger effect-size mutations are rapidly removed from the population through natural selection and thus become rare. However, even for rare variant studies, association does not necessarily immediately reveal causal genes and biological processes. Rare variants can be inherited or be de novo in origin where the variant first arises in the parent germline (oocyte or spermatozoa) or later, after fertilization, when they are known as post-zygotic somatic variants (State and Thapar 2015; Lim et al. 2017). De novo variants are more likely to be causal and, for disorders such as schizophrenia and autism, there have been large-scale de novo CNV and sequencing efforts that are providing early biological insights into these disorders. Large de novo rare variant studies are lacking in ADHD, though as mentioned earlier, preliminary studies using whole exome sequencing in case-control studies are promising (Ganna et al. 2018; Satterstrom et al. 2019).

No genome-wide case-control CNV study to date has been large enough to implicate individual CNVs associated with ADHD risk (Thapar et al. 2016). One exception was a pooled analysis of duplications in the 15q13.3 region (on Chromosome 15) that encompasses the alpha-7 nicotinic acetylcholine receptor gene (CHRNA7) as well as other genes (Williams et al. 2012). The most comprehensive and recent investigation of published CNVs from 11 studies of ADHD identified 2,241 potential genes from these CNVs (Harich et al. 2020; Thapar 2020). This list was refined first by examining whether the CNVs in people with ADHD were likely to be in a position that disrupted genes. Then the authors used

bioinformatic data resources to examine the biological plausibility of these genes being related to ADHD; this included examining brain expression and cross-species data. Ultimately, this process yielded a final list of 26 high-confidence genes. This study highlights that a prohibitively large number of genomic loci can be refined to potentially causal genes by using bioinformatic approaches. However, there are drawbacks. For instance, among the included ADHD CNVs are those that are not genome-wide significant and all the published studies used different approaches to defining CNVs. Bioinformatic approaches are important but still inadequate. These genes will then need to be investigated in cellular systems and through backtranslation into animals to identify mechanisms.

9 Gene–Environment Interplay

To this point, this chapter has focused on the role of genetic factors in isolation. It is important to remember, however, that both genetic and environmental factors are relevant to the development and presentation of ADHD and that the interplay of these different factors is also of relevance. Some have argued that consideration of these interactions could also help account for some of the discrepancies between twin and SNP heritability estimates, as observed in Fig. 2a (Maher 2008).

One way in which genes and the environment work together is through gene-environment correlations (rGE). This is where an individual's genetic background shapes their environmental exposures. For example, individuals may actively seek out environments which match their genetic predispositions (active rGE) or evoke responses from others based on their disposition (evocative rGE). Developmentally, as parents provide both their child's genetic background and their rearing environment, this is also likely to result in an overlap between genetic and environmental exposures (passive rGE). There is evidence to suggest that the observed associations between ADHD and some putative environmental risk-factors may be the result of such correlations. For example, risks associated with parenting, including parent-child hostility, have been shown to be influenced by the child's behavior as well as their genetic liability for ADHD (Lifford et al. 2008; Harold et al. 2013). More recent PRS and Mendelian Randomization (MR) studies also suggest that ADHD genetic liability is associated with maltreatment and that this relationship may be causal (Leppert et al. 2020a; Warrier et al. 2021).

Genetic risk-factors are thought to account for the previously identified environmental risk-associations observed between maternal smoking during pregnancy and ADHD (Rice et al. 2018), highlighting the importance of taking into account potential genetic confounds when investigating environmental risk exposures. Genetically sensitive and natural experimental designs are needed to tease apart these relationships; it is important to remember the potential role of genetic factors when considering putative environmental risk factors and vice versa.

Gene–environment interactions (GxE), whereby genetic liability varies, depending upon environmental exposure, are also likely to be important in

understanding the etiology of ADHD. While of recognized importance, there are no robust GxE findings for ADHD using molecular genetic methods. This is partly due to the fact that identifying interaction effects is more difficult than identifying the main effects of genetic or environmental risks because even larger sample sizes than currently available are required. There were a number of GxE studies using a candidate gene approach, but as noted earlier, molecular genetic methods have moved away from this towards a whole genome approach while the role of previously suggested candidates has not been replicated using GWAS methods (Demontis et al. 2019).

Moving forward, researchers have started exploring ways to use GWAS data for GxE through Genome-wide Environmental Investigation Studies (GWEIS). These studies assess associations between environmental risks and SNPs across the genome, without requiring the main effects of potential risk genetic variants to be associated with the disorder at a genome-wide significant level. To date, there are no GWEIS studies in ADHD (and few for any psychiatric disorder) (Assary et al. 2018) and such methods are likely to be complex due to the issues of: small sample sizes; the fact that interactions can take many forms (each requiring different analytical approaches); and the multiple testing burden associated with genome-wide GxE analysis (Aschard et al. 2012). However, the recognized potential importance of GxE in our understanding of ADHD means that such studies are likely to be undertaken in the future.

A further way in which researchers can investigate the interplay between genes and the environment is by studying epigenetic effects. Epigenetics is the study of factors which alter the expression of genetic factors (rather than changing the DNA sequence itself), including how environmental factors may lead to such changes. While there are few studies investigating epigenetics in ADHD to date, there are many challenges. That is because like GWAS, epigenome-wide association studies (EWAS) require very large samples that are not available currently. Also, association findings can arise as a result of confounders and reverse causation. To date some studies of ADHD have investigated DNA methylation as one marker of epigenetic variation. DNA methylation is a process whereby methylation of specific DNA loci can alter gene expression. For example, Mooney et al. (2020) performed an EWAS comparing DNA methylation markers between those with ADHD and controls. While no genome-wide significant findings were found, there were some promising indications that methylation variants were associated with both ADHD status and ADHD PRS. This finding requires replication, before attempting to identify which environmental factors may contribute to this altered methylation. For example, some smaller studies have looked at how gene expression (mostly through methylation) is associated with environmental exposure to factors such as pre-natal diet or toxins (Rijlaarsdam et al. 2017; Gervin et al. 2017). However these need to be regarded with caution at present given the caveats to epigenetic studies in humans.

10 Clinical Implications and Genetic Testing

As more ADHD risk genes are identified, what are the implications for clinicians? First, there are immediate implications for clinical practice. We already know that ADHD runs in families and is highly heritable. We also know that ADHD genetic risk-factors cross diagnostic boundaries. That means that the clinician needs to be vigilant to the possibility that any siblings and parents of the index child may also have ADHD, or a different neurodevelopmental disorder, and are at higher risk for depression and other psychiatric disorders. That is important insofar as if multiple family members are affected it could impact on household and family stress and so could affect assessment, compliance with clinic attendance and the success of clinical interventions. A second issue is the provision of information in clinics. Families often wish to know about the etiology of ADHD and its biology. Thus clinicians will need to be up-to-date on scientific progress and require skills in communicating the complexities of genetics. They will also need to ensure sufficient provision of genetic counselling to support families with the information they receive (Wilkins et al. 2016; Wolfe et al. 2018).

The next issue is whether genetic testing is warranted? Although rare variants associated with ADHD have large effect-sizes, routine genetic testing for those with ADHD is not currently recommended. However, recommendations may well change in the future. Guidelines in many countries now include genetic testing for those with mild ID and, in the USA, for those with autism. Currently, there is no empirical evidence to provide guidance on how clinically useful genetic testing in ADHD might be because a study in routine clinical practice has not been undertaken although it is possible, as costs decline and more knowledge about causality of specific variants is gained, that testing is introduced, especially if the variants have implications for treatment, prognosis or are potentially medically actionable. However, as we have highlighted, the genetics of ADHD, like other neurodevelopmental and psychiatric disorders, are complex. The effects of any identified larger effect variant will depend on other background genetic factors and non-genetic influences too. Also, the effects of any variant are probabilistic and, we know, likely pleiotropic. For these reasons, genetic counselling is important so that families understand what testing involves and what any findings could mean (Austin 2020). Future studies need to evaluate the potential benefits and risks of providing genetic feedback.

At present the clinical utility of common genetic variants is even less certain. The predictive power of ADHD and psychiatric PRS is weak. However, it is possible that more powerful PRS, generated from much larger GWAS, could contribute to clinical decision making, especially when combined with family history and clinical variables (Murray et al. 2020). For example, a higher rate of vigilance at follow-up may be warranted if a child with ADHD, who presents with first episode depression, has a family history and elevated genetic loading for bipolar disorder. One important consideration is that the population used to derive the risk predictors, including PRS, needs to be similar to the target population (e.g., ethnicity, specialist clinic

versus primary care). A serious concern among geneticists is that most of the world's GWAS focus primarily on individuals of European descent and are therefore less effective in PRS studies of non-European diverse ancestries (Martin et al. 2019). Thus, to enable equal health gains across different populations, it is essential that large-scale genetics research is conducted on diverse groups.

11 Summary

As summarized in Fig. 1, this chapter has highlighted the journey of ADHD genetic research, from the recognition and quantification of heritability estimates to identifying specific common and rare risk-variants for the disorder. However, there is still a long road ahead in such endeavors and, as seen in Fig. 2, our understanding is not as advanced as for some other psychiatric disorders. As can be seen in Fig. 2b, part of the reason for this is that sample sizes for studies of ADHD and other childhood-onset conditions, such as ASD, are much smaller than for schizophrenia, bipolar disorder, and major depressive disorder. As can be seen in the figure, there is a clear correlation between sample size and identification of genome-wide significant SNP associations highlighting the need for much larger studies for ADHD and other neurodevelopmental disorders. Large trio-based samples for investigating de novo rare mutations are also lacking. However samples with detailed clinical information will also be required if these findings are to be translated into clinical benefits.

It will also be important to consider the interplay between genetic and environmental factors, especially as our understanding of those genetic risks increases. However, this identification of genetic risks is only one step on the journey to understanding the etiology of ADHD; understanding the varied effects of such risks on the heterogenous phenotype of ADHD across the lifespan, as well as the biological processes that underpin ADHD, will also be of great importance. While we have some insights already using twin-studies, PRS, and some investigations into the biological underpinnings of ADHD, much more research is needed, including approaches that use newer techniques such as exome and whole genome sequencing. All these studies require extremely large ADHD samples. The study of the genetics of ADHD is therefore at an exciting stage where further developments are both likely and eagerly anticipated and, as our knowledge increases, we can hopefully reach the stage of utilizing molecular genetic knowledge in clinical practice.

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Epigenetics and ADHD

Timothy Silk, Lillian Dipnall, Yen Ting Wong, and Jeffrey M. Craig

Contents

Abstract There is robust evidence of genetic susceptibility to Attention-Deficit Hyperactivity Disorder (ADHD); however, there still remains significant variability

T. Silk (✉)
Centre for Social and Early Emotional Development and School of Psychology, Deakin University, Geelong, VIC, Australia

Murdoch Children's Research Institute, Parkville, VIC, Australia
e-mail: tim.silk@deakin.edu.au

L. Dipnall
Centre for Social and Early Emotional Development and School of Psychology, Deakin University, Geelong, VIC, Australia

Y. T. Wong
Institute for Mental and Physical Health and Clinical Translation (IMPACT), School of Medicine, Deakin University, Geelong, VIC, Australia

J. M. Craig
Murdoch Children's Research Institute, Parkville, VIC, Australia

Institute for Mental and Physical Health and Clinical Translation (IMPACT), School of Medicine, Deakin University, Geelong, VIC, Australia

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that is not attributable to genetic factors. The emerging field of epigenetics is beginning to reveal how genotypic expression can be mediated by an array of variables including external environmental exposure, inter-individual developmental variation, and by the genome itself. Epigenetic modification plays a central role in neurobiological and developmental processes, and disturbances to these processes can have implications for a range of mental health problems. Although the field is still in its early days, this chapter will discuss the current standing of epigenetic research into ADHD. Firstly, key relevant epigenetic processes will be discussed. This will be followed by an overview of the key findings to date investigating the role of epigenetics in ADHD. Human studies have included the theory-driven approach of candidate-gene studies (CGS), as well as the increasingly popular exploratory approach of epigenome-wide association studies (EWAS). Overall, the findings are heterogeneous. However, it is possible that with more longitudinal studies and better characterised cohorts, both predictive and protective links between epigenetic processes and ADHD will be revealed.

Keywords Candidate gene · Epigenetic · Epigenome · EWAS · Methylation

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ASM	Allele-specific DNA methylation
CAARS	Conners' adult ADHD rating scale
CBCL	Child behaviour checklist
CGS	Candidate-gene study
CpG	Cytosine-guanine base pair (probe)
CPRS	Conners' parent rating scale
DAWBA	Developmental and well-being assessment
DISCAP	Diagnostic interview schedule for children, adolescents and parents
DMP	Differentially methylated probe
DMR	Differentially methylated region
DNA	Deoxyribonucleic acid
DNMT	DNA methyltransferase
DZ	Dizygotic (twins)
EEG	Electroencephalogram
ERP	Event-related potential
EWAS	Epigenome-wide association study
GWAS	Genome-wide association study
HAT	Histone acetyltransferase
HDAC	Histone deacetylases
HMT	Histone methyltransferase
MBD	Methyl-binding domains
MHC	Major histocompatibility complex

MPH	Methylphenidate
MRI	Magnetic resonance imaging
MZ	Monozygotic (twins)
NSC	Neural stem cells
PET	Positron emission tomography
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism

1 Introduction

Genetic studies of Attention-Deficit Hyperactivity Disorder (ADHD) have reported the overall heritability of ADHD to be estimated around 74% (Faraone and Larsson 2019). However, no single gene or gene variant is sufficiently common or specific to act as a diagnostic test. Rather, many genes each contribute relatively small risk, and roughly only 22% of phenotypic heterogeneity has been attributed to common genetic variants (Demontis et al. 2019). Despite the importance of genetics in brain and cognitive development and in mental health, there still remains significant variability that is not attributable to genetic factors. This suggests that environmental factors in combination with genes play a significant role.

Epigenetics is the field of research examining this interaction. Epigenetics was first used to describe the process of development from the simple to the complex (Waddington 1942) and has since been extended to the molecular factors that control this process. Epigenetic mechanisms do not change DNA sequence; they are inherited by daughter cells when they divide and are reversible at major developmental stages, and to some extent by environment (Weinhold 2006).

Epigenetic factors play a central role in neurodevelopmental processes, enabling cells to adapt to changing internal (such as age or hormonal) and external environmental factors (such as maternal smoking during pregnancy, exposure to lead or stress) (Numata et al. 2012). Disturbances in epigenetic processes have implications for a range of mental health problems (Klengel et al. 2014; Yeshurun and Hannan 2019) and are suggested mechanisms in the aetiology and heterogeneous phenotype of neurodevelopmental disorders (Dall'Aglio et al. 2018). However, in addition to understanding the molecular underpinnings of mental health conditions, an extremely important feature is that it may be possible to modify epigenetic processes, for example via behaviour, nutrition, social factors or pharmaceutically. This means epigenetic knowledge may not only elucidate the molecular mechanisms of risk and identify vulnerable individuals, but also provide targeting and tracking of individualised, precision medicine. The implementation of epigenetics in ADHD research is burgeoning but at this stage still small and in its infancy. This chapter will give a basic overview of the key epigenetic mechanisms and findings from ADHD research.

2 Overview of Epigenetic Mechanisms

If every cell in each human body contains exactly the same DNA, then why are the organism's cells not all the same? This question underpins the fast-growing field of study known as Epigenetics. Largely revolving around gene/environment interaction, epigenetics aims to examine changes in genes' expression that are not attributable to alteration of DNA sequencing. In short, epigenetic processes result in either the activation or suppression of genes with no change to the underlying nucleotide structure of DNA. A well-known example of this relates to the differentiation of neural stem cells into astrocytes, oligodendrocytes and neurons. For example, DNA methylation of *STAT3*-binding element in the *GFAP* promoter occurs during neurogenesis (Bonni et al. 1997) and DNA demethylation of these elements in the *GFAP* promoter accompanies astrogliogenesis, as well as up-regulation of astrocyte-specific gene promoters (Shimozaki et al. 2005).

Most epigenetic changes are individual-specific. However, increasing evidence supports the possibility that a handful of epigenetic changes can be inherited from one generation to the next (Yahyavi et al. 2014; Skinner 2014; Bohacek and Mansuy 2015). The pathway from nucleotide-based code to real-word phenotypic expression is both beautiful and complex, with many options pre- and post-translation for control of gene expression.

The next section will introduce some of the key epigenetic mechanisms used to date in ADHD research, primarily DNA methylation. There are other epigenetic mechanisms, including chromatin organisation, however because they have not been used in ADHD research, will not be discussed.

2.1 DNA Methylation

To date, DNA methylation is the most widely-measured epigenetic mechanism in ADHD populations. DNA methylation is the process of addition of methyl groups (CH_3) to the fifth carbon position of cytosine-guanine base pair (CpG) sites along a strand of DNA. CpGs are not equally spread across the genome. Upstream of genes, within promoter regions, lie dense regions of CpGs known as CpG islands (Bird 1986). DNA hypermethylation (increased methylation) of these promoter regions is frequently associated with a reduction, and sometimes silencing, of a gene's expression. Interestingly, however, DNA hypermethylation within the main body of a gene can be associated with active gene expression.

The basic premise of DNA methylation is that the addition of a methyl group to CpG can physically impede the binding of transcription factors; because transcription cannot then take place, genetic expression is reduced. An exception to this exists, whereby a family of proteins called methyl-binding proteins can preferentially bind to methylated CpG sites through their methyl-binding domains (MBD).

Such proteins bind to other co-factors that together establish the physically tight chromatin structure associated with gene silencing.

DNA methylation also plays an important role in the cellular inheritance of epigenetic modifications. Here a parent strand of DNA produces two hemi-methylated daughter strands as only one of the DNA strands in each daughter strand is methylated. After recognising the single methylated DNA strand, DNA methyltransferase 1 (DNMT1) proceeds to methylate the conferring base-pair, subsequently resulting in DNA methylation of CpG pairs in each strand. For a review of DNA methylation, see Moore et al. (2013).

The final role of DNA methylation discussed here is that of de novo methylation, which, as the name suggests, is the formation of new methylation patterns (Bird 1999). De novo methylation occurs prolifically during early development: for example, following fertilisation, preceding methylation patterns are erased and re-established by the enzymes DNMT3a and DNMT3b. Maintenance methylation then ensures perpetuation of modifications that have been made.

2.2 Histone Modification

Another key epigenetic process relates to the modification of histones. Histones are globular proteins that play an important role in the formation and compaction of chromatin into the tiny space of each cell's nucleus. Nucleosomes, around which DNA coils, consist of an octamer combination of four histone proteins H2A, H2B, H3 and H4, with H1 being responsible for joining the nucleosomes together. DNA coils around each nucleosome roughly twice. The nucleosomes are then grouped together tightly through the H1 protein.

This tight coiling of the chromatin leaves little 'open' DNA available for the binding of transcription factors, thus inhibiting gene expression. Through epigenetic processes the DNA coiling of chromatin can loosen and 'open' DNA, subsequently encouraging gene expression. These modifications include histone acetylation, methylation, ubiquitination, SUMOylation, biotinylation and ADP-polyribosylation. The primary mechanisms of histone acetylation and methylation will be discussed here. The processes of ubiquitination, SUMOylation, biotinylation and ADP-polyribosylation are not as relevant to the current epigenetic literature in ADHD and will therefore not be discussed.

Histone modifications occur at H2A, H2B, H3 and H4; however, most commonly modified are H2A and H2B. H2A and H2B have some modifications to the C-terminal of the globular core. Most modifications (H3 and H4) are found in the C-terminal of the globular core at the N-terminus.

Histone acetylation involves the addition of an acetyl group (C_2H_3O) from donor acetyl coenzyme A to specific histones (Lee et al. 1993; Vettese-Dadey et al. 1996). Acetylation of histones almost always stimulates transcription. A common example of this is the acetylation of lysine (Ali et al. 2018). The tails that stick out of the histone bundles when the chromatin is tightly coiled are positively charged. This

positive charge interacts with the negative charge of the DNA to produce a tight binding, which also ensures that the DNA is largely inaccessible to other DNA-binding proteins. When lysines are acetylated, then their positive charge is neutralised, allowing the DNA to have more flexibility and thus a looser structure. This encourages DNA-binding proteins, such as transcription factors to access the DNA strands. The enzymes involved in this process are histone acetyltransferase (HAT) and histone deacetylases (HDAC).

Histone methylation involves the addition of a methyl group to the histone tails. This can occur as either mono, di or tri methylation (1, 2 or 3 groups) (Zhang and Reinberg 2001). Usually, the amino acids on the histone tails that are modified are lysine or arginine residues on H3 and H4. Histone methylation can act as both a positive and negative regulator, leading to active or inactive chromatin. The process of histone methylation recruits effector proteins to chromatin, which have enzymatic activities and can lead to chromatin changes such as remodelling. Ultimately this can have an activating or repressing effect on transcription. Unlike acetylation, histone methylation does not alter the overall charge of the histones. The enzymes involved in this process are histone methyltransferase (HMT) and histone demethylases. For a review on histone modification, see Imhof (2006).

3 Overview of Epigenetics and ADHD

The implementation of epigenetics in ADHD research is burgeoning but at this stage still small and in its infancy. Similar to the field of genetics, the first approaches used hypothesis-driven candidate-gene methods to target primarily neurotransmitter systems already implicated in ADHD. While being hypothesis driven, the candidate-gene approach precludes the potential to discover novel biological markers. Epigenome-wide association studies (EWAS) enable us to canvas large parts of the genome in a hypothesis-free manner. An advantage of EWAS is the potential to discover novel biological markers; however, due to so many comparisons, it comes at the price of requiring large samples sizes to have sufficient power to be confident about avoiding type 1 errors. The following section will provide an overview of the findings from the candidate gene and EWAS in ADHD.

3.1 Candidate-Gene Studies

Early candidate-gene approaches have focused primarily on the monoaminergic system, targeting the dopamine transporter gene, *DAT1* (also known as *SLC6A3*) (Xu et al. 2015; Adriani et al. 2018; Wiers et al. 2018), the dopamine receptor gene *DRD4* (van Mil et al. 2014; Xu et al. 2015; Dadds et al. 2016; Weiß et al. 2021), the serotonin transporter, *5-HTT* (also known as *SLC6A4*) (van Mil et al. 2014; Park

et al. 2015) and the norepinephrine transporter, *NET* (also known as *SLC6A2*) (Sigurdardottir et al. 2021).

The dopaminergic system is a clear place to start a candidate approach, given dysregulation of dopamine is the dominant hypothesis in ADHD to explain the behavioural and cognitive difficulties associated with the condition (Swanson et al. 2000; Solanto 2002; Castellanos and Tannock 2002). In a sample of 30 children with ADHD, Adriani et al. (2018) found lower DNA methylation in six CpGs in *DAT1* compared to healthy controls ($n = 15$). Some CpGs also denoted higher DNA methylation with both lower symptom severity (Children's Global Assessment Scale by clinician and Conners' Parent Rating Scale (CPRS) by parent) and a quicker improvement following 6 weeks of treatment. In a small sample of unmedicated adults (13 ADHD, 34 controls), Wiers et al. (2018) did not find a group difference in *DAT1* DNA methylation; however, they did find that within the ADHD group that *DAT1* DNA methylation was associated with subcortical brain measures (discussed later in Sect. 7).

Xu et al. (2015) also failed to find DNA methylation difference in any of their 19 CpGs annotated to *DAT1*. However, Xu et al. (2015) also tested another dopaminergic gene, *DRD4* and found 7 of the 28 annotated CpGs demonstrated a significant difference in DNA methylation between ADHD ($n = 50$) and controls ($n = 50$). Five of the seven CpGs presented with higher DNA methylation in the ADHD group. In addition to examining DNA methylation in dopaminergic genes, Xu et al. (2015) also probed another epigenetic process, histone modification, targeting *HDAC1*, *p300*, *MYST4* and *MECP2*. Messenger RNA levels were significantly lower in ADHD for *p300* and *MECP2* whereas ADHD had significantly higher levels in *HDAC1*.

Association of ADHD with *DRD4* epigenetic state has since been one of the most replicated findings to date. Examining ADHD symptoms in a clinical sample of 330 children, Dadds et al. (2016) reported significant associations in 18 CpGs in the *DRD4* gene, whereby higher DNA methylation was associated with ADHD symptom severity (Diagnostic Interview Schedule for Children, Adolescents and Parents [DISCAP] by clinician and CPRS by parent) for inattention, but not hyperactivity symptoms. In another large study, with a population cohort of 426 children, van Mil et al. (2014) found DNA methylation levels at birth, primarily driven by *DRD4* (as well as serotonergic *5-HTT* regions), were associated with ADHD symptoms (using the Child Behaviour Checklist [CBCL]) at age six. They reported that lower DNA methylation levels were associated with higher overall ADHD symptom scores. In adults (88 ADHD, 91 controls), amongst 37 candidate genes tested, Weiß et al. (2021) also reported a significant group difference in a CpG for *DRD4*, which was also supported by eight additional subthreshold sites in close proximity. This suggests that differences in *DRD4* DNA methylation levels are present in youth and persist into adulthood.

One study implicated epigenetic variation of *DAT1* and *DRD4* in modulating the response to methylphenidate treatment. Ding et al. (2017) examined the association of *DAT1* and *DRD4* DNA methylation with improvement of symptoms following 6 weeks of treatment with methylphenidate (MPH). They found that *DAT1* DNA

methylation (at diagnosis) was associated with greater improvement in ADHD symptoms (oppositional and hyperactive-impulsive symptoms using the Swanson, Nolan and Pelham-IV-parent rating scale [SNAP-IV-P]) at 6 weeks following MPH treatment. However, no significant correlation was observed for *DRD4*.

Serotonin plays a role in emotional, cognitive and behavioural control (Cools et al. 2008). As previously mentioned, in addition to *DRD4*, van Mil et al. (2014) also found DNA methylation levels of *5-HTT* regions at birth that predicted later ADHD symptoms. Park et al. (2015) also examined the serotonin transporter (*SLC6A4*), but examined concurrent DNA methylation levels in 102 children with ADHD. They reported that higher DNA methylation levels of specific CpGs, as well as mean DNA methylation in the *SLC6A4* promoter region, were associated with higher total and hyperactivity/impulsive sub-scores on the ADHD Rating Scale, as well as higher commissions (impulsive errors) on a continuous performance task. The authors suggested that higher DNA methylation of *SLC6A4* promoter may reduce serotonin synthesis, thereby affecting behavioural inhibition reflected in greater commission errors and hyperactive-impulsive symptoms. Although Park et al. (2015) and van Mil et al. (2014) both show evidence of involvement of DNA methylation in the serotonin transporter gene, they report conflicting direction of association. There are, however, numerous methodological differences between the studies that should be considered, including DNA methylation at birth versus concurrent levels, DNA methylation in whole versus cord blood and a population versus a clinical sample.

The norepinephrinergic system, which has a role in arousal has been implicated in ADHD and is also influenced by ADHD medication. In adults (23 ADHD, 23 controls), Sigurdardottir et al. (2021) found significant between-group differences in *NET* DNA methylation levels at several CpG sites. They report a negative association with the severity of hyperactivity–impulsivity symptoms (using the Conners' adult ADHD rating scale [CAARS]). Within the ADHD group the authors additionally found an association between *NET* DNA methylation levels in whole blood and *NET* expression levels (measured by PET-MRI) in a range of deep brain structures (thalamus, locus coeruleus, dorsal and medial raphe nuclei).

Other studies have chosen candidate-genes based on their presumed involvement in brain development, previous genetic findings, or from EWAS. Rijlaarsdam et al. (2017) found that higher mean DNA methylation at birth of the insulin-like growth factor 2 (*IGF2*) gene, involved in foetal and neural development, was associated with higher ADHD symptoms (assessed using the Developmental and Well-being Assessment [DAWBA]) later in childhood. In a small sample (12 ADHD, 9 controls), Li et al. (2021) examined attention performance using a continuous performance task. The authors reported association of DNA methylation in *LIME1* and *SPTBN2* associated with attention performance. It is also worth noting here that the level of DNA methylation at a CpG can be dependent on the variant of a single nucleotide polymorphism (SNP), a phenomenon known as allele-specific DNA methylation (ASM). In an attempt to comprehensively assess the contribution of genetic variants to altered DNA methylation in the brain, Pineda-Cirera et al. (2019) explored the overlap between risk-genes for ADHD (from the largest ADHD GWAS

(Demontis et al. 2019)) with 3896 SNPs reported to influence DNA methylation in human brain regions. They found that genetic risk-variants for ADHD were enriched in those ASM SNPs, and the authors report the potential genetic contribution of ARTN, C2orf82 and PIDD1 to ADHD susceptibility.

In an attempt to replicate the top DNA methylation sites of both candidate and EWAS (the majority of which had been identified in children), Weiß et al. (2021) examined 37 candidate genes in a sample of adults with and without ADHD (88 ADHD, 91 controls). Two CpG were significantly associated with ADHD status. In addition to finding significant association with *DRD4*, the second site was within *KLRD1*. The authors also took a dimensional approach, identifying eight significant CpGs, all located in *TARBP1*, that were associated with inattention (using the diagnostic interview for adult ADHD [DIVA] or ADHD-DSM-IV self-rating scale). KLRD1 and TARBP1 are suggested to play a role in immune function, but the exact functions are unknown.

3.2 Epigenome-Wide Association Studies (EWAS)

EWAS are akin to genome-wide association studies, but specific to epigenetic epidemiology (Rakyan et al. 2011). Rather than specifying the gene under investigation, as is done in candidate-gene studies (which increases the risk of type I error), EWAS aims to compare epigenetic mechanisms across the entirety of the genome. To date, DNA methylation is the primary epigenetic mechanism investigated in EWAS. However, other mechanisms, such as histone modification, are also possible but are yet to be comprehensively explored in ADHD populations.

Like GWAS, EWAS has potential to go beyond identification of biomarkers, into the realm of relative risk. Strength of EWAS is gained by assessing the common variation in clinical populations in comparison with controls, rather than comparing epigenomic mutations. The results of EWAS primarily relate to differentially methylated probes (DMP) and differentially methylated regions (DMR). In brief, a DMP is a CpG (or cg) that is significantly differentially methylated. If a number of DMPs exist in close location, there may be evidence to identify a DMR; therefore, the identification of DMRs is contingent upon the identification of DMPs. EWAS also allows for application of gene ontology, also referred to as pathway analysis and enrichment analysis. In brief, gene ontology is a bioinformatics technique that facilitates the annotation of genetic and epigenomic results. It can aid in the delineation of genetic and biochemical pathways implied by EWAS results. For more information in gene ontology, see Smith (2008) and Rhee et al. (2008).

The first EWAS in ADHD was conducted in 2016 (Wilmot et al. 2016) using saliva samples from boys of 7–12 years of age. A nominal level of significance identified 245 DMPs annotated to 95 genes in a discovery set (43 ADHD, 42 controls). A number of the genes are known to have relevance to neurodevelopment and mental health including: NAV1, NINJ2, SLC12A9, VIPR2, MYT1L, OXTR, HDAC4, and HLA-A, HLA-B and HLA-C. Two particular genes prioritised for

further analysis based on a priori criteria were VIPR2 and MYT1L. Six probes from these two genes were then tested in a confirmation cohort (10 ADHD, 10 controls). The *MYT1L* probes failed to meet confirmation; however, one probe for *VIPR2* (cg134444538) did replicate in the confirmation cohort, and two further probes, while not meeting significance threshold, had the same direction of association. Further, the authors used gene ontology analysis to examine potential enrichment for functional pathways in the DMPs. They found enrichment for genes associated with inflammatory mechanisms and modulation of monoamine and cholinergic neurotransmission.

VIPR2, not previously known as a candidate gene for ADHD, plays a role in neuronal function. Over time, some attempts at replication of this association have been successful (Peter et al. 2016; Chen et al. 2018), but others have not (Walton et al. 2017; Heinrich et al. 2017; Mooney et al. 2020; Neumann et al. 2020). There may also be an influence of sex. Given that Wilmot et al. (2016) studied only boys, an attempt at replication by Mooney et al. (2020), stratified by sex and identified consistent support of ADHD males having lower DNA methylation at two probes (cg26975193 and cg20998127), compared to control males. Interestingly, the inverse was seen for females at one *VIPR2* probe (cg26975193), with significantly higher levels of DNA methylation measured compared to female controls.

Rather than a case-control EWAS, Chen et al. (2018) used a twin model for MZ twins ($n = 14$ pairs) discordant for ADHD (further discussed below). They identified 173 within-twin-pair DMPs, enriched across various important genomic landmark locations (shores, shelves and enhancer regions). They further found the DMPs were enriched with genes expressed during early brain development. Moreover, pathway analysis of the implicated genes demonstrate links to the GABA, dopamine and serotonin neurotransmitter systems.

A number of studies have failed to find significant EWAS differences after controlling for the number of comparisons. Meijer et al. (2020) explored whether they could identify any DNA methylation differences between individuals (aged 12–23 years) with persistent ADHD ($n = 35$), compared to those that have remitted ($n = 19$), and healthy controls ($n = 19$). The study did not find any significant epigenome-wide differences between groups. However, when looking at the global DNA methylation level (mean of methylated CpG sites) there were significant differences between the persistent and the remitted groups.

When further looking at DMRs the finding pointed towards the involvement *APOB* and *LPAR5,* genes associated with fatty acid metabolism, differentiating the remittent and persistent ADHD groups. Goodman et al. (2020) found no significant sites associated with ADHD following correction for multiple comparisons (22 ADHD, 35 controls, aged 7–17 years). However, at a nominal threshold, they identified 188 CpGs associated with ADHD. Taking a subset, with the highest symptoms ($n = 15$) they found 299 CpGs, including multiple mapped to *POUF6*, *PRDM8*, *SNRPN* and *RASGEF1C*. Of note, four CpGs mapped to *MAD1L1* (which had previously been reported in Wilmot et al. 2016) and *DRD4*. In a large (391 ADHD, 213 control) EWAS of ADHD children, Mooney et al. (2020) found no DMPs passed genome-wide significance (of over half a million probes).

However, at an a priori nominal significance level, they identified 7 DMPs associated with ADHD, explaining DNA methylation differences of 0.3–1.4% in probes annotated to *SLC7A8 MARK2 PDLIM5, VPS28, ZNF706, FAM59A* and an intergenic location. Further, in examining the epigenetic association with ADHD polygenic risk score, Mooney et al. (2020) found one probe (cg15472673) met genome-wide significance, whereby reduced DNA methylation was associated with higher polygenic risk.

The largest ADHD EWAS to date, and the first in adults, was van Dongen et al. (2019), with a meta-analysis across three population-based cohorts ($n = 4{,}689$). This study revealed no significant DMPs or DMRs associated with ADHD symptoms. When cohorts were examined separately, one DMP was identified in only one cohort (in an intergenic region), whereas 0, 6 and 19 DMRs were identified in the three cohorts, respectively. There was no overlap across cohorts. At a lower, nominal threshold, some of the top DMPs demonstrated a negative relationship of DNA methylation with ADHD symptoms (using the CAARS), whereas others demonstrated a positive relationship. However, when looking at cohorts separately there was also heterogeneity in the top DMPs. In a clinical sample of adults with ADHD (103 ADHD, 100 controls), Rovira et al. (2020) revealed a single DMP (cg07143296) nearest to a gene associated with autoimmune diseases (PCNXL3). Despite not surviving correction for multiple comparisons, the top 10 DMPs point to genes associated with ADHD symptoms, circadian rhythms, drug addiction (*CREM*), dopaminergic function, attention and learning impairments (*ADK*) and educational attainment (*LAT*).

The majority of epigenetic studies in ADHD to date have looked at DNA methylation as the epigenetic mechanism. However, post-transcriptional modifications have been explored by Sánchez-Mora et al. (2019), looking at the role of microRNA in ADHD. Examining genome-wide microRNA expression in a discovery adult sample (56 ADHD, 69 controls), they identified 79 microRNAs that were differentially expressed. These were tested in a follow-up sample (44 ADHD, 46 controls). Three of the microRNAs (miR-26b-5p, miR-185-5p and miR-191-5p) that demonstrated the best predictive performance for ADHD are regulators of genes previously associated with ADHD or other mental health disorders (ATAT1, SH3PXD2A, NTRK3 and BDNF). This study found evidence of dysregulation of microRNA expression in ADHD, which suggests a potential alternative pathway to the disorder.

4 Epigenetics at Birth Predicting Later ADHD

Epigenetics is temporally dynamic; it changes across development and is driven by both internal (e.g., hormones) and external environmental conditions. This raises the question as to whether an individual's current epigenetic status is the best predictor of concurrent diagnostic status, or whether an epigenetic profile earlier in development already set that individual on a pathway of atypical neurodevelopment. This is

particularly pertinent in the context of neurodevelopmental disorders such as ADHD. In addition to previously mentioned candidate-gene studies (van Mil et al. 2014; Rijlaarsdam et al. 2017), a few EWAS have examined epigenetics at birth predicting later ADHD.

Walton et al. (2017) used an epigenome-wide approach to test if epigenetic markers at birth were associated with trajectories of ADHD symptoms, from up to four timepoints between the ages of 7–15 years in late childhood, in the typical population. In large samples at birth ($n = 817$) and at age 7 ($n = 892$; overlap = 783), they identified 13 DMPs (that meet false discovery rate correction) that were differentially methylated at birth (from cord blood) between individuals with persistent high ADHD symptoms between 7 and 15 years of age versus individuals with persistent low ADHD symptoms. Symptoms were measured via maternal ratings on the DAWBA. It is important to note that the high trajectory group was only moderate on ADHD symptoms, and only ~28% ($n = 10$) were predicted to meet diagnosis status. The associated genes are functionally implicated in neural tube development, ADHD, intellectual disability and peroxisomal processes (including SKI, ZNF544, ST3GAL3 and PEX2). However, the association of those genes did not hold when DNA methylation was tested at 7 years of age.

In 2477 children across 5 cohorts, Neumann et al. (2020) found DNA methylation of 9 CpGs from cord blood at birth predicted later ADHD symptoms from a range of measures (4–15 years of age). Two of the probes in particular have known functions in the brain: *ERC2* is highly expressed in brain, particularly the prefrontal cortex, and plays a role in neurotransmitter release. *CREB5* is also expressed in the foetal brain and plays a role in neurite outgrowth. Although DNA methylation at birth was significantly associated with later ADHD symptoms, none of these probes, nor any genome-wide DNA methylation, was significant when examining the association of concurrent DNA methylation measured at 7–12 years of age (from whole blood) with ADHD symptoms measured at the same time (2,374 children across 9 cohorts). Further, Neumann et al. (2020) attempted to replicate the 13 CpGs from the Walton et al. (2017) findings, but no probes survived multiple testing correction.

5 Twin Models

Twin studies are an extremely powerful design that enables the separation of phenotype into genetic, shared and non-shared environments. Identical, or monozygotic (MZ), twins share 100% of their genetics, and non-identical, or dizygotic (DZ), twins share half their genetics. Models looking at differences within a pair, control for age, sex (all MZ and half DZ), and a number of (primarily early-life) shared environments (such as peri-natal environment, parenting and socioeconomic status). Therefore, within-twin differences in epigenetics associated with a within-twin difference in phenotype (e.g. twins discordant with ADHD) can be highly informative. Research comparing MZ and DZ twins has shown that epigenetics is heritable. However, the heritability varies according to the genomic location (Kaminsky et al.

2009; Wong et al. 2010), cell type (Kaminsky et al. 2009; Ollikainen et al. 2010; Bell et al. 2012; McRae et al. 2014) and developmental stage (McRae et al. 2014).

To date, two EWAS studies have used twins as the model in ADHD. The first study was a small-scale study focused on neuroanatomical, epigenetic and genetic differences related to discordance for ADHD within MZ twin pairs ($N = 15$ twin pairs, median age 10.9 years) (Chen et al. 2018). The discordance for ADHD was correlated with the dimensions of the striatum and the inferior or posterior cerebellum. Affected twins had a significantly smaller right striatum and thalamus, and a trend towards a larger cerebellum. Epigenetic differences were identified in genes expressed in these 'discordant' brain structures. There were 68 of the 173 differentially methylated probes enriched in particular genomic landmark locations (shore and shelf regions). Another 67 probe sets were enriched in enhancer regions. Chen et al. (2018) found several genes previously associated with ADHD. For example, the *VIPR2* gene had higher DNA methylation in three affected twins (Wilmot et al. 2016) and homeobox gene (*MEIS-2*) had increased DNA methylation in 10 of the affected twins (Lasky-Su et al. 2008).

A second study was an EWAS study on ADHD symptoms in twins as part of three population-based adult cohorts, but two out of the three cohorts were relevant to the twins model (van Dongen et al. 2019). The Netherlands Twin Register (individuals from twins family, $N = 2{,}258$, mean age 37 years) and Environmental Risk Longitudinal Twin Study (E-Risk) ($N = 1{,}631$, 56% MZ twin and 44% DZ twin, mean age 18 years). The remaining Dunedin cohort (Dunedin Multidisciplinary Health and Development Study) involved unrelated individuals ($N = 800$, mean age 38 years). There were six non-overlapping differentially methylated regions (DMRs) in distinct subregions of the major histocompatibility complex (MHC), three in each Netherlands Twin Register and Dunedin cohorts, respectively. In contrast, no significant ADHD association was identified in the E-Risk cohort. The top-ranked DMR was associated with the MHC in the Dunedin and Netherlands Twin Register studies, including gene *C4A* and *C4B* genes. These genes belong to the complement component (*C4*) family, previously identified in schizophrenia (Sekar et al. 2016). In the Dunedin study a DMP, cg26197679 (intergenic region on chromosome 8) showed higher DNA methylation level in ADHD and correlated with fewer ADHD symptoms.

Although the MZ twin model has been powerful for understanding the impact of the non-shared environment on neonatal and child development and mental health in humans, the study must be well designed and confounds appropriately controlled to make valid hypotheses and conclusions. Hence, longitudinal studies are needed to understand the role of DNA methylation in disease mechanisms and in mediating the effect of nonshared environment on phenotype. Thus, the MZ twin model will still be the ideal method to assess the environment's influence, while controlling for genetic influence on complex phenotypes and in relatively small sample size (Beaver et al. 2013).

6 Environmental Exposure and Epigenetics in ADHD

In addition to the strong genetic findings in ADHD, there have been many findings on the role of environmental risk and (less so) protective factors in the susceptibility for ADHD. Many of the most replicated findings have related to pre- and peri-natal environment (See Kim et al. 2020 for review). A key advantage of understanding the impact of epigenetic processes is that it provides a mechanism through which environmental exposures could influence the aetiology, progression and potential trajectory of outcomes for ADHD. Given that epigenetic state can be influenced by external environmental exposures, a number of studies have started to examine the mediating role of environment in the relationship between epigenome and ADHD.

To date, the limited research has focused on pre- and peri-natal environmental exposures that may mediate risk for ADHD, such as prenatal maternal unhealthy high-fat and sugar diet (Rijlaarsdam et al. 2017) and inversely post-natal malnutrition (Peter et al. 2016), a range of peri- and post-natal stressful life events (Rovira et al. 2020), and the impacts of maternal medication (Gervin et al. 2017) or smoking (Sengupta et al. 2017; Weiß et al. 2021).

In a study examining epigenetic differences as a result of exposure to malnutrition in infancy, Peter et al. (2016) suggested that infant malnutrition may trigger DNA methylation changes that last into later adult life, some of which are associated with deficits in attention and cognition. In 50 adults that were exposed to moderate-severity malnutrition in the first year of life, compared to 44 matched controls not exposed to malnutrition, they identified 13 DMRs that correlated with ADHD symptoms (CAARS ADHD index). Many of the genes (including *IFNG* and *VIPR2*) are associated with neuronal function and neuropsychiatric disease. However, only one gene, *ABCF1*, remained significant at a more stringent threshold. They subsequent tested an animal model and found evidence of expression of six of the genes (*Ifng, Inhbb, Abcf1, Comt, Syngap1, Vars*) in the prefrontal cortex in adult rats that were malnourished prenatally. Furthermore, these rats also demonstrated glucose hypometabolism in the human homologue of the frontal association cortex, which correlated with attention performance.

At the other end of the dietary scale, Rijlaarsdam et al. (2017) examined the relationship between a high-fat and sugar diet during pregnancy, insulin-like growth factor 2 (*IGF2*), DNA methylation and ADHD symptoms (using the DAWBA). They found that unhealthy (high fat and sugar) prenatal diet was associated with *IGF2* DNA methylation at birth. Higher birth (but not concurrent) DNA methylation levels were associated with higher ADHD symptoms in childhood. Their modelling found that an unhealthy prenatal diet was associated with ADHD in childhood, via *IGF2* DNA methylation at birth.

Prenatal smoking exposure is one of the most commonly examined environmental risk factors for ADHD. In a candidate-gene epigenetic analysis, Sengupta et al. (2017) found that maternal smoking during pregnancy was associated with DNA methylation in candidate sites (*AHRR, GFI1* and *CYP1A1*) in ADHD. Further, the level of DNA methylation was associated with ADHD symptoms and comorbid

conduct problems (based on DISC-IV). Weiß et al. (2021) revealed eight CpGs, all located in the *TARBP1* gene, were associated with inattention scores in adulthood. One of the CpGs was also associated with maternal smoking. Although the function of *TARBP1* is not well understood, it is thought to play a role in immune function.

Gervin et al. (2017) examined the impact of prenatal exposure to paracetamol. Whilst not finding an overall significant effect of paracetamol exposure on DNA methylation, when stratifying between sporadic versus long-term paracetamol use ($\geq$ 20 days), the study identified differential DNA methylation of those with ADHD and long-term exposure ($n = 19$) compared to controls ($n = 96$) (6211 CpGs) and compared to those with ADHD and sporadic ($n = 77$) (2089 CpGs) or no ($n = 96$) (193 CpGs) paracetamol exposure. A number of the top ranks CpGs identified have previously been linked to ADHD (SGTB, CADM1), neural development (REST, ZNRF1, RabGEF1, CUX1) and neural processes (SYN2, DDAH1, PHOX2A, KCNJ8, CACNG8, PHYH). Gene ontology analysis of the top 100 DMPs identified enrichment of genes involved in oxidation stress.

Lastly, part of a larger study, Rovira et al. (2020) examined whether a range of peri- and post-natal stressful life events had an impact on epigenetics in adulthood. Of the adults with ADHD, 65% reported being exposed to stressful life events (a range of events including premature birth, maternal smoking and drugs of abuse, malnutrition, financial and family stress, neglect, violence and abuse or loss of a loved one). However, no effect of stressful life events on DNA methylation was found.

Much more work is needed to explore the epigenetic mechanisms through which environmental exposures could influence mental health. To date, studies have investigated negative environmental exposures that may give rise to ADHD, but there is also scope to examine a range of potentially positive exposures that provide resilience or have a positive influence on the clinical outcomes for the course of ADHD.

7 Epigenetics and the ADHD Brain

Combining epigenetics with neuroimaging techniques, the burgeoning field of imaging epigenetics is also beginning to shed light on functional impact of DNA methylation on neurobiological processes in ADHD.

Using magnetic resonance imaging (MRI) to examine grey matter structure, in a candidate study of the serotonin transporter (SLC6A4) on a sample of 102 children with ADHD, Park et al. (2015) found that higher DNA methylation levels were not only associated with greater symptom severity and more commission errors (impulsive errors), but also with lower regional cortical thickness in the right occipito-temporal regions. The authors suggest that higher DNA methylation of *SLC6A4* promoter region may play a role in the anomalies in the right temporal region, possibly reflected in greater symptom severity and poorer impulse control.

Using a within-twin pair model, Chen et al. (2018) identified 173 DMPs within MZ twins discordant for ADHD ($n = 14$ pairs). Using MRI to examine neuroanatomical differences between the MZ twin pairs, they found that the twins with ADHD had smaller right caudate and thalamic nuclei, and trended towards a larger right cerebellar cortex. They further found that the DMPs identified were enriched with genes expressed during early brain development in brain structures found to be discordant between twins (caudate, thalamus, cerebellum).

Positron emission tomography (PET) provides chemical functional information in the brain. In Wiers et al. (2018) candidate study of the *DAT1* promoter, there were no significant DNA methylation differences between adults with ADHD and controls. Additionally, using PET, no group differences were identified in *DAT1* availability in the striatum. However, within the ADHD group, *DAT1* DNA methylation did correlate with the *DAT1* availability in the caudate (and at the trend level on the putamen and ventral striatum). Further, in post-mortem findings, the authors demonstrated that the *DAT1* DNA methylation levels in peripheral blood correlated with *DAT1* DNA methylation levels in the substantia nigra of the brain. Further to Sigurdardottir et al. (2021) finding of differential DNA methylation of the *NET* promoter between adults with and without ADHD, within the ADHD group, the authors additionally found an association between DNA methylation levels and *NET* expression levels (measured by PET) in a range of deep brain structures (thalamus, locus coeruleus, dorsal and medial raphe nuclei).

Dysfunction in neural networks can also be probed with electroencephalography (EEG). Event-related potentials (ERPs) are the measured response to cognitive or sensorimotor processes. In a non-clinical sample of boys with high ADHD ratings, Heinrich et al. (2017) examined the association between the DNA methylation patterns in 60 candidate genes (2031 CpG sites) and brain function, examining ERP markers during tasks reflecting attention, cognitive control and motivation. In addition to significant associations between ADHD symptoms and CpG sites primarily relating to dopaminergic and neurotrophic systems (*COMT, ANKK1, BDNF, NGFR, DPP10* and *TPH2*), the authors report DNA methylation association with ERP markers of attention orienting (*DPP10*), reaction time variability (*TPH2*) and inhibitory control (*COMT, ANKK1, BDNF* and *NGFR*).

Therefore, using neuroimaging to examine the impact of epigenetic mechanisms offers an invaluable opportunity to elucidate the molecular underpinnings that may drive inter-individual variability in brain structure and function and holds promise as an important guide to the heterogeneity in behavioural phenotypes and clinical outcomes.

8 Summary, Limitations and Future Directions

The findings of epigenetic studies of ADHD have been heterogeneous with little replication. Two of the most replicated epigenetic associations have been with *VIPR2* and *DRD4*. However, some studies have also failed to replicate these. Why

so much heterogeneity in the epigenetic findings? Below we outline a number of methodological variations between studies that may explain some of this lack of reproducibility.

Firstly, sample sizes vary widely from numbers in the teens to the thousands. As studies have progressed, not only have sample sizes increased, but epigenetic technology has also improved. The first EWAS typically used Illumina Infinium HumanMethylation450 (450 k) BeadChip arrays, whereas more recent studies have used the EPIC arrays, which test roughly twice as many locations along the genome. Although the technological advances have led to a more comprehensive look across the genome, a higher threshold for multiple testing is required for significance. Therefore, power and sample size are important issues. For genetic studies (GWAS), it was only when samples sizes reached >20,000 ADHD cases and 35,000 controls (Demontis et al. 2019) that the first regions achieved genome-wide significance. A number of studies, when not demonstrating statistically significant findings, also go on to report findings at nominal thresholds, which is fine to highlight potentially patterns in the data, but they typically use different nominal thresholds.

Another main issue for epigenetic research is that epigenetic variation can differ by cell types and tissues. Ideally, the epigenetic mechanisms of neural tissue samples would be examined (Bakulski et al. 2016). However, even within the brain, DNA methylation can vary from one region to another. Needless to say, collection of neural tissue samples from living humans is certainly not a practical or ethically viable option. The next best option is to collect peripheral tissue samples to serve as a proxy for the brain's epigenetic state. The studies reported in this chapter have been conducted using a range of peripheral tissues including cord blood at birth, whole blood, buccal or saliva samples. These tissues do typically correlate fairly well with the brain epigenetic state (Braun et al. 2019), but it does add another opportunity for variability within and between studies.

Epigenetic state changes hold a lot of promise, not only to elucidate the molecular mechanisms of risk and identify vulnerable individuals, but also to provide targeting and tracking of individuals using precision medicine. However, this is only possible if the associated epigenetic site is known. *Discovering* this site could be difficult when the site is temporally dynamic. Heterogeneity in the findings may therefore also reflect different sensitive periods for epigenetic change, and consequently cohorts with large age ranges may not be homogeneous enough to provide a coherent finding. Due to the age-linked and temporally dynamic nature of epigenetic changes, future research should endeavour to track changes longitudinally to examine the stability of any such difference(s) over age, to examine epigenetic changes associated with changes in symptom profile or diagnosis remission and to examine whether epigenetic differences are precursors of, or a consequence of the disorder.

Some neuroimaging studies have started to touch on the functional relevance of epigenetics changes, but further understanding of the epigenetic influence on the brain and behaviour is warranted. The field of epigenetics is beginning to make an important contribution to our understanding of the risk susceptibility, the biological

underpinnings, the environmental mediators and the developmental course of ADHD, and we look forward to the exciting prospects its future use will bring.

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Preclinical Evaluation of Attention and Impulsivity Relevant to Determining ADHD Mechanisms and Treatments

Johnny A. Kenton and Jared W. Young

Contents

Abstract People with Attention-Deficit Hyperactivity Disorder (ADHD) exhibit inattention, hyperactivity, and/or impulsivity. Symptoms of ADHD emerge in childhood and can continue throughout adulthood. Clinical assessments to diagnose ADHD can include administration of continuous performance tests (CPTs). CPTs provide an objective measure of inattention, requiring individuals to respond to targets (attention), and inhibit response to non-targets (impulsivity). When investigating the mechanisms of, and novel treatments for, ADHD it is important to measure such behavioral domains (attention and impulsivity). Some well-established preclinical tasks purport to assess attention in rodents but, unlike CPTs, do not require non-target inhibition, limiting their ADHD-relevance.

Recently developed tasks recreate CPTs for rodents. The 5-Choice CPT (5C-CPT) contains non-target stimuli, enabling use of signal detection theory to evaluate performance, consistent with CPTs. The 5C-CPT has been adapted for use in humans, enabling direct cross-species comparisons of performance. A newer task,

J. A. Kenton
Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

J. W. Young (✉)
Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

Research Service, VA San Diego Healthcare System, San Diego, CA, USA
e-mail: jaredyoung@ucsd.edu

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the rodent CPT (rCPT), is a touchscreen-based analog of CPTs, utilizing symbols instead of a simple stimulus array. Currently, the rCPT may be more akin to a go/no-go task, equally presenting targets/non-targets, although numerous variants exist – a strength. The 5C-CPT and rCPT emulate human CPTs and provide the most up-to-date information on ADHD-relevant studies for understanding attention/impulsivity.

Keywords Attention · Cognitive control · Deficit · Disorder · Hyperactivity · Response inhibition

Abbreviations

5C-CPT	5-Choice continuous performance test
5-CSRTT	5-Choice serial reaction time test
6-OHDA	6-Hydroxydopamine
ACC	Anterior cingulate cortex
ADHD	Attention-deficit hyperactivity disorder
CANTAB	Cambridge neuropsychological test automated battery
CPT	Continuous performance test
DAT	Dopamine transporter
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
HA	High-attentive (rat)
HI	High-impulsive (rat)
LA	Low-attentive (rat)
LI	Low-impulsive (rat)
NET	Norepinephrine transporter
NK1R	Neurokinin-1 receptor
PFC	Prefrontal cortex
PPC	Posterior parietal cortex
rCPT	Rodent continuous performance test
SAT	Sustained attention task
SHR	Spontaneously hypertensive rat
SI	Sensitivity index
TOVA	Test of variable attention

1 Introduction

The use of rodent paradigms and manipulations to delineate neural mechanisms related to neurodevelopmental disorders in humans has had a long and difficult road. One such disorder is Attention-Deficit Hyperactivity Disorder (ADHD). ADHD is a relatively newly described condition, first appearing in 1980 in the Diagnostic and

Statistical Manual (DSM)-III, initially as Attention-Deficit Disorder *with* or *without* hyperactivity, but thereafter referred to as ADHD in the fourth and fifth versions of the DSM. Although hyperactivity relevant to ADHD has been extensively studied in rodents, primarily via locomotor hyperactivity (Solanto 2000; Davids et al. 2003; Sagvolden et al. 2005), inattention has received far less attention. This is despite inattentive behavior being a core feature of ADHD and having been described since the eighteenth century: e.g., by Sir Alexander Crichton (Lange et al. 2010). Thus, given the central role of inattention on people ADHD, it is the primary aspect requiring understanding and will be the focus here.

There is no unitary conceptualization of attention – given the existence of sub-domains such as selective (process by which environmental stimuli are chosen for attention), sustained, also referred to as vigilance (where attention is focused on particular stimuli for prolonged periods while ignoring irrelevant stimuli), and divided attention (attention is focused during performance of multiple tasks; Parasuraman et al. 1998). In clinical practice, inattention is generally assessed via observations and rating provided by parents and teachers. The emergence of laboratory assessments has enabled objective determination of degrees of dysfunction in those with ADHD. A myriad of laboratory-based attentional assessments exist, but one of the most common types of assessment is the use of Continuous Performance Tests (CPT; Table 1; Mueller et al. 2017). First developed in 1956 by Rosvold (Beck et al. 1956), CPT is now an umbrella term for numerous (go/no-go) tasks that follow a similar structure (Riccio et al. 1999). The subject is presented with numerous stimuli to which they should respond (targets), while also inhibiting their response to other (non-target) stimuli. Thus, both attention (responses to target stimuli) and a deficit in response inhibition (measured as false alarms, an aspect of impulsivity) are assessed. Needless to say, research demonstrates that individuals with ADHD are both inattentive and impulsive across CPTs relative to those without ADHD (Tucha et al. 2006). The most commonly used task in this area of research is the Conners' CPT (Edwards et al. 2007).

The Conners' CPT presents letters which the subject should respond to, but inhibits their response whenever an "X" appears. Thus, subjects develop a prepotent response to target stimuli (i.e., a tendency to respond, by default), which makes the inhibition of responding more difficult, requiring "cognitive control." Additional CPTs include the Test of Variable Attention (TOVA), which first presents numerous non-target stimuli, with few target stimuli, designed to elicit lapses in attention, while the second half presents more target stimuli, thereby increasing the likelihood of impulsive (false alarm) responding (Gualtieri and Johnson 2005). Overall, to assess attention and impulsivity in individuals with ADHD, it is important to test subjects in paradigms that include both target and non-target stimuli (see Table 2 for some examples of studies using CPT measures in adults). Any rodent paradigm to be used to delineate neural mechanisms related to ADHD should therefore include such stimuli.

Classically, in rodent testing, go/no-go tasks include both target (go) and non-target (no-go) stimuli, requiring the response and inhibition of responding to such stimuli, respectively (Numan and Klis 1992; Oakley and Russell 1979). These

Table 1 Continuous performance tests: A group of paradigms for the evaluation of attention and, to a lesser degree, impulsivity

Test	Description
Human assessments of attention	
TOVA (tests of variables of attention)	A small square appears toward the top (target) or the bottom (non-target) of a larger rectangle
X-CPT ('X' continuous performance task)	A string of letters appears sequentially and correct responses are made when an "X" appears (target), inhibiting responses to all other stimuli (non-target)
AX-CPT ('A→X' continuous performance task)	Similar to X-CPT, correct responses occur only when "X" is preceded by "A," inhibit to AY, BX, and BY combinations (non-targets), therefore includes a memory component
Conners' CPT (reverse 'X' continuous performance task)	Similar to X-CPT, responses are made in response to each letter (targets), *except* for "X" (non-target), ensuring a prepotent response to targets
CPT IP (continuous performance task – identical pairs)	Correct responses are made when two identical stimuli are presented in a row (targets), inhibit from responding to non-pairs (non-target)
Animal assessments of attention	
SAT (sustained attention test)	Lever-based task wherein subjects are presented with a signal or not (non-signal), then given the choice to indicate whether it appeared or not, responding left or right; can include a distractor
5CSRTT (5-choice serial reaction time task)	Animals respond to a stimulus appearing in one of five possible locations; does not contain non-target stimuli
5C-CPT (5-choice continuous performance task)	Modification of 5-CSRTT, in which subjects required to respond to a single stimulus (target), but inhibit responses when all five stimuli are presented (non-target)
rCPT (rodent continuous performance task)	Touchscreen-based analogue of common human CPTs presenting symbolic versus simple stimuli

tasks enable direct replication of human go/no-go tests but, of course, do not replicate human CPT studies because go/no-go tasks classically include 50/50 representation of go/no-go stimuli. As can be gleaned from descriptions above, CPTs comprise majority target (e.g., Conners' CPT), or majority non-target stimuli (CPT-X), with some switching between majority to minority presentation (TOVA) (Nicholls et al. 2020; Rotem et al. 2019, 2020). Thus, while go/no-go tasks provide behavioral insight, they do not recreate all aspects of CPTs because the latter require majority target responses, which drive a prepotent response in the subjects enabling measurement of cognitive control (Lustig et al. 2013).

Table 2 Examples of human CPT studies

Authors	Task	Focus	Age	Sex	Objective	Summary
Smid et al. (2006)	X-CPT, AX-CPT, CPT IP	HC ($n = 16$)	$\bar{x} \approx 24.06$ years	6 female 10 male	Determine neurocognitive correlates of CPT variations	Behavioral and EEG assessment in healthy participants indicated worse target detection in AX-CPT than in X-CPT; CPTs differ in ways that influence different cognitive functions
Lopez-Luengo et al. (2016)	Conners' CPT	Schizophrenia ($n = 64$ CP, 64 HC)	CP $\bar{x} \approx 33.97$ years HC $\bar{x} \approx 24.5$ years	CP = 45 female 19 male HC = 54 female 10 male	Measure effect of schizophrenia on CPT requiring high response rate	Patient performance, while different from control fell within clinically "normal" ranges
Hahn et al. (2014)	CPT IP	Schizophrenia ($n = 50$ CP, 47 HC)	CP $\bar{x} \approx 34.4$ years HC $\bar{x} \approx 33.9$ years	CP = 15 female 25 male HC = 19 female 28 male	Assess long-term (1 year) test-retest reliability of CPT IP	While stable in healthy controls, patients showed only moderate test-retest reliability for d' and hit rate
Zane et al. (2016)	Conners' CPT	TBI ($n = 30$ mTBI, 30 msTBI, 30 HC)	HC $\bar{x} \approx 34.7$ years mTBI $\bar{x} \approx 33.9$ years msTBI $\bar{x} \approx 34.6$ years	All male	Determine the utility of Conners' CPT in TBI	TBI negatively affects CPT performance, which correlates with symptom severity
Tu et al. (2018)	Conners' CPT	Cognitive deficits ($n = 39$ SCD, 15 MCI)	SCD $\bar{x} \approx 62.7$ years MCI $\bar{x} \approx 61.7$ years	SCD = 25 female 14 male MCI = 8 female 7 male	Compare visual attention between cognitive decline and healthy controls	Mild cognitive decline impaired sustained attention, with reactions times being worse later in the task

CP clinical patient, *HC* healthy controls, *TBI* traumatic brain injury, *mTBI* mild TBI, *msTBI* moderate-severe TBI, *SCD* subjective cognitive decline, *MCI* mild cognitive impairment

2 History of Attentional/Impulsivity Task Development in Rodents

Attentional functioning has long-been claimed to have been assessed in rodents (for example, refer to Table 3). Certainly, many tasks require attentional functioning during task performance, but also motivation, spatial awareness, etc. Thus, they do not necessarily assess attention in ways that are consistent with CPTs as used in people with ADHD (Fig. 1). One of the earliest of such tasks, which spearheaded the potential for such research, was the 5-Choice Serial Reaction-Time Task (5-CSRTT), first developed by Robbins and colleagues (Carli et al. 1983). Developed to recreate Leonard's 5-CSRTT, which was used in humans to assay choice reaction-time, rodents are required to nose-poke wherever a cue light appears in one of five spatial locations. The performance of rats (Robbins 2002) and mice (Humby et al. 1999) has been extensively assessed. The 5-CSRTT has been suggested as analogous to the CPT (Day et al. 2008; Jones and Higgins 1995), with assumptions that incorrect responses (response where no cue is not present) or premature responses (responding prior to cue presentation, therefore not in response to non-target presentation), in the 5-CSRTT mirror false alarms in the CPT (Day et al. 2008). However, no opportunity for the measurement of correct rejections has existed, despite that being required as the contrary measurement to false alarms. Thus, these interpretations are inaccurate because no non-target trials are presented in the 5-CSRTT (Robbins 2002) and so correct rejection and false alarm rates cannot be evaluated (Young et al. 2009). Without non-target trials in the 5-CSRTT task, signal detection theory (SDT, which mathematically determines sensitivity to signal vs. noise stimuli and commonly used to assay overall performance in human CPTs, generating overall performance metrics like *d'*) cannot be used to evaluate performance in rodents. This limitation in turn makes it difficult to compare preclinical performance with equivalent data derived in a human CPTs. Thus, Robbins (1998) noted that "the test requirements [for the 5-CSRTT] fall short of that which is normally regarded as vigilance" (pp. 191). Furthermore, the human version of the 5-CSRTT for the Cambridge Neuropsychological Test Automated Battery (CANTAB), also developed by Robbins and colleagues, is described specifically as a test of serial choice reaction-time (Sahakian et al. 1993). In fact, despite the wide availability of the human 5-CSRTT within CANTAB, there are no apparent deficits in performance in people with ADHD relative to healthy participants (Chamberlain et al. 2007). Moreover, methylphenidate speeds reaction-time in the 5CSRTT in people with ADHD, with no reports of accuracy, omissions, or premature responses that are commonly reported in rodent studies (Rhodes et al. 2006). Thus, while a great deal of research has been conducted using the 5-CSRTT, with the potential for relevance to attending to target stimuli as measured in CPTs (Table 3), it falls short of requiring response inhibition, which is a commonly replicated area of difficulty in individuals with ADHD (Table 4).

The sustained attention task (SAT) developed and used by Sarter and colleagues (McGaughy and Sarter 1995) includes non-signal trials, unlike the 5-CSRTT.

Table 3 Examples of rodent attentional studies

Authors	Task	Model	Age/ weight	Sex	Drugs	Summary
McGaughy and Sarter (1995)	SAT	Mice	4 months	Males	Benzodiazepine (3, 5, 8 mg/kg)/ amphetamine (0.4, 0.8 mg/kg)	Established face validity of SAT; demonstrated that increased age negatively affects performance, recapitulated with agonism of benzodiazepine receptor
Kim et al. (2015)	rCPT	Mice	7–9 weeks	Males	Donepezil (0.03, 0.1, 0.3 mg/kg)	The rCPT was successfully adapted for mice, with three popular strains demonstrating successful performance
Mar et al. (2017)	rCPT	Rats	12–16 weeks	Males	Various	MAM-E17 schizophrenia model demonstrates impairments in attention and inhibitory control in touchscreen-based rCPT
Hvoslef-Eide et al. (2018)	rCPT	Mice/ 6J	7–9 weeks	Males	NA	Bilateral lesions to the anterior cingulate produces disinhibited phenotype (increased indiscriminate responding and increased false alarms)
Fisher et al. (2020)	rCPT	Rats	225 g ± 20	Males	NA	PLC lesions produce consistent attentional deficits, while lesions to the ACC produced early, but not later deficits and no effects, respectively
Young et al. (2009)	5C-CPT	Mice	10–12 weeks	Males	NA	The 5CCPT has face validity with human CPTs, with C57Bl/6J mice exhibiting better SI levels than DBA/2 mice
Olguin et al. (2021)	5C-CPT TS	Mice	10–12 weeks	Females and males	NA	Prenatal alcohol exposure reduces inhibitory control and, in females, slows responding (regardless of exposure)

SAT sustained attention task, *rCPT* rodent CPT, *5C-CPT* 5-choice continuous performance task, *TS* touchscreen

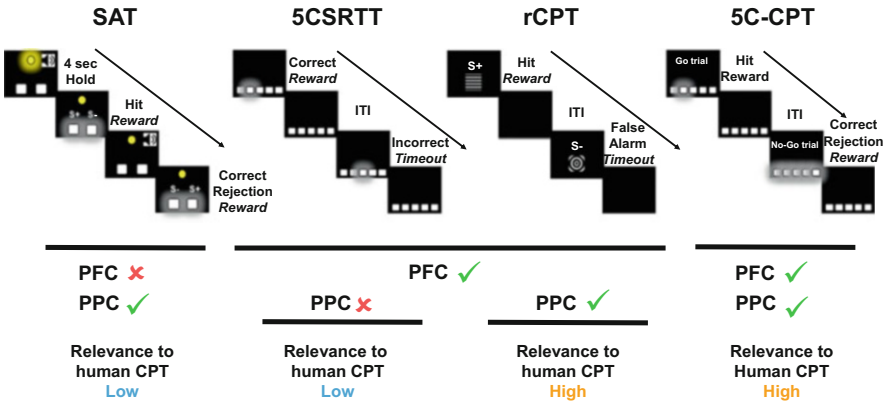

Fig. 1 Potential rodent paradigms to assay attention and impulsivity as done in people with ADHD. Numerous rodent paradigms have been created that putatively assess attentional function, albeit using differing parameters. These variations are key, however, given that the majority of laboratory assessments of attention in people with ADHD incorporate a measure of inhibitory control. In the sustained attention task (SAT), rodents are required to attend to whether a signal appears or does not, after which levers are presented and they press the left or right lever, indicative of detection or not of the stimulus. In the 5-Choice Serial Reaction Time Task (5-CSRTT), rodents respond if a single stimulus appears within an array of five potential locations. Neither the 5-CSRTT nor the SAT require the inhibition of responding to non-target stimuli. The 5-Choice CPT (5C-CPT) was created to go beyond the 5-CSRTT by adding a non-target stimulus (appearance of all five stimuli), requiring the inhibition of responding, consistent with human CPTs. These three tasks reward appropriate responding irrespective of stimulus type. The rodent continuous performance task (rCPT) was then created using touchscreens whereby rodents were presented with different target and non-target stimuli requiring a response or inhibition respectively; this is consistent with the 5C-CPT, albeit presented in the same location, and animals are rewarded only when responding to target stimuli. The 5C-CPT typically contains more target versus non-target trials, encouraging the development of a prepotent response. However, this can also be accomplished in the rCPT: the latter has the option of presenting more non-target stimuli as well. PFC: prefrontal cortex. PPC: posterior parietal cortex. Green checkmarks indicate involvement. Red X's indicate no involvement

Specifically, rats must attend to a single location to ascertain whether a cue stimulus appears or not, before response levers are presented and the animal chooses whether they remember seeing a signal. This task does therefore measure hits, misses, correct rejections, and false alarms to some extent. However, it differs from the CPT in that a memory of an event is required rather than the inhibition of responding to a non-target stimulus and so it can be argued that no non-target stimulus is actually presented. A human version of the SAT also exists, however, and although not tested in people with ADHD, deficits in overall performance in people with schizophrenia have been described (Demeter et al. 2013). Thus, there remains an opportunity to conduct research using animals in order to understand human behavior, but the lack of consistency of the SAT with human CPTs limits the opportunity to delineate neural mechanisms relevant to deficits that are widely described in people with ADHD.

Table 4 Examples of human CPT ADHD studies

Authors	Task	Age	Sex	Drug	Objective	Summary
Edwards et al. (2007)	Conners' CPT	$x^{-} \approx 8.77$ years	26 female 78 male	NA	Determine validity of CCPT in ADHD	CCPT performance did not correlate with reported ADHD behaviors and was only slightly better than chance at classifying children into ADHD subtypes
Verbaten et al. (1994)	X-CPT	$x^{-} \approx 11.2$ years	2 female 10 male	Methylphenidate (10 mg)	Determine effect of ADHD treatment on EEG signals using X-CPT	Methylphenidate increased parietal EEG relative to target and non-target responses in children with ADHD
Dhar et al. (2010)	AX-CPT	ADHD $x^{-} \approx 33.1$ years HC = 33.7 years	32 males	NA	Determine features of information processing in ADHD	ADHD results in an absence of frontal EEG related to an deficiency in inhibitory control
Berger et al. (2017)	MOXO-CPT	ADHD $x^{-} \approx 9.27$ years HC $x^{-} \approx 9.71$ years	ADHD $n = 134$ female 215 male HC $n = 182$ female 279 male	NA	Evaluate utility of CPT incorporating distracting environmental stimuli	Children with ADHD perform worse on MOXO-CPT, which includes visual/auditory distractors
Vogt and Williams (2011)	X-CPT w/IR motion analysis	$x^{-} \approx 10.2$ years	5 female 19 male	Methylphenidate (5/10 mg)	Use X-CPT to identify treatment response to methylphenidate	CPT was effective at determining drug response in children with ADHD allowing for more effective titration process
Park et al. (2019)	Ata	ADHD $x^{-} \approx 7.6$ years HC $x^{-} \approx 8.6$ years	ADHD $n = 20$ female 59 male HC $n = 19$ female 16 male	NA	Evaluate the diagnostic application of ATA in ADHD	Reaction time variability (auditory test) and commission errors (visual test) reliably distinguish between ADHD and control children

(continued)

Table 4 (continued)

Authors	Task	Age	Sex	Drug	Objective	Summary
Baggio et al. (2020)	Conners' CPT	$\bar{x} \approx 35.2$ years	$n = 91$ female 110 male	NA	Determine the usefulness of CPT as a marker of ADHD in adults	Evidence suggests that CPT results should be considered cautiously when assessing or monitoring ADHD in adult populations

HC healthy control, *X-CPT* responses made only to letter "X", *Conners' CPT* responses made to all letter stimuli, *except* "X", *AX-CPT* responses only made to "X" when preceded by "A", *MOXO-CPT* CPT with external interfering stimuli as distractors, *ATA* comprises a visual (non-linguistic) and auditory test with low target:non-target ratio

To address the limitations of these rodent paradigms, we developed the 5-Choice CPT (5C-CPT), which modified the 5-CSRTT to present both target stimuli, as in that task (a single lit hole presentation), but added a non-target stimulus (all five holes lit), which signals that the rodent must inhibit from responding (Young et al. 2009). With a ratio of five target to one non-target trials over 120-250 trials, the 5C-CPT recreates the task requirements of CPTs, particularly the Conners' CPT, measuring attention (responses to targets) and impulsivity (response disinhibition), in a manner consistent with assessment in people with ADHD. Thus, the 5C-CPT more completely fulfills one aspect of validity of CPTs: face validity, versus the 5-CSRTT and SAT.

Other forms of validity exist, however, including predictive and construct validity (Young et al. 2010, 2011; Winstanley and Clark 2016; Wallace et al. 2015; Steckler and Muir 1996; Markou et al. 2009). Predictive validity encompasses the ability to make a correct prediction about the human phenomenon of interest (Geyer and Braff 1987). Although sometimes used to narrowly describe pharmacological predictive validity (Matthysse 1986), a paradigm can be validated via other types of successful predictions (Ellenbroek and Cools 2000).

One prime example of the more general predictive validity is that rodents performing the 5C-CPT exhibit a vigilance decrement (poorer performance over time), as seen in people performing CPTs (Riccio et al. 1999; Young et al. 2009), but not seen in rodents performing the 5-CSRTT or SAT. Additional predictive validity of the 5C-CPT stems from the observation that 36 h of sleep deprivation impairs both rodent and human performance of the 5C-CPT (van Enkhuizen et al. 2014), as seen in other human CPTs (Joo et al. 2012). More specific pharmacological predictive validity of the 5C-CPT is observed whereby amphetamine improved rodent and human performance in the 5C-CPT (Macqueen et al. 2018a), while modafinil improved human performance in the 5C-CPT (Cope et al. 2017), as seen in other CPTs (MacQueen et al. 2018b).

Convergent validity is more complex, describing the closeness of assessing that which is sought after from human testing. This form of validity is commonly used to describe preserved brain regions that subserve cognitive functioning across species and is a helpful starting point for cross-species mechanistic discussions. Interestingly, fMRI studies regularly demonstrate human CPT performance is associated with (or causes) activation of a fronto-striatal-parietal network (Young et al. 2020a; McKenna et al. 2013; Bartes-Serrallonga et al. 2014): in fact, impairment of this network was linked to ADHD psychopathology (Schneider et al. 2010).

Lesions of the parietal cortices did not impact rodent 5-CSRTT performance, however (Muir et al. 1996), whereas parietal lesions of rodents performing the 5C-CPT negatively affected performance (Young et al. 2020a). Thus, the inclusion of non-target trials potentially recruited the brain network required to subserve attentional/impulsive measurement; this finding is closer to that of human CPTs, which potentially increases the validity of findings from the 5C-CPT as relevant to neural functioning in humans.

Construct validity is not that simple, however, as lesion of a brain region may impair performance in rodents, but each brain region has many connections, receptor

expression, etc., and thus the lesion may result in deficits without necessarily recreating what is important in humans. Hence, while human fMRI studies of performance during the 5C-CPT reveal a requirement of parietal functioning during target and non-target trials, to identify exactly what was impacted following lesions of mice would represent a large step forward but requires more validation.

Another more novel CPT-like task developed for use in rodents is the rodent CPT (rCPT). First developed by Kim et al. (2015), the rCPT utilizes touchscreen technology, offering the opportunity to utilize far more symbols akin to human CPTs than is available using a 5-hole operant chamber. Thus, target stimuli could be made from any image and, likewise, non-target stimuli could be any other stimuli. In the main task, mice experience 50/50 presentation of target and non-target stimuli, lasting for 100 trials or 45 min, similar to go/no-go tasks. Here, responding to target stimuli is rewarded, while responding to non-target stimuli is never rewarded. In the rCPT, C57BL/6 mice did not differ from DBA/2 mice and did not exhibit a vigilance decrement, again unlike the better performance of C57BL/6 mice than DBA/2 mice in the 5C-CPT (Young et al. 2009). The differences between these findings may arise from the fact that the rCPT presents as a go/no-go task with 50/50 target/non-target presentation, while the 5C-CPT has a 5/1 presentation, more akin to the Conners' CPT that has an 8/1 presentation (Table 4).

Given that DBA/2 mice and C57BL/6 mice do not differ in go/no-go performance (Gubner et al. 2010), it is possible that the rCPT requires more target to non-target presentations, as in the Conners' and 5C-CPT, which can be readily accomplished. Also, the 5C-CPT is tested over 250 trials within 60 min versus 100 trials within 45 min in the rCPT. Finally, the rCPT rewards only target responses, while the 5C-CPT rewards target responses in addition to the inhibition of responding, evenly distributing reward value for responding and the inhibition of responding. The rCPT likely has some scope for development given its novelty, with fewer publications reporting its use than other techniques, such as the 5C-CPT. For that reason, there has been limited validation of the relevance of rCPT to human CPT testing. Like the 5C-CPT and human CPTs, performance was improved with amphetamine and modafinil treatment (see details below). The rCPT enables more varied stimuli and so offers a new avenue of research toward understanding the neural mechanisms that may contribute to attentional and impulsive deficits seen in people with ADHD (see Table 5 for examples).

3 Research Using Rodent Versions of CPT with Relevance to ADHD

Establishing the validity of a behavioral rodent paradigm as being relevant to human testing in the general population is the first step in the validation pipeline. The next step is identifying manipulations that are then relevant to the disease of interest – in this case ADHD. Such animal models should share aspects of the disease of interest,

Table 5 Examples of rodent attentional ADHD studies

Authors	Task	Species	Age/ weight	♂/♀	Drugs	Summary
Robinson et al. (2009)	5-CSRTT	Rat	10–12 weeks	Males	NA	The 5CSRTT is efficient for characterizing high- vs. low-premature responding in rats
Navarra et al. (2008)	5-CSRTT	Rat	15 months	Males	Methylphenidate (2.5, 5.0 mg/kg)/ atomoxetine (0.1, 0.5, 1.0 mg/kg)	Methylphenidate treatment improved overall attention, but caused hyperactivity at high doses; atomoxetine decreased impulsivity while modestly improving attention
Caballero-Puntiverio et al. (2019)	rCPT	Mouse	~0–12 weeks	Males	Various	ADHD treatment improved performance in low-performing mice as shown by increased hit rate and/or decreased false alarm rate
Porter et al. (2016)	5C-CPT	Mouse	6–7 weeks	Males	NA	Genetic NR1−/− mice do not exhibit increased false alarms, they do perseverate more than control mice
Pillidge et al. (2016)	5C-CPT	Mouse	6–7 weeks	Males	Methylphenidate (3, 10, 30 mg/kg)	Treatment with methylphenidate reduces perseverative behavior in hyperactive mice, but also decreased responding at high doses
Nilsson et al. (2018)	rCPT	Mouse	7–8 weeks	Males	Modafinil (0.4, 4.0, 40 mg/kg), amphetamine (0.25, 0.5, 1.0 mg/kg)	Genetic deletion model of ADHD impairs hit rate and reduces *d'*, which is rescued with amphetamine

not only symptomatology, but also etiology and treatment response. For that reason, the criteria for validating animal models of disease are similar to those for the consistency of behavioral paradigms, with (1) face, (2) predictive, and (3) construct

validity. Additional validation includes (4) etiological validity (mechanisms thought to be relevant to the disease recreated in animals), with (2ii) emphasis that predictive validity includes treatments that are efficacious both in people and the animal model (pharmacologic predictive validity).

Regarding face validity, some rodent strains exhibit worse cognitive function than others, which may be relevant to causes of impairments in humans (Brown and Wong 2007). These strain differences are, importantly, observed in attentional tasks such as the 5C-CPT, as in the poorer performance of male DBA/2 mice versus male C57BL/6J mice (Young et al. 2009). Distinctions between strains, however, may not be due to cognitive differences in behavior per se, but may instead be due to physical limitations (Wong and Brown 2006) (see below). Such evolutionary differences highlight the importance of studying models directly recreating aspects of a specific disorder, and not just differences between standard laboratory strains. That is not to say, however, that "normal" animals cannot be utilized to assess potential treatments. Indeed, previous research has utilized naturally occurring individual differences within strains of rodents (high-performers versus low-performers (Puumala et al. 1996; Koskinen et al. 2000; Robinson et al. 2009). Such strain differences are useful for assessing pharmacologic predictive validity. For instance, ADHD drugs such as methylphenidate (0.1–0.5 mg/kg), atomoxetine (0.5–2.0 mg/kg), and amphetamine (0.1–1.0 mg/kg) have produced varied results in affecting attentional processing, which were more pronounced in low- versus high-performing rats (Puumala et al. 1996; Paterson et al. 2011). These studies, however, were conducted using the 5-CSRTT, which, for reasons explained above, is not equivalent to a human CPT due to the absence of correct rejections (the opposite of false alarms) (Day et al. 2008; Robbins 2002). To further understand the etiology of ADHD, researchers must focus on developing animal models that recapitulate the phenotype and utilize assessments that capture clinically relevant behavior.

Another potential animal model that is widely used to model preclinical ADHD research, the spontaneously hypertensive rat (SHR), has been suggested to exhibit ADHD-relevant behaviors, relative to non-hypertensive controls (Russell 2007). This model, however, exhibits aspects unrelated to ADHD – namely, hypertension. Nonetheless, the SHR provided potential evidence for the role of dopamine in ADHD (Russell 2002), a neurotransmitter that is implicated in ADHD (Blum et al. 2008) and commonly targeted with pharmacological treatments. The association between ADHD and dopamine has resulted in several models focusing on dopaminergic dysregulation, some via neurochemical lesions and others via transgenic manipulation. Neurochemical lesioning with 6-hydroxydopamine (6-OHDA), for example, produces hyperactivity in an open-field test and deficits in the 5-CSRTT (Bouchatta et al. 2018), which was rescued by common ADHD therapeutics. Similarly, mice with hypofunction of the dopamine transporter (DAT) also exhibit reduction in accuracy and increases in premature responding (Ciampoli et al. 2017; Mereu et al. 2017) in the 5-CSRTT. This, however, does not mean the dopamine dysregulation is the ultimate underlying cause of ADHD symptomatology, as people with ADHD display many genetic polymorphisms that interact with environmental factors (Palladino et al. 2019). Thus, research has attempted to recreate aspects of

ADHD in animal models, but rarely has focused on the use of the predominant task used to identify people with ADHD, namely CPTs. Some research has been conducted in the more recently available 5C-CPT and rCPT, however, which are relevant to ADHD clinical outcomes. (For further discussion of animal models, see Chapter "Animal Models of ADHD?")

3.1 5C-CPT for ADHD Research

The 5C-CPT has been used in the assessment of rodent models of ADHD. As described above, the 5C-CPT was established in mice, utilizing two separate strains, and revealed that male DBA/2 mice exhibited poorer attentional performance than male C57BL/6J mice. This poorer performance was confirmed using SDT to calculate a higher sensitivity index (SI; a non-parametric measure of *d'*) in C57BL/6J versus DBA/2 mice, driven by committing fewer omission errors (Young et al. 2009). Importantly, using SDT it was established that the higher omissions of DBA/2 mice were not simply because they were less responsive, because their bias of responding (responsivity index) was not different from C57BL/6J mice (Young et al. 2009). While the differences between these two strains may provide some relevance to ADHD, there are many disorders that exhibit attentional dysfunction, such as Alzheimer's disease, schizophrenia, bipolar disorder, etc. Thus, understanding the differences will not necessarily relate to ADHD.

More specific to ADHD are studies determining the impact of neurokinin-1 receptor (NK1R) knockout (NK1R−/−) in mice, given that NK1Rs are found in brain regions governing mood, cognition, and motor performance (Rigby et al. 2005) and is analogous to the human *TACR1* gene, which is polymorphic in a subset of people with ADHD (Sharp et al. 2014; Yan et al. 2010). Functional ablation of NK1R in male mice interestingly resulted in increased perseverative responses, in the absence of altered hit rate, false alarm, or premature responses (Porter et al. 2016). This perseverative behavior (which has also been referred to as constant checking in) of these mice suggests potential phenotypic differences in ADHD, dependent on subgroup polymorphism. Additional investigation utilizing NK1R−/− mice demonstrated a rescue of the perseverative behavior with methylphenidate treatment (at 3, 10, and 30 mg/kg; Pillidge et al. 2016), providing some face, construct (genetic manipulation), and pharmacological predictive validity for this model, albeit without attentional deficits, the primary hallmark of ADHD.

As described, another approach toward modeling ADHD is to determine differential performance within a group of animals, given that people with ADHD on average exhibit poorer attentional performance than healthy participants (Baggio et al. 2020). Tomlinson et al. (2014) used this approach and trained female Lister hooded rats in the 5C-CPT and, based on initial performance, placed them into four separate groups: low-attentive (LA), high-attentive (HA), low-impulsive (LI), and high-impulsive (HI). Rats were then given common ADHD drug treatments – methylphenidate (0.5, 1.0, 2.0 mg/kg), or atomoxetine (0.5, 1.0, 2.0 mg/kg). In LA

rats, both drugs, at medium-to-high doses, improved attention as measured by increases in accuracy and SI. In HI rats, medium doses of both methylphenidate and atomoxetine improved impulsivity and response inhibition, as measured by false alarms and premature responses. As expected, this study found no meaningful drug effects in the HA group. Interestingly, LI rats also demonstrated drug-related effects at sufficiently high doses, with methylphenidate (2.0 mg/kg) increasing premature responding and atomoxetine (2.0 mg/kg) decreasing the false alarms. Thus, these studies demonstrate the pharmacologic predictive validity of the 5C-CPT, revealing the responsivity of attentional deficits within a group to ADHD-related therapeutic treatments. Unfortunately, there are still many aspects of group differences in the 5C-CPT that remain unknown (e.g., male rat performance, mouse subgroup performance, etc.) and require investigation.

While previous work has demonstrated the effects of commonly prescribed ADHD treatments in the 5C-CPT, further research is needed for the ever developing landscape of ADHD therapeutic targets, such as those relating to dopamine signaling. To this end, potential alternative therapeutics targeting the dopamine system have been assessed (Tomlinson et al. 2015). Female rats were separated into only two groups: high-attentive (HA) and low-attentive with high impulsivity (LAHI). The combination in the latter group was identified to recreate behaviors associated with "combined" subtype of ADHD in humans. i.e., those with both an inattentive and hyperactive/impulsive presentation (Schulze et al. 2021). To address the role of dopamine in the attentional deficits of ADHD, Tomlinson et al. (2015) observed that treating rats with the catechol-*O*-methyl-transferase inhibitor, tolcapone (15.0 mg/kg), theoretically increased frontal catecholamine levels, improved accuracy, reduced false alarms, and increased vigilance, as measured by the SI, in the LAHI group. In the HA group, tolcapone (15.0 mg/kg) reduced both accuracy and SI. When dopamine was directly altered by administration of a dopamine DRD4 receptor agonist (A-412997; 0.3 mg/kg and 1.0 mg/kg), LAHI rats showed decreased false alarms, increased SI, and a reduced responsivity index at the highest dose, suggesting an overall change in response strategy. Thus, targeting dopaminergic systems outside traditional ADHD treatments produced similar effects in this model using the 5C-CPT.

Importantly, both tolcapone and the low potency dopamine/norepinephrine transporter (DAT/NET) inhibitor, modafinil, improved human performance in the 5C-CPT, both of which are yet to be tested in mice. Administration of 200 mg and 400 mg of modafinil improved *d'* in male and female humans (parametric equivalent to SI), while the higher dose also improved hit rate (Cope et al. 2017). Tolcapone acts primarily in frontal regions, increasing dopaminergic tone (Ceravolo et al. 2002), and reduced false alarms while improving a biomarker, derived from an electroencephalogram (EEG), related to false alarms (Bhakta et al. 2017). This effect was evident specifically in poorly performing male and female healthy human participants (Bhakta et al. 2017), thereby providing predictive validity of rodent-based findings. Additionally, amphetamine treatment (10 and 20 mg/kg) in male and female healthy human participants improved 5C-CPT performance by increasing *d'*, accuracy and hit rate and reducing omissions, while amphetamine (0.3 mg/kg) also

improved mouse 5C-CPT by improving *d'*, accuracy and hit rate (Macqueen et al. 2018a), providing further predictive validation for the 5C-CPT. Interestingly, in male rats, performance on the 5C-CPT was improved after amphetamine exposure (0.3 mg/kg), only in low-performing animals (Young et al. 2020b), potentially as a result of different underlying amphetamine treatment mechanisms in rats versus mice and humans (Young et al. 2013). Finally, genetically-altered male mice, with reduced expression of the dopamine transporter, also exhibit deficits in the 5C-CPT, with reduced hit rate, accuracy, and *d'* and increased false alarms, omissions, and premature responses (Young et al. 2020a). While the focus in that study was bipolar disorder, it nevertheless highlights the importance of dopaminergic signaling in 5C-CPT performance.

There has been a strong interest in the potential for cholinergic treatments that may remediate attentional deficits in people with ADHD. Nicotine has long-been associated as a potential cognition enhancer and ADHD is no exception. For example, nicotine improved attention in non-smoking adults with ADHD in a CPT via reducing miss errors (Poltavski and Petros 2006), and reducing reaction time and its variability, indicative of more directed attention (Bekker et al. 2005; Levin et al. 1996). This work is consistent with nicotine-induced improvement attention (reduced miss errors) in healthy participants (Levin et al. 1998). Nicotine-induced improvement in male mouse 5C-CPT performance has been similarly reported in C57BL/6J mice (Young et al. 2013; Higa et al. 2017), an effect interestingly absent in mice lack alpha7 nicotinic acetylcholine receptors (Higa et al. 2017). Thus, treatments targeting the alpha7 nicotinic receptor may prove useful for treating attentional dysfunction in ADHD. In support of this premise, and similar to dopaminergic agents described above, partial agonism of the alpha7 nicotinic receptor remediated attentional deficits in LA female rats (Hayward et al. 2017). Future studies are needed for such treatments targeting attentional dysfunction in people with ADHD.

Taken together, these data demonstrate the utility and clinical relevance of the 5C-CPT in preclinical ADHD-relevant research. However, as with all good science, new methods are constantly being developed and explored, which will be further discussed in the next section.

3.2 rCPT for ADHD Research

Similar to the 5C-CPT, the first rCPT studies characterized differences in performance across strains but, unlike the 5C-CPT, the rCPT was established using touchscreen operant chambers (Kim et al. 2015). When male mice of different backgrounds (C57Bl/6J versus DBA/2J versus CD1) were trained to respond to a single stimulus on the touchscreen 100% of the time, mice from all backgrounds were successful in reaching criterion. However, when presented with a visually distinct non-target stimulus 50% of the time, CD1 mouse performance stopped responding. When tested on the actual rCPT (one target stimulus (50%) versus

four visually similar non-target stimuli (50%), the DBA/2J mice did not differ in performance compared with C57Bl/6J mice, unlike in the 5C-CPT (Young et al. 2009). This distribution is potentially a consequence of stimuli being presented at a 1:1 ratio, akin to a go/no-go task, which could impact study outcome interpretations (Burrows et al. 2022), in which they do not differ in performance (while it is 5:1 in the 5C-CPT). Furthermore, to create a comprehensive picture of the rCPT, Kim et al. (2015) performed probes that involved altering aspects of the task to determine if that would alter mouse performance. Visual probes, such as increasing the size and contrast of the stimulus, improved hit rate in the C57Bl/6J mice, further demonstrating their visual advantage. This approach is a potential strength of the touchscreen rCPT wherein visual parameters can be more readily manipulated as is sometimes done in human CPTs (e.g., degraded stimulus CPT), which offer opportunities that are not available when using operant chambers.

While research into the effects of common ADHD medications on the rCPT across different mouse strains is still lacking, one medication that has been tested is donepezil. Donepezil is a common treatment for cognitive deficits in Alzheimer's disease (Bentley et al. 2008; Romberg et al. 2011) and exerts its action through the inhibition of the enzyme, acetylcholinesterase, thereby elevating the concentration of extracellular acetylcholine. Its impact on rCPT performance has been tested, although it currently has no apparent use in ADHD (Wilens et al. 2005). Donepezil had few overall effects in the rCPT in normal performing mice: DBA/2J mice did appear to have better hit rates, but only at long stimulus durations (4 s) and with sufficiently high drug doses (3 mg/kg; Kim et al. 2015). Thus, evidence for cholinergic-induced changes in performance in the rCPT are still lacking.

More recently, studies have investigated potential pharmacological predictive validity of the rCPT with common ADHD medications, using different baseline-dependent groups as described above (i.e., low-attention (LA), high-attention (HA), low-impulsive (LI), and high-impulsive (HI)) (Caballero-Puntiverio et al. 2019). In male mice, methylphenidate improved hit rate (3.0 mg/kg) and *d'* (1.0–3.0 mg/kg) in the LA group, and reduced premature responses in the HI group at low doses (1.0 mg/kg). Methylphenidate also increased premature responding in LI male mice. Additionally, atomoxetine treatment reduced false alarms (1.0–5.0 mg) and increased *d'* (1.0–5.0 mg/kg) in LA male mice. Atomoxetine (1.0–5.0 mg/kg) also decreased premature responding (HI group), hit rates, and false alarms in HA male mice. Further investigations using female mice report very moderate changes in *d'* in response to methylphenidate (1.0–3.0 mg/kg), but robust *d'* increases after atomoxetine (1.0–5.0 mg/kg) treatment in the LA group (Caballero-Puntiverio et al. 2020). Atomoxetine also reduced premature responses in these female mice. These results are in line with rat 5C-CPT studies showing increases in vigilance (sensitivity index) in LA male rats after exposure to methylphenidate (1.0 mg/kg) and atomoxetine (1.0 mg/kg; discussed above Tomlinson et al. 2014). Importantly, both tasks were able to identify methylphenidate-induced decreases in premature responding in HI groups across different species. While these results speak to the predictive validity of each task, more work is needed to determine how subgroup

differences respond to ADHD drug treatment across species (e.g., mouse performance in the 5C-CPT, rat performance in the rCPT).

Aside from both strain and individual differences, other models of interest to ADHD research include developmental toxin exposures. Prenatal nicotine exposure, for example, is associated with a higher susceptibility for the development of ADHD (Biederman et al. 2017). In a gestational model of nicotine exposure using male NMRI mice, attentional impairments, as measured by decreases in *d'*, were observed and associated with molecular changes in primary neurons in the CA1 regions of the hippocampus (Polli et al. 2020). This finding is particularly interesting, as it suggests (but does not prove) a possible role of the hippocampus in the rCPT (despite a lack of hippocampal involvement in human CPTs).

Other work has demonstrated the role of the anterior cingulate cortex (ACC) in inhibiting responses to non-target stimuli, as measured by an increased false alarm responses in male mice after bilateral lesion of the ACC with quinolinic acid (Hvoslef-Eide et al. 2018). Further work, however, should be conducted to determine what specific role, if any, the hippocampus may play in performance on the rCPT, as hippocampal lesions impair performance in the go/no-go tasks (Foster and Rawlins 1992), but not in the 5-CSRTT (Finlay et al. 2015), or in human CPTs. It is important to note, however, that the NMRI mouse strain is albino, and, while group changes were seen both behaviorally and ex vivo, this highlights the important point that care should be taken when determining which strain of mouse to use when utilizing a visually-dependent task. Additionally, given that adult nicotine treatment improves human Conners' CPT performance (Levin et al. 1998), and mouse 5C-CPT performance (Young et al. 2013; Higa et al. 2017), more work should be done to determine the effects of nicotine in the rCPT, both in developmental exposure and as a recreational drug.

As mentioned previously, people with ADHD often have many attentional deficits common in those with schizophrenia (Buchanan et al. 1997). For this reason, another developmental exposure model – single exposure, gestational methylazoxymethanol acetate treatment (MAM-E17), has been used to recreate attentional deficits in rats. Assessment of the MAM-E17 rat model in the rCPT confirmed such attentional deficits, with male MAM-E17 rats demonstrating a lower *d'*, compared to controls (Mar et al. 2017). Interestingly, this reduction in *d'* is similar to that observed in another developmental rat model of schizophrenia-related attentional deficits (vitamin D deficiency; Turner et al. 2013) in the 5C-CPT, with the addition of increased false alarms, which is rescued with administration of the atypical antipsychotic clozapine (2.5 mg/kg). Furthermore, this model demonstrates no changes in *d'* or false alarms, but instead, indicates that male mice make significantly more perseverative responses during target trials (Harms et al. 2012). These differences underscore the difference in mechanisms underlying animal models of disease and the importance of considering which animal will best recreate the behaviors of interest when investigating attentional dysfunction.

Several different pharmacologic agents have proven useful in modulating performance in the rCPT, relative to the MAM-E17 model. For example, inhibiting either dopamine signaling with sulpiride (30 mg/kg) or GABA signaling with RO4938581

(10.0 mg/kg) reduces vigilance, as measured by *d'*, in MAM-E17 rats. *d'* is also decreased in these rats when norepinephrine or glutamate signaling is increased with atomoxetine (1.0 mg/kg) and LSN2463359 (5.0 mg/kg), respectively (Buchanan et al. 1997). Also, treatment with a nicotinic acetylcholine receptor agonist (ABT-594: 19.4 mg/kg), which binds to both α3β4 and α4β2 receptor subtypes, did not rescue the reduced *d'* expressed by MAM-E17 rats, relative to controls, but had the additional effect of increasing both hit rate and false alarms in both groups. This finding is in contrast to previous reports in the 5C-CPT using the selective α4β2 nAChR agonist, ABT-418, which improved *d'* at low and moderate doses (12 and 40 μg/kg; Young et al. 2013).

Finally, treatment with a commonly prescribed stimulant (modafinil) in the rCPT increased *d'* vigilance in control rats at low doses (8.0 mg/kg), without affecting the MAM-E17 group and increased false alarms in both groups. As stated previously, these varied effects highlight the myriad effects that developmental toxin exposure, such as with methylazoxymethanol acetate, can have on the brain and associated behaviors. Nevertheless, studies like these provide insight to potential mechanism in attention, especially as they relate to tasks, such as the 5C-CPT and rCPT.

Further research has focused on possible genetic underpinnings in attentional deficits. One genetic model of interest – the 22q11.2 deletion syndrome – is associated with neurodevelopmental disorders, such as schizophrenia and ADHD, but also leads to severe physical abnormalities (Ozen et al. 2021). Due to its association with attentional impairments, the rCPT has been used to assess performance in a mouse model of 22q11.2 deletion syndrome (Df(h22q11)/+; Nilsson et al. 2018). Male Df(h22q11)/+ mice demonstrated decreased hit rate and *d'* indicating an impaired ability to discriminate between target and non-target stimuli. In line with previous reports, the authors used common and experimental ADHD treatments (amphetamine and modafinil) to rescue the attentional deficits of the Df(h22q11)/+ mice. Surprisingly, modafinil had little effect on hit rate and *d'*, and actually exacerbated deficits in these measures at high doses (40 mg/kg). Treatment with amphetamine improved hit rate and *d'* in the Df(h22q11)/+ mice at sufficiently high doses (1.0 mg/kg), but impaired hit rate in the wildtype mice. While 22q11.2 deletion syndrome has been linked with alterations in dopaminergic signaling (van Duin et al. 2018), further work is needed to understand how this genetic abnormality may contribute to attentional deficits in mice and how that relates to ADHD.

Overall, the rCPT is a rodent-based analog of the well-established human CPT, that provides a visual layout (center-focused) similar to that used in the human tasks. The predominant use of 50/50 stimulus presentation makes its standard version more akin to a go/no-go than a CPT, but its touchscreen utility offers not only opportunities to change this, but also to go beyond what is capable in the 5C-CPT. Importantly, more work is needed to establish the rCPT as recreating human CPT performance in addition to more detailed understanding of rodent impairments in the rCPT as they relate to ADHD.

4 Summary of the Benefits of Preclinical CPT-Like Tasks for ADHD Research

Preclinical behavioral tasks are now available to determine the neural mechanisms of one of the core symptoms of ADHD, namely inattention, consistent with its measurement in people with ADHD. The 5C-CPT has provided researchers with the means to directly compare cross-species attentional impairments and has both a preclinical and clinical paradigm, with fMRI availability for human use, and EEG in both humans and animals (Bhakta et al. 2017). The validity of the 5C-CPT for other human CPTs is wide-ranging, from face, predictive (including pharmacological), and construct validity. The clinical utility of the 5C-CPT has been demonstrated, with deficits in people with schizophrenia linked to EEG biomarkers of deficient N2 and P300 (Young et al. 2017), to reduced parietal activation in people with bipolar disorder (Young et al. 2020a), but not yet assessed in people with ADHD. The human 5C-CPT strongly correlates with other CPTs (Pocuca et al. 2020), supporting its use. The 5C-CPT utilizes more target than non-target trials, generating measurement of cognitive control, but this limitation means an inability to present more non-target to target trials, as seen in some CPTs. The rCPT is relatively newer, presenting stimuli on a touchscreen that enables a far greater variety of stimuli, but its lack of a clinical counterpart and lack of validation to human CPTs means there is a great deal of research to be done before it can be readily used for ADHD research.

5 Is Measurement of Premature Responses Relevant to Impulsivity in ADHD?

Impulsivity can take many forms, including behavioral inhibition, delay of reinforcement, and temporal perception, with potential overlap between each (Evenden 1999). Impulsive action and impulsive choice are two aspects of impulsive behavior; action refers to behaviors such as responding to stimuli they should instead inhibit (behavioral inhibition), while impulsive choice refers to making suboptimal choices, such as choosing $1 now versus $5 in 10 min, which can be complicated by temporal perception. Certainly, people with ADHD exhibit impulsive action, response disinhibition described above, in response to non-target stimuli (Coutinho et al. 2017). Impulsive choice has also been ascribed to people with ADHD, selecting low rewards rather than tolerating delays (Unsel Bolat et al. 2016). When delays were incorporated into choice tasks, however, any differences from healthy participants disappeared. In other words, people with ADHD likely are averse to delays, which may relate to altered perception of the passage of time (Williams 2010).

This work is pertinent given the importance of temporal perception when rodents commit premature responses in the 5-CSRTT (Cope et al. 2016). Specifically, animals are trained in the task over many 1000s of trials, in which they learn to expect a stimulus presentation after a predetermined period of time (typically 5 s).

Thus, animals learn they do not need to attend for a stimulus until 5 s after their initiation of a trial due to innate perception of time. Speeding such perception would lead to instrumental expectation that the stimuli appear prior to actual presentation, perhaps leading to a "guess" in case they missed it (one in five chance for a reward), producing premature responses as altered perception of time (Cope et al. 2016). Thus, the 5-HT_{2A} receptor antagonist, SB242084, which speeds the perception of time (Cope et al. 2016), increased premature responses in the 5C-CPT without increasing false alarm responses (Young et al. 2011). By contrast, delta9-tetrahydrocannabinol (an active ingredient of cannabis) slowed the perception of time and reduced premature responses (Cope et al. 2016). Interestingly, neither people with schizophrenia, nor bipolar disorder euthymia exhibited any premature responses (specifically, in the 5C-CPT they exhibit zero premature responses), nor have any been reported in the human 5-CSRTT. Furthermore, neither amphetamine nor modafinil treatment induced any premature responses in the 5C-CPT, unlike treatment to rats and mice in the 5-CSRTT. The only premature response recorded in clinical populations using the 5C-CPT was that of people with bipolar disorder mania, averaging four in 250 trials (Young et al. 2017).

A modified version of the 5-CSRTT was created for humans, the 4-CSRTT, which drives people to produce premature responses by: (1) having someone actively encouraging them to go faster during performance; (2) only gaining a reward (money) if they respond faster than their baseline; and (3) losing money if they responded more slowly. Here, premature responses have been measured in people, but none to date in people with ADHD in this or the human 5-CSRTT. Some consistency of premature responding between humans and rodents has been observed: e.g., in another 5-CSRTT variant (participants had to hold a home button and respond to 1 of 5 moving stimuli), revealed some premature responses (2–4%) at levels similar to mice (far less than rats), with elevated levels seen in binge drinkers as also seen in mice albeit with lengthened ITIs (Sanchez-Roige et al. 2014). Hence, some 5-CSRTT variants may yield premature responses, but data are yet to have been reported in people with ADHD. Thus, this review has focused on impulsive action (response disinhibition in response to non-target stimuli) in rodents.

6 Future Directions of Preclinical Attentional Research Using CPTs for ADHD

One key item to raise throughout this chapter is that the vast majority of research utilized adult rodents and humans, unless otherwise stated. ADHD was first identified in children, and with current treatments resulted in some people being treated with stimulants throughout their lives (Renoux et al. 2016). In addition, it is important to note that the majority of people with ADHD today are adults and that number is likely to increase over time, given the longer period of adulthood versus childhood/adolescence (Polanczyk and Rohde 2007). Thus, focus should remain not

only on inattention in people with ADHD, but also the long-term consequences of stimulant treatment on attention and other side-effects (Huang et al. 2012).

Another key aspect of the literature cited throughout this chapter is that most of the preclinical research has been conducted in males only, with few exceptions. While ADHD predominantly affects males over females (approximately 2.28:1; Ramtekkar et al. 2010), it is important to determine whether mechanistic research is consistent across the sexes, in case treatments are sex-specific. Stimulant-induced improvement in poorly performing 5C-CPT rodents has been seen in both male (Young et al. 2020b) and female rats (Tomlinson et al. 2014, 2015), so at least these data provide support that current treatments used for males and females with ADHD have predictive validity in the 5C-CPT. Future studies should endeavor to utilize both sexes for ADHD research.

Ultimately, the availability of these behavioral tasks provides great opportunities for ADHD research. These CPTs can be combined with novel neuroscientific techniques such as optogenetics, chemogenetics, and fiber-photometry to delineate neural mechanisms underlying normal CPT performance. Importantly, the impact of genes and environmental relevant to ADHD on these mechanisms and CPT performance can also be determined, with direct relevance to cognitive dysfunction in people with ADHD (animal models). The identification of such mechanisms may enable the development of more targeted therapeutics that can then be directly tested in these models. Importantly, any positive effects can then be directly tested in the clinical population given the consistency of behavioral testing across species. Thus, it is hoped that these rodent CPTs enable the opportunity for more direct translation of treatments relevant to behavioral dysfunction in people with ADHD.

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The Effects of Drug Treatments for ADHD in Measures of Cognitive Performance

Guy A. Higgins and Leo B. Silenieks

Contents

Abstract Based on core symptoms of inattention and deficient impulse control, and the identification of effective pharmacotherapies such as amphetamine (AMP; Adderall®), methylphenidate (MPH; Ritalin®), and atomoxetine (ATX; Strattera®), ADHD is a clinical condition which provides opportunity for translational research. Neuropsychological tests such as the 5-Choice and Continuous Performance Tasks, which measure aspects of attention and impulse control in animals and humans, provide scope for both forward (animal to human) and reverse (human to animal) translation. Rodent studies support pro-attentive effects of AMP and MPH and effectiveness in controlling some forms of impulsive behavior. In contrast, any pro-attentive effects of ATX appear to be less consistent, the most reliable effects

G. A. Higgins (✉)
Intervivo Solutions, Toronto, ON, Canada

Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
e-mail: guyh@intervivo.com

L. B. Silenieks
Intervivo Solutions, Toronto, ON, Canada

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of ATX are recorded in tests of impulsivity. These differences may account for AMP and MPH being recognized as first-line treatments for ADHD with a higher efficacy relative to ATX. DSM-5 classifies three "presentations" of ADHD: predominantly inattentive type (ADHD-I), predominantly hyperactive/impulsive type (ADHD-HI), or combined (ADHD-C). Presently, it is unclear whether AMP, MPH, or ATX has differential levels of efficacy across these presentation types. Nonetheless, these studies encourage confidence for the forward translation of NCEs in efforts to identify newer pharmacotherapies for ADHD.

Keywords 5-Choice serial reaction time task · Attention · Continuous performance task · Impulsivity · Rat · Translation

Abbreviations

5C-CPT	5-Choice continuous performance task
5-CSRTT	5-Choice serial reaction time task
5-HT	5-Hydroxytryptamine (serotonin)
ADHD	Attention-deficit hyperactivity disorder
ADHD-C	Attention-deficit hyperactivity disorder – combination of both
ADHD-HI	Attention-deficit hyperactivity disorder – predominantly hyperactive/impulsive
ADHD-I	Attention-deficit hyperactivity disorder – predominantly inattentive
AMP	Amphetamine (Adderall®)
ATX	Atomoxetine (Strattera®)
AUC	Area under curve
Cmax	Maximum concentration of drug
CNS	Central nervous system
CPT	Continuous performance task
d'	Discriminability index
DA	Dopamine
DAT	Dopamine transporter
DRL	Differential reinforcement of low-rate
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
GUAN	Guanfacine (Intuniv®)
HA	High attentive
HI	High impulsive
IP	Intraperitoneal
ITI	Inter-trial interval
LA	Low attentive
LI	Low impulsive
MPH	Methylphenidate (Ritalin®)
NCE	New chemical entity
NE	Norepinephrine

NK1	Neurokinin-1 receptor
PREM	Premature responses
PSV	Perseverative responses
rGT	Rodent gambling task
SC	Subcutaneous
SHR	Spontaneously hypertensive rat
SI	Sensitivity index
sITI	Short inter-trial interval schedule
sSD	Short stimulus duration
SSRT	Stop-signal reaction time
SST	Stop-signal task
WKY	Wistar Kyoto rat

1 Introduction

1.1 Clinical Symptomatology and Treatment

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by some combination of inattentiveness, hyperactivity, and impulsivity. ADHD was initially identified in children, but is now recognized to persist into adulthood in approximately two thirds of those individuals presenting at childhood (Faraone et al. 2000; Biederman and Faraone 2005). Meta-analyses estimate the worldwide prevalence of ADHD at 5.3% in individuals of less than 18 years of age (Polanczyk et al. 2007), and at 4.4% in adults based on a US survey (Kessler et al. 2006), and 3.4% in a broader international survey (Fayyad et al. 2007). ADHD often co-occurs with other psychiatric comorbidities, including: substance use; sleep and anxiety disorders; and antisocial personality disorders (Biederman and Faraone 2005; Fayyad et al. 2007; Katzman et al. 2017). A genetic component to ADHD is implied by the observation that first-degree relatives of a child diagnosed with ADHD are four to five fold more likely to have ADHD compared with the general population, with siblings having up to a ten-fold higher risk (Faraone et al. 2000; Biederman and Faraone 2005; Brookes et al. 2008).

The current Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5; American Psychiatric Association 2013) classification seeks to improve the reliability of the diagnosis of ADHD across all age groups, recognizing the prevalence of the adult form. Accordingly, DSM-5 has reclassified ADHD from "Disorders Usually First Diagnosed in Infancy, Childhood or Adolescence" to "Neurodevelopmental Disorders."

ADHD symptoms and signs fall into two primary categories of inattention and hyperactivity/impulsivity. Symptoms of inattention include a short attention-span and lack of response to verbal or other cues. Hyperactive symptoms may manifest as an excess of motor activity, rapid speech, and fidgeting. Impulsive actions often

demonstrate a disconnect between executive functioning and actions. These may be manifest by actions such as premature answers before questions completed, difficulty waiting in turn, interrupting or intruding on others. For a diagnosis under DSM-5, several of these symptoms must be present across two or more settings. Clinical impairment must be shown in social, academic, or occupational functioning.

Three diagnostic "presentations" of ADHD are generally recognized in the current DSM-5 classification: predominantly inattentive (ADHD-I), predominantly hyperactive/impulsive (ADHD-HI), and a combination of both, with the combined type (ADHD-C) being the most prevalent (~60%) (Anastopoulos and Shelton 2001; Faraone et al. 2015). However, the acceptance for the clinical validity and use of these "presentations" is mixed (Biederman and Faraone 2005; Lange et al. 2014; Faraone et al. 2015). While ADHD is recognized in both males and females, there may be sex differences in the clinical expression of symptoms. For example, males are more likely to exhibit symptoms of ADHD-HI and females may present with lower ratings of attention relative to males (ADHD-I). Also, generally speaking, ADHD is more frequently identified in males, although this may be in part linked to symptoms being more evident and thus more readily diagnosed, in boys (see Gaub and Carlson 1997; Biederman and Faraone 2005; Gershon 2002).

For more than 50 years, ADHD has been treated by catecholaminergic stimulants, predominantly enantiomeric forms of amphetamine (AMP; e.g., Adderall®) and methylphenidate (MPH; e.g., Ritalin®) (see Heal et al. 2009; Faraone et al. 2015). Over this time, both treatment approaches have been clinically effective and today represent the primary clinical approach to treating children and adults with ADHD, notwithstanding their potential for diversion and abuse. *d*-Amphetamine and MPH are efficacious in approximately 70–80% of ADHD patients, a responder level that can increase further by switching an individual between both drugs (Biederman and Faraone 2005; Heal et al. 2009; Bolea-Alamañac et al. 2014). Various formulations of both drugs have also become available, designed to provide short (2–4 h), intermediate (6–8 h), and long-acting (10–12 h) durations of pharmacological effect, to further tailor treatment to the individual (Faraone et al. 2015).

The pharmacological properties of AMP and MPH are largely restricted to enhancement of CNS dopamine (DA) and norepinephrine (NE) transmission, which has led to the dominant view that functional imbalances between these two neurotransmitters within key CNS regions, notably the prefrontal cortex, underlie core ADHD symptoms (Arnsten 2009; Heal et al. 2009; Bolea-Alamañac et al. 2014; Spencer et al. 2014). While both inhibit the catecholamine reuptake transporters, AMP has the additional property directly enhancing DA release from vesicular stores (Heal et al. 2013; Hutson et al. 2014), which likely accounts for its greater effect on DAergic function relative to MPH, especially in subcortical regions such as the striatum/accumbens (Kuczenski and Segal 1997, 2001; Heal et al. 2009).

More recently, the selective NE reuptake inhibitor, atomoxetine (ATX; Strattera®), (Bymaster et al. 2002) has emerged as a third major treatment option, becoming widely approved for ADHD (Simpson and Plosker 2004; Heal et al. 2009; Bolea-Alamañac et al. 2014). Also the preferential α_{2A}-adrenoceptor agonist, guanfacine (GUAN; Intuniv®), has proven efficacious as a treatment for ADHD

and an extended release formulation has been approved in some territories, although on a more restricted basis compared to AMP, MPH, and ATX. This is in part due to a side-effect risk of hypotension, sedation, drowsiness, and depression (Biederman and Faraone 2005; Faraone et al. 2015). Both ATX and GUAN are recognized as non-stimulants without the abuse liability of the stimulant class of ADHD treatments (Jasinski et al. 2008; Heal et al. 2009; Faraone et al. 2015).

Because of the clinical failure of various drug candidates with predominantly DA reuptake inhibitory properties (Heal et al. 2009), this may suggest a greater contribution of enhanced NE tone to the clinical efficacy of an ADHD therapeutic. However, this view should be balanced by meta-analytic studies showing a higher responder rate and overall efficacy for AMP and MPH compared to ATX as treatments for both adult and juvenile forms of ADHD (Cunill et al. 2016; Faraone and Glatt 2010; Faraone et al. 2006; Mészáros et al. 2009; Bolea-Alamañac et al. 2014). Also a DAergic component may contribute to the mechanism of action of ATX. For example, microdialysis studies show ATX to increase both extracellular DA and NE levels in the prefrontal cortex of rodents (Bymaster et al. 2002; Swanson et al. 2006).

In summary, enhancement of both DA and NE neurotransmission within the prefrontal cortex is generally recognized as critical to the therapeutic efficacy of ADHD drugs (Arnsten 2009; Del Campo et al. 2011; Bolea-Alamañac et al. 2014; Spencer et al. 2014; Stanford and Heal 2019).

1.2 ADHD as an Opportunity for Translational Research

Bidirectional cross-species translation of findings between preclinical experimental animals and humans represents an important strategy for new drug discovery, and an attempt to reverse the high attrition rate of new chemical entities (NCEs) as they pass through the clinical development process (Kola and Landis 2004; Hay et al. 2014). An important feature of this approach is the utilization of tests that can generalize across species in terms of underlying neurobiology, behavioral expression, and response to treatments (Day et al. 2008; Enna and Williams 2009; Markou et al. 2009; McArthur 2017; Tricklebank et al. 2021). Translational research is also greatly assisted by the parsing of complex clinical disorders into discrete symptom clusters, or endophenotypes (Hyman and Fenton 2003; Markou et al. 2009; Insel et al. 2010; Robbins et al. 2012; Kozak and Cuthbert 2016; Robbins 2017; Young et al. 2017). This deconstruction represents a more focused means to investigate the underlying neurobiology and a more rational approach to study treatment effect across species (Pangalos et al. 2007; Day et al. 2008; Markou et al. 2009; Insel et al. 2010; Robbins et al. 2012; McArthur 2017; Young et al. 2017; Tricklebank et al. 2021).

Based on core symptoms and the identification of effective pharmacotherapies, ADHD is a clinical condition, which serves as a useful avenue for translational research (Robbins 2017; Phillips et al. 2018). The core symptoms of ADHD (inattention and impulsivity) represent two of the most widely studied

endophenotypes that can be reliably measured both in animals and humans with analogous cross-species tests. For these reasons, ADHD presents opportunities both for forward translation from preclinical to clinical trials and reverse translation for clinical observation to be reinvestigated in the preclinical setting (Winstanley et al. 2006; Chamberlain et al. 2011; Robbins 2017).

The remainder of this article is focused on studies investigating the three primary ADHD therapies in use today (i.e., AMP, MPH and ATX) in predominantly rodent-based operant tests, designed to measure aspects of attention and impulse control. Some of the work presented will be based on the authors' own research but, given the broad scope of this research topic, equivalent studies conducted by other research groups will be discussed, to identify areas of consensus or otherwise. Finally, the reverse translatability of these findings to the clinical experience of ADHD therapy will be considered.

2 Effect of AMP, MPH, ATX in Preclinical Tests Related to Endophenotypes of ADHD

2.1 General Comment

Multiple tests have been developed to measure the domains of attention and impulsivity in rodents and non-human primates using human test counterparts. Reflecting the multidimensional nature of both constructs, multiple tests or adaptive test configurations are necessary to study each domain. The 5-Choice Serial Reaction Time Task (5-CSRTT) was initially developed by Robbins and colleagues as a preclinical equivalent to the human Continuous Performance Task (CPT) (Robbins 2002), a test that is widely used in clinical ADHD research. The 5-CSRTT has probably become the most widely used test to measure attention and impulsive action in rodent species. Accuracy may be measured either as % correct (# correct/(# correct + # incorrect) (commission errors) * 100) or % hit which also includes errors of omission, although for this measure to be valid, omissions should be confirmed as being related to task difficulty as opposed to motor or motivational factors.

A strength of the 5-CSRTT is the capability to modify task conditions to differentially challenge attention and response control (Robbins 2002; Bari et al. 2008; Amitia and Markou 2011; Higgins and Silenieks 2017). For example, varying the event rate of stimulus presentation may challenge aspects of attention and response control in different ways. A short event rate (e.g., inter-trial interval (ITI) range of 2–4 s, resulting in a high frequency of stimulus presentation, will challenge an aspect of attentional processing with little impact on impulse control, while a lower rate (e.g., ITI range 8–10 s) challenges response control in addition to attention. Similarly, variations in the duration of the visual stimulus (SD) can be used to vary its detectability. Conversely, extending trial presentations from a

normal range of 100–150 to 250 trials may challenge vigilance (i.e., extended performance) over time. These schedule variations have been exploited by various groups, including ours, to investigate the effect of AMP, MPH, and ATX on animals' performance.

The 5-Choice Continuous Performance Task (5C-CPT) is a closer rodent analog of the human CPT. Unlike the 5-CSRTT, where all trials are target trials requiring a "*go*" response, the 5C-CPT test includes non-target stimuli to which the animal must withhold responding (Lustig et al. 2013; Cope and Young 2017). In a typical 5C-CPT test design, approximately 80% are "*go*" trials, with the remainder "*no-go*" trials; thus, non-target trials are interspersed to provide an additional challenge compared to the 5-CSRTT. Responding during such a "*no-go*" trial is termed a "false alarm" and is categorized as response disinhibition, a form of impulsive action (Winstanley 2011; Lustig et al. 2013; Cope and Young 2017). The CPT thus allows the experimenter to probe test manipulations on multiple types of impulsivity, as well as attention, using measures of signal detection theory. To further highlight the translatable capability of the 5-CSRTT and 5C-CPT, computerized touch screen variants have been developed for the rat, mouse, rhesus monkey, and marmoset primate species (Weed et al. 1999; Spinelli et al. 2004; Hvoslef-Eide et al. 2015; Sullivan et al. 2021), which mirror the methodology used in humans (e.g., Riccio et al. 2001; Chamberlain et al. 2011; Worbe et al. 2014).

Impulsivity is generally subclassified into two domains: impulsive action (motor impulsivity) and impulsive choice (decisional impulsivity) (Evenden 1999; Winstanley 2011; Hamilton et al. 2015; Dalley and Robbins 2017). Impulsive action is associated with a loss of control over responding, a failure of behavioral inhibition (i.e., "stopping"), or acting prior to having all necessary information needed to guide responding (i.e., "waiting"). It is most frequently investigated using the 5-CSRTT, with responses made prior to a stimulus presentation (termed premature [PREM] responses) regarded as an impulsive act (Robbins 2002; Winstanley 2011).

Alternative tasks include the Stop-Signal Task (SST), which requires the test subject to cancel an already-initiated action, as opposed to withholding a response, as in the 5-Choice task. The close temporal proximity between the *go* and *stop* signals makes the stop-signal reaction time (SSRT) the principal measure, which is a time estimate for a subject to attend to, process, and complete an inhibitory response to a *stop* signal (Eagle et al. 2008). The *go/no-go* task requires the subject to adjust to external stimuli (e.g., light/tone) used to signal either a response (*go*) or to withhold a response (*no-go*) trial. Typically, evaluation of the *stop* and *go* signals occurs before the subject can make a *go* response, introducing a decisional component (Eagle et al. 2008). Responses made in *no-go* trials are termed false alarms and are analogous to those responses recorded in the CPT. Both the SST and *go/no-go* tasks are utilized in both the preclinical and clinical setting to measure response inhibition.

In contrast to the predominantly motor-based tasks of impulsive action, tasks of impulsive choice (or risky choice) are reflected by more cognitive-based tasks of choice and preference, with decision-making influenced by delay to reward, or the probability/risk of gaining reward versus punishment. These Delayed Discounting paradigms assess decision-making based on the premise that the subjective value of

a reward diminishes as the delay in its delivery increases. The rate of discounting between an immediate small reward versus a larger reward, when dependent on an adjustable delay, provides a measure of impulsive choice (Evenden and Ryan 1996; Winstanley 2011; Hamilton et al. 2015).

Decision-making based on reward probability is assessed experimentally by probability discounting or gambling-type paradigms, such as a procedure first reported by Zeeb et al. (2009), which was devised as a rodent equivalent of the human Iowa Gambling Task. The rodent Gambling Task (rGT) requires test subjects to make choices based on advantageous/low risk versus disadvantageous/high risk options. Since all choice options are presented simultaneously there is not the complicating issue of ascending or descending schedules, which is inherent in many discounting task designs.

An alternative risk-based task has been developed by Setlow and colleagues (Simon et al. 2009, 2011). In this task, rats are given choices between a small, safe (unpunished) reward, and a larger reward, which is accompanied by risk of a mild footshock (0.3–0.35 mA) punishment. The probability or risk of punishment varies from 0 to 100% within a test session, thus allowing a measure of decision-making. The use of a mild footshock punishment likely introduces a more salient cost compared to reward omission used in tests of probability discounting.

Given this range of measures related to the domains of attention and impulsivity, an important question in ADHD research is which are the most relevant, from a translational perspective, both for diagnosis and measurement of a drug effect? Laboratory-based tests identify impairments in response inhibition (e.g., slower SSRT, higher incidence of false alarms) as an important marker of ADHD (Castellanos and Tannock 2002; Aron and Poldrack 2005; Lijffijt et al. 2005) and so tests such as SST, *go/no-go,* or CPT tasks serve an important role in the translational study of ADHD treatments. ADHD subjects also show a greater propensity for impulsive or risk-based choice, such as the preference for smaller but more immediate rewards, over larger but delayed rewards (Castellanos and Tannock 2002; DeVito et al. 2008; Patros et al. 2016). Consequently, measures of impaired response inhibition and impulsive/risk-based choice represent two core features of ADHD (Winstanley et al. 2006). In terms of inattention, deficits in both selective and sustained attention have been described in ADHD subjects, as well as an abnormal variability in reaction time to certain tasks (response precision) (Castellanos and Tannock 2002; Karalunas et al. 2012; Mueller et al. 2017).

2.2 Neurocognitive Endophenotypes to Study ADHD Drugs

Rats tested in many of the tasks described in Sect. 2.1 tend to show a continuum of performance on measures of accuracy and impulsivity. Subjects at the extreme ends of this continuum therefore represent an approach to study these endophenotypes (Jupp et al. 2013; Hayward et al. 2016; Barlow et al. 2018; Higgins et al. 2020a, b). However, subgrouping, based on performance, requires at least three conditions to

be met for validity. First, there is a requirement to demonstrate that any performance subgroup classification is enduring in nature and based on performance history. The second is to establish that the extreme subgroups, particularly low/poor performers, are not a consequence of non-specific factors, such as ill health. The third requirement is for large sample sizes to ensure that subgroups are adequately separated and powered (Button et al. 2013; Hayward et al. 2016).

ADHD research lends itself to the use of neurocognitive endophenotypes of attention and impulse control. Selecting animals, based on a phenotype of low choice accuracy or high PREM responses in 5-CSRTT performance, represents a logical population with which to study ADHD (Puumala et al. 1996; Blondeau and Dellu-Hagedorn 2007). A feature of behavioral subgrouping is that it places no bias on any underlying neurobiology. Attempts have been made to identify biochemical or genetic biomarkers relevant to a specific endophenotype with probably the most important advances in the study of impulsive trait based on high/low PREM responders in the 5-CSRTT (Jupp et al. 2013, 2020; Sholler et al. 2020). Indeed, the selection of subgroups based on high versus low PREM responding to extended ITIs (high versus low impulsives; HI versus LI; see Hayward et al. 2016; Higgins and Silenieks 2017; Barlow et al. 2018) has proved to be a useful approach in preclinical ADHD research (see Sect. 2.4).

In terms of subgrouping, based on attentional performance, several researchers have applied high and low attentive rats to the study of drug effects in the 5-CSRTT and 5C-CPT (Puumala et al. 1996; Blondeau and Dellu-Hagedorn 2007; Paterson et al. 2011a; Tomlinson et al. 2014; Higgins et al. 2020b). The study of Blondeau and Dellu-Hagedorn (2007) reported a sub-population exhibiting both high impulsivity and low attention. While the majority of these studies categorized performance on baseline task conditions, we have applied subgroupings based on percent accuracy (% correct and/or % hit) under conditions of sITI (i.e., short variable ITI; range 2–5 s) and a variable sSD (short stimulus duration i.e., brief visual stimulus duration, range 0.03–1 s) schedule (Higgins et al. 2020b). Interestingly we found that performance under the sSD does not predict performance under the sITI. That is, in animals that have been run across both schedules, there was no correlation between performance accuracy in each task variant, suggesting that the sITI and sSD schedules test distinct neuropsychological systems. Similarly, animals identified as high impulsive in a test such as the 5-CSRTT may not necessarily show an equivalent profile on discounting (Broos et al. 2012).

The report of Broos et al. (2012) highlighted a wide variability in terms of discounting measured across a cohort of rats over increasing delay. This variability persisted over multiple trials thus fulfilling the criteria of performance history. These findings have also been reported by other groups, including our own (Cardinal et al. 2000; Diergaarde et al. 2008; Barbelivien et al. 2008; Slezak and Anderson 2009; Maguire et al. 2014; Higgins et al. 2016). A similar variability was also reported by Simon and coworkers (Simon et al. 2009, 2011) in a model of risky decision-making, in which rats are presented with a choice between a “safe” small food option and a “risky” large food option, with risk defined by an increasing probability of a mild footshock. These workers also evaluated the high/low risk-takers on a

delay discounting task, and found no correlation: i.e., high risk-takers, based on continued selection of large reward despite high risk of punishment, did not necessarily select large reward at longer delay intervals. Therefore, within the multidimensional domains of both attention and impulsivity, there is a high likelihood of unique performance subgroups of distinct underlying neurobiology and which may differ in their value as models of endophenotypes relevant to ADHD.

Preclinical ADHD research has also benefitted from the use of specific rodent strains as potential models of ADHD. For example, the Spontaneously Hypertensive Rat (SHR) has been described as a useful model of ADHD due to behavioral signs of increased locomotor activity, motor impulsivity, and inattention relative to the WKY control (Sagvolden 2000; Russell 2007), although concern has been raised about the suitability of the WKY rat for this purpose (Alsop 2007; Heal et al. 2009). Some genetically-modified (gene knockout (KO)/mutation) rodent models have also been used, based on behavioral phenotype, with the dopamine transporter (DAT) KO (Gainetdinov et al. 1999; Young et al. 2017) and NK1 receptor KO mouse lines (Yan et al. 2009; Porter et al. 2016) probably the best described. The present article is not intended to be exhaustive and largely focuses on pharmacological studies conducted in genetically "normal" rodent strains with some emphasis on behavioral subgroups based on attention/impulse control, which in these authors' opinion is providing a useful approach to the study of ADHD and its treatment.

2.3 Effects of AMP, MPH, and ATX on Measures Related to Attention

2.3.1 AMP and MPH

Generally speaking, the profiles of the psychostimulant drugs, AMP and MPH, on measures of accuracy recorded in tasks, including the 5-CSRTT or 5C-CPT, are somewhat similar. At doses described to be in the low range (i.e., 0.1–0.4 mg/kg; see Grilly and Loveland 2001), AMP reliably improves both accuracy, measured either as % correct or % hit, and increases response speed (i.e., faster without error trade-off) in rats and mice, particularly in test subjects identified as poor performers based on accuracy (Bizarro et al. 2004; Andrzejewski et al. 2014; Turner and Burne 2016; Caballero-Puntiverio et al. 2017, 2019; MacQueen et al. 2018b; Higgins et al. 2020b). For example, using a modified signal detection task, Turner and Burne (2016) (see also Turner et al. (2016)) reported that acute AMP doses of 0.1–0.25 mg/kg improved % signal trial accuracy in rats with low performance baseline. Higher AMP dose challenges (0.75–1.25 mg/kg) resulted in performance impairment, particularly in the high baseline group (Turner and Burne 2016), reflecting the characteristic inverted U-shaped relationship between AMP dose/exposure and cognitive performance (Grilly and Loveland 2001; Wood et al. 2014). Peak plasma concentrations (C_{max}) at the 0.1–0.3 mg/kg dose of d-AMP are in the range 35–100 ng/mL, which overlaps the therapeutic exposure levels measured in human

subjects following treatment with Adderall (see Angrist et al. 1987; Asghar et al. 2003; Slezak et al. 2018; Higgins et al. 2020b; Adderall XR Product Monograph 2017).

Similar positive effects have been reported for MPH in attention-based tasks, with improvements in accuracy across multiple studies utilizing the 5-CSRTT and 5C-CPT; again, in many cases, this is reported to be most evident in test subjects classified as low performers (Puumala et al. 1996; Bizarro et al. 2004; Navarra et al. 2008; Berridge et al. 2012; Spencer et al. 2014; Andrzejewski et al. 2014; Tomlinson et al. 2014; Caballero-Puntiverio et al. 2017, 2019; Ding et al. 2018; Higgins et al. 2020b; Toschi et al. 2021). However, in contrast to d-AMP, there may be a wider variability in the effective dose range of MPH, with Puumala et al. (1996) reporting that doses as low as 0.1 mg/kg improve accuracy in low performers trained in the 5-CSRTT, while the majority of studies report attentional improvements in the 1–6 mg/kg range. Spencer et al. (2014) highlight distinct cognitive effects of MPH, each with somewhat distinct dose profiles. Thus, a relatively low MPH dose (0.5 mg/kg) with concomitant plasma exposure in the clinical range, may be optimal for working memory improvement, yet sub-optimal for pro-attentional effect, which they report a maximal improvement at 2 mg/kg (Berridge et al. 2012; Spencer et al. 2014).

Taking advantage of the different test challenges that can be utilized in rats trained to the 5-CSRTT, we have investigated the effect of d-AMP (dose range: 0.03–0.3 mg/kg IP) and MPH (dose range: 1–6 mg/kg) in relatively large populations of adult Long Evans rats. Under test conditions of high event rate of stimulus presentation (i.e., sITI) (see Fig. 1a), and extended trials (i.e., 250 trials schedule) (see Fig. 1b), both drugs improved attentional performance measured as % correct, but more significantly as % hit, reflecting reduced omissions as well as improved choice accuracy. Also, both drugs, particularly AMP, increased speed of responding (i.e., faster response latencies). Each of these changes was most notable in the low performing cohorts and so consistent with much of the aforementioned literature (Higgins et al. 2020b). The performance improvement in the 250 trial test variant was most evident at the latter trial stages (i.e., Bins 3–5, corresponding to trials 100–250; see Fig. 1b), and reflects the positive effects of both d-AMP and MPH on vigilance: i.e., sustained attention over time (see Fig. 1b; also Grottick and Higgins 2002). However, at equivalent doses, neither d-AMP nor MPH improved accuracy under the sSD and long 10s ITI condition (Higgins et al. 2020b) (see Fig. 1c).

We also evaluated the effects of d-AMP (0.03–0.6 mg/kg) in male, Long Evans rats trained to a 5C-CPT (see Fig. 2a), according to methods described in Higgins and Silenieks (2017). While there was no overall effect of any dose on attentional measures when all test subjects were included ($N = 20$), subgrouping rats into low and high attentives based on % correct measure (i.e., tertile groups, $N = 7$ per tertile) identified trends to improvement both in accuracy (% correct) and sensitivity index: a measure of the test subjects' ability to discriminate between target and non-target trials (see Higgins and Silenieks 2017; Cope and Young 2017). MacQueen et al. (2018b) also reported an improvement on this measure (discriminability index (d'))

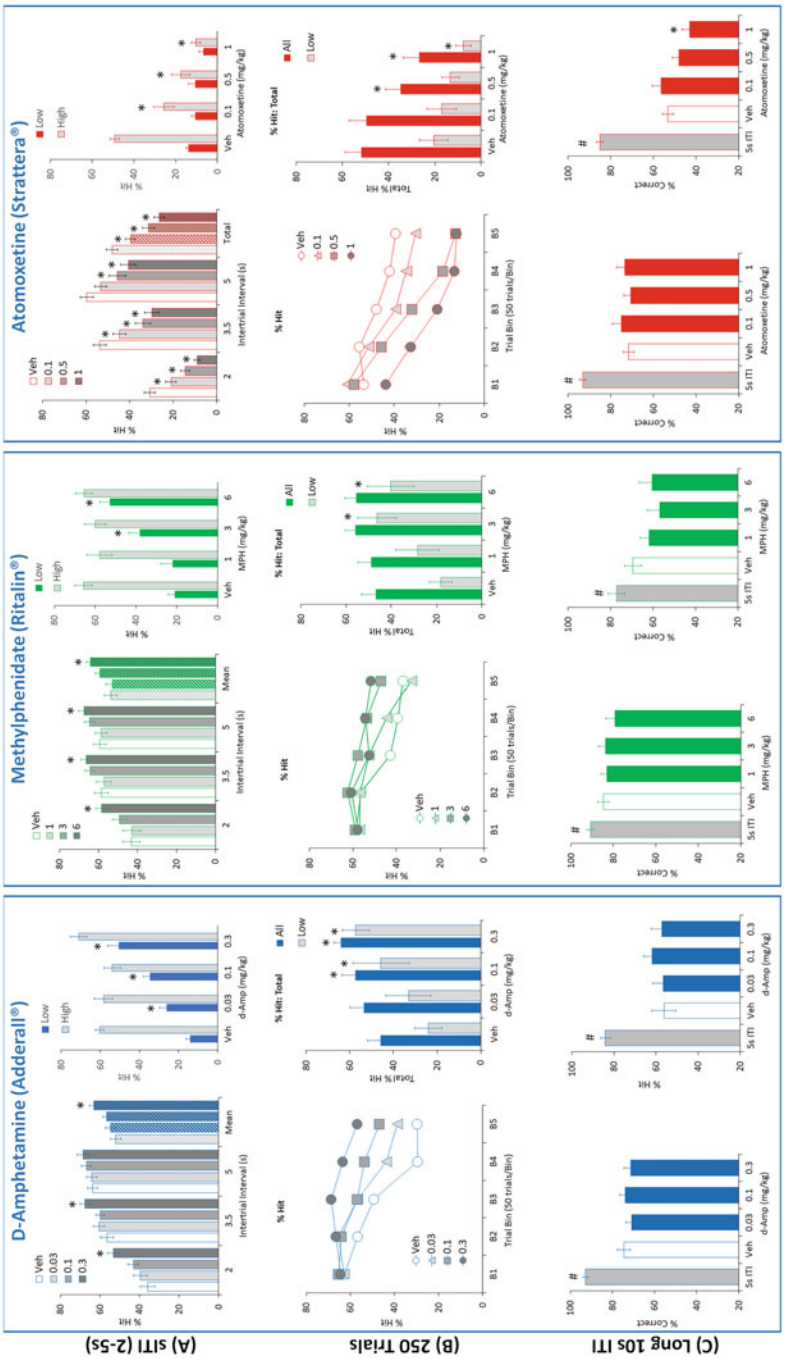

Fig. 1 Effect of amphetamine (AMP; 0.03–0.3 mg/kg IP), methylphenidate (MPH; 1–6 mg/kg IP), and atomoxetine (ATX; 0.1–1 mg/kg IP) on three different versions of the 5-Choice task, designed to produce different challenges to attention. (**a**) High event rate of stimulus presentation (sITI; 2–5 s), with attentional accuracy presented as % hit by ITI (all subjects), and also % hit at 2 s ITI (i.e., highest attentional demand) presented by both high and low attentive subgroups.

Fig. 1 (continued) Data previously presented in Higgins et al. (2020b). (**b**) Extended 250 trials presentation to test vigilance. Data presented as % hit calculated for each 50 trial bin (i.e., Bin 1–5) (all subjects), and also as Total % hit collapsed over all 250 trials for all rats, and by the lowest performing tertile (Low). Higgins and Silenieks (unpublished data) but see Grottick and Higgins (2002) for schedule detail. (**c**) Low event rate of stimulus presentation (10s ITI). Data presented for all rats with accuracy presented as % Correct and % hit. Data previously presented in Higgins et al. (2020b). Both AMP and MPH improved performance accuracy measured as % hit in sITI and 250 trials, notably in low performing rats. Neither drug affected accuracy in the low event rate condition. In contrast ATX actually impaired performance as % hit in each test condition, and notably in high performing rats. $^{*}P < 0.05$ vs. respective vehicle control group; $^{\#}P < 0.05$ vs. vehicle 10s ITI group. Figures presented in (**a**) and (**c**) are reprinted with permission

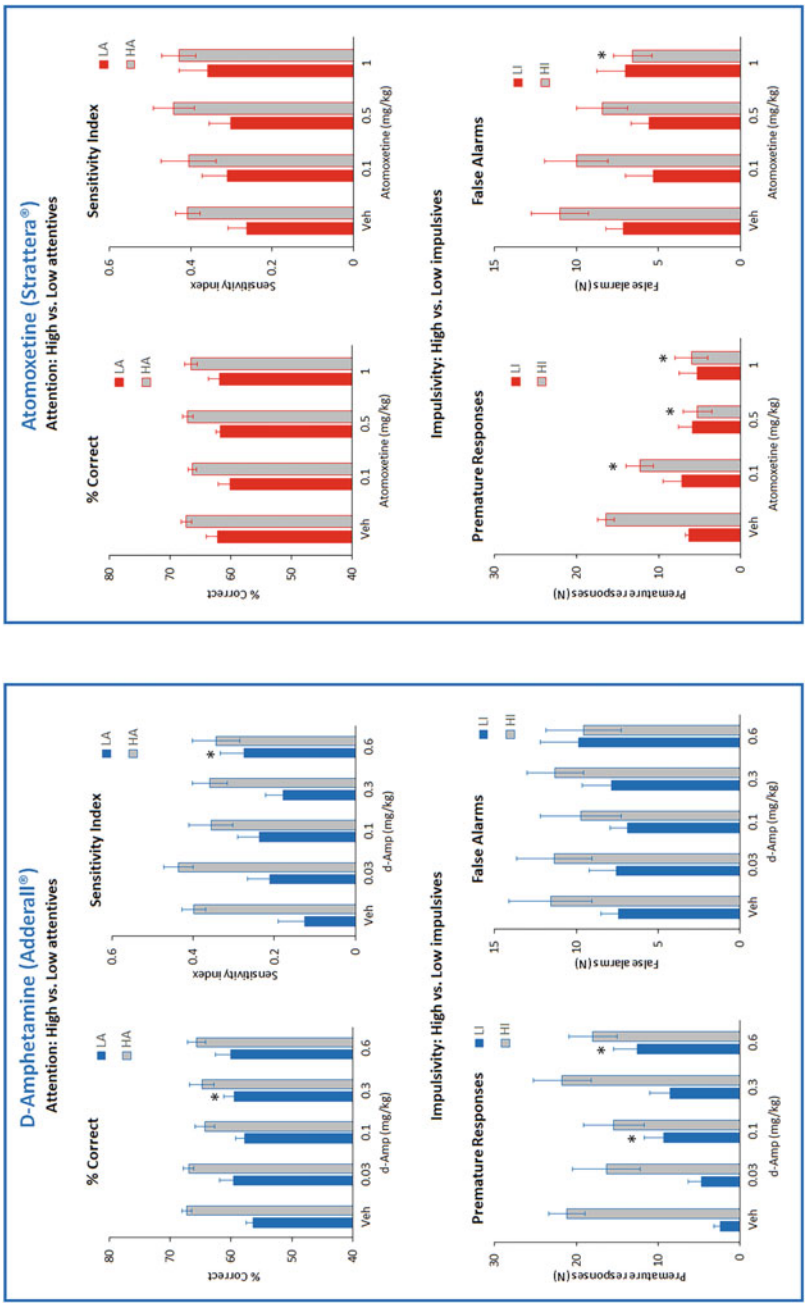

Fig. 2 Effect of d-amphetamine (AMP; 0.03–0.6 mg/kg IP) and atomoxetine (ATX; 0.1–1 mg/kg IP) on the performance of rats trained to a 5C-CPT. Male Long Evans rats were trained to a 5C-CPT task (see Higgins and Silenieks 2017 for methodological detail). Final task conditions: 1 s SD; 5 s ITI, 120 trials (84 target trials, 36 non-target trials). Both AMP and ATX were evaluated in all rats ($N = 20$) in a repeated measures design. The rats were subgrouped either (**a**)

Fig. 2 (continued) based on attentional performance (% correct; "high" attentive (HA, $N = 7$), "low" attentive (LA, $N = 7$), or (**b**) based on impulsivity measure (PREM responses; "high" impulsive (HI, $N = 7$), "low" impulsive (LI, $N = 7$)). Therefore these subgroups comprised distinct study cohorts. AMP (0.3–0.6 mg/kg) improved attention measured either as % correct, or sensitivity index in LA rats only. AMP (0.1–0.6 mg/kg) also increased PREM responses in LI rats. ATX (0.1–1 mg/kg) had no effect on attentional measures in LA/HA rats. In LI rats, however, ATX had a robust effect to reduce both PREM responses and false alarms, with greater potency against PREM responses. *$P < 0.05$ versus respective vehicle control group. Higgins and Silenieks (unpublished data)

in mice trained to a touchscreen CPT following pretreatment with AMP (0.1–0.3 mg/kg), largely due to an improvement in hit rate, rather than a decrease in false alarms – a profile similar to ours.

2.3.2 ATX

While the effects of AMP and MPH on attentional measures seem broadly similar and consistent across different laboratories, the overall profile of ATX is clearly distinct with some inconsistencies. Our own investigations utilizing the 5-CSRTT, thus controlling for procedural differences between laboratories, highlight some of these differences. Tested under identical task conditions, and in direct contrast to AMP and MPH, ATX (0.1–1 mg/kg) tends to impair attentional accuracy in the sITI and 250 trials conditions, particularly in rats identified as high performers (Higgins et al. 2020b; see Fig. 1a, b). Indeed, in all the test conditions utilized (i.e., sITI, sSD, 10s ITI, 250 trials) we have been unable to detect a pro-attentive effect of ATX, measured either as accuracy (% correct or % hit) or faster response speed, without error trade-off – even in test subjects classified as low attentive. These null effects of ATX have also been reported by other groups using the 5-CSRTT (Blondeau and Dellu-Hagedorn 2007; Robinson et al. 2008; Fernando et al. 2012; Toschi et al. 2021) or a touchscreen CPT (Ding et al. 2018). The recent report of Toschi et al. (2021) highlighted a finding similar to our own (Higgins et al. 2020b) in that ATX appears to be particularly detrimental to performance accuracy (hit rate) under a high event rate of stimulus presentation.

However, positive effects of ATX on attentional measures have been reported in some 5-CSRTT studies typically under conditions of extended ITI (see Navarra et al. 2008; Baarendse and Vanderschuren 2012; Callahan et al. 2019) and which may be secondary to improvements in response control (see Sect. 2.4.3). Furthermore, at least three studies have described accuracy improvements following ATX pretreatment in low attentive subgroups (Robinson 2012; Tomlinson et al. 2014; Caballero-Puntiverio et al. 2019). In the study of Tomlinson et al. (2014), utilizing rats trained to a 5C-CPT under a variable 10s ITI schedule, while ATX (1–2 mg/kg) improved accuracy in the low attentive subgroup, equivalent doses impaired performance in the high attentive counterparts.

Somewhat similar findings were reported by Caballero-Puntiverio et al. (2019, 2020) who investigated both male and female mice trained to a touchscreen CPT. In both groups, ATX improved performance based on the discriminability index, d', essentially by reducing false alarms, yet reduced hit-rate in high performers. The preferential α_{2A}-adrenoceptor agonist, GUAN, produced a response profile that was similar to ATX (Caballero-Puntiverio et al. 2019), although null effects on attentional measures are generally reported in a 5-CSRTT procedure following treatment with GUAN at pharmacologically relevant doses (Milstein et al. 2007; Fernando et al. 2012).

Our own experience with ATX (0.1–1 mg/kg) in a 5C-CPT task is that, while attentional accuracy may not be improved based on % correct to "*go*" trials, there

was a trend to an improvement in the sensitivity index, which like d' is a measure of the test subject's ability to differentiate between "*go*" and "*no-go*" stimuli (see Fig. 2b). This improvement was only evident in the study cohort identified as low attentive, based on their % correct performance. In contrast to AMP, the improvement trend in sensitivity index was largely attributable to decreases in false alarms rather than hit rate. These effects somewhat mirror the findings of Caballero-Puntiverio et al. (2019, 2020) and Tomlinson et al. (2014).

2.3.3 Summary

Taken together, the results from preclinical species highlight generally pro-attentive effects of both AMP and MPH, particularly in animals with a low baseline performance. Improvements may be manifest both as % correct and % hit rate, the latter reflecting treatment-induced reductions in trials of omission. In CPT-based tasks, improvements in signal detection (measured either as d' or the sensitivity index; see Cope and Young 2017) are also commonly reported, reflecting an improvement in the ability to discriminate and respond appropriately between target ("*go*") and non-target ("*no-go*") trials. Relative to MPH, d-AMP may produce more reliable increases in response vigor and speed in the absence of error trade-off, perhaps reflecting the greater effect on subcortical DA systems (Kuczenski and Segal 1997, 2001; Heal et al. 2009). Where conducted, extended dose-response experiments show the inverted U-shaped relationship between dose/exposure and attentional performance (Wood et al. 2014). In the case of d-AMP, there is a good agreement between the plasma exposure level at doses corresponding to the peak positive effect in preclinical species with clinically therapeutic levels (Angrist et al. 1987; Asghar et al. 2003; Slezak et al. 2018; Higgins et al. 2020b).

In contrast, any pro-attentive effects of ATX appear to be more subtle and largely confined to low performing subgroups. In high performing counterparts, or conditions of a high rate of stimulus presentation, the effect of ATX tends to be detrimental. Indeed, the contrast between the positive effect of AMP/MPH and the negative effect of ATX on 5-CSRTT performance, particularly under high-event rate conditions that require rapid information processing and action, is quite striking (Higgins et al. 2020b; Toschi et al. 2021). This effect of ATX may be a consequence of indirect activation of α- or β-adrenoceptors (see Sirviö et al. 1994; Ruotsalainen et al. 1997; Pattij et al. 2012). The fact that these attentional impairments following ATX pretreatment seem particularly prominent in high performers might explain why clinically, this feature of ATX may not be widely recognized in ADHD subjects.

2.4 *Effects of AMP, MPH, and ATX on Measures Related to Impulsivity*

2.4.1 AMP

Differential effects of AMP across "waiting" and "stopping" forms of impulsive action support their distinct neurobiology (Dalley and Robbins 2017). In tasks presenting a challenge to the "waiting" form, such as PREM responses prior to visual stimulus presentation in the 5-CSRTT, or timing behavior in a differential reinforcement of low-rate (DRL) task, a large body of literature consistently shows AMP to promote (i.e., increase) this impulsive measure (Sanger et al. 1974; Seiden et al. 1979; Robbins 2002; van Gaalen et al. 2006a; Ferguson et al. 2007; Paterson et al. 2011a; Higgins et al. 2020b) (see Fig. 3a). Typically, these effects begin to emerge at doses which produce pro-attentive effects, but continue to increase in magnitude. This is likely to contribute to the decline in attentional performance at higher doses because their frequency may impact on choice and overall task performance.

In the SST and *go/no-go* tasks, which require the subject to inhibit a prepotent response, AMP typically shows a propensity to improve performance and thus a trend to reduce this form of impulsive action (Feola et al. 2000; Eagle et al. 2009; Maguire and France 2019; Higgins et al. 2020b). Feola et al. (2000) reported that the positive effect of AMP (0.5 mg/kg) of reducing SSRT was restricted to slow stoppers, thus mirroring the baseline-dependent effects observed for attentional measures (see Sect. 2.3). Similarly, a significant decrease in false alarm rate was noted in rats trained to a *go/no-go* task (Higgins et al. 2020b). In our experiments investigating effects of AMP (0.03–0.6 mg/kg) on rat 5C-CPT performance, we have found robust increases in PREM responses but not false alarms (see Fig. 2a). Contrary to the *go/no-go* task findings, AMP did not reduce false alarms measured in the 5C-CPT.

The majority of investigations into AMP effect on impulsive choice are largely restricted to delay discounting where a wide variety of studies primarily seem to highlight the importance of procedural variables to influence outcomes. For example, AMP either reduced discounting (i.e., reduce impulsive choice: Wade et al. 2000; Winstanley et al. 2005; Van Gaalen et al. 2006b; Floresco et al. 2008; Sun et al. 2012), increased impulsive choice (Evenden and Ryan 1996; Helms et al. 2006; Slezak and Anderson 2009) or had no effect (Uslaner and Robinson 2006). Some of this variability in AMP effect is likely attributable to study variables, such as the use of a cue to signal delay (Cardinal et al. 2000), delay length (Slezak and Anderson 2009; Yates et al. 2019), environmental enrichment (Perry et al. 2008), reinforcer magnitude (Krebs et al. 2016), and schedule (Yates et al. 2019) (see Table 1). We and others (Barbelivien et al. 2008; Tanno et al. 2013; Maguire et al. 2014; Bickel et al. 2016; Orsini et al. 2017; Higgins et al. 2021) have also highlighted an influence of delay sequence and baseline discounting level as further factors influencing the AMP response (see Fig. 3c).

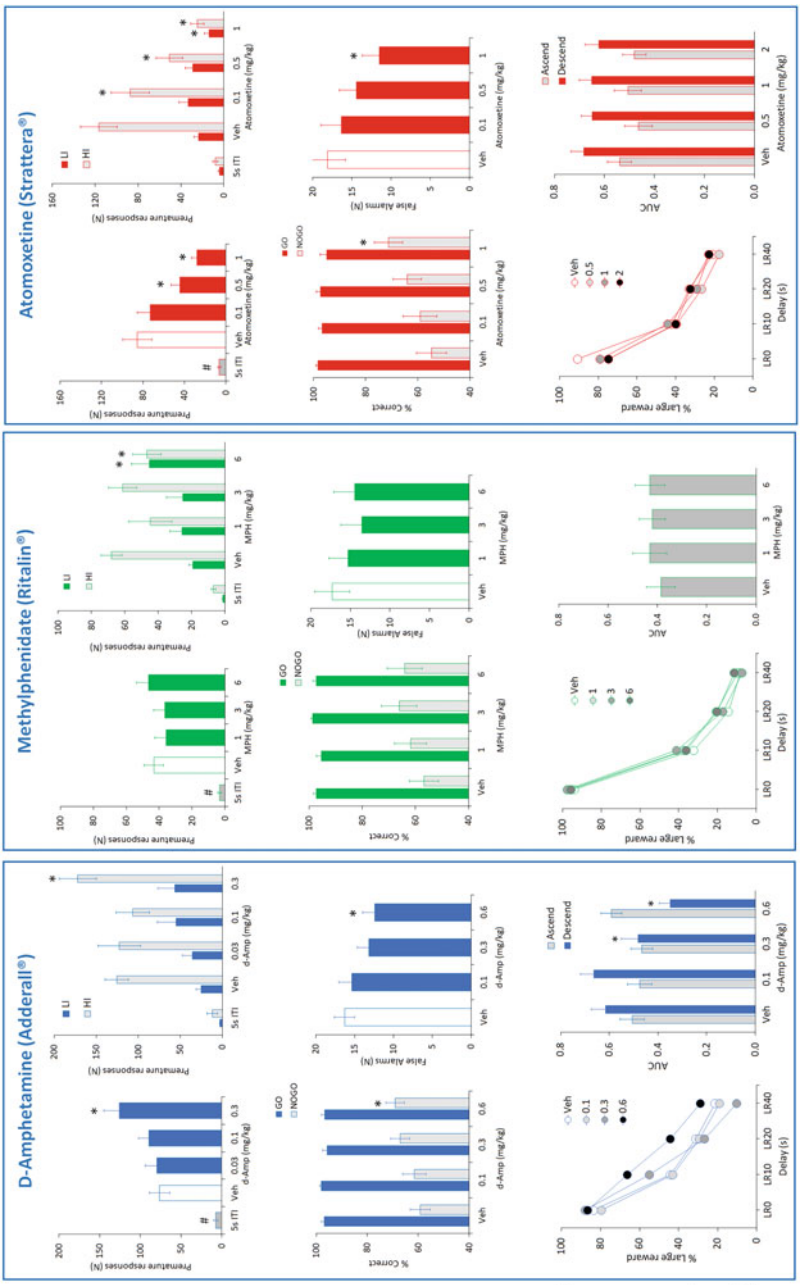

Fig. 3 Effect of d-amphetamine (AMP; 0.03–0.6 mg/kg IP), methylphenidate (MPH; 1–6 mg/kg IP), and atomoxetine (ATX; 0.1–2 mg/kg IP) on three different tasks, designed to produce different challenges to impulse control. (**a**) Low event rate of stimulus presentation (10s ITI). Data presented as the total number of

Fig. 3 (continued) PREM responses for all rats, and by both high (HI) and low impulsive (LI) subgroups. AMP increased PREM responses, both in LI and HI rats. MPH increased PREM responses in LI, and decreased PREM responses in HI rats – therefore showing a clear dependence on baseline level of PREM responses. ATX decreased PREM responses in all rats, but particularly in HI rats. Data previously presented in Higgins et al. (2020b). (**b**) *go/no-go* task performance with data presented either as % correct for both *go* and *no-go* trials, and the total number of false alarms recorded in *no-go* trials. Both AMP and ATX reduced false alarms and increased % correct in *no-go* trials, without affecting *go* trials. MPH showed a trend to reduce false alarms and increased % correct in *no-go* trials relative to vehicle pretreatment. Data previously presented in Higgins et al. (2020b). (**c**) Delay discounting with delays presented in ascending sequence. The discounting curves are shown for all male, Long Evans rats trained to ascending delays. The total AUC measures for all rats are also presented based on ascending or descending sequence (MPH ascending delays only). The data show that AMP reduced discounting under an ascending order of delay, and increased discounting under a descending order of delays. In contrast, ATX did not reliably influence discounting under either delay sequence. Data previously presented in Higgins et al. (2021), except MPH (Higgins and Silenieks, unpublished data). *$P < 0.05$ versus respective vehicle control group. Figures presented in (**a**), (**b**), and (**c**) are reprinted with permission

Table 1 Influence of different experimental variables on the effect of D-amphetamine on operant delay discounting in rodents. Variations in the operant delay discounting procedure, first developed by Evenden and Ryan (1996), influence the effect of AMP on discounting. This raises the question as to what is the most appropriate way of designing the operant delay discounting procedure (see Yates et al. 2019). ↓ discounting/↑ AUC relates to increased preference for the larger/delayed reward and ↑ discounting/↓ AUC relates to decreased preference for the larger/delayed reward. ↔ discounting/↔ AUC relates to no effect

Variable	Brief description of AMP effect	References
Delay sequence	AMP ↓ discounting (↑ AUC) on an ascending delay schedule AMP ↑ discounting (↓ AUC) on a descending delay schedule	Tanno et al. (2013), Orsini et al. (2017), Higgins et al. (2021)
Baseline performance	(1) review highlights five preclinical studies showing effects of AMP on discounting are dependent on baseline impulsive choice level. (2) AMP effect on discounting affected by baseline and sequence.	[1] Bickel et al. (2016) [2] Higgins et al. (2021)
Cue light to signal delay	AMP ↓ discounting (↑ AUC) under CUE condition AMP ↑ discounting (↓ AUC) under NO CUE condition	Cardinal et al. (2000)
Delay length/ response schedule	Interaction between delay length and response requirement. AMP ↓ discounting (↑ AUC) on FR1/short delay or FR10/long delay. Not on the converse combinations.	Yates et al. (2019)
Environmental enrichment	AMP ↑ discounting (↓ AUC) in environmentally enriched rats. AMP ↓ discounting (↑ AUC) in isolated (impoverished) rats.	Perry et al. (2008)
Reinforcement magnitude	AMP ↔ discounting (↔ AUC) between 1 vs. 3 pellet reward. AMP ↑ discounting (↓ AUC) between 2 vs. 6 pellet reward.	Krebs et al. (2016)
Test subject strain	(1) AMP ↔ discounting in SHR rats; ↑ discounting in WKY rats. (2) AMP ↓ discounting (↑ AUC) in LEW but not F344 rats. (3) differential effects of AMP between C57BL/6 and BALB/c mice.	[1] Hand et al. (2009) [2] Huskinson et al. (2012) [3] Pope et al. (2020)

This raises the important question of which is the most appropriate design for this test procedure to study drug effects? This topic needs to be resolved in order to more accurately define the profile of AMP on discounting. Effects of AMP on other measures of impulsive choice, such as reward probability, may also show a similar association to sequence order (St Onge et al. 2010), suggesting that the confounding property of this treatment on response flexibility/perseveration (e.g., Evenden and Robbins 1983; Koek and Slangen 1984; Loh et al. 1993) needs to be factored into study design and interpretation.

As described above, the rGT requires test subjects to make choices based on advantageous/low risk versus disadvantageous/high risk options and, because all choice options are presented simultaneously, there is no issue of ascending or descending schedules that are inherent in most discounting tasks. A further feature of the rGT is that PREM responses can also be determined, thus enabling the simultaneous assessment of a treatment on a measure of impulsive action as well as risk-based choice. Studies have reported a tendency for AMP to increase the low risk choice (P1), reflecting a preference shift from the optimal (P2) option (Zeeb et al. 2009; Baarendse et al. 2013; Silveira et al. 2015; Higgins et al. 2021). This shift is interpreted as AMP promoting a more risk-aversive strategy, possibly suggesting that the extended punishment timeout may be deemed more aversive under AMP treatment (Zeeb et al. 2009). This effect of AMP to promote risk-aversion may also be supported by findings from the risky decision-making model of Simon et al. (2009). In two separate studies AMP (0.33–1.5 mg/kg) was reported to produce a dose-related preference shift to the "safe" reward, that increased in magnitude in parallel with reduced risk of punishment (Simon et al. 2009; Mitchell et al. 2011).

2.4.2 MPH

In contrast to AMP, the effects of MPH on PREM responding in the 5-CSRTT (and 5C-CPT on "*go*" trials) tend to be more subtle and most evident in subjects subcategorized on the basis of their performance. Under a 10s ITI (i.e., low event rate) 5-choice schedule we found MPH (1–6 mg/kg) had little or no effect on overall PREM responses. However, subgrouping into LI and HI resulted in a significant subgroup x MPH interaction, with MPH reducing PREM responses in HI, and increasing PREM responses in LI (Higgins et al. 2020b; see Fig. 3a). Indeed, at the 6 mg/kg dose of MPH, the level of PREM responses was equivalent between these two extreme subgroups. Other groups have also reported the same bidirectional effect of MPH on PREM responses (see Tomlinson et al. 2014; Caprioli et al. 2015; Caballero-Puntiverio et al. 2019), although null effects or increased PREM responses have also been widely reported (Blondeau and Dellu-Hagedorn 2007; Navarra et al. 2008; Fernando et al. 2012; Paterson et al. 2011b; Ding et al. 2018).

In terms of tests designed to measure the "stopping" form of impulsive action, MPH has been reported to reduce SSRT in slow stoppers, yet increase SSRT in fast responders (Eagle et al. 2007), thus showing a commonality of rate-dependence to the aforementioned effects on PREM responses made in the 5-CSRTT/CPT. However, Maguire and France (2019) failed to find any reliable effect of MPH on SSRT, although no subgrouping based on SSRT was attempted in this study and the overall group size was quite low. Similarly, in a *go/no-go* task, we reported a non-significant trend for MPH to reduce false alarms (Higgins et al. 2020b; see Fig. 3b); however, the overall study size was not sufficient to conduct a subgrouping analysis, which might have revealed a clearer effect.

In terms of studies designed to investigate the effect of MPH on measures of impulsive choice, several have shown that under an ascending schedule of delay

presentation, MPH may reduce discounting (Van Gaalen et al. 2006b; Slezak and Anderson 2011; Paterson et al. 2011b; Slezak et al. 2014; Tanno et al. 2013). While these studies imply that MPH may reliably have a beneficial effect on this measure of impulsive choice, only one study (Tanno et al. 2013) has investigated treatment effects under the reverse (i.e., descending) delay sequence. In this case, equivalent doses of MPH that reduced discounting under an ascending delay schedule increased discounting on the descending schedule. This again raises a possibility that choice perseveration influences study outcome (Tanno et al. 2013; Maguire et al. 2014). We have evaluated MPH (1–6 mg/kg) only under an ascending delay sequence and found no effect on choice (see Fig. 3c).

2.4.3 ATX

A wide range of investigations have reported ATX to reduce PREM responding emitted by rodents performing the 5-CSRTT and CPT tasks (Blondeau and Dellu-Hagedorn 2007; Navarra et al. 2008; Robinson et al. 2008; Robinson 2012; Fernando et al. 2012; Paterson et al. 2011a, b; Baarendse and Vanderschuren 2012; Tomlinson et al. 2014; Pillidge et al. 2014; Caballero-Puntiverio et al. 2019, 2020; Callahan et al. 2019; Higgins et al. 2020a, b; Mei et al. 2021; Toschi et al. 2021). This property of ATX is particularly evident under test conditions designed to induce high levels of PREM responses, where ATX is effective at low doses (0.1–1 mg/kg) and generally devoid of effects on other performance measures, such as response speed and trial omissions (Fernando et al. 2012; Paterson et al. 2011a; Tomlinson et al. 2014; Caballero-Puntiverio et al. 2019, 2020; Higgins et al. 2020a, b) (see Fig. 3a). The report of Mei et al. (2021) extended this observation across both male and female study subjects.

Similarly, a consistent dataset supports a positive effect of ATX in tests of response inhibition. False alarms as measured in the CPT or *go/no-go* task are attenuated by ATX at doses that are equivalent to those effective against PREM responding (Tomlinson et al. 2014; Ding et al. 2018; Caballero-Puntiverio et al. 2019, 2020; Higgins et al. 2020b) (see Fig. 3b). In the 5C-CPT we have found that ATX (0.1–1 mg/kg) reduced both PREM responses and false alarms in test subjects classified as high impulsive (HI). Measured concurrently in the 5C-CPT the effects of ATX seemed more potent against PREM responding, being reduced at all ATX doses (0.1–1 mg/kg); yet, false alarms were affected only at the 1 mg/kg dose (see Fig. 2b). This latter effect also likely contributed to an improvement trend in the sensitivity index measure (see also Tomlinson et al. 2014; Caballero-Puntiverio et al. 2019, 2020).

In the SST, ATX has also been reported to reduce SSRT in "all" rats, as well as those classified as "slow" responders, and without affecting reaction time on *go* trials (Robinson et al. 2008). However, on an adjusting SST, Maguire and France (2019) failed to detect any effect of ATX on response latencies. Despite this difference in outcome, which may in part be a reflection of small sample size (Maguire and France 2019), considered overall, the effects of ATX measured across multiple tests of

impulsive action are probably the most consistent between study groups, when compared against AMP and MPH.

In delay and probability discounting tests of impulsive choice, ATX has generally been reported to have no effect (Paterson et al. 2011b; Sun et al. 2012; Turner et al. 2013; Montes et al. 2015; Ozga-Hess and Anderson 2019; Higgins et al. 2021), although Robinson et al. (2008) reported an intermediate dose of ATX (1 mg/kg) to reduce delay discounting, while Broos et al. (2012) reported the same dose of ATX to increase discounting. In the study of Higgins et al. (2021), the effect of ATX was evaluated in rats trained to either an ascending and descending delay order, as well as animals subgrouped according to baseline level of discounting (based on AUC), thus controlling for two variables that influence the profile of AMP and MPH in this task (Tanno et al. 2013; Bickel et al. 2016). In each case ATX did not appear to have any effect on reinforcer choice (see Fig. 3c). Montes et al. (2015) similarly examined ATX on ascending and descending reward probabilities without effect, although a modest effect on a subgroup of rats identified as "risk aversive" was noted at the lowest ATX dose (0.3 mg/kg). In the rGT test, three independent studies have failed to detect any effect of acute ATX on any of the choice options, indicating no shift in risk-based choice (Baarendse et al. 2013; Silveira et al. 2016; Higgins et al. 2021).

Similar to ATX, the α_{2A}-adrenoceptor agonist, GUAN, is a preferential modulator of central norepinephrine function. Although less widely reported than ATX, there seem to be certain commonalities between both drugs. For example, GUAN reduces PREM responses in 5-CSRTT/CPT, although precise interpretation is complicated by detrimental effects of GUAN on other performance measures (Milstein et al. 2007; Fernando et al. 2012; Terry Jr et al. 2014; Caballero-Puntiverio et al. 2019). In a rodent SST, GUAN prolonged SSRT and had multiple effects consistent with a general slowing of performance (Bari et al. 2009). A single study in an ascending delay discounting task has reported a null effect of GUAN (Schwager et al. 2014). It has been proposed that the positive effects of GUAN, supporting its clinical benefit as an ADHD treatment, may be more evident in primate species compared to rodents, due to the more advanced cortical development of the former species (Arnsten 2020).

2.4.4 Summary

Across the three primary ADHD treatments of AMP, MPH, and ATX, probably the most reliable effects on preclinical tests of impulsivity are recorded following ATX pretreatment. ATX has robust effects on tests of both "waiting" and "stopping" forms of impulsive action, which is observed across multiple groups and seemingly less influenced by task variables. Furthermore, the clearest effects of ATX on these measures are evident under test conditions relevant to ADHD: i.e., HI subjects tested under a low event rate 5-Choice task, slow performers in an SST, and HI subjects in a CPT. In tests of impulsive choice, equivalent doses of ATX seem largely neutral suggesting a lack of effect on this impulsivity construct.

Differences between ATX and AMP/MPH seem most evident in tasks measuring the "waiting" form of impulsive action, primarily as measured by 5-CSRT task performance. In contrast to ATX, both MPH and particularly AMP increase PREM responses under multiple task conditions, possibly reflecting enhanced subcortical DAergic function (Kuczenski and Segal 1997, 2001). The effects of MPH are particularly notable in LI and HI subgroups, where MPH has a bidirectional effect of reducing PREM in HI, and increasing PREM in LI. This is a feature reported by multiple groups (Tomlinson et al. 2014; Caprioli et al. 2015; Caballero-Puntiverio et al. 2019; Higgins et al. 2020b) and suggests that the LI/HI endophenotype may reflect an imbalance between central NE and DA tone, which may be corrected by MPH.

An additional point to consider is a requirement for greater test consistency particularly in tasks of impulsive choice, and more specifically delay discounting. For example, the profile of AMP on discounting has been inconsistent across studies, and influenced by a variety of task variables, including: delay sequence; use of cues; delay duration; environmental enrichment; reinforcer magnitude; animal strain; schedule requirement; and baseline levels of discounting (see Table 1). It is likely that other drugs will show a similar sensitivity to these variables. The field could be helped by guidelines as to what are the most appropriate task conditions to run discounting experiments, and consequently for different labs to adopt similar methods for consistency (Table 1).

3 How Do the Preclinical Findings Translate to Clinical ADHD?

3.1 Subtypes of ADHD? (ADHD-I, ADHD-HI, ADHD-C)

Individuals diagnosed with ADHD show a variation in symptom profiles and so appropriate partitioning of this heterogeneity, to refine diagnosis and to provide targeted treatments, remains an important research goal (Faraone et al. 2015). To address this issue, the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 classifies three "presentations" of ADHD: predominantly inattentive type (ADHD-I), predominantly hyperactive/impulsive type (ADHD-HI), or combined type (ADHD-C) (DSM-V, 2013). The term "presentation" rather than "subtype" is used to reflect that each can change over time and, even within presentations, individuals may differ in symptom profiles (Epstein and Loren 2013; Faraone et al. 2015). Consequently, these DSM symptom categories have raised debate among researchers in part related to a limited knowledge of the neural mechanisms, which underlie the ADHD subtypes (Anastopoulos and Shelton 2001; Lange et al. 2014). However, such a categorization does provide a framework for developing insights into the underlying neurobiology of ADHD. For example, Saad et al. (2020) have recently reported a meta-analysis of imaging studies, conducted across symptom

categories, and identified differences in network activities. Additional insights may also be gained from treatment efficacy across these "presentation" types (see Sect. 3.2).

In terms of relating these "presentation" types to the preclinical data reviewed in this article, as noted by Tomlinson et al. (2014), the subgrouping of inattentive (I) and impulsive (HI) subgroups provides logical models of the ADHD-I and ADHD-HI conditions, respectively. A population of rats that share an inattentive-impulsive phenotype would serve as a viable model for ADHD-C (Blondeau and Dellu-Hagedorn 2007). The identification of inattentive and impulsive subgroups provides a method of generating models without any underlying assumption as to the mechanism(s) of action. This may be considered advantageous, given uncertainty around the precise etiology of many neuropsychiatric conditions (Hayward et al. 2016). Three recent reports describing separate lines of HI rats, based on motor impulsivity, may conceivably provide insights into gene targets and neurobiology contributing to a clinical diagnosis of ADHD-HI (Moloney et al. 2019; Jupp et al. 2020; Sholler et al. 2020). The study of Jupp et al. (2020) has used a selective breeding strategy combined with genome sequencing and transcriptome analysis to identify a number of gene variants associated with a linkage region on chromosome 1. These data support PREM responding in the 5-CSRTT as a heritable trait and a valid endophenotype to investigate the circuit neurobiology of PREM responding and, by extension, waiting impulsivity.

3.2 How Do the Preclinical Effects of AMP, MPH, and ATX Translate to Clinic?

Generally speaking, despite the variability in study methods used to evaluate ADHD treatments, which make cross-study comparisons challenging, meta-analyses of ADHD study trials, comparing the primary ADHD medications, support a better efficacy of the stimulant class (AMP, MPH) relative to the non-stimulant class (ATX, GUAN). This profile is observed in children, adolescents, and adults (Cunill et al. 2016; Faraone and Glatt 2010; Faraone et al. 2006; Mészáros et al. 2009). For example, Faraone and Glatt (2010) in a review of 19 double-blind, placebo controlled trials in adult ADHD subjects, reported a placebo corrected 50% responder rate for stimulants compared to a 20% rate for non-stimulants. Comparisons in effect-sizes between the two classes also support a larger effect of AMP/MPH formulations, and reflect a similar outcome from a similar meta-analysis that these authors conducted in children with ADHD (Faraone et al. 2006). Consequently, AMP and MPH are recognized as the first choice treatments for ADHD in all age groups (Bolea-Alamañac et al. 2014; Faraone et al. 2015).

Despite this evidence, at present, there does not seem to be any consensus between the effect of each treatment class and ADHD symptom presentation (i.e., ADHD-I, ADHD-HI, ADHD-C), which perhaps reflects the debate about the

validity of these symptom profiles. For example, based on the preclinical literature, outlined in Sects. 2.3 and 2.4, given the reliable effects of ATX on measures of motor impulsivity rather than attention, one might predict ATX to be of most benefit in ADHD subjects categorized as ADHD-HI rather than ADHD-I. However, there is little evidence to support any particular subgroup of patients as specifically responsive to ATX treatment (Faraone and Glatt 2010; Bushe and Savill 2014; Bolea-Alamañac et al. 2014).

A similar statement can probably be made for AMP and MPH across ADHD subjects (Faraone and Glatt 2010; Castells et al. 2011a, b; Bolea-Alamañac et al. 2014; Epstein et al. 2014; Storebø et al. 2015), although in both instances, and consistent with the preclinical literature, positive treatment effects on attentional and impulsive measures have been reported. Improvements in both domains might explain the higher responder rate and/or efficacy for both stimulant drugs compared to ATX as treatments for adult and juvenile forms of ADHD (Faraone and Glatt 2010; Bolea-Alamañac et al. 2014).

At this time, a more useful reverse translational exercise is to compare the profiles of AMP, MPH, and ATX across specific tests conducted in both the preclinical and clinical contexts. Some of the most direct comparisons can be drawn with the CPT, which has been extensively conducted in human subjects, and increasingly in rodents. AMP has a positive effect on CPT performance both in healthy adults and in individuals diagnosed with ADHD, with positive effects on processing speed and attentional domains such as vigilance (Rapoport et al. 1978; Castells et al. 2011a; MacQueen et al. 2018a). The study of MacQueen et al. (2018a), conducted in healthy adults, reported an effect of AMP to reverse the decline in d' associated with a vigilance decrement observed following placebo pretreatment. This shows a translational consistency with the rodent CPT and 5-CSRTT (Grottick and Higgins 2002; Bizarro et al. 2004; Higgins et al. 2020b; MacQueen et al. 2018b), notably under conditions such as extended trials specifically designed to challenge vigilance (Grottick and Higgins 2002; see Fig. 1b). AMP has also been reported to reduce false alarms in a human go/nogo task (de Wit et al. 2002) which is mirrored by a preclinical *go/no-go* study (Higgins et al. 2020b), However, in the human CPT study of MacQueen et al. (2018a), false alarms were not reduced by AMP, the improvement in d' being largely reflective of an improved hit rate. The efficacy of AMP in rodent tests of risky decision-making may also reflect the property of the stimulant class to counter the elevations shown by ADHD subjects in tests of risk-taking (White et al. 2007; DeVito et al. 2008). De Wit and coworkers (de Wit et al. 2000, 2002) have reported positive effects of AMP in healthy volunteers performing multiple laboratory based tests of impulse control. These findings include a decrease in stop (but not go) reaction time in an SSRT, reduced false alarms in a *go/no-go task*, and reduced k value (a measure of indifference between immediate vs. delayed reward; see Richards et al. 1999 for detail) in a delay discounting task. In each study (de Wit et al. 2000, 2002), the AMP effect in SSRT was confined to individuals with slow stop reaction times at baseline. Overall, these findings show a consistency with

the profile of AMP conducted in the analogous rodent-based impulsivity tasks (see Sect. 2.4.1).

Losier et al. (1996) reported a meta-analysis of CPT studies using MPH treatment in children with ADHD. They found that MPH treatment was associated with fewer commission and omission errors, and faster processing speed (see also Riccio et al. 2001). These findings correspond to observations from rodent 5-CSRT/CPT assays. For example, MPH improved performance in a sITI 5-CSRTT schedule, largely through reducing commission and omission errors and increasing response speed in low performers (Higgins et al. 2020b; see also Bizarro et al. 2004; Navarra et al. 2008; Tomlinson et al. 2014). However, the preclinical literature for MPH is somewhat inconsistent, which likely reflects the importance of task variables and baseline subject performance to study outcomes (Paterson et al. 2011a; Fernando et al. 2012; Caprioli et al. 2015; Ding et al. 2018). At least two studies have reported a superior effect of MPH relative to ATX on CPT measures related to sustained attention in youths categorized with ADHD (Bédard et al. 2015; Wu et al. 2021). More specifically, in the study of Bédard et al. (2015) MPH produced greater improvements relative to ATX in omission errors and reaction time (both in terms of response speed and variability). Furthermore, while Spencer et al. (2001) reported on improvements of certain core ADHD signs in children treated with ATX, no effects of this treatment were observed on a Conners CPT performance.

The limited effect of ATX as reported by Bédard et al. (2015), Wu et al. (2021), and Spencer et al. (2001) on attentional measures in the CPT might be seen to mirror the generally null preclinical findings for ATX in attention-based tests. Spencer et al. (1998) and Chamberlain et al. (2007) also reported on effects of ATX in adults diagnosed with ADHD, in a neuropsychological test battery, which included tests of attention. In neither study was an outcome described that was indicative of a significant improvement, although in the latter study a modest decrease in commission errors was recorded following ATX treatment in a sustained attention task. Rather, in the study of Spencer et al. (1998) an improvement in Stroop color word test was identified, which the authors attributed to improved inhibitory capacity. These effects were subsequently confirmed in a much larger adult ADHD study cohort (Faraone et al. 2005). Chamberlain et al. (2007) reported improvements in SSRT in 20 adult ADHD subjects following ATX relative to placebo pretreatment. *Go* reaction time was unaffected. This positive effect of ATX on SSRT has since been extended to juvenile ADHD subjects, as well as healthy volunteers (Robbins 2017) and neatly parallels the findings for ATX conducted on the equivalent rodent task (Robinson et al. 2008). Therefore, considered overall, effects of ATX as measured in clinical neuropsychological tests seem most clear on measures of impulse control rather than attention, which seems consistent with preclinical outcomes.

4 Final Comments

Results from studies conducted in preclinical species highlight generally pro-attentive effects of both AMP and MPH, notably in studies employing low performing test subjects. In contrast, any pro-attentive effects of ATX appear to be more subtle and inconsistent. The most reliable effects of ATX are recorded in tests of impulsivity, especially when considered across tests of both "waiting" and "stopping" forms of impulsive action (see Table 2). Guidelines as to the most appropriate task conditions to run discounting tests of impulsive choice may benefit consistency.

Back-translating observations from the clinic to these preclinical findings, it might be argued that the higher efficacy of AMP/MPH relative to ATX/GUAN is attributable to the former having a broader efficacy across measures of attention and impulse control, as opposed to the narrower profile of the non-stimulants to tests of impulsive action. This hypothesis would be greatly helped by insights into the efficacy of each treatment approach in individuals presenting as predominantly ADHD-I, ADHD-HI, or ADHD-C (DSM-V 2013). Certainly, the preclinical data would seem to suggest that ATX might be more effective against symptoms of impulse control as opposed to symptoms of inattention. However, such data are presently lacking and there remains debate about the value of these subclassification terms.

Currently more data are available to compare the profiles of AMP, MPH, and ATX across specific neuropsychological tests conducted between the preclinical and clinical context, notably the CPT and SSRT. Some of the most direct comparisons can be drawn from the CPT, which has been extensively conducted in human subjects and increasingly in rodents. Findings such as improved vigilance following AMP pretreatment, and SSRT following ATX pretreatment, support the premise that endophenotypes such as attention and impulsivity can be objectively investigated across the preclinical-clinical spectrum using appropriate tests and experimental conditions. Further, there seems reasonable cross-species consistency for effect of AMP, MPH, and ATX across these domains, although research gaps remain. Nonetheless, when considered overall, these studies should encourage confidence for the forward translation of NCE's from the preclinical to clinical setting in efforts to identify newer and hopefully improved pharmacotherapies for ADHD.

Table 2 Summary of profiles for AMP, MPH, and ATX in operant tasks designed to measure attention and impulsivity in rodents. The table is intended as a summary of preclinical findings reported for each drug in each specific test, and reflects much of the authors own experience. (↑) = improvement/increase; (↓) = impairment/decrease; (↔) = no effect. *sITI* short inter-trial interval (2–5 s), *SI* sensitivity index, *CPT* continuous performance task, *SST* stop signal task, *SSRT* stop signal reaction time

	Attention		Impulsivity			
Drug	5-choice	CPT	5-Choice (PREM; "waiting")	CPT	SST/ GO/NOGO ("stopping")	Delay discounting (impulsive choice)
AMP	Improvement (extended trials, sITI) (↑% correct, ↑% hit, ↑response speed)	Improvement (↑% hit rate, ↑SI, ↑d')	↑ impulsive action (↑PREM)	No reliable effect (↓/↔ false alarms, ↑/↓ PREM)	↓ impulsive action (↓ false alarms; GO/NOGO) (↓ SSRT)	No reliable effect (Effects dependent on test variables)
MPH	Improvement (extended trials, sITI) (↑% correct, ↑% hit) *Effects baseline dependent*	Improvement (↑% hit rate, ↑SI, ↑d') *Effects baseline dependent*	↑/↓ impulsive action (↑/↓ PREM) *Effects baseline dependent*	↑/↓ impulsive action (↑/↓ PREM) *Effects baseline dependent*	↓/↔ impulsive action (↓/↔ false alarms; GO/NOGO) (↔ SSRT) *Effects baseline dependent*	No reliable effect (Effects dependent on test variables)
ATX	No reliable effect Occasional improvement, long ITI Impairment often noted in high attentives, or sITI schedules	Improvement ↑ in SI, d' may be secondary to ↓ false alarms.	↓ impulsive action (↓ PREM) *Effects baseline dependent*	↓ impulsive action (↓ false alarms; ↓ PREM; improve SI)	↓ impulsive action (↓ false alarms; GO/NOGO) (improve SSRT)	No reliable effect

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Animal Models of ADHD?

S. Clare Stanford

Contents

Abstract To describe animals that express abnormal behaviors as a model of Attention-Deficit Hyperactivity Disorder (ADHD) implies that the abnormalities are analogous to those expressed by ADHD patients. The diagnostic features of ADHD comprise inattentiveness, impulsivity, and hyperactivity and so these behaviors are fundamental for validation of any animal model of this disorder. Several experimental interventions such as neurotoxic lesion of neonatal rats with 6-hydroxydopamine (6-OHDA), genetic alterations, or selective inbreeding of rodents have produced animals that express each of these impairments to some extent. This article appraises the validity of claims that these procedures have produced a model of ADHD, which is essential if they are to be used to investigate the underlying cause(s) of ADHD and its abnormal neurobiology.

Keywords 5-Choice serial reaction-time test (task) · Colobama mouse · Continuous performance test (task) · Dopamine transporter gene knockout mouse · Neonatal 6-hydroxydopamine lesioned rat · Neurokinin-1 (NK1) receptor gene knockout mouse · Obesity · Spontaneously hypertensive rat · Tachykinin receptor-1 (TACR1)

S. C. Stanford (✉)
Department of Neuroscience Physiology and Pharmacology, University College London, London, UK
e-mail: c.stanford@ucl.ac.uk

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Abbreviations

ADHD	Attention-deficit hyperactivity disorder
CPT	Continuous performance test
5C-CPT	5-Choice continuous performance test
5-CSRTT	5-Choice serial reaction-time task
DAT	Dopamine transporter
DAT KO	Dopamine transporter knockout (mouse)
DRL	Differential reinforcement of low rates of responding
DSM-5	Diagnostic and statistical manual of mental disorders (edition 5)
GWAS	Genome-wide association study
LITI	Long-intertrial interval
NK1R	Neurokinin-1 receptor
6-OHDA	6-Hydroxydopamine
SNAP25	Synaptosomal-associated protein, 25 kDa
SHR	Spontaneously hypertensive rat
SSRI	Selective serotonin reuptake inhibitor
TACR1	Tachykinin receptor-1
TOVA	Test of variables of attention
VITI	Variable intertrial interval
VNTR	Variable number of tandem repeats allele
WKY	Wistar-Kyoto (rat)

1 Introduction

A diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) rests on patients' expression of three core signs: hyperactivity, inattention, and impulsivity (American Psychiatric Association 2013; International Classification of Diseases (ICD-11) 2022). As reviewed in detail, by Leffa et al. 2022 (Chapter "ADHD in Children and Adults: Diagnosis and Prognosis") and other contributors to this volume, the relative prominence of inattention and hyperactivity/impulsivity determines whether the disorder is categorized as predominantly inattentive, predominantly hyperactive-impulsive, or combined type. It follows that a fundamental criterion for validating preclinical models of ADHD should be that the animals express equivalent signs. Only if this criterion is satisfied would it be justified to assume that these models are translationally relevant and to use them in research of the underlying cause(s) of ADHD in humans.

Unlike most psychiatric disorders, for which many of the diagnostic criteria are subjective (e.g., suicidality and hypochondria in depression, hallucinations in schizophrenia, flashbacks and survivor-guilt in post-traumatic stress disorder), the key diagnostic elements of ADHD can arguably be evaluated objectively in both humans and other animals. This means that preclinical studies of ADHD are

relatively well-placed to confirm (or refute) the validity of claims that an experimental intervention (e.g., gene mutation, neurotoxic lesion, or selective inbreeding) has produced an animal model of this disorder. Yet, as will become clear, even validating an animal model of ADHD is challenging. There is the added complication that many putative models express additional abnormalities that are not commonly (if ever) associated with ADHD or its comorbidities.

There are several other factors that should be taken into account when appraising the phenotype of an animal as a model of ADHD. First, there are different categories of attention and impulsive behavior (see Libedinsky and Fernandez 2019; Evenden 1999; Kenton and Young 2022 Chapter "Preclinical Evaluation of Attention and Impulsivity Relevant to Determining ADHD Mechanisms and Treatments") and it is not always obvious how a specific behavioral impairment in animals, which is attributed to one of these domains, is analogous to those expressed by ADHD patients. Secondly, there are many different experimental procedures for evaluating attention and impulsive behavior in animals and, as a consequence, it can be difficult to compare findings across different studies or to be confident about assimilating their respective findings into a coherent model of ADHD. Thirdly, patients with ADHD often express comorbid disorders, some of which have features that overlap with those of ADHD (e.g., impaired attention or disrupted sleep/arousal architecture, which are also common in depression) and so it cannot be certain that an abnormality expressed by an animal is analogous to a primary feature of ADHD, rather than a secondary comorbid problem, or both. Fourthly, ADHD is not a single entity or fixed phenotype: different patients express different clinical profiles and their diagnostic features wax and wane, change with age, and can depend on their environment (Leffa et al. 2022 Chapter "ADHD in Children and Adults: Diagnosis and Prognosis"). For all these reasons, there are grounds to be skeptical that an experimental animal (typically a rodent) that expresses a fixed abnormal phenotype can be regarded as a valid model of ADHD.

Validation of a putative model could also incorporate the amelioration of these signs by drugs that have established clinical efficacy in ADHD patients: the psychomotor stimulants (amphetamine, methylphenidate and lisdexamfetamine), the α_2-adrenoceptor agonist, guanfacine, and the norepinephrine reuptake inhibitor, atomoxetine. However, that should not be a stringent requirement because none of these drugs is efficacious in every patient (see Groom and Cortese 2022 Chapter "Current Pharmacological Treatments for ADHD"; Coghill 2022 Chapter "Benefits and Limitations of Stimulants in Treating ADHD"; Heal et al. 2022 Chapter "New Drugs to Treat ADHD - Opportunities and Challenges in Research and Development") and so a negative finding does not necessarily invalidate the model. That is not to say that these models should not be used as a resource for screening promising new treatments for ADHD. For predictive validity, such tests merely need both candidate drugs and established treatments to have a consistent effect on specific aspect(s) of animals' behavior; they do not require the animals to be a model of ADHD in the drug-free state (see Stanford 2020). For that reason, a positive finding, when using these models, does not necessarily confirm their validity as a model of ADHD either.

Another aspect of this field focuses on neurochemical evidence for abnormal neurotransmission in ADHD patients and animals, together with studies of how this is modulated by drugs used to treat this disorder (see Heal et al. 2022 Chapter "New Drugs to Treat ADHD - Opportunities and Challenges in Research and Development"). Although the importance of that evidence cannot be overstated, our understanding of how any such abnormalities explain the behavioral manifestations of ADHD, or how they are ameliorated by drug treatments, is not sufficiently comprehensive to use this information to inform the process of validating animal models.

For all these reasons, this chapter focuses on the behavioral phenotype of animals, but does not critique the neurobiological or pharmacological evidence, when considering their validity as animal models of ADHD in humans.

In the first edition of this book, four animal models of ADHD were discussed in detail by Fan et al. (2012) and Sagvolden and Johansen (2012): the neonatal 6-OHDA lesioned rat; the *coloboma* mouse; the dopamine transporter-gene knockout (DAT KO) mouse; and the spontaneously hypertensive rat (SHR). Another, the neurokinin-1 receptor gene knockout mouse ($NK1R^{-/-}$), was flagged as potentially interesting, subject to more research. This chapter reappraises those models, particularly in respect of how their status as rodent analogues of ADHD in humans has evolved in the light of recent evidence, and also considers some interesting new candidates that have emerged over the last ten years.

2 Pioneer Animal Models of ADHD

2.1 The Neonatal 6-Hydroxydopamine (6-OHDA) Lesioned Rat

This model, which was first developed to study the role of dopamine in motor function and habituation, involves intracisternal or bilateral intraventricular infusion of the neurotoxin, 6-hydroxydopamine (6-OHDA). When administered to animals that have been pretreated with a norepinephrine reuptake inhibitor, 6-OHDA causes a neuropathy of dopaminergic neurons in the brain, with only slight effects on norepinephrine-expressing neurons (Erinoff et al. 1979) and so it has been assumed that there is a deficit in dopaminergic transmission in these mice. However, the possibility that a deficit in dopaminergic transmission explained the hyperactivity of these animals was challenged, early on (Erinoff et al. 1979). Moreover, a recent study, in which 6-OHDA was infused directly into the substantia nigra revealed extensive compensatory sprouting of the surviving neurons (Tanguay et al. 2021). This evidence is consistent with earlier reports that neurotoxins (whether targeted at a specific brain region, or given by a route that ensures their more general distribution throughout the brain) do not necessarily reduce the concentration of extracellular catecholamines, including dopamine, in the terminal field (Abercrombie et al. 1990; Hughes and Stanford 1998). On the basis of such evidence, it cannot be assumed that neurotransmission is reduced by such lesions, as is often the case.

Nevertheless, neonatal rats that have been treated in this way, at around 5 days of age, display increased motor activity and delayed motor habituation in a novel environment, 10–17 days later (Shaywitz et al. 1976, 1977): a change that persists in adulthood (Erinoff et al. 1979). Evidence that the hyperactivity is prevented by the stimulants, amphetamine and methylphenidate, prompted the inference that the lesion had produced a model of ADHD (Sahywitz et al. 1976, 1981; Luthman et al. 1989; see also Kostrzewa et al. 2016). It should be noted that the effects of these drugs on motor activity are neither consistent nor straightforward (see: Pappas et al. 1980; Thieme et al. 1980; Fan et al. 2012), but this does not necessarily undermine the validity of the model (see Sect. 1, above). A recent finding is that the hyperactivity is also prevented by the non-stimulant treatment for ADHD, atomoxetine (Ogata et al. 2019). However, there are no published reports of the effects of either guanfacine or the amphetamine prodrug, lisdexamfetamine, on these lesioned rats.

Given the role of inattention in most cases of ADHD in humans, focusing on hyperactivity alone is insufficient to fully understand the complexity of the condition, or to validate an animal model of this disorder. For that reason, considerable effort has been invested in evaluating the animals' inattention and impulsivity in 6-OHDA-lesioned rats. A range of different procedures have been used to evaluate attention, which is impaired in these animals; these include animals' vulnerability to distracting, irrelevant stimuli when trained to discriminate cues for reward/nonreward in a T-maze (Oke and Adams 1978) and associative conditioning in a two-way active avoidance task (Oades et al. 1987). Impairment of visuo-spatial working memory in an alternating Y-maze task, which was ameliorated by atomoxetine, has also been reported by Martínez-Torres et al. (2018), whose inferences were based on these animals being a model of ADHD.

A more detailed evaluation of these animals' attention and impulsivity has been carried out recently, using the 5-Choice Serial Reaction-Time Task (5-CSRTT). In this test the 6-OHDA lesioned animals express a higher incidence of *premature responses* (an index of motor impulsivity), as well as an increased incidence of *omissions* (an index of inattention) (Bouchatta et al. 2018, 2020). They also displayed an increase in *perseverative responses*; perseveration is a common, albeit not a diagnostic, feature of ADHD (Houghton et al. 1999; Walshaw et al. 2010; Lichtenstein et al. 2019). All these deficits in cognitive performance were ameliorated by methylphenidate (Bouchatta et al. 2018, 2020).

Further supporting evidence is that both male and female 6-OHDA lesioned rats display intolerance of delayed reward (Freund et al. 2014), a form of impulsive behavior (choice impulsivity), which is evident in ADHD patients. They also display sleep disruption, with prolonged arousal (delayed sleep) at the onset of the light (inactive) phase (Suzuki et al. 2018), compared with unlesioned animals. Both these abnormalities are common in ADHD patients (Imeraj et al. 2012; Solanto et al. 2001; Patros et al. 2016; Fabio et al. 2020).

Despite these promising findings, a criticism of this model has been that there is no evidence for a dopaminergic neuropathy in the brains of ADHD patients (Kostrzewa et al. 1994). However, as discussed elsewhere (Groom and Cortese

2022 Chapter "Current Pharmacological Treatments for ADHD"; Heal et al. 2022 Chapter "New Drugs to Treat ADHD - Opportunities and Challenges in Research and Development"; Zetterstrom et al. 2022 Chapter "Effects of Methylphenidate on the Dopamine Transporter and Beyond"), there is substantial evidence for a deficit in dopaminergic transmission in the brain of ADHD patients and also evidence that the therapeutic efficacy of stimulants and the non-stimulant, atomoxetine, rests on augmenting catecholamine transmission, especially in the prefrontal cortex.

Collectively, all these findings suggest that 6-OHDA lesioned rats meet the criteria for an animal model of ADHD (hyperactivity, inattention and impulsivity). However, the procedure has the disadvantage of requiring skilled surgery in neonates, which raises ethical and welfare concerns. Also, these lesioned animals have yet to be studied using the rodent 5-Choice Continuous Performance Test. Unlike the 5-CSRTT this test enables the evaluation of a different form of impulsive responding (*go/no-go* (commission) errors, termed "*false alarms"*), which Kenton and Young argue is essential for validation of any animal model of ADHD 2022 Chapter "Preclinical Evaluation of Attention and Impulsivity Relevant to Determining ADHD Mechanisms and Treatments").

2.2 The Coloboma Mouse

The *coloboma* mutant mouse expresses a range of physical and behavioral abnormalities, including hyperactivity, which is diminished by amphetamine (but not methylphenidate; Hess et al. 1996) and intolerance of delayed reward (Bruno et al. 2007). However, there is a striking gap in the literature regarding attempts to evaluate inattention or other types of impulsive behavior of these mice. This is most likely because the *colobama* mouse is profoundly hyperactive and has impairments that affect their visual and auditory function, as well as balance and motor co-ordination (Hess et al. 1994), all of which would confound evaluation of their behavior in tests of cognitive performance (see Gunn et al. 2011). In fact, it has even been suggested that these mice might be a better model of ataxia than ADHD (Gunn et al. 2011).

Nevertheless, decoding the genetic mutation in these mice was proposed as a research strategy that would help explain the hyperactivity of ADHD patients (Hess et al. 1992). The mutation was traced to a deletion within mouse Chromosome 2 of heterozygous mice, and spanned the gene for synaptosomal-associated protein, 25 kDa (SNAP25); this gene product has a crucial role in the neurochemical cascade that couples neuronal stimulation with regulation of intracellular Ca^{2+} and exocytotic release of neurotransmitters, as well as neuronal plasticity, axonal growth, and insulin release.

Evidence that the hyperactivity of these mice was abolished by a *Snap25* transgene (Hess et al. 1996) firmly linked this behavioral abnormality with the genetic mutation. However, subsequent studies revealed that several flanking genes, which

could influence the behavior of these animals, could be affected by the mutation (Hess et al. 1994, 1996). The influence of microdeletions, or the background strain of the mouse, on the behavior could also not be ruled out.

Another set-back was that small-scale linkage studies of extended families of ADHD patients failed to find convincing evidence of an association between polymorphism of *SNAP25* and ADHD (Hess et al. 1995; Barr et al. 2000; Brophy et al. 2002). However, several later studies have reported positive findings (e.g., Mill et al. 2004; Feng et al. 2005; Hawi et al. 2013; Gálvez et al. 2014) and a recent meta-analysis also found evidence for "modest" support for polymorphism of *SNAP25* as a risk factor for ADHD (Liu et al. 2017).

Finally, there is accumulating evidence for an association between *SNAP25* mutations and several other psychiatric disorders (e.g., Najera et al. 2019; Braida et al. 2015). On that basis, mice with mutations of the *Snap25* gene are likely to be more useful for studies of endophenotype(s) that are associated with a range of different disorders, or possibly with individual differences in patients' responses to drug treatment (Najera et al. 2019), than as a model of any single disorder, including ADHD.

2.3 The Dopamine Transporter Knockout ($DAT^{-/-}$) Mouse

This mouse, with a null function mutation of the dopamine transporter ($DAT^{-/-}$), was first developed as a research resource for studying the role of the DAT in dopaminergic transmission and the actions of psychomotor stimulants (e.g., cocaine and amphetamine), as drugs of abuse (Giros et al. 1996). Evidence for delayed clearance of extracellular dopamine in striatal slices from these mice, in vitro, further prompted the suggestion that they could be used to study the positive symptoms of schizophrenia as well as the neurobiology of reward and addiction (Giros et al. 1996). However, the same study noted that $DAT^{-/-}$ mice were hyperactive and that their motor habituation to a novel environment is slower than their controls ($DAT^{+/+}$ (wild-types)). Furthermore, high doses of amphetamine and cocaine, which both bind to the DAT and prevent neuronal reuptake of dopamine, caused stereotypies in the wild-types, but had no effect on the hyperactivity of the mutant mice.

Despite these promising findings, it should be borne in mind that in the prefrontal cortex, a brain region that is strongly implicated in ADHD (See Heal et al. 2022 Chapter "New Drugs for Treatment of ADHD - Opportunities and Challenges in Research and Development"), most extracellular dopamine is sequestered by the norepinephrine transporter, for which dopamine is a high affinity substrate. As a consequence, a functional deficit of dopamine transporters does not increase the concentration of extracellular dopamine in this or other brain regions (Yamamoto and Novotney 1998).

Meanwhile, evidence was emerging for the heritability of ADHD and this was underpinned by the finding of an association between a variable number of tandem repeats allele (VNTR) in the noncoding region of the DAT gene of humans and a

diagnosis of ADHD (Cook et al. 1995): a finding replicated by Gill et al. (1997; see also Langley et al. 2022 Chapter "Genetics of Attention-Deficit Hyperactivity Disorder"). Such findings strengthened the rationale for investigating these mice as a model of ADHD (Gainetdinov et al. 1999), even though the authors expressed skepticism that the phenotypes of these mice and ADHD were identical. However, it should be pointed out that the selective serotonin reuptake inhibitor (SSRI), fluoxetine, similarly blunted the hyperactivity of the $DAT^{-/-}$ mice (Gainetdinov et al. 1999), but SSRIs are not effective treatments for ADHD (see: Aydın et al. 2021).

In addition to their hyperactivity, $DAT^{-/-}$ mice express a range of cognitive abnormalities. These include a higher rate of perseverative errors and impaired spatial working memory when tested in a radial maze or a Y-maze, compared with wild-types (Gainetdinov et al. 1999; Li et al. 2010). The $DAT^{-/-}$ mouse also displays impaired performance in the Morris Water Maze, but this was interpreted as poor cognitive flexibility because there was no deficit in the animals' general learning ability, spatial navigation or motivation to escape (Morice et al. 2007). However, evidence for impaired cognitive flexibility as a feature of ADHD is inconsistent, for reasons that are as yet unresolved (see: Aydın et al. 2021).

Sensorimotor gating, as assessed by the startle reflex or paired-pulse inhibition, is also disrupted in $DAT^{-/-}$ mice (Ralph et al. 2001; Yamashita et al. 2006), but this is not the case for heterozygote mice ($DAT^{+/-}$; Mereu et al. 2017); the latter is consistent with the typical (but not invariable) finding that sensorimotor gating is not impaired in ADHD patients (see Lemvigh et al. 2020; Le Sommer et al. 2021). In fact, it has been suggested that $DAT^{-/-}$ mice are a better model of early Parkinson's disease or dystonia. This is not least because humans with a loss of function of DAT (dopamine transporter deficiency syndrome) suffer from these neurological disorders, but not motor hyperactivity (see Kurian et al. 2009, 2011).

Recent research that has used $DAT^{+/-}$ mice instead has confirmed their hyperactivity, which persists throughout the lifespan of both sexes and, with the possible exception of adolescent females, is prevented by *d*-amphetamine (Mereu et al. 2017). The same study further revealed impairment of specific elements of cognitive performance when $DAT^{+/-}$ mice were tested the 5-CSRTT (Mereu et al. 2017). It should be pointed out that the hyperactivity of homozygote $DAT^{-/-}$ mice disrupts their behavior to the extent that only heterozygotes ($DAT^{+/-}$) can be studied in this test. There was no difference in animals' *omission errors* (inattention) or the incidence of *perseverative responses*. However, their choice *accuracy* was reduced (which is interpreted as an alternative index of inattention) and *premature responses* were increased, compared with the wild-types. Both these performance deficits were ameliorated by subchronic treatment with *d*-amphetamine (Mereu et al. 2017).

A recent advance is the development of the $DAT^{-/-}$ rat. Like the $DAT^{-/-}$ mouse, these animals have impaired sensorimotor gating (increased startle response and impaired pre-pulse inhibition) compared with wild-types (Leo et al. 2018). They also express locomotor hyperactivity both in the home cage and a novel environment, which is prevented by amphetamine and methylphenidate (Adinolfi et al. 2019). In addition, $DAT^{-/-}$ rats show working memory deficits (Leo et al. 2018) and also an apparent impaired intolerance of delayed reward, compared with wild-types. The

latter behavior contrasts with the delay intolerance seen in ADHD, but was attributed to a stereotypical response by the animals, which targets the lever delivering the large reward ("compulsive fixation") rather than disruption of attentional processing (Cinque et al. 2018).

Overall, the complex abnormal phenotype of homozygote ($DAT^{-/-}$) rodents confounds their validation as a model of ADHD, in terms of their inattentiveness and impulsivity. The heterozygote ($DAT^{+/-}$) mouse does not suffer this drawback, but it is telling that this strain has also been suggested to be useful for research of schizophrenia, bipolar disorder, and Huntington's disease, as well as ADHD, because all these disorders are thought to share excessive dopaminergic transmission as a possible common factor.

Nevertheless, considerable effort has been invested in looking for a biomarker (or biomarkers) for ADHD that focus on the DAT gene (*DAT1* (*SLC6A3*) Adriani et al. 2018; Grünblatt et al. 2019; Tonelli et al. 2020; Lambacher et al. 2020; Dai et al. 2017; Carpentieri et al. 2021). Although it is acknowledged that any such biomarkers are unlikely to be aligned with the ADHD presentations defined in the Diagnostic and Statistical Manual of Mental Disorders (edition 5) (DSM-5), this approach is essential for back-translation into rodents in order to study the functional consequences and underlying neurobiological mechanisms that are affected by promising mutations ((endophenotypes) e.g., Mergy et al. 2014). Such studies could further help to explain individual differences in patients' response to treatment with CNS stimulants (e.g., Soleimani et al. 2018). This again points to the more circumspect approach of using mutant rodents to study the etiology and treatment of specific elements of ADHD, rather than as a rodent analogue of the full-blown disorder.

2.4 The Spontaneously Hypertensive Rat (SHR)

The spontaneously hypertensive rat (SHR) is certainly the most widely studied candidate for a model of ADHD. Although evidence, discussed below, suggests that it is no longer a plausible model of ADHD, many groups continue to use these animals in research of the causes of, and treatments for, ADHD. A comprehensive review of the literature reporting studies that have used SHRs is far beyond the scope of this chapter. Instead, the purpose of this section is to highlight key behavioral findings that are relevant to (and considerably undermine) its validity as a model of ADHD.

The hyperactivity of rats from the SHR strain in a novel environment, by comparison with their controls (rats from the Wistar-Kyoto (WKY) strain), was first noted in the late 1970s (e.g., McCarty and Kopin, 1979). This difference in motor activity is evident in young animals even before they develop hypertension, which could be a confounding factor in studies using older animals. An early report suggested that *d*-amphetamine reduced the hyperactivity of SHRs at a dose (3.5 mg/kg i.p.) that increased the activity of WKYs, but attributed this to a rate-dependent

response arising from the high baseline (spontaneous) activity of SHRs (Myers et al. 1982). However, a later study reported that a lower dose of amphetamine (1 mg/kg i.p.) increased the motor activity in both SHRs and WKYs (Tsai and Lin 1988). This evidence was challenged to some extent by Wultz et al. (1990) who found that methylphenidate increased the activity of both strains, but less so in the SHR than their controls and so they endorsed tentative suggestions that these animals offer a model of ADHD.

A later important finding was the discovery of a preference of SHRs to respond for an immediate reward vs. their reduced response to a delayed reinforcer, compared with WKYs ("delay-discounting") (Sagvolden et al. 1992). This difference was diminished by methylphenidate, which prompted a torrent of preclinical research to explore the possibility that intolerance of delayed gratification explains distractibility and impulsivity in ADHD. A later study further reported that the difference in the tolerance of delayed reward of SHRs, compared with WKY rats, was diminished by methylphenidate, albeit only in juvenile SHRs (Bizot et al. 2007). This form of choice impulsivity of SHRs was confirmed recently in a comprehensive study, which also provided evidence that prolongation of the training period increases the animals' expression of impulsive choice (Aparicio et al. 2019). However, a detailed interrogation of this behavior, using Wistar rats for comparison, indicated that SHRs are more sensitive to the actual delay in reinforcement, rather than the amount of reward, a finding that is possibly exacerbated by distortion of the animals' perception of time (Orduña 2015; Orduña and Mercado 2017; but see Ferguson et al. 2007). Moreover, a recent report has challenged the fundamental translational relevance of protocols for assessing delay-discounting in animals (Sjoberg et al. 2021). This view is based on evidence that it is the length of the delay in receiving the reward, *after* the animals have carried out their response, that is the key experimental parameter and determines animals' apparent impulsive choice in delay-discounting tests (Sjoberg et al. 2021).

Meanwhile, evidence that SHRs also display a deficit in sustained attention, motor and cognitive impulsivity, and motor hyperactivity, with no sensory deficit, was gathering apace, as was the view that these animals satisfied the criteria for a model of ADHD (e.g., Sagvolden 2000). Findings from studies using a two-lever visual discrimination task further consolidated that status because the inattention of SHRs was diminished by low doses of amphetamine (Sagvolden and Xu 2008) and higher doses normalized both their hyperactivity and impulsive behavior (Sagvolden 2011). However, Alsop (2007) drew attention to a potential problem: that the baseline response rate of different rat strains is not the same in operant behavioral tasks and this can affect the magnitude of apparent abnormalities of SHRs. The highly variable response rate of SHRs has also been highlighted as a confounding factor in such tests of impulsive choice (Garcia and Kirkpatrick 2013).

Using a different protocol to evaluate choice impulsivity (the differential reinforcement of low rates of responding (DRL)), there is evidence for impaired performance of SHRs in this task, compared with WKY rats (Sable et al. 2021, Bull et al. 2000), but both strains performed better than Sprague-Dawley rats, which prompted the authors to question the use of WKYs as controls for such studies (Bull

et al. 2000). Furthermore, the lack of any differences in the effects of amphetamine or methylphenidate on the response of WKY and SHRs, in either a test of temporal response differentiation or the DRL, led to questions concerning the validity of the SHR as a model of ADHD (Ferguson et al. 2007; van den Bergh et al. 2006).

Several protocols have been used to compare other aspects of the cognitive performance of SHRs and control strains, but the evidence for any consistent deficit in SHRs is not convincing. For instance, after training in a 2-Choice visual discrimination test, Wistar and SHRs did not differ on measures of attention or premature responses (Bizot et al. 2015). Moreover, in the same study, amphetamine improved attention of Wistar rats, but not SHRs, and did not affect impulsivity or activity of either strain. Few studies have used choice reaction-time tests to evaluate the cognitive performance of SHRs, probably for reasons outlined by Dommett (2014) and Rostron et al. (2017) (see below). Using SHRs from Harlan (Indianapolis) paired with WKYs as controls, response *accuracy* (an index of attention) was slightly impaired in male, but not female SHRs. *Omissions* (used as an alternative index of attention) did not differ in either sex (Bayless et al. 2015) but both sexes carried out more *premature responses* in this study, a finding that echoed an earlier report (van den Bergh et al. 2006).

Findings from experiments testing the effects of drug treatments on the cognitive performance of SHRs response are similarly inconsistent. The α_2-adrenoceptor agonist, guanfacine improved attention and impulsivity, but reduced response rate in a two-lever visual discrimination task of SHRs; these changes were not thought to be a consequence of the sedative effects of this drug (Sagvolden 2006). Guanfacine also prolonged active inhibitory avoidance, which was interpreted as another measure of attention/cognitive performance (Kawaura et al. 2014). However, methylphenidate did not affect their behavior in the 5-CSRTT (van den Bergh et al. 2006), with the exception that this drug actually increased measures of inattention in the SHRs (Dommett 2014). Nevertheless, in a meta-analysis of data assembled from a range of different procedures, methylphenidate improved attention of SHRs and also reduced impulsivity (data gathered from a batch of studies that used electro-shock aversive water drinking tests), but this stimulant did not affect their hyperactivity (Leffa et al. 2019).

By this time, reports had emerged that even challenged the view that SHRs are hyperactive. For instance, Ferguson and Cada (2003) compared both the activity of male and female SHRs, of different ages, and SHRs with WKY and Sprague-Dawley strains. They concluded that the evidence that the SHRs of either sex are hyperactive is unconvincing. In another study, male, but not female SHRs, were hyperactive when compared with WKY rats, but this was strongly dependent on the age of the animals (van den Bergh et al. 2006). Moreover, in that study, methylphenidate blunted the motor activity of WKYs, but not SHRs.

One reason for these disparate findings certainly relates to a recurrent criticism of studies using the SHR, which is that rats of the WKY strain are typically used as parallel controls. Although all these animals derive from the same ancestral source, they are now regarded as a different inbred strain. Also, it is acknowledged that not only the choice of the control strain but also the specific breeding colony of the SHRs

determines the conclusions from research findings. In detail, Sagvolden suggested that the SHR/NCrl strain (Charles River, Germany) should be paired with the WKY/NHsd strain (Harlan, UK) for studies of ADHD combined type, whereas WKY/NCrl (Charles River, Germany) displays abnormalities analogous to ADHD predominantly inattentive subtype when paired with WKY/NHsd as their controls (Sagvolden et al. 2009; Sagvolden and Johansen 2012).

The genetic divergence of WKY rats and different colonies of SHRs has been confirmed in detail by Zhang-James et al. (2013) who endorsed the need for caution when selecting SHR and control substrains for any study. Such genetic divergence is likely to affect all inbred strains/substrains, sourced from different colonies, and there is no reason to expect SHRs to be especially vulnerable to this problem. In fact, this divergence could offer an invaluable opportunity to investigate the genetic basis of the behavioral differences in closely-related substrains (e.g., Richards et al. 2013; Dela Peña et al. 2015) and so help to identify specific endophenotypes that contribute to a diagnosis of AHHD in humans.

Apart from the influence of the comparator strain and source of the animals on conclusions to emerge from these studies, there are further confounding factors that should be taken into account when appraising evidence from experiments that have used SHRs as a model of ADHD. For instance, SHRs have abnormal visual processing and impaired hearing (Brace et al. 2015a, b), which could affect their training and performance in instrumental tasks. They also have raised fluid intake (Dommett and Rostron 2013), which would be particularly problematic when using fluid reinforcers. Also, as is the case with other strains, husbandry affects the behavior of SHRs (Botanas et al. 2016) but, interestingly, their hyperactivity was not affected by housing style (single- vs. group-housed or same vs. mixed strains (Tsai et al. 2017) but was affected by cross-fostering to a mother from a different strain (Gauthier et al. 2015). Obviously, the effects of environmental factors on animals' behavior (and physiology) should be considered when using any strain of rodent, but they are potentially especially problematic for experiments using SHRs, which are unavoidably always paired with a different strain, as a control (usually WKYs). This is because the two strains could be affected by these factors in crucially different ways, which could distort conclusions about the status of SHRs as a model of ADHD.

Despite these drawbacks, studies of SHRs continue unabated with the rationale and the ensuing conclusions usually resting on the assumption that their validity as a model of ADHD is assured. However, the disparate findings and confounders, highlighted above, mean that this is most unlikely and that apparent abnormalities in the behavior of SHRs should be interpreted with caution, especially in respect of their translational relevance.

2.5 The Null Function NK1 Receptor-Gene Mouse ($NK1R^{-/-}$)

2.5.1 $NK1^{-/-}$ Mice Express Hyperactivity, Inattention, and Motor Impulsivity

Mice with functional ablation of the substance P-preferring neurokinin-1 receptor gene ('$NK1R^{-/-}$; 129/Sv × C57BL/6 background, backcrossed with an outbred MF1 strain) were developed to help elucidate the role of substance P in nociception and stress-induced antinociception (De Felipe et al. 1998). A deficit in their response to opiate (morphine) reward, but not to cocaine (Murtra et al. 2000), attracted further interest in the context of research of opiate addiction. Preclinical studies of NK1R antagonists had also suggested that these drugs could have antidepressant actions, which led to $NK1R^{-/-}$ mice being used to investigate the role of NK1R in the mechanisms underlying the therapeutic effects of antidepressants ("antidepression") Froger et al. 2001; Herpfer et al. 2005). In the course of these experiments, it was noticed that these mutant mice express marked locomotor hyperactivity (Herpfer et al. 2005; Fisher et al. 2007), a finding that has been confirmed in many different experimental settings (e.g., McCutcheon et al. 2008; Moyes et al. 2016; Porter et al. 2015). The finding that NK1R antagonists increased the motor activity of wild-type mice aligned this behavior with a deficit in NK1R function as a causal factor (Yan et al. 2010).

A further finding was that the hyperactivity of both $NK1R^{-/-}$ mice and wild-types that had been treated with an NK1R antagonist was blunted by *d*-amphetamine or methylphenidate, which raised the possibility that these mutant mice might offer a better model for studies of ADHD, rather than antidepression (Yan et al. 2010). In view of evidence for an association between polymorphism of the tachykinin receptor-1 gene (*TACR1:* the human equivalent of the mouse *Nk1r* gene) and alcoholism (Seneviratne et al. 2009), together with the high incidence of alcoholism in ADHD (Blaine et al. 2013), the findings from the mutant mice prompted a genome-wide association study (GWAS), which found an association between polymorphisms in, or near, the *TACR1* receptor gene, pointing to haplotypes that increase susceptibility to ADHD (Yan et al. 2010), a finding that has been confirmed (Sharp et al. 2014). In short, the abnormal behavior of genetically-altered $NK1R^{-/-}$ mouse led to a discovery of an association with a genetic polymorphism of the *TACR1* gene with ADHD.

Because hyperactivity alone is not sufficient to validate a model of ADHD, a series of studies then compared the cognitive performance of $NK1R^{-/-}$ mice with that of their wild-types ($NK1R^{+/+}$ with the same background strain) in the 5-Choice Serial Reaction-Time Test (5-CSRTT). The incidence of animals' *omissions* and *accuracy* were used as surrogate markers for inattention, while their *premature responses* were taken as an index of motor impulsivity. *Perseveration* (multiple repetitions of a correct response, before collecting a reward) turned out to be another interesting aspect of their behavior.

The first study in the series found that, on reaching the baseline criterion for training in this task, the incidence of *omissions* (inattention) and *premature responses* (motor impulsivity) expressed by $NK1R^{-/-}$ mice was higher than their wild-types. The animals' cognitive performance was then compared with wild-types by increasing attentional demand in the task in two different ways. One was to introduce an unexpected prolongation of the (constant) intertrial interval (long intertrial interval: "LITI"): *omissions* and *perseveration* were higher in the mutants under this test condition. The second was to introduce a randomized sequence of intertrial intervals of variable duration ("VITI"): in this test condition, *omissions*, *premature responses,* and *perseveration* were all higher, and *accuracy* was lower, in the $NK1R^{-/-}$ mice than in the wild-types (Yan et al. 2011). All these differences were found typically, but not invariably, in subsequent studies.

The higher incidence of *omissions, premature responses,* and *perseveration*, expressed by $NK1R^{-/-}$ mice in the VITI has been confirmed (Dudley et al. 2013; Weir et al. 2014) and suggests that activation of NK1R stabilizes these behaviors. The higher incidence of *premature responses* by $NK1R^{-/-}$ mice, compared with wild-types, when tested with a VITI, but not when using a constant LITI, has also been confirmed (e.g., Weir et al. 2014) and could indicate that $NK1R^{-/-}$ mice rely more on interval-timing to cue their response than do wild-types.

Subsequent experiments tested the effects of NK1R antagonists in the 5-CSRTT in order to check whether or not the abnormal behavior of $NK1R^{-/-}$ mice could be explained by a lack of functional NK1R. However, this proposal was supported to only a limited extent and only in respect of *premature responses* (see Weir et al. 2014). Although NK1R antagonists also increased *omissions* this affected both genotypes and so this response was unrelated to antagonism of NK1R and pointed to an additional action of the antagonists. A well-documented, non-selective target for these compounds are L-type Ca^{2+} channels and so further experiments investigated the effects of the L-type channel antagonist, nifedipine, on animals' behavior in the 5-CSRTT. The possibility that blockade of these channels confounded the effects of NK1R antagonism in this test was confirmed in a study in which nifedipine increased *omissions* and reduced *premature responses* in both genotypes, with the caveat that $NK1R^{-/-}$ mice seemed to be less sensitive to the effects of nifedipine than the wild-types (Dudley et al. 2013; Weir et al. 2014). Evidence that an interaction between NK1R and L-type Ca2+ channels could be important for modulation of behaviors that are relevant to ADHD is reviewed, in detail, elsewhere (Stanford 2014).

Another factor that came to light in the course of these studies was that the animals' behavior changed on repetition of the 5-CSRTT. Despite ensuring that baseline performance was restored (i.e., as expressed at the end of training) before each test session, *accuracy* increased slightly and *premature responses* declined appreciably, on repeated testing with the VITI. These adaptive changes affected $NK1R^{-/-}$ mice, especially, and eventually abolished the genotype difference (Dudley et al. 2013; Weir et al. 2014; van der Veen et al. 2021). Likewise, *omissions* declined, but *perseveration* increased, in both the LITI and the VITI: these changes affected both genotypes and so do not involve NK1R. Nevertheless, such

progressive adaptation of animals' performance on repeated testing with the 5-CSRTT should be taken into account when carrying out a long sequence of tests on the same batch of animals and possibly humans as well (e.g., by using a counterbalanced or a fully randomized experimental design).

Finally, ADHD patients are typically assessed using the Conners' Continuous Performance Test (CPT) or the Test of Variables of Attention (TOVA), which include a target signal for the animals to withhold any response (a rewarded *no-go* cue) as well as (*go*) signals to which the animals must respond for a reward. The incidence of animals carrying out an inappropriate response to the *no-go* signal ("false alarm") is interpreted as a form of impulsive behavior that differs from *premature responses* in the 5-CSRTT. As discussed in detail elsewhere (Kenton and Young 2022 Chapter "Preclinical Evaluation of Attention and Impulsivity Relevant to Determining ADHD Mechanisms and Treatments"), the rodent equivalent of the CPT (the 5C-CPT) is argued to have more translational relevance than the 5-CSRTT, which incorporates only *go* signals.

When NK1R$^{-/-}$ mice were tested in the 5C-CPT, *perseveration* was higher during both training and testing sessions (Porter et al. 2016). They also showed a higher rate of *premature responses* and lower *accuracy*, but only at the onset of training. The dissipation of excessive *premature responses* is likely explained by the animals repeated experience of the VITI schedule during training (*c.f.,* the 5-CSRTT; see: Weir et al. 2014; van der Veen et al. 2021): i.e., *premature responses* seem to be aggravated by an unexpected change in the ITI.

Contrary to the predicted finding, NK1R$^{-/-}$ mice carried out fewer *false alarms* than wild-types but the implications of this finding, in terms of the validity of NK1R$^{-/-}$ mice as a model of ADHD, is uncertain because it is not clear whether or not they are increased in ADHD patients (see citations in Porter et al. 2016).

In summary, NK1R$^{-/-}$ mice expressed some abnormal behaviors in the 5C-CPT that overlapped with those seen when using the 5-CSRTT. However, there were important differences that highlight the need for a better understanding of the procedural factors that influence animals' cognitive performance in these tests.

2.5.2 Other Aspects of the NK1R$^{-/-}$ Phenotype

A further interesting finding was that the incidence of certain behaviors (*omissions*, *premature responses,* and *perseveration*), but not other aspects of the animals' behavior in these tests, depended on time of day. Regarding the 5-CSRTT, a confirmed difference was that the incidence of *premature responses* carried out by NK1R$^{-/-}$ mice in the LITI was higher in the afternoon than the morning (Yan et al. 2011; Weir et al. 2014), which could affect the interpretation of findings that are pooled over a whole day. Similarly, wild-types expressed fewer *premature responses* than NK1R$^{-/-}$ mice when tested in the 5C-CPT in the morning, but NK1R$^{-/-}$ mice expressed more *premature responses* in the afternoon. Whether this relates to the disruption of circadian rhythms in ADHD is unknown, but it points to

time of day being an additional experimental variable that should be taken into account by using it as a blocking factor in the experimental design.

All the studies described above were carried out on homozygote NKR1$^{-/-}$ and wild-type mice that had been inbred for several years. The possibility that genetic drift or extraneous environmental factors (e.g., maternal behavior or interactions with litter-mates) had influenced the behavioral phenotypes of the two breeding colonies could not be ignored. To explore that possibility, further studies compared the behavior of homozygote NK1R$^{-/-}$ and NK1R$^{+/+}$ mice, from the original inbred colonies ("Hom"), with that of the homozygote progeny of heterozygote mice (NK1R$^{-/-}$ and NK1R$^{+/+}$; "Het") that were produced by cross-breeding the same two inbred strains (Porter et al. 2015).

These studies included the monitoring of the animals' motor activity, in the home cage, over the 24 h cycle, for seven days. In a head-to-head comparison, NK1R$^{-/-}$ mice derived from either the original inbred homozygote colony or from heterozygote parents were hyperactive during the late dark (active) phase (Porter et al. 2015). This difference can evidently be attributed directly to the lack of NK1R and echoes the delayed sleep onset in many patients with ADHD (Kooij and Bijlenga 2013; van der Veen et al. 2021). However, during the light phase, the influence of genotype on animals' activity interacted with breeding colony such that the onset of arousal of wild-type Hom (but not Het) mice preceded that of all other groups. This finding, which cannot be attributed to a functional deficit of NK1R, alone, raises questions about the extent to which an interaction between early-life experience and genotype determines disruption of sleep architecture in ADHD. It is also important to consider the evidence that circadian preference for the late active phase is associated with daytime sleepiness in ADHD (Becker et al. 2020) and that this compounds impaired cognitive performance in ADHD (Mann et al. 2021). For a detailed discussion of sleep disorders in ADHD patients and their treatment, see Sciberrras 2022 (Chapter "Sleep in Individuals with ADHD: Prevalence, Impacts, Causes and Treatments").

In the 5-CSRTT (VITI), both Hom and Het homozygotes carried out more *premature responses* than their NK1R$^{+/+}$ counterparts during training. This was still the case when the Hom colony was tested in the VITI, but the Het NK1R$^{-/-}$ mice did not show this difference. Moreover, these two groups of NK1$^{-/-}$ mice differed from each other, suggesting that environmental factors ameliorated this behavior in the Het mice. However, *perseveration* was higher in both colonies of NK1R$^{-/-}$ mice, pointing to the lack of functional NK1R as a causal factor. There was a borderline difference in *omissions* but, as in previous studies, this behavior was confounded by time of day. There were no differences in *accuracy*.

An important inference from all these findings is that a genetic mutation (in this case, null function NK1$^{-/-}$) can affect certain elements of behavior and so account for specific endophenotypes, but not others. It is also clear that animals' genotype interacts with environment in ways that influence specific aspects of motor behavior and cognitive performance that are arguably relevant to ADHD. These findings echo those reported for the SHR in respect of cross-fostering (Gauthier et al. 2015; see above).

Another distinctive feature of NK1R$^{-/-}$ mice is that they are typically shorter (approx. 7%) than wild-types; small body size is a common feature of ADHD and has even been suggested as a risk factor (Momany et al. 2018). Yet, ADHD patients have a predisposition to obesity (Hanć and Cortese 2018; Cortese 2019; Lanoye et al. 2022 Chapter "Obesity and Attention-Deficit Hyperactivity Disorder". Although both male and female NK1R$^{-/-}$ mice weigh less than their wild-type counterparts, when their size (nose to tail-base length) was taken into account, the body mass of both sexes was higher than that of wild-types (Pillidge et al. 2016a). Furthermore, when fed a high-fat ("western") diet, the body fat content of NK1R$^{-/-}$ mice increased considerably, especially in males (35%), but there were no genotype differences in body composition of ash, water, or protein (Pillidge et al. 2016a). These findings are interesting in light of evidence that NK1R promotes lipolysis and that the NK1R antagonist CJ12255 prevents weight gain and accumulation of fat in mice (Karagiannides et al. 2008). They further suggest the possibility that an interaction between genotype (in this case, *TACR1* polymorphism) and sex could affect the incidence of obesity in ADHD patients, as has similarly been suggested recently by Do et al. (2019).

Finally, in light of extensive evidence for a role for substance P in regulation of blood pressure and that a deficit in substance P signalling contributes to essential hypertension, a radiotelemetry study was carried out for continuous monitoring of hemodynamic parameters in NK1R$^{-/-}$ mice and their wild-types (Moyes et al. 2016). Mean arterial pressure (systolic and diastolic) and heart rate were all higher in the NK1R$^{-/-}$ mice, especially during the dark (active) phase. These findings suggest the interesting possibility that patients with polymorphism of TACR1 are vulnerable to hypertension, as well as ADHD, which could point the way to stratification of their medication. In this context, an interesting report has described the expression of abnormal behaviors that are common in ADHD, by a large proportion of children with renal hypertension. Moreover, these abnormal behaviors were ameliorated in about half of those patients by successful treatment for their hypertension (Krause et al. 2009). The increased risk of developmental disorders, including ADHD, in the offspring of hypertensive mothers is well documented. However, there is also evidence for an association between hypertension and ADHD, with high body mass index as a key covariate (Fuemmeler et al. 2011). It is tempting to speculate that it is individuals with polymorphism(s) of *TACR1* who are at high risk of obesity and hypertension, as well as ADHD.

2.5.3 NK1R$^{-/-}$ Mice: Pharmacological Challenges in the 5-CSRTT and 5C-CPT

A further series of studies indicated that each drug that is used to treat ADHD affects certain behavior(s) of NK1R$^{-/-}$ mice in the 5-CSRTT, not others. For instance, treatment with *d*-amphetamine (0.3 & 1.0 mg/kg i.p.) reduced *perseveration* by NK1R$^{-/-}$ mice in the LITI (Yan et al. 2011) but neither dose abolished the genotype difference. *d*-Amphetamine did abolish the genotype difference in *omissions* and

perseveration in the VITI, but that was due to a convergence of an increase in these behaviors by wild-types and a reduction in the mutants, rather than improvement in NK1R$^{-/-}$ mice, specifically. In short, with the possible exception of *perseveration*, there was no convincing evidence that *d*-amphetamine has any beneficial effects on the behavior of NK1R$^{-/-}$ mice in the 5-CRSTT.

Atomoxetine reduced the *hyperactivity* of NK1$^{-/-}$ mice, at a dose that did not affect the wild-types, and also reduced *premature responses* by both genotypes, but had no overall effect on other behaviors (*omissions*, *accuracy,* or *perseveration;* Pillidge et al. 2014a). This finding is broadly consistent with those discussed by Higgins and Silenieks 2022: i.e., that atomoxetine is most effective at reducing *premature responses* in these tests and can even exacerbate inattentiveness. The lack of improvement in attention is hard to explain because there is plenty of evidence that atomoxetine ameliorates inattentiveness in ADHD (e.g., Schwartz and Correll 2014; but see Higgins and Silenieks 2022 Chapter "The Effects of Drug Treatments for ADHD in Measures of Cognitive Performance"). One possibility is that indices of attention in these tests do not translate well from rodents to humans. Another is that a lack of functional NK1R accounts for this response profile, in which case ADHD patients with polymorphism of the *TACR1* gene could comprise a subgroup whose impulsive behavior, but not attention, is improved by this drug.

A low dose of guanfacine reduced both *hyperactivity* and *omissions* in NK1R$^{-/-}$ mice. However, higher doses affected both genotypes as was the case for *premature responses* and *accuracy,* most likely because of its sedative effects (Pillidge et al. 2014b). These findings are consistent with evidence that a low dose of guanfacine has beneficial effects on inattentiveness in ADHD patients (e.g., Kollins et al. 2011; Biederman et al. 2008).

The effects of methylphenidate on the behavior of NK1R$^{-/-}$ mice has been tested in the 5C-CPT, but not the 5-CSRTT (Pillidge et al. 2016b). Only *perseveration* was increased in NK1R$^{-/-}$ mice throughout the training and testing procedure (see above), but methylphenidate blunted this behavior at doses that did not affect the wild-types. By contrast, methylphenidate increased *omissions* in this test in both genotypes. Although there were fewer *false alarms* by NK1R$^{-/-}$ mice (see above), it is interesting that a low dose of methylphenidate reduced this behavior in the mutant, but not wild-type mice. However, a higher dose reduced this behavior in both genotypes, as was also the case for *premature responses.* These findings suggest that methylphenidate might have beneficial effects on *perseveration,* and possibly *false alarms* in subjects with a functional deficit of NK1R (TACR1).

2.5.4 A Portfolio of Biomarkers for *TACR1* Vulnerability to ADHD?

Compared with their wild-type counterparts, NK1$^{-/-}$ mice are hyperactive and also typically, but not invariably, express *impulsivity*, *inattention,* and *perseveratio*n in the 5-CSRTT and 5C-CPT. Other phenotype features of these mice include: raised mean arterial pressure and heart rate; small body size but proportionally higher body mass; excessive increase in body fat in males that have been fed a high fat diet; and

disruption of the 24 h sleep/arousal cycle. The abnormal behaviors of these animals are affected by different drugs in different ways: in the 5-CSRTT, amphetamine reduced *perseveration*, but not other behaviors; atomoxetine reduced impulsivity (*premature responses*); guanfacine improved attention; and, in the 5C-CPT, methylphenidate reduced both *perseveration* and impulsivity (*false alarms*). It is worth considering whether this abnormal phenotypic and pharmacological response profile could serve as a biomarker for a deficit in functional NK1R/TACR1. If so, ADHD patients with polymorphism of *TACR1* could comprise a subgroup of genetically-defined patients with analogous vulnerabilities and pharmacological responses, which could inform research of the cause(s) of this disorder and the development of stratified treatment strategies.

3 Recent Models and Developments

Two models are of particular interest and comprise a substantial body of recent literature. One is prenatal exposure of rodents to alcohol. Several studies have reported that the progeny of dams that have experienced high alcohol consumption during pregnancy express hyperactivity (Brys et al. 2014), impaired attention (increased *omissions*), and impulsive behavior in Choice Reaction-Time tests (Brys et al. 2014; Wang et al. 2020, 2021). These abnormalities are thought to be relevant to the equivalent features of ADHD. Although the evidence for an association between alcohol consumption and a diagnosis of ADHD is inconsistent (Eilertsen et al. 2017; Pagnin et al. 2019; San Martin Porter et al. 2019; Mitchell et al. 2020; Weile et al. 2019), the possibility that these abnormal behaviors are analogous to specific deficits that are seen in ADHD patients, albeit with small effect-size, merits consideration Eilertsen et al. 2017; Furtado and Roriz 2016). However, until these inconsistencies are resolved, it is not clear whether the abnormal behavior of rodents is relevant to fetal alcohol syndrome, ADHD, or both. In fact, this could be a good example of how models might replicate abnormal aspects of behavior and cognition that are shared by more than one disorder.

The other is prenatal exposure to tobacco smoke, notwithstanding the inconsistent reports on the incidence of ADHD in the children of smoking mothers (Pagani 2014; see Zhu et al. 2014). In tests of whether or not nicotine was the culprit, the progeny of rats given nicotine in the drinking water displayed several neuromotor impairments including key features of ADHD (increased *premature responses* and *hyperactivity*) in the 5-CSRTT. However, compared with controls, they carried out fewer commission errors and there was no change in their performance in a delay-discounting test (Schneider et al. 2011, 2012; Zhu et al. 2014). There are further reports that male progeny show deficits in the Y-maze (spontaneous alternation), which is interpreted as an index of their working memory, and impaired avoidance in the cliff avoidance tests (impulsive behavior), whereas both sexes showed impaired object recognition (attention) (Zhang et al. 2018). The extent to which these behaviors replicate the diagnostic criteria for ADHD is unclear, but they are all prevented

by methylphenidate (Zhu et al. 2017; Buck et al. 2019) and atomoxetine (Alkam et al. 2017; Piña et al. 2020). Moreover, the impulsive behavior of these progeny, as well as their impaired attention, has been confirmed recently in the rodent Continuous Performance Test (Polli et al. 2020: c.f. rats in the 5-CSRTT). Another interesting finding is that the effects of prenatal exposure to nicotine on mice depend on genotype, with *Snap25* heterozygous mice being more vulnerable to hyperactivity than wild-types (Baca et al. 2013). Collectively, this evidence makes this a promising model for further research of a possible cause of ADHD, which has obvious etiological justification.

There are several other recent candidates for animal models of ADHD, based on interventions that cause disruption of specific molecular targets in genetically-altered animals. In some cases, the target has a scientific rationale that is mechanistically interesting, but lacks evidence for association with ADHD. Also, an ADHD phenotype is sometimes inferred merely on the basis of hyperactivity or impulsive behavior/inattention in procedures such as the Open Field Test and the Morris Water Maze. Also, as Langley and Thapar make clear 2022 Chapter "Genetics of Attention-Deficit Hyperactivity Disorder"), confirmation of a genetically-defined vulnerability to ADHD is not at all straightforward and should also consider interactions between genes and the environment. Although much can be learned from these models about the influence of specific genetic polymorphisms on behavior and cognition, which will enable the progressive assembly a library of relevant endophenotypes, confirming their contribution to the etiology of full-blown ADHD will be crucial.

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Modelling ADHD-Like Phenotypes in Zebrafish

Barbara D. Fontana, William H. J. Norton, and Matthew O. Parker

Contents

Abstract The use of multiple species to model complex human psychiatric disorders, such as ADHD, can give important insights into conserved evolutionary patterns underlying multidomain behaviors (e.g., locomotion, attention, and impulsivity). Here we discuss the advantages and challenges in modelling ADHD-like phenotypes in zebrafish (*Danio rerio*), a vertebrate species that has been widely used in neuroscience and behavior research. Moreover, multiple behavioral tasks can be used to model the core symptoms of ADHD and its comorbidities. We present a critical review of current ADHD studies in zebrafish, and how this species might be used to accelerate the discovery of new drug treatments for this disorder.

B. D. Fontana and M. O. Parker (✉)
Brain and Behaviour Laboratory, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK
e-mail: matthew.parker@port.ac.uk

W. H. J. Norton (✉)
Department of Neuroscience, Psychology and Behaviour, College of Medicine, Biological Sciences and Psychology, University of Leicester, Leicester, UK

Department of Genetics, Institute of Biology, ELTE Eötvös Loránd University, Budapest, Hungary
e-mail: whjn1@leicester.ac.uk

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Abbreviations

3-CSRTT	3-Choice serial reaction-time task (Test)
5-CCPT	5-Choice continuous performance task (Test)
5-CSRTT	5-Choice serial reaction-time task (Test)
ADHD	Attention-deficit hyperactivity disorder
GOFD	Glucose-fructose oxidoreductase domain
MIA	Mirror-induced aggression
MO	Morpholino oligonucleotide
RIC	RAB6A GEF complex

1 Introduction

Translational models are essential to understand the mechanisms underlying normal and abnormal behavior, including complex human psychiatric disorders (Ellenbroek and Youn 2016; Stewart et al. 2014; Mench 1998). Animal models have been used successfully to investigate the pathophysiological processes involved in psychiatric and neurological disorders, such as autism (Lewis et al. 2007; Tordjman et al. 2007), schizophrenia (Tordjman et al. 2007), epilepsy (Grone and Baraban 2015), and Attention-Deficit Hyperactivity Disorder (ADHD) (de la Pena et al. 2018; Arime et al. 2011).

ADHD is a common neurodevelopmental disorder that affects around 8–12% of children worldwide regardless of nationality or cultural background (Polanczyk et al. 2015). It is characterized by three core syndromal dimensions: hyperactivity, impulsivity, and inattention (Faraone et al. 2003; Polanczyk et al. 2015; Halperin et al. 1992; Spencer et al. 2007; Wolraich et al. 1996). There are three major presentations of ADHD: (1) predominantly hyperactive/impulsive; (2) predominantly inattentive; and (3) combined-type (APA 2013). ADHD patients often display comorbidities with other psychiatric disorders, such as: autism spectrum disorders; oppositional defiant and conduct disorders (Sebastian et al. 2013; Breyer et al. 2009); substance use disorder (Anastopoulos et al. 2018; Kessler et al. 2006; Marraccini et al. 2017); anxiety and depression (Levy et al. 2020; Heim et al. 2008; Blazer 1982). This suggests that common genetic or neurobiological signaling pathways may be shared across these diseases.

ADHD appears to be caused by alterations in several neurotransmitter signaling pathways including the dopaminergic, noradrenergic, and serotonergic systems (Purper-Ouakil et al. 2011; Potter et al. 2014; Cortese 2012). Many ADHD treatments (e.g., amphetamine and methylphenidate) act by increasing the concentration

of extracellular dopamine and norepinephrine (noradrenaline), thereby supporting the involvement of these neurotransmitters in ADHD (Krause et al. 2000; Fan et al. 2010). Interestingly, the clinical efficacy of ADHD treatments, such as methylphenidate and atomoxetine, parallels genetic polymorphisms in the *SOLUTE CARRIER FAMILY 6 MEMBER A2* (*SLC6A2*) gene that codes for the norepinephrine transporter (Ramoz et al. 2009; Park et al. 2012). Regarding the serotonergic system, serotonin (5-hydroxytryptamine; 5-HT) is involved in many behavioral functions including attention, sleep, memory, learning, locomotion, and anxiety (Lucki 1998). Although the role of serotonin signaling in ADHD is less understood, serotonin dysregulation has been associated with impulsive behavior in children, and alterations in the expression of serotonergic genes are associated with ADHD (Oades et al. 2008; Quist et al. 2003).

Numerous rodent models have been developed to investigate the pathobiology of ADHD (Kostrzewa et al. 2008; Sagvolden et al. 2005; van der Kooij and Glennon 2007). However, it is difficult, if not impossible, to fully recreate such a complex human disease in an animal model. An ideal model should express alterations in all core ADHD-like behaviors (hyperactivity, inattention, and impulsivity). It should also be based upon the mechanisms that underlie human ADHD and be able to provide novel insights into the disease, including the development of novel treatments. To date, few, if any, of the models that have been created fulfill all these criteria (Sontag et al. 2010). However, an example of a well-characterized model that has informed our understanding of human ADHD is the substance P-preferring, tachykinin-1 receptor ($NK1R^{-/-}$) knock-out mouse. These animals display hyperactivity and impulsivity/inattention: phenotypes that can be rescued by administration of methylphenidate and guanfacine (Pillidge et al. 2016; Yan et al. 2010, 2011). The striking similarity between the behavioral phenotype of $NK1R^{-/-}$ mice and ADHD led to mutations in the human homologue of this gene being found and has focused research onto norepinephrine signaling (Yan et al. 2010). Although ADHD-related phenotypes have previously been characterized in rodent models, the use of multiple species can shed light upon conserved evolutionary mechanisms that underlie specific behaviors across species.

The zebrafish (*Danio rerio*) is an increasingly popular animal model for behavioral neuroscience (Orger and de Polavieja 2017; Meshalkina et al. 2017) due to the availability of robust behavioral tests and a well-described behavioral repertoire (Kalueff et al. 2013; Parker et al. 2012, 2013a). Zebrafish have been used to study developmental biology for decades because of their rapid external development and transparency at embryonic stages. Over the past years, tools have been established to manipulate genes, ablate cells, and both visualize and manipulate neural activity using light (optogenetics) (Curado et al. 2007; Albadri et al. 2017). In addition, in the United Kingdom, larval zebrafish are not protected by the Animal Scientific Procedures act (1986) until 5 days post-fertilization. This means that in some cases, larval forms can be used to screen for drugs or test behavior, reducing the need to use more sentient adult fish or rodent models. These advantages, together with the availability of software and hardware for automated behavioral testing (Carreno

Gutierrez et al. 2018; Parker et al. 2013a), and the capacity to screen large numbers of animals, often make zebrafish a first choice for drug discovery.

As a model for translational studies, young zebrafish are particularly useful for optogenetic dissection of behavior, time-lapse analysis of neural development, and screens for novel therapeutic treatments. The ability to apply water-soluble chemical compounds by immersion, rather than injection into the stomach or brain, makes the zebrafish a good choice for drug screens. They have previously been used to screen for drugs that can modify aggression, sleep, and feeding (Rihel et al. 2010a, b; Jordi et al. 2018; Gutiérrez et al. 2020). Zebrafish have also been used to study some aspects of ADHD.

In this chapter, we will first discuss the advantages and limitations of using zebrafish as a translational model. We will then describe the behavioral tasks that are available to study ADHD-like phenotypes and their behavioral comorbidities. Finally, we will review studies of ADHD in zebrafish and provide a synthesis of how this species can best be used to search for novel ADHD treatments.

2 Advantages and Limitations of Modelling ADHD in Zebrafish

The zebrafish continues to develop as an alternative model organism to study the shared genetic and neurological basis of complex disorders like ADHD (Stewart et al. 2015; Howe et al. 2013; Postlethwait et al. 2000). They are genetically and physiologically similar to other vertebrates: for example, there is approximately 70% homology between human genes and their zebrafish orthologues (Howe et al. 2013). The zebrafish brain also includes all the major neurotransmitter systems and signaling pathways found in humans (Tropepe and Sive 2003; Panula et al. 2010; Thakkar 2011). We have described the similarity of ADHD-related genes in humans and zebrafish in a recent review (Fontana et al. 2019, 2020).

Despite their utility for translational studies, zebrafish do have some limitations as a model system. There are topographical differences between zebrafish and mammalian brain structures, which can complicate the comparison of neural circuits (Mueller and Wullimann 2009; Amo et al. 2010; Mueller 2012; Parker et al. 2013b). Additionally, an extra round of whole genome duplication occurred in teleost fishes about 450 million years ago. Although some of the duplicated genes became redundant, other genes developed a novel function or subdivided the function of the ancestral gene, a fact that has likely driven the expansion of teleost fish species (Postlethwait et al. 2000; Dahm and Geisler 2006; Balciunas 2018). The duplication of important ADHD-related genes can complicate analysis of their function, particularly if the effect of a mutated gene is masked by an unaltered paralogue (Stewart et al. 2015). However, in some cases this can be turned into an advantage: for example, to investigate later (non-developmental) functions of genes that lead to embryonic lethality upon mutation in other species.

In summary, the combination of genetic and neurological similarity with other vertebrates, combined with tools to manipulate this species, makes the zebrafish an important alternative model organism to study ADHD. In the following sections we will discuss the behavioral repertoire of zebrafish (Stewart et al. 2014; Maximino et al. 2015; Buske and Gerlai 2011; Jones and Norton 2015; Stewart et al. 2011; Levin et al. 2007) and how this can be used to model some aspects of ADHD.

3 Behavioral Tasks and Zebrafish Phenotypes Related to ADHD

3.1 Locomotion and Exploration

One of the cardinal symptoms of ADHD is hyperactivity (Faraone et al. 2003; Polanczyk et al. 2015; Halperin et al. 1992; Spencer et al. 2007; Wolraich et al. 1996). Locomotion and exploration have been well characterized in zebrafish and can be used as a readout of this ADHD-like behavior. Locomotor and exploratory profiles can be measured in multiple behavioral tests (e.g., the open field and novel tank diving tasks) depending on the animals' age (Lange et al. 2013; MacPhail et al. 2009; Lange et al. 2012; Ingebretson and Masino 2013; Ulhaq et al. 2013; Budick and O'Malley 2000; Grossman et al. 2010; Egan et al. 2009; Mezzomo et al. 2016; Rosemberg et al. 2012; Blaser and Rosemberg 2012; Wong et al. 2010). In larval zebrafish, locomotion patterns can be assessed by simply placing animals in small multi-well plates and recording their movements for 5–10 min (Lange et al. 2013; MacPhail et al. 2009; Lange et al. 2012; Ingebretson and Masino 2013; Ulhaq et al. 2013). The locomotor profile of larval zebrafish has previously been divided into two main categories, based upon the point at which the larva's body bends maximally: burst swims (near the mid-body) and slow swims (closer to the tail) (Budick and O'Malley 2000). Parameters such as swim episode frequency (Hz) and duration (ms), swim speed (mm/s), active swim time (s), and the total distance swum (cm) can be used to investigate the locomotor profile in detail.

The novel tank diving test and open field tests are often used to measure hyperactivity, anxiety-like behavior (shown as the preference to remain at the bottom of a tank), and exploration of an arena in adult zebrafish through the analysis of different parameters (e.g., distance traveled, mean velocity, absolute turn angle, and time spent immobile) (Stewart et al. 2011; Blaser and Rosemberg 2012). In the novel tank diving test, zebrafish normally spend most of the time at the bottom of the tank and gradually explore the top area (Egan et al. 2009; Mezzomo et al. 2016; Rosemberg et al. 2012; Blaser and Rosemberg 2012; Wong et al. 2010). This task is sensitive enough to detect sex differences in zebrafish: female fish present a stronger anxiety-like phenotype than males, spending more time at the bottom of a novel tank (Genario et al. 2020; Fontana et al. 2020). Since anxiety is a comorbid symptom of ADHD (Jarret and Ollendick 2008) that is more often found in women

(Quinn 2005), this task could be also used to assess sex differences when studying ADHD in zebrafish, an area of research that has been relatively understudied, since most experiments use a mixture of male and female fish. Similar to the novel tank diving test, the open field test assesses zebrafish behavior in a novel environment, and locomotor and exploratory activity are assessed. However, in the open field test, fish are recorded from above and the time spent close to the walls (thigmotaxis) is used as a parameter to measure anxiety (Colwill and Creton 2011; Kalueff et al. 2013; Shams et al. 2015).

Tasks based upon scototaxis have also been used to assess the anxiogenic and anxiolytic effects of drugs (Gerlai et al. 2000; Alia and Petrunich-Rutherford 2019). Scototaxis is an animal's preference for dark areas compared to bright/white areas of a tank, meaning that anxiogenic drugs will increase the time spent in the dark zone whereas anxiolytic drugs will increase the time spent in the white zone. In zebrafish, the preference for time spent in black or white areas changes during its life. While adult animals naturally prefer dark areas, larvae tend to spend more time in the white area of the tank (Blaser and Penalosa 2011; Facciol et al. 2019). Importantly, scototaxis is extremely sensitive to both the background shade and the intensity of ambient illumination. This complicates the comparison of behavior described in different studies (Facciol et al. 2019). When analyzing anxiety-behavior in zebrafish, parameters such as freezing, fast-starts, leaping out of the tank, erratic swimming, and the level of arousal (the rate of opercular beats, indicating respiration) should also be considered (Egan et al. 2009; Levin et al. 2007; Kalueff et al. 2013). Exposure to a predator has previously been used to assess anxiety-related phenotypes, such as freezing and defensive behavior (jumping) (Gerlai et al. 2009). However, the use of predator models to investigate anxiety requires careful interpretation, due to the difficulty of differentiating between fear and anxiety in these tests. The ethical concerns about exposing animals to a predator also need to be considered (Gerlai et al. 2009; Ahmed et al. 2011).

3.2 Attention Set Formation and Impulsivity

Self-regulation and the control of attention and impulsivity are essential traits that are present in different species (Nigg 2017; Parker et al. 2014). The dysregulation of both, attention and impulsivity-related behaviors, are also two of the core symptoms of ADHD (Winstanley et al. 2006). In rodents, one of the most popular tasks to assess attention and impulsivity is the Five-Choice Serial Reaction-Time task (5-CSRTT) (Higgins and Silenieks 2017; Bari et al. 2008; Pillidge et al. 2016). In this assay animals are trained to respond to a brief, unpredictable visual stimulus, shown in one of five locations, in order to qualify for a reward. Changes in the latency of the animals' response, choice accuracy, and attentional performance are quantified following different experimental manipulations (e.g., changes in the duration and latency of the light stimulus) (Higgins and Silenieks 2017; Parker et al. 2014, 2015; Bari et al. 2008).

Parker et al. (2012) were the first to characterize impulsivity and attention in zebrafish by using a 3-Choice Serial Reaction-Time Task (3-CSRTT). The 3-CSRTT task is based on principles that are similar to the rodent 5-CSRTT and consists of a 17-day training period followed by 5 days of testing. The training time for fish is significantly less than that of rodents; rodents can take many weeks or even months to reach learning criterion (typically 80% correct; Bari et al. (2008)). However, it should be noted that for fish, the test was designed for measuring impulse control, not attention. As such, the initial light stimulus duration was longer (5 s, as opposed to rodents, typically ~0.5 s). Exposure of day 20 and 22 animals to a low dose of amphetamine injected intraperitoneally (0.025 mg/kg) reduced anticipatory responses (i.e., attempts to collect a food reward before the stimulus light is activated) in the 3-CSRTT. This finding validated this task (Parker et al. 2012), as amphetamine is often used as a positive control in rodent models and is effective in reducing impulsivity in humans with ADHD.

Later, a fully automated system was successfully developed for the 5-CSRTT task by combining image analysis software with National Instruments drivers and actuators (Parker et al. 2013a). The 5-CSRTT consists of five steps. The first four steps are part of the training period: animals spend the first week habituating to the task environment (all lights on and food delivered at a pre-scheduled time). The second week is the magazine training (learning to associate the magazine light with the food reward). In the third week, the animals are challenged to recognize the stimulus light (after activation of the magazine light, all 5-chamber lights are activated). During weeks 4–8, the fish experience interval training: i.e., they learn that they need to enter the illuminated chamber in order to activate the magazine light, which signals reward. During weeks 9–12, the fish are tested, following the same procedure as that for the last training step, except that the time delay interval is now extended to 10 s. This assesses whether animals will try to anticipate a correct choice even though no light has been switched on, which indicates a premature response (impulsive behavior) (Parker et al. 2013a). Interestingly, application of 0.6 mg/kg atomoxetine reduced zebrafish impulsive behavior in the 5-CSRTT, whereas immersion in high doses of methylphenidate (4 mg/kg) increased the number of anticipatory responses (Parker et al. 2014), suggesting that the previous effect of amphetamine in reducing impulsive behavior is most likely associated with norepinephrine signaling. Overall, these studies demonstrate that conserved neurotransmitter signaling pathways control impulsivity in zebrafish and other vertebrates.

To date, few studies have measured attention in zebrafish and it is not clear whether they can maintain an attention set in a similar manner to other vertebrates (reviewed in Echevarria et al. (2011)). In rodents, five categories of attention have been proposed: orienting, expectancy, stimulus differentiation, sustained attention, and parallel processing (Bushnell 1998). Orienting has been measured in a social attention paradigm in which male zebrafish were permitted to eavesdrop upon different stimuli: two male zebrafish fighting each other; two non-interacting males separated by a barrier; or an empty tank (Abril-de-Abreu et al. 2015). The focal fish's orientation and proximity to the stimulus was used as a readout of attention. Zebrafish spent more time watching a fight than watching the two fish separated

by a barrier. They paid particular attention to lateral displays at the beginning of fights, suggesting that this represents an important social cue (Abril-de-Abreu et al. 2015).

In a recent study, the ability of zebrafish to orient themselves toward each other has been shown to be controlled by *LIM homeobox 8a*-positive cholinergic neurons in the ventral forebrain (Stednitz et al. 2018), an area of the teleost brain that may be homologous to the lateral septum in mammals. Sustained attention has also been measured using a novel object recognition test (Braida et al. 2014) in which the time spent interacting with an object presented on a video screen was recorded. Wild-type zebrafish could differentiate between a familiar and novel object up to 24 h later. Despite these promising findings, further studies validating attention and impulsive-related tasks such as the Stop-Signal Task (SST) (Bari and Robbins 2013), Go/No-go task (Eagle et al. 2008), and the 5-Choice Continuous Performance Task (5C-CPT) (Cope and Young 2017) would increase the validity of using zebrafish to model ADHD.

3.3 Other Comorbid Behaviors: Sociality, Aggression, and Risk-Taking Behavior

Patients with ADHD present with a variety of comorbid problems. These abnormal phenotypes may be sex-dependent and include externalizing problems (e.g., aggression and antisocial personality disorder), internalizing problems (e.g., anxiety and depression), and intellectual impairments (Gershon 2002; Arnett et al. 2015). In zebrafish, sociality, aggression, and anxiety can be assessed using several behavioral protocols (Dreosti et al. 2015; Egan et al. 2009; Wong et al. 2010; Cachat et al. 2010; Saverino and Gerlai 2008; Way et al. 2015; Rosemberg et al. 2011; Blaser and Penalosa 2011; Gerlai et al. 2000). The zebrafish is a social species, and behaviors such as shoaling (Miller and Gerlai 2012) and the preference to interact with conspecifics, can be used to assess social interactions (Dreosti et al. 2015; Saverino and Gerlai 2008; Green et al. 2012; Muller et al. 2017; Schmidel et al. 2014; Canzian et al. 2017; Miller and Gerlai 2012). In their free-ranging habitat, zebrafish form large shoals creating complex hierarchies that are hard to study in laboratory conditions. However, previous data show reproducible social interactions using 4–8 fish per shoal (Green et al. 2012; Muller et al. 2017; Schmidel et al. 2014; Canzian et al. 2017). Shoaling behavior can easily be assessed by measuring the distances between each fish in a tank and calculating the inter-individual and nearest-neighbor distances (Fontana et al. 2018; Canzian et al. 2017; Buske and Gerlai 2011).

Another important behavioral test that can be used to analyze social interactions is the conspecific preference task. This consists of placing individual fish in a tank that provides the opportunity to choose between swimming close to an empty compartment, or a second compartment, which contains a group of conspecifics (Saverino

and Gerlai 2008; Norton et al. 2019). The natural response of a zebrafish is to remain close to the group for around 60–80% of the time. However, if the fish shows disrupted social behavior, a decrease of time spent close to the conspecific tank may be observed (Dalla Vecchia et al. 2019). Importantly, the preference of zebrafish for conspecifics cannot be assessed in larval animals: it is first observed in young fish from around 3 weeks of age, perhaps because the neural circuits needed to drive this behavior have not developed until that time (Dreosti et al. 2015).

Aggressive behavior is sometimes reported in patients with ADHD (Blader et al. 2016; Halperin et al. 1997). In humans, aggression can be classified into two subtypes: reactive aggression (the response to a perceived threat) and proactive aggression (behavior that anticipates a reward) (Kempes et al. 2005). Retz and Rosler (2010) found that adult violent offenders with current or childhood ADHD have an increased risk of reactive aggression and decreased risk of proactive aggression relative to non-ADHD offenders (Retz and Rosler 2010). In zebrafish, aggression can be measured in two ways: (1) placing two animals together in a tank and quantifying their aggressive interaction, including chases, bites, and circling each other (Way et al. 2015; Oliveira et al. 2011); or (2) in the Mirror-Induced Aggression (MIA) task (Fontana et al. 2016; Gerlai et al. 2000; Way et al. 2015). The MIA task consists of transferring an individual zebrafish to a new environment that contains an inclined or flat mirror, close to the tank. Parameters such as biting, lateral displays, charges, and time spent near the stimulus are used to evaluate aggression (Fontana et al. 2016; Gerlai et al. 2000; Way et al. 2015). Although both methodologies are comparable, they can elicit slightly different behavioral phenotypes. For example, the use of a flat mirror or a live conspecific triggers an increased number of bites compared to an inclined mirror. However, the inclined mirror elicits more darts than both other methods (Way et al. 2015). This means that care must be taken when comparing data from these protocols. In general, it is relatively easy to evaluate aggression in zebrafish, meaning that zebrafish can be used to explore comorbid aggressive phenotypes in ADHD-like models.

ADHD patients can also exhibit increased risk-taking. This is usually associated with individual traits, such as the co-expression of other disorders (e.g., oppositional defiant disorder) and changes in the perceived benefits of risk-taking behavior (Pollak et al. 2019). Boldness, the disposition of an animal to take a risk in a novel environment, can be used as an index measure of risk-taking (Sih et al. 2004). In zebrafish, boldness can be assessed by different tasks, such as interaction with a novel object (Norton et al. 2011; Wright et al. 2003) or emergence from a shelter (Dahlbom et al. 2011; Mustafa et al. 2019). Both tasks examine the conflict between protection and risk. For example, bold animals will tend to approach a novel object more often, or will tend to spend more time outside a sheltered, protected zone (Dahlbom et al. 2011; Mustafa et al. 2019; Norton et al. 2011; Wright et al. 2003). Importantly, zebrafish show sex- and strain-specific differences in boldness, with different patterns of behavior elicited by each task (Mustafa et al. 2019). More research is needed to fully understand the extent to which boldness can be used as a comorbid abnormal behavior seen in ADHD models.

3.4 Other Comorbid Behaviors: Anxiety and Depression

Anxiety and depression are relatively non-specific comorbid symptoms of a variety of psychiatric disorders, including ADHD (Levy et al. 2020; Heim et al. 2008; Blazer 1982). It is straightforward to measure anxiety-like behavior in zebrafish, as described above, and the behavioral and neuroendocrine responses to stress are robust (Cachat et al. 2010; Blaser and Rosemberg 2012). Although some protocols assess aspects of depression in this species, such as hypolocomotion and disrupted shoaling (de Abreu et al. 2018), zebrafish models of this disease are not well established. In fact, it may be particularly difficult to model this depression in zebrafish considering that related behaviors that can be measured in fish (including anxiety-like behavior, changes to locomotion and social deficits) cannot be unambiguously assigned to this disease.

4 Zebrafish Lines to Model ADHD Endophenotypes

The majority of zebrafish ADHD models are based upon mutant lines that display ADHD-like changes in behavior, such as hyperactivity and impulsivity. One of the best studied ADHD candidate genes is *adhesion G protein-coupled receptor L3* (*adgrl3.1*; previously called *latrophilin 3.1*). The human *LATROPHILIN 3* gene is strongly associated with ADHD susceptibility, making it an important candidate to understand this disorder (Lange et al. 2012; Franke et al. 2012). In larval zebrafish, morpholino oligonucleotide (MO) knock-down of *adgrl3.1* leads to ADHD-like phenotypes, such as hyperactivity and changes in the pattern of swimming (fast peaks of acceleration followed by freezing) that have been called "motor impulsivity." Both phenotypes can be rescued by the prototypical ADHD medications, methylphenidate and atomoxetine, resulting in normal patterns of locomotion in *adgrl3.1* morphants.

The dopaminergic system is strongly affected in ADHD patients (Li et al. 2006; Vles et al. 2003; Levy 1991) and *adgrl3.1* MO animals showed a reduction and abnormal localization of dopaminergic neurons in the ventral diencephalon, a brain area associated with locomotion (Lange et al. 2012). Zebrafish *adgrl3.1* morphants are also hyposensitive to dopamine antagonists and agonists. For example, application of SCH-23390, an antagonist of the D_1-like receptor family (i.e., D_1 and D_5 dopamine receptors), decreased locomotion in control animals but had effect in *adgrl3.1* morphants. Similarly, quinpirole, a selective agonist of the D_2-like receptor family (i.e., D_2, D_3, and D_4 dopamine receptors) decreased locomotion in control fish but not *adgrl3.1* morphants. This suggests that dopaminergic signaling is saturated or desensitized when *adgrl3.1* is knocked down (Lange et al. 2018). The combination of hyperactivity, loss of dopaminergic neurons and reduction of the hyperlocomotion phenotype by methylphenidate and atomoxetine supports the validity of zebrafish *adgrl3.1* morphants as a model for some aspects of ADHD.

However, further behavioral studies investigating other cardinal features of ADHD such as inattention and impulsivity in adult animals are still necessary.

Similar to *adgrl3.1*, zebrafish mutants lacking the function of the circadian clock gene *period1b* (*per1b*) show changes in the dopaminergic system and ADHD-related behavioral phenotypes (Huang et al. 2015). Adult zebrafish *per1b* mutants display hyperactivity, inattention in a 2-Choice Serial Reaction-Time Task (similar to the 5-CSRTT, described above) and impulsivity (Huang et al. 2015), although this was measured using a mirror test that is frequently used to study aggression (Gerlai et al. 2000). They also have disrupted circadian changes to their locomotion pattern. The hyperactivity phenotype can be rescued with methylphenidate adding weight to *per1b* mutants as a model for ADHD. The heightened activity can also be reduced by the monoamine oxidase inhibitor, deprenyl, a drug that is not commonly used to treat ADHD.

Fish with *per1b* mutation(s) display a reduction and misplacement of posterior tuberculum dopaminergic neurons (similar to the *adgrl3.1* phenotype), as well as changes in the expression of genes related to dopamine neuron formation and dopamine synthesis and metabolism. *Monoamine oxidase* (*mao*) and *dopamine beta hydroxylase* gene expression are increased, whereas *orthopedia a*, *orthopedia b*, *mesencephalic astrocyte-derived neurotrophic factor* (*manf*), *wingless and integrated* (*wnt*) *1*, *wnt3a*, *wnt5a1* (genes that are required to specify many neurons, including dopaminergic neurons) and *adgrl3.1* expression are decreased (Huang et al. 2015). Excitingly, this suggests that both *per1b* and *adgrl3.1* may interact to control the formation and placement of dopaminergic neurons in the posterior tuberculum. Treatment of *per1b* mutants with auriculasin, a prenylated isoflavone, extracted from the root of *Flemingia philippinensis,* decreases hyperactivity and normalizes the expression of dopamine-pathway genes (Wang et al. 2018). This shows that auriculasin may represent a novel treatment option for some aspects of ADHD and demonstrates the power of fish models to identify novel drug treatments.

Similarly, *microtubule associated monooxygenase, calponin and LIM domain containing like protein 2b* (*micall2b*) knock-out zebrafish display hyperactive/impulsive-like behavior that can be rescued by treatment with atomoxetine (Yang et al. 2018). However, the authors did not explore whether changes to the development of dopaminergic neurons occur in this model. The *micall2b* gene codes for a cytosolic multidomain protein that has an important function in axon guidance, myofilament organization, and synaptogenesis. Since these fundamental processes are also affected in some human ADHD patients (Terman et al. 2002; Beuchle et al. 2007) it would be interesting to characterize this mutant line in more detail.

Characterization of a zebrafish lines with mutations in *glucose-fructose domain containing gene family* (*gfod*) *1* and *2* provides evidence that GABAergic neurons also play an important role in ADHD. A single nucleotide polymorphism (SNP) in the last intron of *GFOD1* was linked to ADHD in humans (Franke et al. 2009). Lechermeier and Collaborators (2020) mapped the expression of two (GFOD)-related genes (*gfod1* and *gfod2*) in the zebrafish brain, comparing early embryonic, late embryonic, and adult stages. They found that *gfod1* is expressed in a subset of GABAergic neurons, and both *gfod1* and *gfod2* are essential for neural development.

Creation of mutant lines for both genes has the potential to provide further insights into the mechanisms that can lead to ADHD.

The RAB6A GEF Complex Partner 1 (Ric1) protein is important for collagen trafficking from the Golgi apparatus through the cell. Human patients with polymorphisms in RIC1 display CATIFA syndrome that includes cleft lip, cataract, tooth abnormalities, intellectual disability, facial dysmorphism, and ADHD (Unlu et al. 2020). Zebrafish with a mutation in *ric1* exhibit reduced locomotion, a reduced forebrain and cerebellum volume, as well as a lack of jaw protrusion and changes to the musculature including shorter, misaligned cranial muscles and decreased secretion of tenocytes in the tendons (Unlu et al. 2020). Some of these phenotypes such as the reduced forebrain and cerebellum volume may represent endophenotypes for ADHD. However, the reduction of locomotion and lack of information, regarding attention and impulsivity, means that the association between this mutant line and ADHD is not clear.

Exposure to some drugs can also induce ADHD-like phenotypes. Zebrafish embryos exposed to methylphenidate have been associated with long-lasting behavioral alterations, such as inattention and hyperactivity (Levin et al. 2011). Chronic or acute exposure of juvenile zebrafish to methylphenidate diminished responses to visual stimuli modelling the approach of a conspecific or predator. Moreover, adult animals also display impaired predator avoidance and a decreased locomotor response to social stimuli upon exposure to this drug (Brenner et al. 2020). The impact of methylphenidate and atomoxetine treatment on zebrafish behavior and the brain transcriptome has recently been assessed. Interestingly, methylphenidate increased anxiety while atomoxetine decreased it, and the mechanisms underlying these changes involve opposite regulation of the cholesterol biosynthesis pathway (Suzuki et al. 2020). Since methylphenidate is prescribed for children and adolescents, further studies should be performed to determine its effects on brain and behavior after chronic treatment (Gray et al. 2007; Soileau 2008; Brenner et al. 2020).

5 Conclusions

Despite some limitations of working with zebrafish, such as differences in brain organization and genome duplication, the behavioral repertoire of this species can be used to model some aspects of ADHD. Assays to study ADHD range from locomotor and exploratory tasks to more complex behaviors, such as attention and impulsivity. Moreover, other comorbid phenotypes can be studied, such as altered aggression, social deficits, increased risk-taking, and anxiety-like behaviors including thigmotaxis. It is important to develop complementary models of ADHD to better understand the evolutionary-conserved mechanisms that underpin different behavioral domains, such as locomotion, cognition, and emotion. Due to the transparency and external fertilization of zebrafish embryos, this species also provides the opportunity to study ADHD at a neurodevelopmental level using optogenetics,

molecular biology, and imaging. Finally, several researchers have been working to develop ADHD models in zebrafish providing valuable insights into the neural mechanisms underlying ADHD-related genes, and how treatments modulate different neurotransmitter pathways and behaviors. Altogether, since zebrafish can easily be used in high-throughput screens, the development and the use of this species provides the opportunity to discover new therapeutic treatments for patients who do not respond to existing pharmacological approaches.

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What Has Been Learned from Using EEG Methods in Research of ADHD?

Gráinne McLoughlin, Máté Gyurkovics, and Ümit Aydin

Contents

Abstract Electrophysiological recording methods, including electroencephalography (EEG) and magnetoencephalography (MEG), have an unparalleled capacity to provide insights into the timing and frequency (spectral) composition of rapidly changing neural activity associated with various cognitive processes. The current chapter provides an overview of EEG studies examining alterations in brain activity in ADHD, measured both at rest and during cognitive tasks. While EEG resting state studies of ADHD indicate no universal alterations in the disorder, event-related studies reveal consistent deficits in attentional and inhibitory control and consequently inform the proposed cognitive models of ADHD. Similar to other neuroimaging measures, EEG research indicates alterations in multiple neural circuits and cognitive functions. EEG methods – supported by the constant refinement of analytic

G. McLoughlin (✉) and Ü. Aydin
Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
e-mail: grainne.mcloughlin@kcl.ac.uk

M. Gyurkovics
Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, USA

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strategies – have the potential to contribute to improved diagnostics and interventions for ADHD, underlining their clinical utility.

Keywords Electroencephalography (EEG) · Endophenotype · Error monitoring · Event-related potential (ERP) · Inhibitory control · Spectral composition

Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CEM	Cognitive-energetic model
CNV	Contingent negative variation
CPT	Continuous performance task(s)
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography (electroencephalogram)
ERN/Ne	Error-related negativity
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
IC	Independent component(s)
ISI	Inter-stimulus interval
MEG	Magnetoencephalography
NEBA	Neuropsychiatric EEG-based Assessment Aid
NIRS	Near infrared spectroscopy
Pe	Error positivity
Pre-SMA	Pre-supplementary motor area
RDoC	Research Domain Criteria
SCL(s)	Skin conductance level(s)
SMA	Supplementary motor area
TBR	Theta-beta ratio
VLF	Very low frequency (EEG)

1 Introduction

For almost 100 years, neurophysiological methods have been successfully applied to understand altered brain function in Attention-Deficit Hyperactivity Disorder (ADHD) (Jasper et al. 1938). The unparalleled temporal resolution of electroencephalography (EEG) can provide information on the strength, type and timing of the fast-changing cognitive processes that appear to be central to neurobiological understanding of the disorder. In this chapter, we introduce EEG methods and

review core findings related to ADHD. We further examine the evidence in the context of key neurobiological theories of the disorder. We also consider the impact of heterogeneity in ADHD on EEG-indexed neural activity and the role of EEG measures in explaining the heritability of the disorder. Finally, we close the chapter by discussing future perspectives in research on the neurobiology of ADHD.

2 Electromagnetic Imaging

Neuronal activity in the brain is associated with electrical currents that give rise to both electrical potentials on the scalp (measurable by means of EEG) and magnetic fields outside the head (magnetoencephalography/MEG). The EEG signal reflects the summated post-synaptic potentials of large populations of similarly aligned cortical pyramidal neurons (Luck and Kappenman 2011). MEG, on the other hand, records the magnetic field perpendicular to the electric field generated by the synchronously active neurons (Hari and Puce 2017). Both EEG and MEG measure the same underlying activity and they can provide information on the brain dynamics and temporal changes that are pertinent to understanding the abnormalities in sensory, cognitive and motor processing in ADHD. Both methods measure changes in synchronised cortical neuronal activity with millisecond precision, thus displaying the evolution of brain activity in real time. Consequently, they can be used to track covert, rapidly changing neural computations or changes in the cortex.

Despite measuring the same underlying activity, different sensitivity profiles of EEG and MEG make them complementary. MEG is mainly sensitive to quasi-tangential activity in the brain (activity on sulcal walls) while EEG is sensitive to both quasi-radial (sulci and gyri) and quasi-tangential sources. However, the signal to noise ratio for tangential sources is usually lower in EEG due to radially oriented background noise (Hari and Puce 2017). Because of these sensitivity differences, measurements might differ: e.g., some epileptic spikes could be visible only in EEG or MEG (Knake et al. 2006). It has been suggested that combined analysis of EEG and MEG might provide a better overview of the underlying activity and increase spatial resolution (Aydin et al. 2015; Baillet et al. 1999).

While the time courses of activations are critical in understanding brain function, it is also useful to know where in the brain signals of interest are generated. Spatial information from MEG and EEG is measurable in centimetres (especially without source localisation) and is thus less precise relative to other neuroimaging methods, such as functional magnetic resonance imaging (fMRI), which has a spatial resolution in the millimetre range and further has small co-registration errors as functional images can be superimposed on structural images. In contrast, with EEG and MEG the location of sources of activity in the brain could be estimated only after applying source localisation techniques to the sensor measurements. This estimation process is directly affected by volume conduction, which can create significant uncertainty regarding the localisation of EEG and MEG signals. One main difference between EEG and MEG is that the EEG source localisation is highly affected by the blurring

of the propagating electrical signal in space due to the low conducting skull; thus the signals measured on electrodes are a larger mixture of different sources, while MEG is mostly immune to this problem (Wolters et al. 2006; Aydin et al. 2014). However, recent major advances in computer hardware and signal processing are greatly increasing the amount of spatially precise information that can be extracted from EEG data using high-density channel recordings (Hari and Puce 2017; McLoughlin et al. 2014a).

Despite its importance as a neuroimaging method, MEG studies are comparatively rare in the literature due to the substantially higher cost of the method compared to EEG. In addition to its cost effectiveness, a further advantage of EEG is its portability and robustness to body movement relative to MEG. The development of dry, wireless, wearable, high density EEG systems makes the use of EEG in most recording locations feasible. Specifically, the lightweight EEG sensors and the lack of strict head movement constraints imposed by modern EEG recording and analysis methods allow accessible testing of developmentally young samples, a desirable approach for studies seeking to enable earlier detection of disorders (McLoughlin et al. 2014a; Lau-Zhu et al. 2019b). This brings a big advantage of EEG in comparison with fMRI, which requires restrictions on the movements of the participants during recording. In addition to the advantages mentioned above, EEG – and indeed, MEG – also has the benefit of being non-invasive in comparison with other neuroimaging measures, such as positron emission tomography that requires injection of radiotracers (McLoughlin et al. 2014a; Lau-Zhu et al. 2019b). These strengths and the ready accessibility of EEG have led to its proliferation in studies of neurodevelopmental disorders, including ADHD. Since MEG studies in ADHD are relatively rare, this chapter focuses on EEG.

3 Methods of Analysis

Due to its superlative temporal resolution, EEG is most commonly used to track the time course of various cognitive processes. The signal is a rich repository of temporal, spatial and spectral features that can be extracted using a variety of different techniques. In Fig. 1 we summarise the most common techniques for extracting meaningful information from the EEG signal (Tadel et al. 2011; Delorme and Makeig 2004). This is typically achieved in one of three ways.

First, the spectral composition of EEG signals can be quantified, for instance, by decomposing them into a set of cyclic waves of different frequencies and quantifying how much each wave contributes to the original signal. This process results in a spectrum of amplitude or power (squared amplitude) values across frequencies. This frequency domain representation of EEG is often investigated in resting-state studies when a person is not engaged in any specific task. Analyses are then commonly focused on the magnitude of power in one or more of the following canonical frequency bands: delta (<4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (<30 Hz). Such narrowband power is typically interpreted as an

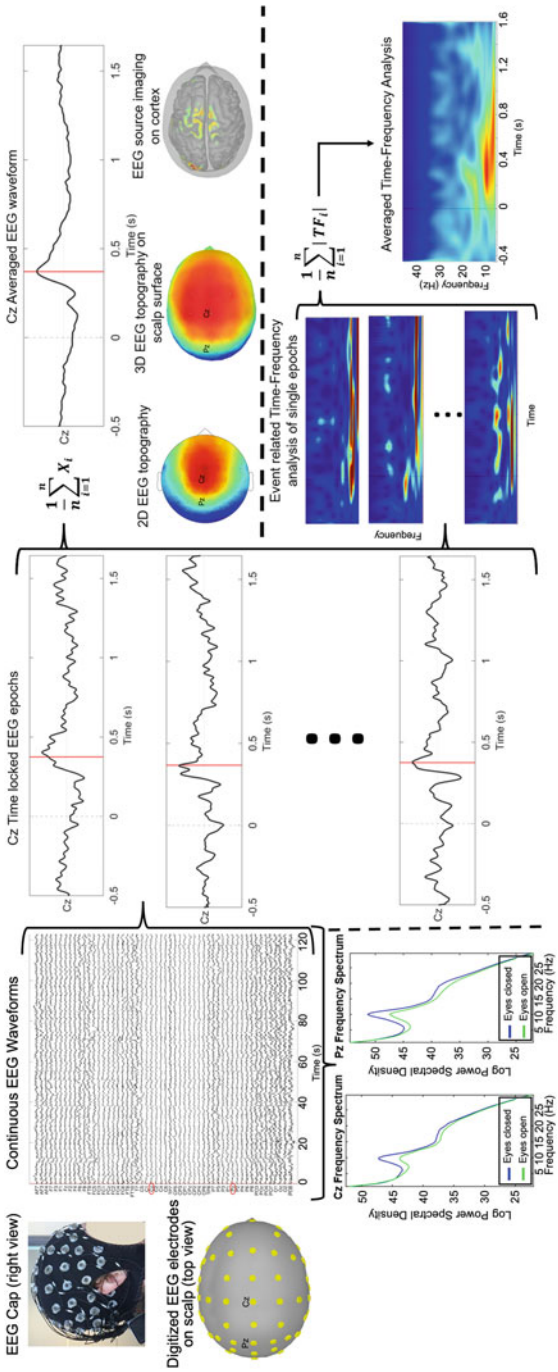

Fig. 1 (**a**) EEG data acquisition, digitization of the electrodes, and continuous EEG waveforms. (**b**) Spectral analysis of the continuous EEG waveforms to obtain the power in different frequencies for EEG channels Cz and Pz. Green line shows the spectrum with eyes closed and blue line shows for eyes open condition. Notice the attenuated alpha frequency (8–12 Hz) for the eyes open condition. Cz and Pz show different spectra especially for the alpha band. (**c**) In event related analysis continuous EEG waveforms are epoched using the event triggers. Here only the signals for the Cz channel are shown and the trigger used is the no-go events for the Continuous Performance Task (CPT). The time of the event trigger is shown as zero seconds. (**d**) Averaged event related potential (ERP) waveform for the Cz electrode with vertical red line showing the peak of the P3 component. (**e**) The spatial information at the peak of the P3 event is shown as 2D topography as well as 3D topography on the scalp. The EEG source imaging improves precision and allows the activity to be localised on the cortex. (**f**) Time-frequency analysis shows both time and frequency information. It is calculated for each epoch separately and then averaged to capture induced oscillations

oscillation at a frequency included in the specific band, although this may not always be justified and methodological care needs to be taken to ascertain that oscillations are indeed present (Wen and Liu 2016; Donoghue et al. 2020). In the case of resting-state data, the power across a range of frequencies is usually calculated at durations in minutes as opposed to milliseconds. The power in a particular frequency band can be expressed in absolute or relative terms, with relative power expressed as a percentage of power relative to all bands.

Secondly, event-related potentials (ERPs) reflect transient time- and phase-locked neural activity obtained by computing the average of the electrical potential in the range of milliseconds following or preceding some event. To do this, neural activity is typically recorded concurrently with a task and the data segments, or epochs, around task events of interest (e.g., the onset of a given stimulus) are aligned and averaged (Luck 2005). Activity that is consistently time- and phase-locked to the event across segments will be reflected in the average waveform, enabling the investigation of neuronal changes evoked by the event in the time domain. The functional significance of an ERP component is determined by its eliciting conditions (experimental variables), polarity (positive or negative), timing (latency) and spatial position (scalp distribution).

Finally, time and frequency domain information can be combined to yield the aptly named time-frequency domain representation of the data. This domain shows changes in the spectral composition (frequency domain representation) of neural activity as a function of time, typically following some task-relevant events, just like in ERP research (Herrmann et al. 2014; Cohen 2014). Time-frequency data allow researchers to draw conclusions about the time course of activity in different frequency bands (purportedly reflecting oscillatory activity). It also indicates how this activity changes in response to task events, compared to a (typically) pre-event baseline, showing stimulus- and task-related suppressions and enhancements. This helps link frequency bands to specific cognitive processes (i.e., those engaged by a given type of task event) and clarifies their dynamic interactions (Palva et al. 2005; Gratton 2018) (Fig. 1).

4 Resting State EEG

A body of quantitative EEG research highlights widespread alterations in resting state EEG in individuals with ADHD. The most consistent finding is an increase in slow wave, specifically theta, activity when compared with healthy controls, particularly with respect to frontal and central regions of the brain (Matsuura et al. 1993; Janzen et al. 1995; Chabot and Serfontein 1996; Lazzaro et al. 1998; Bresnahan et al. 1999) and, to a lesser degree, reduced faster-wave, beta activity (Mann et al. 1992; Clarke et al. 1998, 2001a, b; Lazzaro et al. 1998; Bresnahan et al. 1999; Bresnahan and Barry 2002). The combination of increased theta and decreased beta activity is sometimes quantified as the theta-beta ratio (TBR) and, when originally described by

Lubar in 1991, it was proposed to inversely index cortical arousal in ADHD (Lubar 1991). Support for the TBR as a biomarker of ADHD comes from multiple reports of more than 90% sensitivity and specificity (Monastra et al. 2001; Quintana et al. 2007; Snyder et al. 2008) and large effect sizes (>3.08) (Snyder and Hall 2006).

The theoretical link between TBR and cortical hypoarousal in ADHD was called into question by a series of studies that failed to show a link between TBR and objective measures of arousal (skin conductance levels, SCLs, Barry et al. 2004) and manipulations of arousal (caffeine, Barry et al. 2005). The role of TBR in the cognition of ADHD has, to date, been largely limited to exploration of its relationship to other EEG/ERP measures and its potential role in cognitive efficiency in ADHD (see below). Despite uncertainty about the theoretical implications of TBR, the evidence for its link with ADHD was sufficient for it to be approved as the first EEG biomarker of the disorder in 2013 by the United States Food and Drug Administration. The Neuropsychiatric EEG-Based Assessment Aid (NEBA) System (Saad et al. 2018) uses data from single electrodes at central and frontal locations to aid diagnosis of ADHD.

The announcement of NEBA has stimulated criticisms of the use of TBR in the diagnosis of ADHD. Studies have emerged that directly contradict its accuracy and reliability as a diagnostic biomarker in both children (Ogrim et al. 2012) and adults (Loo et al. 2009; van Dongen-Boomsma et al. 2010). A meta-analysis published in the same year as the NEBA release showed a significant association between TBR effect size and year of publication, showing a diminishing effect over time (Arns et al. 2013). This reduction in effect-size over time may be linked to the increase in rate of ADHD diagnosis, which the authors linked to false positives in the ADHD groups (reflecting overdiagnosis of the disorder in the population) (Snyder et al. 2015).

It is, however, important to note here that TBR in ADHD has remained stable over time and the diminishing effect size reflects an increase in TBR in the control samples (Arns et al. 2013). The largest study of the TBR in ADHD to date further failed to show an association between TBR and ADHD (Loo et al. 2013). The researchers behind NEBA propose that it should not be used as a standalone diagnostic tool but in conjunction with conventional diagnostic practices (Stein et al. 2016). This caveat notwithstanding, as growing numbers of practitioners incorporate its use into their patient assessments, further well-powered validation studies of the NEBA are required.

A critical point in resting state EEG studies of ADHD is the effect of age. Indeed, studies found that TBR was more effective at predicting age (up to 96.5% accuracy) than ADHD (up to 55% accuracy) (Buyck and Wiersema 2014; Liechti et al. 2013). The link between age and EEG variables is well-established: in general, slow wave EEG (i.e., delta, theta) decreases and fast wave EEG (i.e., alpha, beta) increases with increasing age (Benninger et al. 1984). A shift towards normalisation of beta activity in adult ADHD (Bresnahan et al. 1999, 2006; Bresnahan and Barry 2002; Hermens et al. 2004) was tentatively suggested to be related to the reduction in hyperactive-impulsive symptoms reported in adults with the disorder (Biederman et al. 2000);

however, a direct test of this hypothesis indicated that increased beta power is associated with a reduction in both attention and hyperactivity-impulsivity symptom domains (Loo et al. 2004).

Heterogeneity in ADHD, in Diagnostic and Statistical Manual (DSM) subtype/presentation, sex, age of onset and behavioural severity may also translate to variability in EEG profiles in ADHD. In contrast to decreases in higher-frequency activity (alpha and beta ranges) (Lazzaro et al. 1998; El-Sayed et al. 2002; Loo et al. 2009), other studies have found no differences (Bresnahan et al. 1999; Clarke et al. 2001a, b; Koehler et al. 2009; van Dongen-Boomsma et al. 2010) or even increases in these frequency bands (Chabot and Serfontein 1996; Clarke et al. 2011). Elevated beta activity was proposed as an EEG subtype of ADHD most common in the DSM-IV combined subtype (identical to DSM-5 combined presentation), representing 15–20% of this group (Clarke et al. 2001a, 2011).

A recent study by Loo et al. (2018) using a statistical method similar to cluster analytic techniques, called latent class analysis in a large sample, suggests five resting state subgroups in ADHD with differing patterns of associated behaviours and cognitive functioning. While the EEG subtypes loosely aligned with additional measures of behaviour, cognitive dysfunction, age and gender, crucially, the EEG subgroups were distributed in the same way across both ADHD and typically developing groups (Loo et al. 2018). This suggests that heterogeneity in brain function exists at the population level, rather than solely among children with psychiatric disorders, which is consistent with findings in ADHD using other neuroimaging methods and neuropsychological measures (Fair et al. 2012; Gates et al. 2014) and is furthermore in line with the dimensional approach of the Research Domain Criteria (RDoC) (Insel et al. 2010).

While there is limited evidence for consistent spectral differences between ADHD patients and non-affected individuals using resting EEG, these measures can be useful in tracking treatment response (Arns and Olbrich 2014), developmental outcomes (Clarke et al. 2011) and psychiatric comorbidities (Loo et al. 2018). Future research may need to consider individual differences in peak frequencies and thus the limitations of fixed frequency bands (Saad et al. 2018). A further consideration is the confounding effect of aperiodic, or in other words, non-oscillatory, background EEG activity on oscillatory measures, given emerging evidence linking the aperiodic component of EEG to ADHD and medication status (Robertson et al. 2019). Unless this aperiodic component is somehow accounted for, EEG ratio measures (including TBR), based on predefined frequency bands, could reflect changes in oscillations, the aperiodic component only, or a combination of both. This would create confusion about the meaning of the measured effect or, indeed, if the same effect is being measured across different studies. Further refinement of resting state EEG measures in combination with comprehensively described large samples is likely to lead to improvements in the understanding of the neurobiology of ADHD and also in the potential use of EEG in clinical settings.

5 Event-Related EEG

Event-related designs in EEG studies enable researchers to directly link spectral or amplitude changes in the recorded signal to cognitive processes. This can be done by using different cognitive tasks that tap into different domains of cognition: e.g., inhibitory control, working memory, cognitive flexibility. These tasks typically contain trials (or events), which engage the specific cognitive process or processes, and other trials that do not, or to a lesser extent. Electrophysiological changes that are unique to the former class of trials are then considered correlates of the cognitive process(es) in question. A common strategy for the understanding of brain pathophysiology across psychiatry, using all cognitive neuroscience methodologies, is to examine cognitive and neural dysfunction that is closely related to the core behavioural symptoms. Accordingly, the majority of event-related studies in ADHD aim to address questions focused on selective or sustained attention, inhibitory control and effort allocation (Johnstone et al. 2013), typically using variations of stop signal, flanker, go/no-go and continuous performance tasks (CPT) (Lau-Zhu et al. 2019a).

6 Inhibitory Control

One of the most established ERP findings in children and adults is that the P3, also known as the P300, in multiple contexts has been associated with the disorder (Kaiser et al. 2020). The P3 component is a positive voltage deflection occurring around 300 ms after a stimulus. When the P3 ERP is elicited by a stop signal or no-go stimulus, where a participant must refrain from making a prepotent or automated response, it is called the inhibition-related or no-go P3, and projects to frontal regions of the scalp (Fallgatter et al. 2002). A particularly robust finding is that ADHD is associated with a reduced amplitude and longer latency of the inhibition-related frontal P3 component (Lau-Zhu et al. 2019a; Kaiser et al. 2020). In the visual go/no-go task, a participant responds to a continuous stream of go stimuli (go trials), by pressing a button, but has to withhold a response when a no-go target appears (no-go trials). The go trials typically outnumber no-go trials to induce the prepotency of the go-response. Similarly, in the Stop Signal Task, a subject is asked to respond as quickly as possible to a stimulus but not to respond when a stop-signal (visual or auditory) follows the target stimulus.

These conditions elicit robust inhibitory processing and, in addition to the no-go P3, the no-go and stop stimuli evoke the frontal-midline N200 or N2, often together referred to as the N2/P3-complex (de Jong et al. 1990). The frontocentrally distributed N2 is a negative voltage deflection that peaks approximately 200–350 ms after a stimulus (Larson et al. 2014). However, in contrast to the no-go P3, the N2 is not consistently associated with ADHD (Kaiser et al. 2020). While the N2 was altered in ADHD patients in several studies (Pliszka et al. 2000; Barry et al. 2003; Albrecht

et al. 2008; Johnstone and Clarke 2009; McLoughlin et al. 2009; Wild-Wall et al. 2009; Rommel et al. 2019), there are exceptions (Overtoom et al. 1998; Banaschewski et al. 2004; Fallgatter et al. 2004; Spronk et al. 2008; Fisher et al. 2011; Tye et al. 2014). This discrepancy may relate to the respective functions of the N2 and the P3. Even though both have been described uniformly as indices of inhibition, it is now widely accepted that the N2 in fact reflects conflict detection and monitoring, 'the process of monitoring performance for simultaneously competing response options' (Groom and Cragg 2015; Hong et al. 2017). The inhibitory P3 is thought to reflect a 'braking' mechanism when inhibiting automated or prepotent response tendencies (Huster et al. 2013). Thus, while the N2 is elicited by these inhibitory conditions, unlike the no-go P3, it is not related to response inhibition per se, but rather reflects the conflict between the prepotent response tendency and the infrequent requirement to inhibit the response. In support of this, N2 amplitude for go trials increases when the ratio of go/no-go trials is reversed: an inversion that is not observed for the P3 (e.g., Enriquez-Geppert et al. 2010).

7 Error Processing

An ERP related to the N2 is the error-related negativity (ERN/Ne): a response-locked ERP occurring after the commission of errors. It has a strong negative frontocentral deflection that peaks 50–120 ms after erroneous responses (Falkenstein et al. 1990; Gehring et al. 1993). Source localisation and EEG-fMRI studies also suggest that the ERN and the N2 share common neural substrates in the medial frontal cortex, specifically the anterior cingulate cortex (ACC) and the pre-supplementary motor area (pre-SMA), despite their temporally distinct appearance in the processing of information, either prior to correct responses or after erroneous responses (Van Veen and Carter 2002; Yeung et al. 2004; Iannaccone et al. 2015).

EEG-indexed error monitoring has been found to be deficient in ADHD (Albrecht et al. 2008; Skirrow et al. 2009; McLoughlin et al. 2009; Geburek et al. 2013; Marquardt et al. 2018; Rommel et al. 2019; Michelini et al. 2021) although not in every study (Zhang et al. 2009; Wild-Wall et al. 2009; Groom et al. 2010) and a recent meta-analysis could not confirm an altered ERN in ADHD (Kaiser et al. 2020). The inconsistency in results could be explained by evidence that the N2 and ERN may be related to heterogeneity within samples in terms of age, IQ, ADHD presentation, medication status or comorbidities (Kaiser et al. 2020). Inconsistencies may also partially be due to differences in the type or degree of conflict engendered by tasks used in different studies (Brandeis et al. 2018). For instance, a large portion of studies that do find group differences in ERN magnitude use classic conflict tasks, such as the flanker task, whereas studies yielding null findings tend to use variants of the go/no-go task. Conflict stems from different stimuli priming incompatible responses simultaneously or quasi-simultaneously in the former, while it comes from the need to unexpectedly withhold a prepotent response tendency in the latter

task. While an early meta-analysis of the literature found evidence for a reduced ERN in ADHD using both tasks, this was based on a smaller set of studies (Geburek et al. 2013).

Nevertheless, a systematic investigation of how conflict type or task difficulty interacts with group differences in the magnitude of performance monitoring components is needed to address whether or not task design factors contribute to the heterogeneity of findings. Indeed, a recent study showed an interaction between the affective valence of task stimuli and the ERN in adult ADHD (Balogh et al. 2017). Furthermore, it is possible that time-frequency domain measures such as post-error phase and power dynamics, especially in the theta range, are more sensitive measures of performance monitoring than time-domain ERPs (Groom et al. 2010; Keute et al. 2019), leading to less stable findings in ERP studies. All in all, it appears that components related to performance monitoring (N2, ERN) are not reliably different in individuals with ADHD compared to healthy controls, or may be different only in a subgroup of these individuals.

Similar to the N2, the ERN is followed by a positive potential peaking at around 200-500 ms, known as the error positivity or 'Pe' (Falkenstein et al. 1990). The ERN is consistently observed when a mismatch occurs between representations of anticipated and actual responses, whereas the Pe appears to reflect error awareness (Falkenstein et al. 2000; Klein et al. 2007), reflecting conscious error processing or updating of the error context (Nieuwenhuis et al. 2001; Mathewson et al. 2005). Pe amplitudes are typically reduced in participants with ADHD compared to healthy controls and this finding is more consistent than the reduction in ERN (Kaiser et al. 2020). The Pe has been proposed to represent a P3-like facilitation of information processing modulated by sub-cortical arousal systems (O'Connell et al. 2007), which links with general deficits in P3 components in ADHD that may be modulated by arousal state (Wiersema et al. 2005, 2006).

8 Cognitive Models of ADHD

A highly influential theory places behavioural inhibition at the centre of cognitive dysfunction in ADHD (Barkley 1997). The model integrates neuropsychological and behavioural levels and proposes that inhibitory control is at the top of a hierarchy of self-regulatory behaviour in the disorder. In Barkley's model, the inability to inhibit or stop prepotent or on-going behavioural output interferes with normal functioning. This interference results in the development of further neuropsychological deficits in ADHD, specifically working memory, internalisation of speech and behavioural self-regulation of motivation, arousal and motor control (Barkley 1997).

Studies of inhibitory control in ADHD have typically operationalised this cognitive construct as the withholding of a prepotent or on-going response. Here, prepotent responses are actions that have previously been useful or reinforced, but that are not useful in the current situation owing to changes in the context, and on-going responses are behaviours that are already being executed and require interruption

(Barkley 1997). This operationalisation captures a form of cognitive control called reactive control, as it refers to situations where control processes are engaged following the onset of the target stimulus that requires a response. However, the evidence points towards this being too limited a model to explain the complex behaviours and altered brain function of ADHD. Poor inhibitory control can emerge due to dysfunctions in a number of processing stages: i.e., from the perceptual and attentional selection stage (Ocklenburg et al. 2011; Lackner et al. 2013; Grunewald et al. 2015) to the response selection stage (for a review, see Bari and Robbins 2013). This is because both perceptual processes (e.g., deficient attention) and response-related mechanisms (e.g., deficient inhibition) are crucial for adequate response inhibition. Rather than a central deficit of inhibitory control, event-related research in ADHD suggests that deficits exist on a number of these stages of action. In addition to the no-go P3, convincing and consistent evidence indicates reduced P3 amplitude to both go and cue stimuli within go/no-go and continuous performance tasks. In contrast to the anterior projection of the no-go P3 described above, these P3s are maximal over posterior scalp electrodes and reflect stimulus evaluation and response selection (P3b, Polich 2007). The 'go P3' is reduced in both children and adults with ADHD (Szuromi et al. 2011; Johnstone et al. 2013). Similarly, the P3 in response to predictive cues, which is maximal at posterior scalp sites, is also attenuated in ADHD in both children (Banaschewski et al. 2003) and adults (McLoughlin et al. 2010). A recent meta-analysis concluded that P3 components to all stimuli are the most sensitive ERP biomarkers of ADHD (Kaiser et al. 2020).

Additional cue processing deficits in ADHD are seen in the contingent negative variation (CNV), a frontocentral slow negative potential observed during the anticipatory interval after a cue stimulus. The same meta-analysis showed that reduced amplitudes of CNV were a consistent finding in over 52 studies of the disorder (Kaiser et al. 2020). Furthermore, cue-related deficits in ADHD are also indicated by a lack of cue-related suppression of alpha-band activity, which has been found in both children and adults with the disorder across a variety of tasks (for a review, see Lenartowicz et al. 2018). Suppression of alpha reflects increased control for processing upcoming stimuli via inhibition of irrelevant input (De Loof et al. 2019). In ADHD, these findings have been interpreted as deficient processing of the cue information prior to target onset, which may translate into impaired behavioural performance as well (Mazaheri et al. 2010).

The additional event-related deficits in ADHD, particularly for cue processing that precede the need for reactive control, indicate that a breakdown of inhibitory control is unlikely to be the central deficit in ADHD. Specifically, these findings suggest additional deficits in proactive control or the preparation of a reactive cognitive control network when it seems likely that reactive control may be required (de Zeeuw and Durston 2017). A recent study manipulated cues to either carry information about subsequent stimuli (e.g. to attend to a shape) or to simply alert the participant to a stimulus (with no task information). The aim was to tease apart whether reduced preparation in ADHD reflects proactive control impairments or is

the result of reduced general alerting in the disorder, as in general cues may both convey advance information about the task and also have a general alerting property. ADHD participants displayed alterations in the usage of informative cues to prepare for an upcoming task, indicative of a deficit in proactive control as opposed to general alerting (Sidlauskaite et al. 2020).

While these findings undoubtedly advance our understanding of the neurobiology of ADHD, alternative explanations remain possible in the context of the proposed cognitive models of ADHD. The dysregulation of downstream attention and perceptual systems in ADHD is consistent with another influential theory of ADHD, the cognitive-energetic model (CEM), which proposes that abnormalities in the regulation of basic information-processing may explain higher-order deficits in ADHD (Sergeant 2000). A central hypothesis of the CEM is that individuals with ADHD have difficulty in mobilising energetic resources and that this may be manipulated by specific task properties, including task difficulty and rewards. It is not clear if deficient alpha suppression in ADHD reflects a fundamental dysfunction in top-down frontoparietal circuitry or if this is a downstream problem with arousal (Lenartowicz et al. 2018). Consistent with the latter interpretation, reduced desynchronisation of alpha in ADHD is particularly pronounced during low working memory load conditions compared to high-load conditions (Lenartowicz et al. 2014). Similarly, larger effect-sizes are found for mean reaction-time, reaction-time variability and response accuracy in slower tasks (with long inter-stimulus intervals, ISIs) (Metin et al. 2012, 2016).

The periodic lapses of attention that are evident in ADHD during tasks with low event rates have alternatively been related to intrusions of the default mode network (DMN), known as the DMN interference model (Sonuga-Barke and Castellanos 2007). The DMN is typically deactivated during cognitive tasks and its activity is associated with mind-wandering and self-referential processing (Gusnard et al. 2001; Fox et al. 2015) and, as such, may interfere with appropriate task performance. While there is an inevitable degree of incongruence between hemodynamic and electrophysiological signals, researchers have proposed to examine DMN activity in ADHD using very low frequency (VLF) EEG (<0.2 Hz). VLF-EEG is increased in individuals with ADHD during the CPT and is associated with omission errors, an index of attention (Cooper et al. 2014). However, it has also been found to be decreased, though mainly during resting state (Helps et al. 2008, 2010). It is likely that EEG research has more to contribute to investigations of DMN interference in ADHD but, to date, has been bound by the observed weak to moderate correlations between EEG frequency domain features and regions associated with the DMN. Future research would benefit from an EEG-specific approach to identify correspondence between EEG features and known functional processes ascribed to the DMN (e.g., self-referential thought) and early work in this area is showing some promise (e.g., Bozhilova et al. 2020).

9 Heterogeneity in ADHD

As indicated in this chapter, and indeed, in this volume, the population of those affected by ADHD is heterogeneous, in terms of age, symptomatology, comorbidities and outcomes.

Defined according to the DSM-IV or DSM-5 (DSM), ADHD is also heterogeneous at the diagnostic level with three subtypes or presentations: primarily hyperactive-impulsive, primarily inattentive or a combination of both (combined presentation) (see Chapter "ADHD in Children and Adults: Diagnosis and Prognosis"). To date, limited evidence exists that the clinical presentations align with distinct neurobiological underpinnings. Early research taking this approach relied heavily on resting state EEG, which would provide clear potential benefits in ease of use in a clinical setting. The findings were often variable and lacked replication (for a review, see Loo et al. 2018). That limitation has justified an approach that extends beyond the clinical presentations of ADHD, using statistical clustering methods (e.g., latent class analysis, Loo et al. 2018), to derive subgroups based on neural activity (see Sect. 4, above: Resting State).

Recent work using event-related EEG measures hold more promise for uncovering differences between existing diagnostic presentations. For example, Mazaheri et al. (2014) provided some evidence that impaired suppression of alpha activity in task-relevant regions of the brain may be more typical of the inattentive presentation of ADHD, whereas those showing both inattentive and hyperactive symptoms displayed impaired suppression in the beta range, possibly suggesting poor motor planning during the preparatory period. Both groups, however, showed weakened functional connectivity between midfrontal theta activity and posterior alpha activity, which suggests a deficit in the top-down attentional control of perceptual processes after the cue across all subtypes/presentations of ADHD (Mazaheri et al. 2014).

Similarly, a series of studies examining differences in developmental outcomes in ADHD has indicated clear differences between those who persist with the diagnosis into adulthood and those who experience remission. Specifically, event-related theta power and phase was lower in those who have persistent ADHD while no differences in alpha suppression emerged between those in remission and those who retained the diagnosis (Vainieri et al. 2020). Event-related EEG data has also highlighted key differences in those with a single diagnosis of ADHD versus those who have a comorbid diagnosis. Investigations by Tye and colleagues indicate that those with ADHD have a different ERP profile compared with those who have a dual diagnosis of ADHD and autism spectrum disorder (ASD) with abnormalities in P3 amplitudes to cue and no-go stimuli evident in those with ADHD only (Tye et al. 2014).

The objective nature of EEG measurements and its ready availability in the clinic have led to work that aims to identify EEG subgroups. This work could lead to a personalised treatment approach based, in almost all cases, on the spectral contents

of resting state EEG recordings. Some of this work has indicated that EEG measures may be useful in predicting medication response. A 2014 review identified four different EEG subgroups based on their response to different medications (Arns and Olbrich 2014). Two subgroups (excess theta and high beta activity) were proposed to respond well to stimulant medication (Clarke et al. 2003b; Arns et al. 2008) whereas children with a slow individual alpha peak frequency were reported to be resistant to stimulant medication with poor outcomes (Arns et al. 2008). Another group was identified as having paroxysmal and epileptiform EEG, without the existence of seizures, and thus was suggested to have a good response to anticonvulsant medication (Silva et al. 1996). These findings suggest the potential for using EEG parameters for personalised medication in ADHD, but further research is required to confirm if, in practice, EEG subgroups could predict treatment outcome.

Event-related EEG approaches may hold more promise for tracking treatment response in ADHD. For example, in a large sample of medication naïve children with ADHD, Ogrim et al. (2014) conducted follow-up assessments after 4 weeks based on 23 parameters related to demography, IQ, DSM-IV subtype, as well as behavioural, ERP and EEG spectra parameters of a visual go/no-go task. They found that only three EEG parameters (amplitude of independent components (IC) representing cue P3 and no-go P3, and theta power) independently predicted a medication response as rated by clinicians blind to all EEG measures. Furthermore, in another study of IC amplitudes of the CNV, an early visual ERP as well as reaction-time were reported to predict side effects of medication (methylphenidate, Ogrim et al. 2013). Longer term neural changes have also been indicated by resting state EEG studies. Isiten et al. (2017) reported an increase in beta power after continuous use of methylphenidate for 1.5 years, in comparison with the EEG data prior to the treatment, and Clarke et al. (2003a) reported normalisation of theta, alpha and beta band EEG after 6 months of stimulant medication. Further work is required to investigate the long-term EEG correlates of medication use, including whether the reported effects are sustained after medication is ceased.

10 Endophenotypes: The Role of EEG in Explaining Heritability in ADHD

The heritability of EEG has long been investigated in twin and family studies (Vogel 1970). Consistent evidence indicates that the impact of genetic influences on EEG measures is moderate to high, similar to behaviour and brain structure measures, and surpassing heritability estimates found in twin and family studies of fMRI data (van Baal et al. 1998; Anokhin et al. 2004; Smit et al. 2005; Anokhin et al. 2006, 2008; Blokland et al. 2012). A meta-analysis in 2002 confirmed high heritability (50–80%) for frequency and ERP measures (van Beijsterveldt and van Baal 2002) indicating that they may have value as endophenotypes. An endophenotype is defined as a quantitative, subclinical and biological phenotype that is intermediate between the behavioural symptoms and genetic variation associated with the disorder.

Endophenotype studies aim to map neurobiological processes that mediate the relationship between behaviour, symptoms and genes (Ishii and Naito 2020).

Many studies have indicated that EEG/ERP variables share genetic or environmental variance with ADHD (Loo and Smalley 2008; Tye et al. 2012). A major requirement for an endophenotype is that it shows familial clustering with the disorder so that it is evident even in unaffected family members thus covarying with genetic vulnerability for the disorder even in the absence of symptoms (Gottesman and Gould 2003; Durston et al. 2009). In ERP studies of ADHD, familial segregation has been shown. Moreover, unaffected siblings or parents of individuals with ADHD display similar performance to those with the diagnosis across a range of executive control tasks (Albrecht et al. 2008; McLoughlin et al. 2009, 2011; Albrecht et al. 2013). For example, Michelini and colleagues investigated a large sample of adolescents and young adults with ADHD, their affected and unaffected siblings and controls on a range of tasks: familial influences on ADHD overlapped strongly with the ERN and the no-go P3 (Michelini et al. 2021).

Endophenotype investigations adopting strategies for advanced EEG analysis have had mixed results. A recent investigation aimed to predict ADHD symptoms using machine learning of connectivity signals across all canonical frequency bands (resting state EEG) in adults with the disorder, first degree relatives and healthy controls. While they found that EEG connectivity in specific frequency bands predicted hyperactive-impulsive and inattentive symptoms, separately, they failed to show a difference in any type of EEG connectivity measures between first degree relatives and healthy controls, thereby showing no familial clustering between the EEG measures and ADHD symptoms (Kiiski et al. 2020). Thus, the findings do not support network alterations as potential endophenotypes of ADHD. However, this may be because functional connectivity was analysed between electrodes (sensors) in this study, as opposed to between potential cortical sources of neural activity (Kiiski et al. 2020). In support of this notion, a study indicated that spatially-resolved cortical source measures of frontal-midline theta may share more genetic variance with the disorder than traditional scalp-based measures (McLoughlin et al. 2014b). The authors proposed that the improved signal-to-noise ratio of source imaging measures in EEG may provide a better representation of the underlying cortical activity and therefore may improve the ability to detect genetic effects on brain function measures and their overlap with the disorder. This approach was supported by a study showing an association between dopaminergic candidate genes and the go and no-go P3 in the source space, but not at the electrode (sensor) level (McLoughlin et al. 2018).

A key feature for any endophenotype, EEG-based or otherwise, is reliability in measurement and, in turn, statistical power to identify an association between the disorders and potential genetic causal factors (Iacono et al. 2017). ADHD, in common with all psychiatric disorders, is heterogeneous even at the genetic level and so the extraction of a common genetic background is a challenge (Faraone and Larsson 2019; McLoughlin et al. 2014a). Large studies are required to parse the neurobiological pathways, but these are potentially enabled by the use of advanced analysis methods and genetic approaches.

11 Future Directions

Future studies of the neurophysiology of ADHD could consider adopting novel methodologies and analytic approaches. In terms of methods, improvements in neuroimaging techniques provide powerful new tools for the investigation of the neural bases of ADHD. Recent advancements in MEG technology, such as optically pumped magnetometers that allow MEG sensors to be placed on the scalp, much like the EEG, improve the portability and resilience to movement (Boto et al. 2018; Hironaga et al. 2020). MEG is more sensitive to higher-frequency signals (i.e., gamma band activity) in the brain and these signals may be sensitive to alterations in emotional regulation in the disorder (Dor-Ziderman et al. 2021). Increasing evidence points towards emotional symptoms as a potential core feature of the ADHD diagnosis (Faraone et al. 2019; Biederman et al. 2020).

Further advantages arise from the use of optical techniques, such as near infrared spectroscopy (NIRS), which can be used to obtain hemodynamic information and has several clear advantages for studying children with developmental disorders, such as ADHD (Scholkmann et al. 2014). However, unlike fMRI, it measures both relative oxygenated and deoxygenated haemoglobin changes by measuring changes to the absorption of infrared light (Scholkmann et al. 2014). Furthermore, unlike fMRI, NIRS is silent and the acquisition environment is not intrusive, so it is a practical method for children with hyperactive symptoms. Although limited in number, to date, NIRS studies in ADHD have contributed to the understanding of the neurobiology of ADHD by pointing to hypo-metabolism in frontal brain regions during the go/no-go and Stroop tasks (Mauri et al. 2018). Furthermore, pharmacotherapy increased oxyhemoglobin in the prefrontal cortex (Nagashima et al. 2014; Ishii-Takahashi et al. 2015; Dolu et al. 2019; Grazioli et al. 2019). However, another study found increased prefrontal activity after treatment with atomoxetine, but not methylphenidate, even though participants receiving either medication showed a reduction of ADHD symptoms (Nakanishi et al. 2017). These studies included fewer than 60 participants and therefore studies with larger sample sizes are still needed. Perhaps one of the most important prospects is that EEG and NIRS could be measured simultaneously; analysing both sets of data would bring information on both direct neuronal activity and hemodynamics and so improve precision (Fazli et al. 2012; Shin et al. 2018; Dolu et al. 2019).

While resting state EEG investigations of ADHD have contributed to our understanding of the disorder, the interpretation of spectral changes is substantially more straightforward in event-related designs that target various, specific cognitive processes. Furthermore, event-related designs often permit researchers to link directly trial-to-trial fluctuations in neural activity with moment-to-moment variability in behaviour (e.g., accuracy or reaction-time) through single trial analyses (McLoughlin et al. 2014b). Such methodological, analytic and design considerations could help further uncover details of the neural basis of ADHD that have hitherto remained hidden or unclear. On-going advances in signal processing and visualisation of EEG activity could provide novel insights and/or more sensitive measures of

underlying cognitive processes in ADHD (McLoughlin et al. 2014a). Time-frequency decomposition of neural signals, particularly in the context of distinct cortical source activities, take advantage of the ability of EEG measures to both spatially and temporally characterise fast-changing events in the brain that are key to understanding the pathophysiology of ADHD.

The study of brain activity from EEG (and MEG) has benefited from the development of techniques that aim to characterise the degree of functional or effective brain connectivity between time series, in which cognitive functions are no longer associated to specific brain areas, but to networks of synchronously activated areas (Friston 2011). This approach reflects a shift from understanding the neurobiological basis of neurodevelopmental disorders, as focal brain abnormalities affecting specific systems, towards an overall pattern of brain reorganisation. While this research is still relatively underexplored in ADHD, initial investigations using this approach indicate disruptions in interrelated networks in ADHD (e.g., Pereda et al. 2018).

Together with machine-learning methods, these approaches can improve the predictive power of the proposed neurobiological models of ADHD and, consequently, may contribute to the development of screening and diagnostic tools. The importance of large sample sizes for such research is highlighted by a recent meta-analysis, which indicated that classification accuracies for ADHD appear to be inflated by small sample sizes that do not account for the heterogeneity in the disorder (Pulini et al. 2019). Furthermore, to achieve clinical benefits, machine-learning classifiers need to achieve good performance in independent samples: i.e., individuals not included in the original study. Brain connectivity research in fMRI has led the way in the validation of models in independent samples by indicating the value of validating all predictive models across independent data sets to identify a potential tool to assess attention independent of ADHD diagnosis (Yoo et al. 2018).

Although symptom-based diagnoses are the ‘gold-standard’ for clinical outcomes of ADHD, symptoms may be distinct from the actual burden of the conditions. Individuals with ADHD are at higher risk of experiencing a range of behavioural and functional problems, such as mood disorders, sleep problems and unfavourable psychosocial outcomes, including poorer academic performance and lower employment levels (Davidson 2008). Even individuals who no longer have the diagnosis but retain some symptoms have been shown to have lower work productivity, quality of life, functioning and self-esteem (Pawaskar et al. 2020). The role of cognitive dysfunction in the burden of ADHD over and above diagnosis has to date been under-researched. The use of cognitive biomarkers to predict and track outcomes – e.g., education, physical health, emotional and adaptive functioning – may have greater clinical impact than a focus on diagnosis alone by advancing the potential for personalised interventions. Such an approach could directly improve the lives of those affected by the disorder by improving wellbeing and quality of life.

12 Conclusions

As with other neuroimaging investigations of ADHD, EEG research has not been able to identify a final common pathway to the disorder. Nevertheless, this large body of research does show that, although there is limited evidence for universal alterations in ADHD, there are robust and consistent patterns emerging that incorporate these deficits in broader neurobiological frameworks: this applies particularly for P3 measures in multiple contexts and indices of proactive control, such as alpha suppression. Heterogeneity in ADHD and evidence that multiple neural circuits and cognitive functions are affected in the disorder have led to a preference for multiple pathway theories of the disorder that propose deficits in multiple, partially separable brain systems (Castellanos et al. 2006). Further insight into the neurobiology of ADHD is likely to be gained by large studies that take into account this heterogeneity and also take advantage of the rich information about cortical function provided by EEG data.

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Alterations in Structural and Functional Connectivity in ADHD: Implications for Theories of ADHD

Karen González-Madruga, Marlene Staginnus, and Graeme Fairchild

Contents

Abstract Attention-Deficit/Hyperactivity Disorder (ADHD) is increasingly viewed as a disorder of brain connectivity. We review connectivity-based theories of ADHD including the default mode network (DMN) interference and multiple network hypotheses. We outline the main approaches used to study brain connectivity in ADHD: diffusion tensor imaging and resting-state functional connectivity. We discuss the basic principles underlying these methods and the main analytical

Karen González-Madruga and Marlene Staginnus contributed equally to this work.

K. González-Madruga
Department of Psychology, Middlesex University, London, UK

M. Staginnus and G. Fairchild (✉)
Department of Psychology, University of Bath, Bath, UK
e-mail: g.fairchild@bath.ac.uk

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approaches used and consider what the findings have told us about connectivity alterations in ADHD. The most replicable finding in the diffusion tensor imaging literature on ADHD is lower fractional anisotropy in the corpus callosum, a key commissural tract which connects the brain's hemispheres. Meta-analyses of resting-state functional connectivity studies have failed to identify spatial convergence across studies, with the exception of meta-analyses focused on specific networks which have reported within-network connectivity alterations in the DMN and between the DMN and the fronto-parietal control and salience networks. Overall, methodological heterogeneity between studies and differences in sample characteristics are major barriers to progress in this area. In addition, females, adults and medication-naïve/unmedicated individuals are under-represented in connectivity studies, comorbidity needs to be assessed more systematically, and longitudinal research is needed to investigate whether ADHD is characterized by maturational delays in connectivity.

Keywords ADHD · Attention-deficit/hyperactivity disorder · Brain networks · Connectivity · Diffusion tensor imaging · fMRI · Functional connectivity

Abbreviations

AD	Axial diffusivity
ADHD	Attention-deficit/hyperactivity disorder
BOLD	Blood oxygen level-dependent
CC	Corpus callosum
CD	Conduct disorder
DMN	Default mode network
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
FPCN	Fronto-parietal control network
ICA	Independent component analysis
MD	Mean diffusivity
PFC	Prefrontal cortex
RD	Radial diffusivity
ROI	Region-of-interest
rsfMRI	Resting-state functional magnetic resonance imaging
SBC	Seed-based connectivity
SGC	Subgenual cingulum
SLF	Superior longitudinal fasciculus
SS	Sagittal stratum
TBSS	Tract-based spatial statistics
WM	White-matter
(WB)VBA	(Whole-brain) voxel-based analysis

1 Introduction

Over the last decade, Attention-Deficit/Hyperactivity Disorder (ADHD) has increasingly been conceptualized as a disorder of abnormal brain connectivity rather than alterations in individual brain regions (Konrad and Eickhoff 2010; Cortese et al. 2021). Accordingly, neuroimaging research on brain connectivity in ADHD has dramatically increased. In the present chapter, we review the two main approaches that have been used to study brain connectivity in ADHD: diffusion tensor imaging (DTI), which assesses the microstructural properties of white-matter pathways in the brain (essentially 'structural connectivity'), and functional connectivity, as assessed using functional magnetic resonance imaging (fMRI) methods. We provide an overview of the basic principles behind these neuroimaging methods and the main analytical approaches used, and then consider what these methods have told us about alterations in brain connectivity in ADHD. We review the findings of recent meta-analyses of neuroimaging studies of ADHD. We also provide recommendations for future research in this area, focusing particularly on harmonization of data analysis approaches, the value of meta- and mega-analyses, and the importance of measuring and accounting for head motion during scanning – given the inconsistent findings and lack of replicability in the field. It should be noted that, due to space limitations and methodological heterogeneity, graph theory and task-related functional connectivity studies will not be considered in detail here (but see Posner et al. (2014) for a review covering these approaches).

1.1 Theories of Brain Connectivity in ADHD

1.1.1 The Default Mode Network Interference Hypothesis

The central idea underpinning this theory is that activity in a core brain network thought to support internally-generated or self-referential thought, the 'default mode network' (DMN), persists or intrudes into periods in which the individual is actively engaging in a task, thereby leading to impaired performance and attentional lapses (Sonuga-Barke and Castellanos 2007). This failure to suppress DMN activity in an adaptive manner – when switching between so-called task-negative and task-positive states or orienting towards external stimuli – is thought to underlie many of the characteristic features of ADHD. It is also thought to explain why ADHD symptoms might fluctuate over time, such that intact performance is observed in some task conditions or trials, but ADHD-related deficits in performance are seen in others (Castellanos et al. 2005). This hypothesis is supported by empirical data showing that the typical pattern of anticorrelation between the DMN and task-positive networks, such as the cognitive control network, observed in healthy individuals, is significantly weaker in those with ADHD (Castellanos et al. 2008).

Overall, it appears better placed to explain inattentive ADHD symptoms (i.e., difficulties in concentration and following instructions, forgetfulness and problems organizing tasks) than hyperactive symptoms, due to its focus on cognition and issues with transitioning between states.

An extension of this hypothesis is that the individual subcomponents (or 'nodes') of the DMN, as well as connections between the DMN and other networks (e.g., the fronto-parietal control network) are less well-integrated with each other in ADHD, which might have negative implications for the DMN's ability to support self-referential cognition and a coherent sense of self (Posner et al. 2014).

1.1.2 Menon's Multiple Network Hypothesis

This hypothesis builds on our expanding knowledge base regarding functional networks in the brain, which has largely been obtained via resting-state fMRI methods. The hypothesis argues that different forms of psychopathology or symptom profiles are caused by disturbances in the *interactions* between different brain networks. The three networks considered particularly important for ADHD are the salience, central executive and default mode networks and the connections between them (Menon 2011). The salience network plays a key role in attending to motivationally-relevant stimuli and recruiting fronto-parietal systems involved in working memory and cognitive control (Seeley et al. 2007). This hypothesis is more general than the above ADHD-specific model, because it seeks to explain psychopathology across multiple disorders rather than fully accounting for a specific disorder.

As we shall see in the following sections, both theories are supported to some extent by existing neuroimaging data. However, there are also conflicting findings and many connectivity studies have failed to support either of these models or provide robust evidence for ADHD-related connectivity disturbances. It is currently unclear whether this is due to methodological heterogeneity (e.g., variations in the diagnostic assessment of ADHD), heterogeneous sample characteristics (e.g., different rates of comorbid conditions), or a failure to consider developmental influences on the findings (e.g., the possibility that abnormal brain connectivity observed in ADHD reflects *delays in brain maturation* rather than absolute differences that persist across the lifespan). We shall return to some of these issues in later sections, but now consider the diffusion tensor imaging literature on ADHD.

2 Diffusion Tensor Imaging (DTI) Studies of ADHD

As mentioned above, DTI methods enable researchers to investigate the microstructural organization of white-matter (WM) fibres that connect different parts of the brain. In this section, we review studies investigating structural connectivity in ADHD using DTI methods. Before discussing the evidence, we provide a primer

on how structural connectivity is assessed using DTI and the metrics which are typically studied.

2.1 What Is DTI and How Is It Quantified?

DTI is a sensitive tool that can be used to measure cellular structure and is frequently used to investigate the microstructural properties of brain tissue – specifically WM. It works by measuring the displacement of water molecules, which varies in direction according to tissue type (Soares et al. 2013). For instance, WM is composed of myelinated bundles of axons that form structural connections between brain regions (i.e., grey matter areas). Thus, the diffusion of water molecules in WM is constrained overall, but is less restricted along the axons which run in particular directions. This directionally-dependent form of diffusion is known as anisotropy. In grey matter, where the majority of neurons are located, diffusion is more homogenous and less anisotropic. In the cerebrospinal fluid, diffusion is unrestricted and occurs in all directions and this motion is referred to as isotropic.

In WM, the axon bundles (also known as fibres or 'tracts') can be categorized, depending on their direction, as either *association* fibres (axons that connect cortical areas within the same hemisphere), *projection* fibres (efferent fibres which carry neural impulses from the central nervous system to the periphery, and afferent fibres which carry signals from the spinal cord to the brain), or *commissural* fibres (axons that cross the midline and connect the brain's hemispheres (Catani and de Schotten 2012)).

It is possible to measure the diffusivity of water molecules along different directions and thus estimate the WM fibre orientation (Basser and Pierpaoli 1996). The quantification of water molecule diffusivity is achieved by generating diffusion maps of deep tissue organization (Basser et al. 2000). The most commonly reported measures in DTI studies include: mean diffusivity (MD; average diffusion in all directions), fractional anisotropy (FA; an index of WM coherence and diffusion directionality), radial diffusivity (RD; diffusion perpendicular to the main fibre direction; modulated by myelin in WM) and axial diffusivity (AD; diffusivity along the fibres, an indicator of axonal integrity) (Alexander et al. 2007). Given that FA values are thought to provide information about the microstructural organization of WM tracts, such as their axonal density and diameter, and myelination (Beaulieu 2009; Paus 2010), FA is the most commonly used metric in DTI studies, with higher values thought to index greater coherence. However, as this is a composite measure, it is recommended that researchers assess multiple metrics simultaneously (e.g., radial and axial diffusivity, as well as FA) to understand what may be driving differences in FA.

2.2 DTI Methods

There are a number of different ways of obtaining DTI parameters in a format suitable for performing statistical comparisons. DTI studies of ADHD have mainly used four different analytical approaches: region-of-interest analysis, whole-brain voxel-based analysis (WBVBA), Tract-Based Spatial Statistics (TBSS) and tractography. Below, we briefly explore how each approach works and review DTI studies of ADHD that have used each of these approaches.

2.3 Region-of-Interest (ROI) Analysis

Region-of-interest (ROI) methods are usually used to indicate an a priori specified brain area for subsequent analysis (see Fig. 1 for an example). An ROI can either be positioned manually on a suitable co-registered image or can be derived from anatomical atlases (see, for example, Mori et al. 2008; Oishi et al. 2008) embedded in automated methods (without manual input) (Froeling and Leemans 2016). Earlier

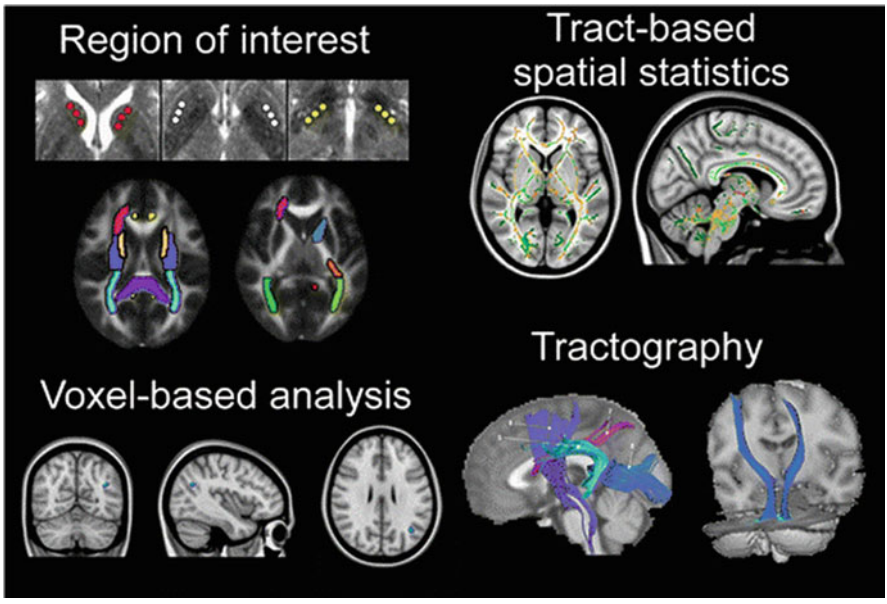

Fig. 1 Illustrations of the main DTI methods used in the ADHD field. Clockwise from top left: manual selection of regions of interest; Tract-Based Spatial Statistics, an automated and unbiased approach, which involves aligning fractional anisotropy maps onto a 'fractional anisotropy skeleton' (shown in green); Tractography involves tract reconstruction based on the orientation and magnitude of diffusion, after which probabilities of connectivity can be analysed; Automated voxel-based analysis registers diffusion maps into a standard space. Figure reproduced with permission from Hess et al. (2013). *Current Neurology and Neuroscience Reports*

studies on ADHD relied on the former method, while more recent studies have used the latter. An advantage of ROI analysis is that it has high sensitivity to detect small or focal changes, but it requires prior knowledge of neuroanatomy and a clear hypothesis regarding the location of the pathology (Froeling and Leemans 2016). It also does not provide information about areas outside the ROI. Thus, ROI-based studies are usually the method of choice when a researcher has a clear hypothesis and wants to detect more subtle differences in the WM of selected brain regions. These could be chosen either because they have been identified as abnormal in structural imaging studies, WBVBA (see below), or because they are implicated in the functional deficits associated with ADHD, such as inhibitory control regions.

ROI studies of ADHD have been highly heterogeneous in terms of the regions selected. This is partly due to differences in research interests and hypotheses. Some ROIs have been used to identify correlations between symptoms of ADHD and WM alterations (Li et al. 2010). For instance, one study first compared the FA of brain regions (e.g., the corpus callosum (CC), corona radiata; the superior longitudinal fasciculus (SLF); the sagittal stratum (SS) and the cingulum) that have been associated with functional deficits in ADHD (e.g., motor dysfunction) in children with ADHD ($n = 16$) and typically-developing controls ($n = 16$). The researchers found increased FA in the left SS (i.e., a tract that connects the temporal lobe to distant cortical regions) in children with ADHD compared to controls. A correlational analysis in the same sample showed that FA values in the left SS were positively associated with ADHD symptom severity across both ADHD individuals and controls (Peterson et al. 2011). The SS is part of the occipital-temporal projection system and contains fibres of the inferior frontal-occipital and inferior longitudinal fasciculi. This region is implicated in attentional set-shifting and memory (Peterson et al. 2011).

Another study investigated FA differences specifically in the CC of boys with ADHD ($n = 28$) and typically-developing controls ($n = 27$). It used a more comprehensive method (i.e., the CC was subdivided into seven functionally-distinct sections) and found reduced FA specifically in the isthmus of the CC of ADHD youth compared to controls (Cao et al. 2010). Interestingly, these findings are consistent with those of a similar study in adults with ADHD (Dramsdahl et al. 2012). The isthmus of the CC contains fibres connecting primary motor and sensory areas (Wahl et al. 2007). fMRI studies have suggested that the isthmus is involved in attention and response inhibition (McNally et al. 2010), suggesting that abnormal WM in this part of the CC may contribute to the attentional deficits observed in ADHD.

The basal ganglia (i.e., caudate nucleus, globus pallidus and putamen) are involved in voluntary movement but also cognitive functions such as emotion regulation – and sMRI studies have reported reduced volume in these regions in children with ADHD (Hoogman et al. 2017). The WM of the basal ganglia has also been investigated using an ROI approach. Silk et al. (2009) compared children with ADHD ($n = 15$) and typically-developing controls ($n = 15$) in terms of FA and MD in the basal ganglia. Although no group differences in FA and MD were found in the ROIs, a correlational analysis investigating associations between age and caudate

nucleus FA suggested that the ADHD group continued to show increases in FA into late adolescence whereas the control group showed minimal changes in FA with advancing age (Silk et al. 2009). Although the latter study was not a longitudinal study and had a small sample, the findings support the hypothesis that WM maturation is delayed in ADHD but 'catches up' in adolescence (Bouziane et al. 2018).

The cerebellum has also been selected as an ROI due to its involvement in motor control, timing and executive functions (e.g., inhibitory control and working memory), which have been shown to be impaired in neurocognitive studies of ADHD (Martel et al. 2007; Noreika et al. 2013). FA values in the cerebellum were compared in boys with ADHD and controls, but no group differences were found (Bechtel et al. 2009). However, the latter study did find reduced FA in the ADHD group compared with typically-developing controls in the cerebellar peduncle (i.e., afferent fibres connecting sensory and motor areas of the cortex with the pons and cerebellum), which might contribute to issues with fine motor skills.

Although earlier studies mainly focused on cognitive and motor functions in ADHD, recent studies have recognized that ADHD symptoms frequently co-occur with emotional problems and have expanded their focus to investigate brain regions associated with emotion regulation. For instance, the subgenual cingulum bundle connects the ventral and rostral anterior cingulate cortices with the amygdala (Heilbronner and Haber 2014). These regions are of interest in ADHD due to their role in emotion–cognition interactions (Keedwell et al. 2016). An ROI-based study investigated several DTI indices (i.e., FA, MD and RD) within the subgenual cingulum in children with ADHD ($n = 32$) and typically-developing controls ($n = 32$) and found increased RD in the ADHD group; this finding suggests that there is excessive diffusion perpendicular to the axon and possibly greater fibre branching. In addition, RD of the subgenual cingulum bundle was positively correlated with ADHD symptoms in both the ADHD and control groups (Zhan et al. 2017).

ROI studies have also investigated WM asymmetry in ADHD, due to its involvement in the development of cognitive functioning. A recent study examined WM asymmetry in a large sample ($N = 205$) of children with ADHD and controls (Wu et al. 2020). It positioned 20 pairs of ROIs and included the cingulum, SLF, external capsule and posterior thalamic radiation. Compared to controls, children with ADHD showed greater asymmetry in the posterior thalamic radiation alone. FA values in the external capsule were negatively correlated with inattentive symptoms across the whole sample (Wu et al. 2020).

To understand more about WM development in ADHD, and the potentially confounding effects of stimulant medication, it is important to assess WM alterations in children and adults who have never been medicated. However, the majority of DTI studies have assessed medicated children and adolescents with ADHD. It has been suggested that previous findings showing WM differences between children with ADHD and controls are attributable to prior stimulant use (Bouziane et al. 2018). Therefore, to rule out this possibility, medication effects have also been investigated in ROI-based studies.

One study compared medication-naive adults with ADHD ($n = 37$) and controls ($n = 34$) in ROIs within the attentional network, including the SLF, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, splenium and genu of the CC, anterior cingulum bundle and posterior cingulum bundle. FA values in ADHD individuals were lower in the left inferior longitudinal fasciculus, while MD values were higher in ADHD individuals compared to controls in the left inferior fronto-occipital fasciculus (Konrad et al. 2010).

Another study assessed the WM of medication-naive children and adults with ADHD. The authors selected ROIs implicated in executive function (e.g., CC, SLF and anterior thalamic radiation). Interestingly, while never-medicated ADHD children did not differ from control children in FA, never-medicated adults with ADHD had reduced FA values compared to controls in the anterior thalamic radiation and CC, but not the SLF (Bouziane et al. 2019). This represents preliminary evidence that WM alterations in children with ADHD may be influenced by prior medication use. The discrepancies between these studies may be due to ROI selection and other methodological differences (e.g., smoothing, cluster size in voxels).

2.4 Tractography

This analysis method involves reconstructing WM pathways in vivo, based on the direction of diffusion. It enables researchers to investigate specific anatomically-defined pathways and facilitates the integration of diffusion properties along their entire length (for an example of a tractography method, see Fig. 1). Similar to the above-mentioned studies, the reconstruction of WM tracts can be done by placing an inclusion (i.e., area of interest where all the fibres of that region are included) and exclusion (i.e., area of no interest where all fibre pathways from that region are excluded) seed (ROIs) in WM areas where a tract of interest originates or terminates. These seeds can be collocated manually or by using semi-automatic software. Tractography studies usually collocate seeds (ROIs) following the Boolean logic (AND, and NOT gates) to delineate their WM tract of interest. This method has several limitations as it struggles to resolve complex fibre configurations such as fibre crossing, branching problems or a mix of different tissues can corrupt the indices such that they are no longer fibre-specific (Dell'Acqua et al. 2013). Despite these challenges, this method provides more accurate information about the microstructural properties along the whole tract of interest (rather than the WM of a specific brain region). This approach would usually be used when researchers have a clear hypothesis and knowledge of the underlying WM anatomy or the tract's functions.

Tractography methods have been used to assess the anatomical specificity of the fronto-striatal WM alterations observed in ADHD. One study showed reduced FA in WM tracts that connect the striatum and prefrontal cortex (PFC) in children with ADHD compared to the control group (De Zeeuw et al. 2012), adding to the existing literature showing the involvement of fronto-striatal networks in ADHD. Treatment

effects were also assessed in this study; these analyses showed that FA differences between the groups were not influenced by medication. Supporting this conclusion, another study that investigated the WM properties of the corticospinal tract in drug-naïve children also showed reduced FA of the corticospinal tract in children with ADHD compared to controls (Bu et al. 2020).

Another study investigated associations between ADHD traits and microstructural organization of the subgenual cingulum (SGC) in a sample of male adolescents with ADHD. The SGC is a subdivision of the cingulum bundle. This is the most anterior tract: fibres of the SGC arise from the anterior cingulate region and terminate in the medial PFC, insula and amygdala. The authors found a positive association between the FA of the SGC and ADHD symptom severity (Cooper et al. 2015). Interestingly, this result was not observed in a previous voxel-wise analysis of the same ADHD sample, suggesting that tractography methods provide enhanced sensitivity to detect WM alterations along specified tracts. It should be noted that brain regions overlapping with the DMN are connected by the SGC. Therefore, this study provides evidence that the WM pathways which connect the different nodes of the DMN together may be disrupted in ADHD.

2.5 Whole-Brain Voxel-Based Analysis

Voxel-based analysis (VBA) is an automated technique, which enables the researcher to analyse the WM segments of the brain in an unbiased/hypothesis-free manner (for an example of VBA methods, see Fig. 1). It works by aligning the images from different individuals onto a common image called the atlas or template to achieve a correspondence between a particular voxel position in each image and the same anatomical structure across subjects (van Ewijk et al. 2012). However, the problem here is that there are many options to choose from when pre-processing the data and setting up the comparisons (e.g., the choice of template or smoothing process (which involves blurring the data using a filter)), that can lead to substantial variability in results. These processes (e.g., smoothing) may increase the risk of partial volume effects (i.e., when FA from non-WM regions is also considered in error), or failure to align FA images from different subjects into a common space.

To address these limitations, Smith et al. (2006) developed an alternative method called Tract-Based Spatial Statistics (TBSS). TBSS introduced a new step, which follows image alignment into a standard space. This step is the projection of FA values from the main WM tracts of all subjects onto an alignment-invariant tract representation called the mean FA 'white-matter skeleton' (see Fig. 1). However, TBSS's main limitation is the anatomical specificity of the findings, because it is optimized to detect differences only in the centre of the respective tracts, and a stringent correction for multiple comparisons (controlling for all voxels in the WM skeleton) is applied. Consequently, this approach can be considered relatively conservative and results should be interpreted with care (Bach et al. 2014).

2.6 *Whole-Brain DTI Meta-Analysis*

Meta-analysis provides a quantitative means of integrating across different empirical studies to identify the most reliable and robust findings in ADHD. Techniques exploring WM abnormalities at the whole-brain level, such as VBA and TBSS, are easier to incorporate into quantitative meta-analyses than approaches like tractography. To date, three meta-analyses have been conducted to identify robust WM alterations in individuals with ADHD compared to controls (Aoki et al. 2018; Chen et al. 2016; van Ewijk et al. 2012). All three meta-analyses included whole-brain DTI studies and, given that FA is the most widely reported index in DTI studies of ADHD, all three focused on FA in their primary analyses.

2.6.1 van Ewijk et al. (2012)

The first meta-analysis was conducted by van Ewijk et al. (2012). At the time of publication, there were insufficient studies using TBSS, therefore the authors incorporated studies using both VBA and TBSS in their analysis rather than distinguishing between these approaches. They included nine datasets, seven of which used VBA methods and two used TBSS methods. One hundred and seventy three ADHD patients and 169 controls were included. Although the majority of the included studies assessed children or adolescents only, the analysis combined datasets of participants spanning a wide age range (M_{ages} ranged from 7 to 49 years). They used activation likelihood estimation analysis to analyse and visualize agreement in the reported clusters of abnormal FA across studies. The results showed reduced FA in the right anterior corona radiata, right forceps minor, left cerebellum and bilateral internal capsule in patients with ADHD compared to controls (van Ewijk et al. 2012). These WM tracts form part of the fronto-striatal-cerebellar neurocircuitry, thus this meta-analysis supports the fronto-striatal-cerebellar theory of ADHD (Durston et al. 2011).

Although this meta-analysis represented an important first step in helping us to understand WM differences in patients with ADHD, it had several limitations. First, it did not control for age, sex or medication use or investigate whether these variables moderate ADHD-related effects. However, this is not surprising as earlier studies did not consider age or sex when analysing their findings and only 22% of the ADHD sample were female and just 21% were adults. Finally, and most importantly, it merged datasets from TBSS and VBA studies, which is problematic as these approaches differ substantially in methodology, as mentioned above.

2.6.2 Chen et al. (2016)

The methodological limitations of combining TBSS and VBA studies in van Ewijk's meta-analysis were addressed in a subsequent meta-analysis by Chen et al. (2016). By this time, TBSS was the preferred method to assess for WM alterations within the ADHD neuroimaging field: surpassing the number of VBA studies available. Thus, Chen et al. meta-analysis focused solely on TBSS studies (Chen et al. 2016). The study used a seed-based mapping method. Compared to ALE methods, seed-based mapping methods enable individual studies to be controlled for several moderators (e.g., age), and null findings can also be included. Chen and colleagues included a total of 12 datasets extracted from ten studies.

A total of 470 ADHD patients and 477 controls were included. Only three studies recruited adults with ADHD. However, as one of them included participants aged 8–30 years, this dataset was incorporated into the youth subsample. Similar to the van Ewijk et al. (2012) meta-analysis, Chen and colleagues observed reduced (rather than increased) FA in the splenium of the CC, the right SS and the left tapetum of the CC in patients with ADHD compared to controls (see Fig. 2). A jackknife sensitivity analysis (which involves leaving out each of the studies in turn) was performed to test for reliability. This showed that the findings were highly reliable, especially the CC and right SS clusters. The CC connects the two cerebral hemispheres and undergoes dramatic developmental changes from childhood to adolescence due to myelination, redirection, pruning and specialization (Dramsdahl et al. 2012). The splenium of the CC conveys commissural fibres of the occipital, temporal and parietal areas, which influence transmission of visual information. The SS contains fibres connecting the parietal, occipital, cingulate and temporal regions to subcortical regions such as the thalamus and brainstem (Di Carlo et al. 2019). It is involved in verbal and non-verbal processing, reading, visual processing and attention (van Ewijk et al. 2012). Thus, deficits in both structures may be related to the inattention and distractibility seen in ADHD individuals.

Interestingly, to understand discrepancies between the original studies (e.g., FA changes in opposite directions), a meta-regression analysis was performed using age as an independent variable. A significant negative correlation was found between age and FA values in the splenium of the CC. This suggests potential developmental effects in the WM microstructure of patients with ADHD, with children showing the most abnormal FA values, and is in line with ROI-based studies reporting a developmental delay in the CC of ADHD individuals compared to controls (Dramsdahl et al. 2012). Chen et al. also noted that there were insufficient data available to test for sex differences in the relationship between ADHD and WM microstructure or effects of medication status – only 29% of the participants with ADHD were female, and just 7% were unmedicated. This highlights the need for future research to recruit more representative samples and test for potential moderating effects of sex and medication use.

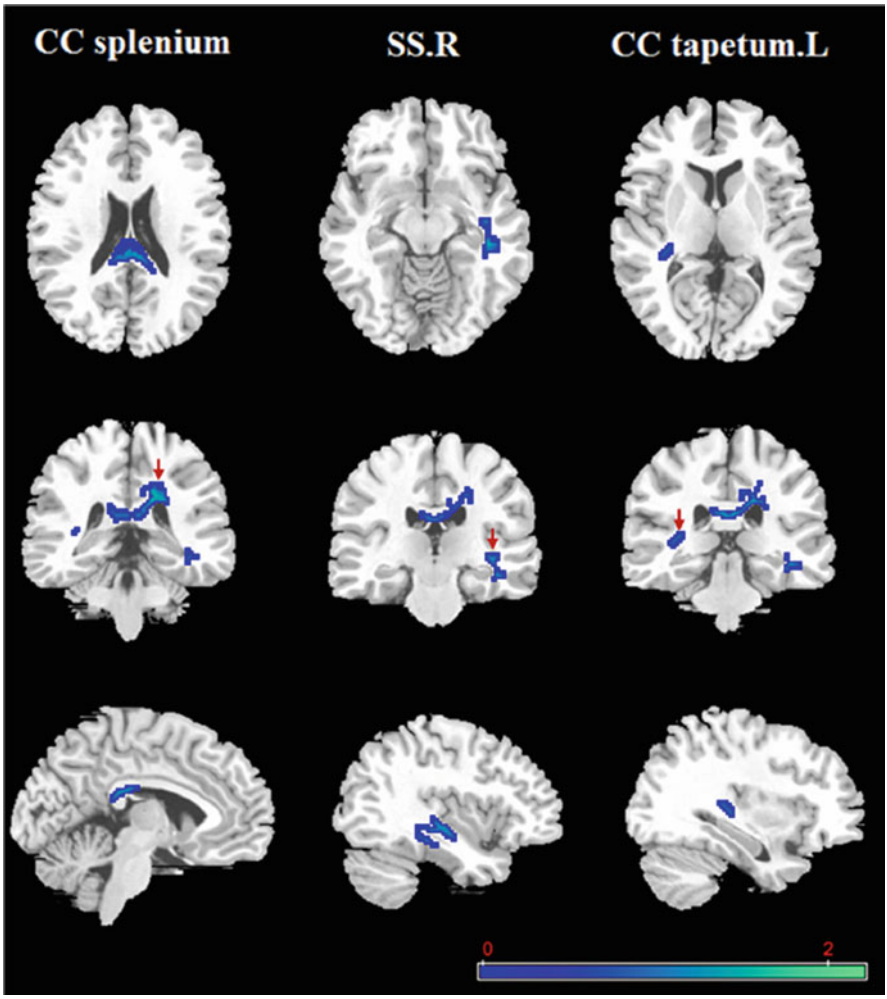

Fig. 2 Patients with ADHD had lower fractional anisotropy than controls in the splenium and tapetum of the corpus callosum (CC) and the right sagittal stratum (SS) in the Tract-Based Spatial Statistics meta-analysis performed by Chen et al. (2016). Figure reproduced with permission from Chen et al. (2016). *Neuroscience and Biobehavioral Reviews*

Taken together, these findings indicate that the main WM differences between ADHD individuals and controls are localized to commissural (e.g., CC) and association fibres (e.g., SS). Reduced FA may be related to changes in myelination, axonal density and axonal diameter (Beaulieu 2009). However, as the interpretation of diffusion parameters is complex, the combined use of additional DTI indices is needed (Curran et al. 2016). Investigating MD, RD and AD together with FA may help researchers to better understand the microstructural changes contributing to FA alterations. For instance, the two main diffusion indices used are MD and FA. Both

represent the magnitude of the diffusion process and are mirror images of each other that generally change in opposite directions, with FA values tending to increase, while MD values decrease, across childhood and adolescence (Soares et al. 2013).

2.6.3 Aoki et al. (2018)

Aoki et al. (2018) also recognized the limitations of combining TBSS and VBA methods in the same analysis. However, they acknowledged that both approaches have been used in DTI research on ADHD and that separate meta-analyses for each study type may be needed to provide complementary evidence. In addition, Aoki et al. noted the issues arising from head motion in the neuroimaging field. In DTI studies, this is particularly important as head motion may produce spurious findings of decreased FA in groups that have a greater tendency for motion such as children with ADHD (Yendiki et al. 2014). Thus, they performed an updated meta-analysis in which TBSS and VBA studies were considered separately and the influence of head motion investigated.

Twelve TBSS studies yielding 13 separate datasets were extracted for the TBSS meta-analysis, while 13 studies with 14 datasets were included in the VBA meta-analysis. Many of the included studies overlapped with those included in the previous meta-analyses. A total of 557 ADHD individuals and 568 controls were included in the TBSS meta-analysis, whereas 314 individuals with ADHD and 278 controls were included in the VBA meta-analysis (Aoki et al. 2018). In addition, while the authors focused on FA in their primary analysis, they also extracted MD for a secondary analysis. However, only 8/13 studies reported this metric. Finally, the authors also performed a separate meta-analysis in a youth subsample. To analyse WM differences between the groups, the authors used signed differential mapping, a voxel-based meta-analytic method. Aoki et al. also contacted the authors of the included studies to ask whether they had assessed for head motion and, if so, whether the groups differed in this measure. In total, the authors of five studies were able to confirm that there were no significant differences in head motion between the ADHD and control groups.

Surprisingly, the separate meta-analyses yielded opposite results. The VBA meta-analysis demonstrated *increased* FA in the left mid-cingulate (extending to the CC), the anterior CC and the left inferior fronto-occipital fasciculus, and reduced FA in the anterior cingulate and orbitofrontal cortex in the ADHD group. However, the TBSS meta-analysis demonstrated only *reduced* (rather than increased) FA in the isthmus and posterior body of the CC, right inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus and in the right SLF in ADHD participants (see Fig. 3). Interestingly, four out of the six datasets that reported no group differences in head motion did not identify any group differences in FA, suggesting that head motion may have been an important influence on findings and a potential confound in previous DTI studies of ADHD. Although the authors argued that discrepancies in the direction of FA changes in the VBA and TBSS meta-analyses are unlikely to be explained by the analytic procedures, the brain templates used for the respective

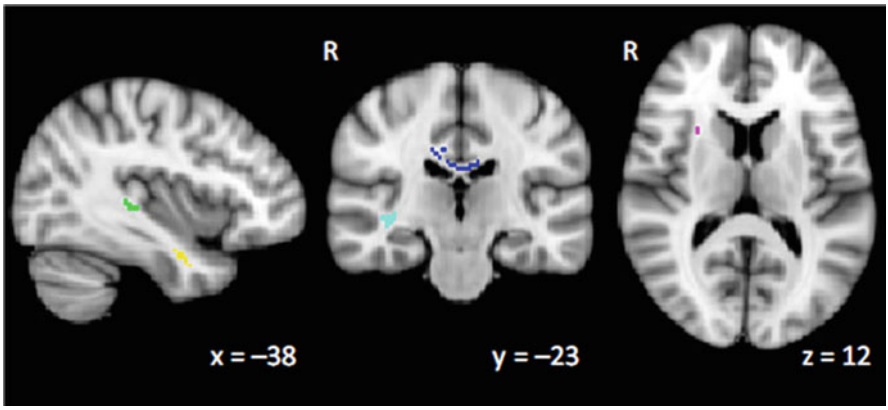

Fig. 3 Results of the voxel-based meta-analysis of Tract-Based Spatial Statistics studies of ADHD by Aoki et al. (2018), showing regions that were lower in fractional anisotropy in the ADHD group than controls. The corpus callosum is shown in dark blue, whereas the left and right inferior frontal-occipital fasciculus are shown in green and light blue, respectively. The left inferior longitudinal fasciculus and right superior longitudinal fasciculus are shown in yellow and purple, respectively. Figure reproduced with permission from Aoki et al. (2018). *Journal of Child Psychology and Psychiatry*

analyses differ. While a whole-brain template was used for the VBA analysis, a 'WM skeleton' was used for TBSS, therefore while the focus of TBSS analysis is on the centre of the WM tracts, VBA largely focuses on the periphery of WM tracts.

Finally, the meta-analysis focusing on MD showed increased MD in the left inferior fronto-occipital fasciculus, and reduced MD in the right inferior longitudinal fasciculus and SS in individuals with ADHD compared to controls. The sensitivity analysis focusing just on children and adolescents showed reduced FA in the CC, bilateral inferior longitudinal fasciculus and right SLF in ADHD youth compared to controls. In line with Chen et al. (2016), microstructural alterations in the CC seem to be the most robust finding across studies. However, this meta-analysis highlighted head motion as an important factor that should be considered in future studies.

2.7 Conclusions of DTI Section

In this section, we explained that DTI data can be analysed using different approaches depending on the research question and study aims. While ROI-based and tractography studies are hypothesis-dependent, in that they typically focus on

predefined tracts or regions, whole-brain voxel-wise analysis facilitates the identification of WM differences in novel regions that may not have been implicated in ADHD to date (Smith et al. 2006).

To date, three DTI meta-analyses on ADHD have been performed. The first meta-analysis supported the involvement of fronto-striatal-cerebellar neurocircuitry in the pathophysiology of ADHD, whereas the most recent meta-analyses highlighted the role of tracts involved in interhemispheric communication, and particularly the corpus callosum. Interestingly, limbic system regions (e.g., sagittal stratum) were also identified by these meta-analyses. Thus, while early DTI research investigated the WM of cognitive control networks, novel findings demonstrating the involvement of limbic regions and associated tracts are emerging. On the other hand, the lack of convergence across different analytical approaches was highlighted by Aoki et al. (2018) who obtained findings in opposite directions (increased vs. reduced FA) and different tracts when contrasting TBSS versus VBA studies.

There are insufficient data to draw robust conclusions regarding WM alterations in females, adults and medication-naïve patients with ADHD so it will be important to address these gaps in the evidence base in future studies. Another major limitation of DTI research relates to the heterogeneity of the ADHD samples studied to date and the failure of many studies to take comorbidity into account. As a consequence, none of the existing meta-analyses were able to extract sufficient data on comorbidity to investigate the influence of this variable. This is important as WM microstructure may not be altered in the same way in all ADHD individuals, and differences in clinical presentation or comorbidity may contribute to heterogeneity in findings.

For instance, WM alterations in the cingulum, a limbic tract, have been reported in youth with Conduct Disorder (CD) (González-Madruga et al. 2020), which frequently co-occurs with ADHD. However, the proportion of participants with comorbid CD in the above meta-analyses is unknown. Future research should consider the impact of comorbidity (especially Oppositional Defiant Disorder, CD and depression) and contrast the connectivity profiles of 'pure' and comorbid forms of ADHD, or explicitly compare ADHD and other psychiatric disorders in terms of WM alterations. In addition, the relative lack of females in DTI studies of ADHD has prevented researchers from exploring whether sex moderates ADHD-related effects, as has been found in other disorders (González-Madruga et al. 2020; Nordahl et al. 2015; Rogers et al. 2019).

We now turn our attention to functional connectivity studies of ADHD, first starting with an overview of the underlying methods.

3 Resting-State Functional Connectivity Studies of ADHD

3.1 What Is Functional Connectivity and How Is It Quantified?

In addition to DTI studies (i.e., structural connectivity), studies of functional connectivity provide a means to assess alterations in network organization in ADHD and, hence, enable an investigation of the disorder from a systems perspective (Konrad and Eickhoff 2010). As opposed to structural connectivity, which assesses the fibre pathways linking brain regions, functional connectivity can be conceptualized as an index of dynamic functional communication between spatially distant brain regions (Margulies et al. 2010). Although research suggests that structure is predictive of function, available evidence indicates that the correspondence between structural and functional connectivity is not perfect (Honey et al. 2009, 2010; Tsang et al. 2017). In the following sections, we shall highlight what functional connectivity measures and how it is assessed before discussing data on functional connectivity alterations in ADHD with an emphasis on meta-analytical evidence.

Functional connectivity is an index of the temporal correlations between neuronal activity of spatially distant regions in the brain (Konrad and Eickhoff 2010). Although functional connectivity can be investigated under task conditions, many studies have focused on task-unrelated, 'intrinsic' functional connectivity as assessed by resting-state functional Magnetic Resonance Imaging (rsfMRI). This is based on the observation that even in the absence of external stimulation, the brain shows spontaneous activity (i.e., fluctuations in the Blood Oxygen Level-Dependent [BOLD] signal; Smitha et al. 2017). Regions that show temporally correlated spontaneous fluctuations under resting conditions are considered to be functionally connected and form inter-connected 'resting-state networks' (Castellanos and Aoki 2016). These include the default mode network (DMN), the fronto-parietal control network (FPCN, also called cognitive control network or executive control network), the salience (or ventral attention) network, the dorsal attention network, the affective network (also called limbic network), the visual network and the somatomotor/sensory network (Yeo et al. 2011).

While all of these networks are active during rest and task performance, the DMN is particularly active during rest and is deactivated during external stimulation and hence shows anticorrelations with task-positive networks such as the attention and control networks (Andrews-Hanna et al. 2014; Buckner et al. 2008). Corresponding to these activation patterns, the DMN is implicated in self-generated thoughts, mind-wandering, autobiographical memory retrieval and prospection (Andrews-Hanna et al. 2014; Buckner et al. 2008). Figure 4 displays the aforementioned brain networks (except for the visual network), while Fig. 5 presents the DMN and its subsystems.

One challenge in investigating intrinsic functional connectivity lies in the considerable flexibility in how it can be operationalized and analysed (Castellanos and Aoki 2016). One of the most commonly employed approaches, which will be

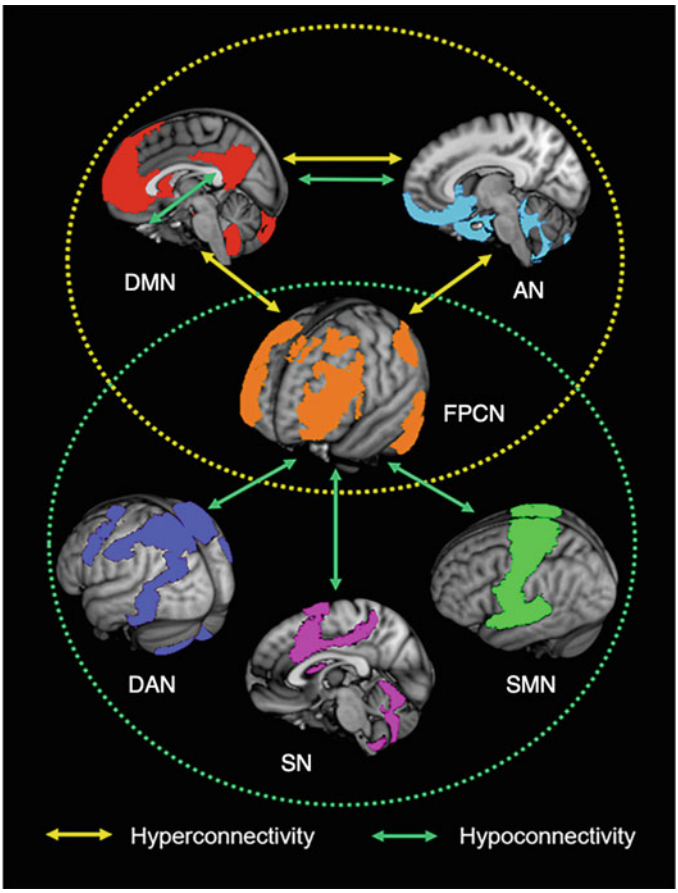

Fig. 4 Illustration of six resting-state networks: The default mode (DMN), affective (AN), fronto-parietal control (FPCN), dorsal attention (DAN), salience (SN) and the somatomotor/sensory networks (SMN). Arrows reflect findings of within and between network hypo- and hyperconnectivity in individuals with ADHD as identified by Gao et al. (2019). Figure adapted from Gao et al. (2019). *Psychological Medicine*

discussed below, is Seed-Based Connectivity (SBC; Gao et al. 2019). In brief, SBC focuses on the analysis of correlations of spontaneous brain activity between predefined ROIs (i.e., the 'seed[s]') and the rest of the brain (Smitha et al. 2017). While this approach is relatively straightforward to implement, easily interpretable and enables the investigation of specific networks, it is not hypothesis-free due to the selection of seed regions (Margulies et al. 2010). Additionally, even minor variations in the location and size or shape of the seed(s) can impact cross-study comparability and integration of studies in meta-analyses (Castellanos and Aoki 2016; Smitha et al. 2017).

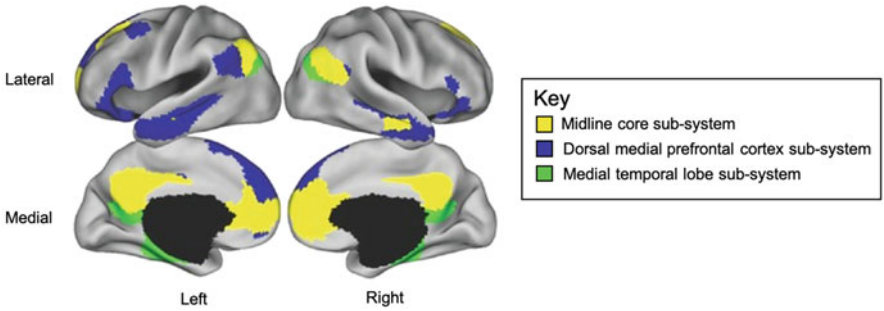

Fig. 5 The three subsystems of the default mode network (DMN). Yellow: The midline core subsystem, including the posterior cingulate cortex, anterior medial prefrontal cortex and the inferior parietal lobule, linked to self-referential processing. Blue: The dorsal-medial prefrontal cortex subsystem, comprising dorsal-medial prefrontal cortex, lateral temporal cortex, temporo-parietal junction and temporal pole, implicated in mentalizing. Green: The medial temporal lobe subsystem, including ventromedial prefrontal cortex, (para)hippocampus, retrosplenial cortex and inferior parietal lobule, linked to memory. Figure adapted from Andrews-Hanna et al. (2014). *Annals of the New York Academy of Sciences*

Other more data-driven methods such as Independent Component Analysis (ICA) partly address these shortcomings. Using ICA, all observed voxel-to-voxel interactions are decomposed into spatially and temporally independent components (i.e., networks) without the specification of ROIs (Margulies et al. 2010; Smitha et al. 2017). However, similar to SBC studies, issues with replicability have been reported and there is a risk of bias as the 'true' number of independent components is not known. This means that the researcher has to make decisions about whether observed networks are meaningful or reflective of noise (Margulies et al. 2010). Further approaches include: (1) clustering – the identification of patterns in the data which are partitioned into subsets; (2) pattern recognition – the identification of classes of data by means of multivariate pattern classification algorithms; (3) graph theory – the characterization of network structure in terms of its topological properties; and (4) local methods such as regional homogeneity (correlations of BOLD signals among neighbouring voxels) and amplitude of low frequency fluctuation (assesses variability of BOLD fluctuations at specific voxels). For a detailed overview of these methods, see Margulies et al. (2010).

3.2 Heterogeneous Alterations in Functional Connectivity Across Primary Studies

Using SBC methods and in line with findings on structural connectivity, alterations in intrinsic functional connectivity in youths and adults with ADHD compared to age-matched typically-developing controls have been reported (Castellanos and Aoki 2016). These include hypoconnectivity (i.e., increased negative or decreased

positive functional connectivity) and hyperconnectivity (i.e., increased positive or decreased negative functional connectivity), both at the whole-brain level and within and between specific networks (Castellanos and Aoki 2016). While graph theory studies will not be discussed in detail here, it is interesting to note that studies investigating the topological properties of network structure in ADHD have demonstrated higher local and lower global efficiency, reflected by greater network segregation (i.e., stronger short-range connections) against lower integration (i.e., weaker long-range connections; Cao et al. 2014; Lin et al. 2014).

At the network scale, alterations in intrinsic functional connectivity within and between various networks have been observed including the DMN, FPCN, salience, affective and somatomotor/sensory networks, as summarized in the narrative reviews by Castellanos and Aoki (2016) and Posner et al. (2014). For example, multiple studies have reported higher or lower intrinsic connectivity between DMN hubs (i.e., within the DMN; e.g., Fair et al. 2010; Kessler et al. 2014; Sripada et al. 2014a; Sun et al. 2012), as well as (primarily hypoconnectivity) between the DMN and networks that are typically active during tasks such as the FPC and salience networks (e.g., Fair et al. 2010, 2013; Hoekzema et al. 2014; Mills et al. 2018; Qiu et al. 2011; Sun et al. 2012). Such findings have been interpreted as evidence that the DMN may interfere with task-active networks in ADHD, resulting in mind-wandering and executive dysfunction, as proposed by the default mode interference hypothesis (Sonuga-Barke and Castellanos 2007). Based on these findings, it has been proposed that ADHD is a disorder of dysfunctional connectivity and that, in turn, functional connectivity alterations may underlie the behavioural and neurocognitive deficits observed in ADHD (Konrad and Eickhoff 2010).

However, while multiple primary studies support the conceptualization of ADHD as a dysconnectivity syndrome, findings have been highly heterogeneous in terms of the affected networks and network subcomponents, as well as the direction of effects. For instance, both reduced (Fair et al. 2010; Sripada et al. 2014a) and increased (Barber et al. 2015) within-DMN connectivity have been reported in youths with ADHD. Similarly, some studies were unable to replicate the widely reported alterations in static functional connectivity between the DMN and FPCN in children and adolescents with ADHD (Dajani et al. 2019; de Lacy and Calhoun 2018; Zhou et al. 2019). While cross-study inconsistencies are likely influenced by heterogeneous experimental and analytical approaches, they suggest that a consistent pattern of ADHD-related functional connectivity alterations remains to be identified.

This observation is further supported by the findings of three recent coordinate-based meta-analyses, which pooled the peak coordinates from resting-state functional connectivity studies to assess overlap or convergence between studies (Cortese et al. 2021; Gao et al. 2019; Sutcubasi et al. 2020). Despite inclusion of a partly overlapping pool of studies, these meta-analyses arrived at different conclusions. Both Gao et al. (2019) and Sutcubasi et al. (2020) adopted a hypothesis-driven approach focusing on SBC studies with seeds in either three or four resting-state networks, respectively. Both identified seed-based connectivity alterations within and between overlapping networks, but they showed substantial heterogeneity in their findings. Conversely, adopting a data-driven approach and including both SBC

and non-SBC studies, Cortese et al. (2021) found no reliable convergence in connectivity alterations. These meta-analytic findings will be discussed further in the following sections.

3.3 *Meta-Analyses of Resting-State Functional Connectivity Studies*

3.3.1 Gao et al. (2019)

Gao et al. (2019) performed a coordinate-based meta-analysis of 21 rsfMRI studies using whole-brain SBC methods (yielding 25 datasets), comprising 700 patients with ADHD and 580 controls. While their original aim was to focus on all seven networks identified by Yeo et al. (2011), due to the limited availability of studies investigating certain seed regions, their analysis focused on seeds in the DMN, FPCN and affective network. After categorizing seed and effect regions from each study into specific resting-state networks, they performed a meta-analysis for each seed-network using anisotropic effect-size seed-based mapping, which allows for inclusion of null findings (Radua and Mataix-Cols 2012).

These analyses identified ADHD-related altered functional connectivity both within and between the three analysed networks and other regions (see Fig. 6a). Specifically, they identified hypoconnectivity within the DMN (between DMN seeds and the middle frontal gyrus across all samples and the medial PFC in youth samples), as well as hyperconnectivity between the DMN and the FPCN (including supramarginal and angular gyrus) and hyper- and hypoconnectivity between the DMN and regions of the affective network (between DMN seeds and the left superior temporal gyrus and cingulate cortex, respectively). With regard to the FPCN, hypoconnectivity was found with regions of the salience network (putamen, left insula) and the somatomotor network (precentral gyrus), while hyperconnectivity was found between the FPCN and the affective network (orbitofrontal cortex). Lastly, hyperconnectivity between seeds in the affective network and regions of the DMN (middle frontal gyrus) and FPCN (dorsolateral prefrontal cortex) was reported.

Age, sex and history of medication did not moderate the findings for the DMN and FPCN seeds (studies using affective network seeds could not be analysed due to insufficient data). A subgroup analysis focusing on youth studies ($n = 13$) confirmed and extended the findings by identifying five additional clusters of altered connectivity within the DMN and between the DMN and the salience and somatomotor networks (see Fig. 6b). Hence, Gao and colleagues' findings highlight connectivity alterations within and between the DMN and FPCN and moreover indicate that intrinsic functional connectivity alterations in ADHD appear to be more evident or consistent in youth samples.

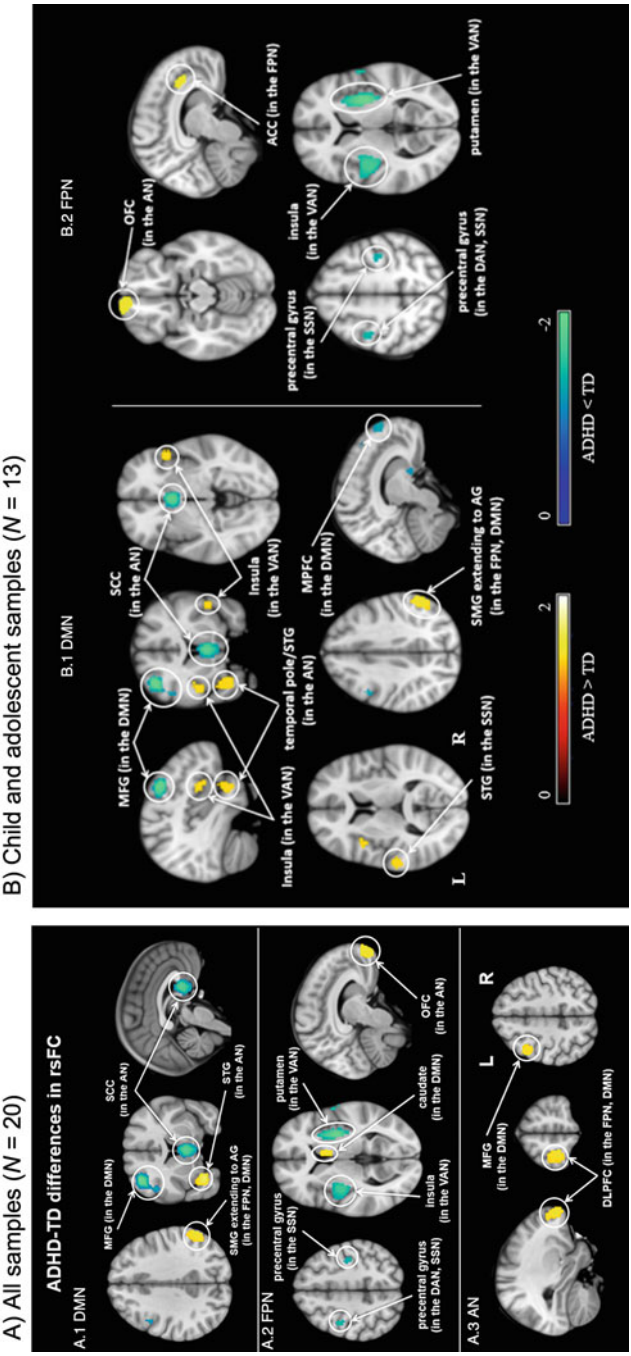

Fig. 6 Overview of the results of the meta-analysis by Gao et al. (2019). (**a**) Results of the meta-analysis including all samples (both youths and adults). (**b**) Results of the meta-analysis including only child and adolescent samples. Regions shown in red-yellow show *hyperconnectivity* with the predefined seeds in ADHD, whereas those shown in blue-cyan show *hypoconnectivity* with the predefined seeds. *DMN* default mode network, *FPN* fronto-parietal control network, *AN* affective network, *DAN* dorsal attention network, *VAN* ventral attention/salience network, *SSN* somatosensory network, *MFG* middle frontal gyrus, *STG* superior temporal gyrus, *OFC* orbitofrontal cortex, *SCC* subcallosal cingulate cortex, *SMG* supramarginal gyrus, *AG* angular gyrus, *DLPFC* dorsolateral prefrontal cortex, *MFG* middle frontal gyrus, *STG* superior temporal gyrus, *MPFC* medial prefrontal cortex, *SFG* superior frontal gyrus, *IPL* inferior parietal lobe, *ACC* anterior cingulate cortex, *L* left, *R* right. Adapted from Gao et al. (2019). *Psychological Medicine*

3.3.2 Sutcubasi et al. (2020)

Partly overlapping results implicating the DMN and FPCN were reported by Sutcubasi et al. (2020), based on a meta-analysis of 20 whole-brain seed-based resting-state functional connectivity studies, comprising 944 patients with ADHD and 1,121 controls. Adopting a theory-driven approach, they focused on four resting-state networks implicated in attention and ADHD (Castellanos and Aoki 2016): the DM, FPC, salience and affective networks. Differences between participants with ADHD and healthy controls were analysed using Multilevel Kernel Density Analysis, which uses the peak coordinates from individual studies to determine the proportion of studies which show connectivity alterations between the predefined seed and a specific voxel (Wager et al. 2007).

When controlling for multiple comparisons, there was no convergence across studies investigating functional connectivity with seeds in the salience and affective networks. However, both hypo- and hyperconnectivity were observed within the DMN in ADHD (see Fig. 7a). While reduced connectivity was observed between DMN seeds and the posterior cingulate cortex (i.e., the DMN core subsystem), increased connectivity was observed between DMN seeds and the dorsal-medial PFC subsystem. Additionally, hyperconnectivity within the FPCN was reported. Similar to Gao et al.'s (2019) results, these findings were confirmed and extended when the analyses were constrained to studies using youth samples ($n = 16$), suggesting greater convergence of functional connectivity alterations in youth with ADHD (see Fig. 7b). Specifically, more widespread connectivity reductions within the DMN were identified, now including not just the core subsystem but also the medial temporal lobe and dorsal-medial PFC subsystems. Additionally, reduced connectivity between the DM and the FPC, affective and salience networks was reported.

3.3.3 Similarities and Differences Between the Meta-Analyses by Gao et al. (2019) and Sutcubasi et al. (2020)

Integrating the findings of these two meta-analyses, a pattern emerges that supports the conceptualization of ADHD as a dysconnectivity syndrome whilst highlighting heterogeneity between primary and meta-analytical studies. Specifically, as both meta-analyses identified convergence of connectivity alterations within the DMN and between the DMN, FPCN and other networks, as well as greater convergence when focusing on youth studies, their findings provide some support for different models of atypical connectivity in ADHD, including the DMN interference (Sonuga-Barke and Castellanos 2007), multiple network (Menon 2011) and maturational delay hypotheses (Shaw et al. 2007).

Firstly, using a partly overlapping pool of studies ($N_{overlap} = 12$, ~60%), but different analytical approaches, both meta-analyses reported significant convergence of hypoconnectivity (but also hyperconnectivity) within the DMN and altered

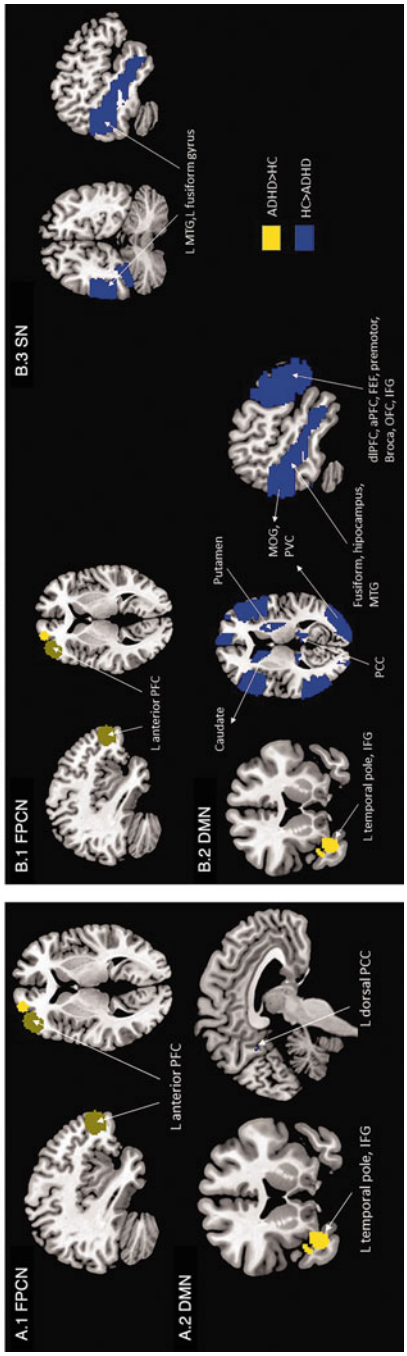

Fig. 7 Results of the meta-analysis by Sutcubasi et al. (2020). (**a**) Results of the meta-analysis including all samples (youth and adults). (**b**) Results of the meta-analysis including only child and adolescent samples. Regions that were hyper-connected with the respective seed/network in the ADHD group are shown in yellow, whereas those that were hypo-connected with the predefined seed(s) in ADHD are displayed in blue. *HC* healthy controls, *ADHD* attention-deficit hyperactivity disorder, *FPCN* fronto-parietal cognitive control network, *DMN* default mode network, *SN* salience network, *PFC* prefrontal cortex, *IFG* inferior frontal gyrus, *PCC* posterior cingulate cortex, *MOG* middle occipital gyrus, *PVC* primary visual cortex, *dlPFC* dorsolateral prefrontal cortex, *aPFC* anterior prefrontal cortex, *FEF* frontal eye field, *OFC* orbitofrontal cortex, *MTG* middle temporal gyrus. Figure adapted from Sutcubasi et al. (2020). *The World Journal of Biological Psychiatry*

connectivity between the DMN and the 'task-active' FPCN (especially in youth studies) as can be seen in Figs. 6 and 7. These findings suggest a less efficient organization of the DMN in individuals with ADHD, consistent with previous studies in which hypoconnectivity within the DMN is amongst the most commonly reported findings (Posner et al. 2014). Given the additional convergence of altered connectivity between the DMN and FPCN, as well as meta-analytical evidence of ADHD-related DMN hyperactivation during tasks (Cortese et al. 2012), the findings support the notion that insufficient attenuation of the DMN during task performance could underlie observed attention deficits and mind-wandering in ADHD (Sonuga-Barke and Castellanos 2007). However, it must be noted that the affected network subcomponents differed between the two meta-analyses. While this is likely influenced by differences in the definitions of networks and seed regions, it also suggests that the findings of the two meta-analyses are not entirely consistent. Moreover, conclusions regarding the default mode interference hypothesis must be confirmed by studies exploring the behavioural and neurocognitive correlates of atypical intra-DMN and DMN-FPCN connectivity to test whether atypical connectivity within and between these networks is associated with increased mind-wandering and impaired task performance (Gao et al. 2019).

Secondly, both meta-analyses identified convergence of ADHD-related functional connectivity alterations between networks beyond the DMN and FPCN, especially when focusing on youth samples. In line with Menon's (2011) multiple network model of psychopathology which proposes that impairments in the dis (engagement) of the DMN, FPCN and salience network contribute to the pathophysiology of various disorders, Gao et al. (2019) found evidence of convergence of altered connectivity between the FPCN and DMN and salience network (DMN-salience network connectivity alterations were limited to youth samples). Critically, their findings also suggest that the altered network organization in ADHD comprises networks beyond the DMN, FPCN and salience networks, as the affective and somatomotor/sensory networks were also affected. Altered integration of these additional networks might contribute to ADHD-related deficits in emotion dysregulation (Shaw et al. 2014) and motor inhibition (Cortese et al. 2012). Sutcubasi et al. (2020) findings focusing on youth studies are broadly consistent with this hypothesis. While most of the functional connectivity alterations they identified were within or between the DMN and FPCN, they also found significant convergence of hypoconnectivity between the DMN and the affective and salience networks, respectively. Overall, while both studies support Menon's (2011) multiple network hypothesis, Gao et al. findings highlight the FPCN (see Fig. 6), whereas Sutcubasi et al. (2020) findings identify the DMN as the core locus of ADHD-related functional connectivity alterations. Notably, as mentioned above, the specific network subcomponents identified differed between the meta-analyses.

Thirdly, in both meta-analyses, alterations in intrinsic functional connectivity in individuals with ADHD were more apparent when focusing on youth samples (which comprised most of the included studies, see Figs. 6b and 7b). Focusing on youth studies, Gao et al. (2019) identified five additional clusters of convergence, particularly implicating the DMN, whilst Sutcubasi et al. (2020) not only identified

further loci of hypoconnectivity within the DMN but also dysfunctional interactions between the DMN, FPCN and affective networks that were not identified when including adult samples.

While it must be considered that the reduced number of studies in these analyses likely reduced statistical power, thereby increasing the risk of spurious findings (Button et al. 2013; Müller et al. 2018), the greater convergence of connectivity alterations in youth samples suggests that children and adolescents with ADHD might show more dysfunctional connectivity or, at least, more consistent alterations than adults with ADHD. Integrating these observations into a developmental framework, a greater convergence in youth samples might reflect a lag in the development of intrinsic functional connectivity in youth with ADHD, which potentially normalizes in later life. This would be consistent with the maturational delay theory of ADHD (Shaw et al. 2007). Indeed, investigations of other brain modalities support this hypothesis, indicating that children with ADHD reach peak cortical thickness later than healthy controls (~10.5 years versus ~7.5 years; Shaw et al. 2007).

Related to this, large-scale meta-analyses conducted by the Enhancing NeuroImaging through Meta-Analysis (ENIGMA) ADHD consortium indicate that brain structural alterations are more evident in children with ADHD, with minimal differences between adults with ADHD and controls (Hoogman et al. 2017, 2019). As resting-state networks, including the DMN, continue to mature throughout the adolescent period (Fair et al. 2009; Jolles et al. 2011), hypo- and hyperconnectivity in youths with ADHD might indicate delayed development and reflect less mature network organization (Bos et al. 2017).

Conversely, less convergence across adult studies may point towards a (partial) normalization of network organization. However, while cross-sectional studies investigating age effects and diagnosis-by-age interactions support the maturational delay hypothesis (e.g., Choi et al. 2013; Fair et al. 2010; Sripada et al. 2014b), longitudinal fMRI research is lacking. It is interesting to note that if a maturational delay in functional connectivity exists, this might also explain cross-study inconsistencies due to differences in sample age. At the same time, it would indicate that averaging across wide age ranges may conceal age-specific group differences (or result in spurious findings; Courchesne et al. 2011).

3.3.4 Cortese et al. (2021)

While this discussion highlights that the meta-analyses by Gao et al. (2019) and Sutcubasi et al. (2020) provide some support for intra- and inter-network dysconnectivity in ADHD, their findings were acquired in a theory-driven manner, focusing on three or four core resting-state networks and only including SBC studies. Conversely, Cortese et al. (2021) performed a data-driven whole-brain voxel-based meta-analysis assessing convergence of group differences in functional connectivity using activation likelihood estimation. Their meta-analysis included 18 SBC studies – many of which overlapped with those included in Gao et al. (2019)

and Sutcubasi et al. (2020) – as well as 12 non-SBC studies, comprising 1,094 participants with ADHD and 884 controls overall.

In contrast to the other meta-analyses, Cortese and colleagues identified no spatial convergence of hypo- or hyperconnectivity in ADHD participants, regardless of inclusion or exclusion of non-SBC studies. That is, at no location in the brain did the findings of previous connectivity studies converge to a greater extent than would be expected by chance. This was also the case when only youth samples or non-medication-naïve participants were considered. However, in additional analyses focusing on atypical intrinsic functionality more broadly, by ignoring the sign of the group effects and analysing loci of hypo- and hyperconnectivity together, Cortese et al. did identify convergence in the left superior temporal gyrus.

Cortese et al. (2021) null findings for their main analysis contrast with those of the aforementioned meta-analyses and suggest instead that patterns of functional connectivity identified by primary studies are heterogenous and are not replicated when optimal, data-driven meta-analytical approaches (Müller et al. 2018) are adopted. While it is important to consider that ADHD might not be characterized by consistent patterns of abnormal intrinsic functional connectivity, it is also likely that methodological and conceptual limitations of the rsfMRI field contribute to the observed inconsistencies. These limitations and ways of addressing them will be discussed below.

3.4 Limitations of the Current Evidence Base on Functional Connectivity

Methodological issues and experimental and analytical flexibility likely contribute to inconsistencies between studies, with many issues mirroring those faced by analyses of structural connectivity. Issues include heterogeneity in resting-state fMRI data acquisition and experimental approaches (e.g., length of scan, eyes open versus eyes closed; Smitha et al. 2017) as well as (a lack of) consideration of head motion, which may produce regional artefacts in fMRI analyses (Power et al. 2015). Additionally, statistical inferences have been limited by small sample sizes. Although sample sizes have been increasing (Castellanos and Aoki 2016), the median ADHD group size across studies included in Cortese et al. (2021) conducted since 2015 remained low to moderate at 33 (versus 21.5 for those performed before 2015). Critically, small sample sizes and ensuing low power can increase the risk of both false negatives (i.e., the failure to identify existing group differences) and false positives (i.e., finding group differences where none exist; Button et al. 2013).

While analytical flexibility is an issue across many fields of research, the various analytical techniques used to assess functional connectivity present a further obstacle to the integration and replicability of findings across studies (Castellanos and Aoki 2016). For example, the removal of artefacts from resting-state data by means of global signal regression – whereby the mean signal averaged over the whole brain is

removed via linear regression – is amongst the most controversial analytical decision. While some report that this correction is beneficial (e.g., reducing motion effects and improving the ability to detect brain-behaviour associations; Li et al. 2019; Power et al. 2014), others found it to have the potential to both obscure effects and lead to artificial group differences (Gotts et al. 2013; Hahamy et al. 2014). Hence, application of global signal regression (or lack thereof) might contribute to differences between studies, indicating that studies should report their results with and without this correction (Gao et al. 2019). Lastly, variations in the nomenclature and definition of functional networks represent a further challenge (Castellanos and Aoki 2016). This problem was also evident when integrating the findings from the different meta-analyses.

In addition to methodological shortcomings, clinical heterogeneity within ADHD constitutes a further issue when exploring intrinsic functional connectivity in this population. Sources of heterogeneity in ADHD may include (but are not limited to): sex, ADHD subtype or presentation (inattentive versus hyperactive/impulsive versus combined) and severity, age (youth versus adult), disorder course (persistent versus remitting), medication status and comorbidity. While a detailed discussion of these factors goes beyond the scope of this chapter, existing studies indicate that some of these might be important variables to consider when investigating network (dis)-organization in ADHD. For instance, the meta-analyses by Gao et al. (2019) and Sutcubasi et al. (2020), as well as primary studies directly comparing age groups (e.g., Guo et al. 2020), suggest there may be differences in the functional connectivity alterations displayed by children and adults with ADHD. For example, using machine learning, Guo et al. (2020) identified shared and distinct functional connectivity alterations in youths and adults with ADHD. The child-specific alterations were associated with hyperactivity symptoms which are known to decrease with age (Faraone et al. 2006) suggesting that hyperactivity may explain developmental differences in ADHD-related effects. In terms of ADHD presentation, Zhou et al. (2019) reported that functional connectivity alterations between youths with ADHD and controls across four datasets of the ADHD-200 cohort (i.e., decreased connectivity between inferior frontal and middle frontal gyrus) were only consistently seen for combined presentation ADHD and not the predominantly inattentive presentation. Zhou et al. results therefore point towards presentation and/or severity effects, given that individuals with combined presentation ADHD are symptomatically more severe by definition.

Overall, these data suggest that age and ADHD presentation might be important moderators of ADHD-related alterations in intrinsic functional connectivity. Moreover, linked to the issue of population heterogeneity is the idea that while ADHD may be characterized by dysfunctional brain connectivity, the affected networks or specific network subcomponents may differ between individuals (Cortese et al. 2021). Such considerations challenge whether case-control comparisons are the most appropriate study design to investigate 'disorder-associated' brain alterations as they are ill-suited to account for all sources of heterogeneity and their interactions within the individual (Cortese et al. 2021). This illustrates the potential usefulness of alternative approaches such as normative modelling where deviations of individual

participants are assessed with reference to a normative pattern of functioning or connectivity derived from a healthy reference cohort, an approach that functions similarly to growth charts in paediatric medicine (see Marquand et al. 2019 for a detailed overview).

Normative modelling has already been successfully applied to investigations of brain structure in ADHD (Wolfers et al. 2020), which demonstrated that group differences do not accurately reflect individual deviations in ADHD participants and that while most ADHD participants showed deviations from the norm in grey matter volume, the inter-individual overlap in these deviations was minimal, i.e., the ADHD participants differed from controls in different ways.

Additionally, case-control studies are also limited by their use of what may be considered arbitrary diagnostic cut-offs, biased sampling methods from specialized settings (e.g., clinics) that reduce the generalizability of findings, as well as confounds associated with the investigated disorder (e.g., high comorbidity rates; Casey et al. 2014; Horga et al. 2014; Insel et al. 2010). Hence, dimensional analyses of the influence of ADHD symptoms or ADHD-related constructs (e.g., hyperactivity) on functional connectivity in population-based samples may also provide informative data and triangulation of findings across different study designs.

3.5 Conclusions of Functional Connectivity Section

In conclusion, a review of recent meta-analyses investigating convergence of differences in intrinsic functional connectivity between individuals with ADHD and controls highlights that while there is substantial support for altered network organization in ADHD, the current evidence base is highly inconsistent (Pereira-Sanchez and Castellanos 2021). Individual studies and theory-driven meta-analyses have provided evidence for ADHD-related connectivity alterations within and between the DMN and FPCN, potentially extending to other networks such as the salience and affective networks (Castellanos and Aoki 2016; Gao et al. 2019; Posner et al. 2014; Sutcubasi et al. 2020). These findings provide some support for the default mode interference and the multiple network hypotheses, and there are preliminary indications that functional connectivity alterations may underlie aspects of ADHD's clinical phenotype (Castellanos and Aoki 2016). However, alterations in functional connectivity were not replicated in the most comprehensive, data-driven meta-analysis performed to date (Cortese et al. 2021): i.e., findings from primary studies remain heterogeneous with respect to the implicated networks, network subcomponents and direction of effects. This suggests that despite an ever-growing body of studies, conclusions remain tentative and echo those made by Castellanos and Aoki (2016): '. . .it is not yet possible to distil the mosaic of heterogenous reports into a single conclusive story. . .' (p. 257).

Addressing current methodological and conceptual limitations will be required to arrive at more definitive conclusions. This will include making use of existing datasets through large collaborative efforts using harmonized analysis protocols

(e.g., ENIGMA) as well as large prospective datasets (e.g., the Adolescent Brain Cognitive Development or ABCD study; Casey et al. 2018), which employ harmonized MRI acquisition protocols and allow for longitudinal analyses. The latter will be key in terms of evaluating the maturational delay hypothesis of ADHD, insofar as it applies to structural or functional connectivity. It will also be important to utilize study designs beyond the case-control framework, such as normative modelling and dimensional analyses of variation in ADHD symptoms in the general population. Lastly, more work is required to increase our understanding of the functional implications of abnormal network connectivity by exploring whether alterations in functional connectivity relate to ADHD symptom profiles, neuropsychological deficits or behaviours such as mind-wandering or delay aversion.

4 General Conclusions

Overall, the research reviewed here has provided evidence that ADHD, like many other neurodevelopmental disorders, can be conceptualized as a disorder of multiple brain systems and the interactions among these systems may also be disrupted. However, as we have seen, the evidence is inconsistent across studies and recent meta-analyses, particularly of resting-state functional connectivity studies, have not yielded convergent findings. Harmonization of data acquisition and analytic approaches across studies, potentially within the framework of the ENIGMA consortium, may help in identifying robust structural and functional connectivity alterations in ADHD and understanding whether the relationship between ADHD and altered connectivity differs according to age (as is the case for brain structure; (Hoogman et al. 2019)). Prospective longitudinal studies examining how changes in structural or functional connectivity relate to changes in ADHD symptoms over time (e.g., comparing patients with persistent versus remitting forms of ADHD) would be informative. Future research could also adopt a multi-modal approach by investigating convergence between structural and functional connectivity alterations in the same individuals or groups of patients (see Bos et al. 2017 for an early example of this approach).

A final question relates to the clinical utility of the results obtained to date: have connectivity studies provided any findings that might aid in the identification or treatment of ADHD? If not, how might they do so in the future? Although a recent review concluded that research on brain connectivity has yielded few clinically-useful insights to date (Pereira-Sanchez and Castellanos 2021), the hope is that connectivity assessments could eventually assist with diagnosis, predictions regarding prognosis, and treatment selection for individual patients. These methods may also help researchers and clinicians to identify more homogeneous ADHD subgroups or subtypes for treatment stratification (see Drysdale et al. 2017 for a similar approach that used resting-state fMRI data to identify functional connectivity-based ‘biotypes’ of depression in a large adult sample). This could ultimately contribute to

a personalized medicine approach in which different brain networks are targeted by specific types of medication, psychological treatment or even brain stimulation.

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Promising Developments in the Use of Induced Pluripotent Stem Cells in Research of ADHD

Cristine Marie Yde Ohki, Rhiannon V. McNeill, Matthias Nieberler, Franziska Radtke, Sarah Kittel-Schneider, and Edna Grünblatt

Contents

Cristine Marie Yde Ohki, Rhiannon V. McNeill, Sarah Kittel-Schneider, and Edna Grünblatt shared first and last authorship.

C. M. Yde Ohki
Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zurich (PUK), University of Zurich, Zürich, Switzerland

R. V. McNeill, M. Nieberler, and S. Kittel-Schneider
Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Wuerzburg, Wuerzburg, Germany

F. Radtke
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Wuerzburg, Würzburg, Germany

E. Grünblatt (✉)
Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric University Hospital Zurich (PUK), University of Zurich, Zürich, Switzerland

Neuroscience Center Zurich, University of Zurich and the ETH Zurich, Zürich, Switzerland

Zurich Center for Integrative Human Physiology, University of Zurich, Zürich, Switzerland
e-mail: edna.gruenblatt@kjpd.uzh.ch

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Abstract Although research using animal models, peripheral and clinical biomarkers, multimodal neuroimaging techniques and (epi)genetic information has advanced our understanding of Attention-Deficit Hyperactivity Disorder (ADHD), the aetiopathology of this neurodevelopmental disorder has still not been elucidated. Moreover, as the primary affected tissue is the brain, access to samples is problematic. Alternative models are therefore required, facilitating cellular and molecular analysis. Recent developments in stem cell research have introduced the possibility to reprogram somatic cells from patients, in this case ADHD, and healthy controls back into their pluripotent state, meaning that they can then be differentiated into any cell or tissue type. The potential to translate patients' somatic cells into stem cells, and thereafter to use 2- and 3-dimensional (2D and 3D) neuronal cells to model neurodevelopmental disorders and/or test novel drug therapeutics, is discussed in this chapter.

Keywords Attention-deficit disorder (ADD) · Attention-deficit hyperactivity disorder (ADHD) · Cell models · Induced pluripotent stem cells (iPSC) · Neuronal cells · Personalized modelling

Abbreviations

ADD	Attention-deficit disorder
ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
CRISPR-cas9	Clustered regularly interspaced short palindromic repeats-D/CRISPR-associated protein 9
CSF	Cerebrospinal fluid
CNS	Central nervous system
CNV	Copy number variants
2D /3D	Two/three dimension(al)
DNA	Deoxyribonucleic acid
ESC	Embryonic stem cell
fMRI	Functional magnetic resonance imaging
GLUT3	Glucose transporter-3 (*SCL2A3*)
GSK3-β	Glycogen synthase kinase 3-β
GWAS	Genome-wide association study (studies)
iPSC	Induced pluripotent stem cell
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
PRS	Polygenic risk score(s)
SNP	Single nucleotide polymorphism

1 Introduction

Although the use of animal models, peripheral and clinical biomarkers, multimodal neuroimaging techniques and (epi)-genetic data has advanced our understanding of Attention-Deficit Hyperactivity Disorder (ADHD), the exact aetiology of this neurodevelopmental mental disorder is still far from known. However, because the primary tissue affected in this disorder is the brain, access to samples enabling cellular and molecular analyses is principally not available; therefore, alternative models are required.

Over a decade ago, the technology of reprogramming somatic cells back into induced pluripotent stem cells (iPSCs) was introduced (Hanger et al. 2020; McNeill et al. 2020; Sabitha et al. 2020; Cheffer et al. 2020; Luciani et al. 2020). This has provided novel opportunities in the research of brain disorders at the cellular and molecular levels, due to the possibility to model aetiopathology and pathways leading to neurodevelopmental delays, and in the development and testing of drug therapies.

In this chapter, current research approaches and their drawbacks are discussed, followed by the potential applications and limitations of modelling ADHD using iPSC technology (see: summary Fig. 1).

2 Current Research Approaches for Investigating ADHD: Pros and Cons

Investigating neuropsychiatric disease requires the use of various research approaches. It is therefore essential to choose the most appropriate models for specific research questions. Clinical studies that monitor patients by evaluating brain physiology/functions through neuroimaging techniques, such as diffusion tensor imaging, magnetic resonance imaging (MRI) or resting-state functional MRI (fMRI), are of high importance (Sun et al. 2018; Silk et al. 2016; Qiu et al. 2011). These types of techniques provide valuable information regarding brain alterations associated with the disorder, or as a response to treatment. The use of cerebrospinal fluid (CSF) and blood samples from patients has also advanced research for genetic risk-factors and biomarkers for ADHD, such as peripheral cytokine profiles (Anand et al. 2017; Bonvicini et al. 2018; Thome et al. 2012). Although these approaches have advanced the field of ADHD research, they do not fully reflect the functionality of the central nervous system (CNS). Complementing clinical studies, in vivo and in vitro models are essential tools to further enhance knowledge of the pathophysiology and molecular mechanisms that may underlie neurodevelopmental disorders such as ADHD.

Animal models have been widely used in ADHD research (see chapter "Animal Models of ADHD?"), particularly rodent models, which are more genetically heterogeneous and cheaper compared to non-human primates (Russell 2011). However,

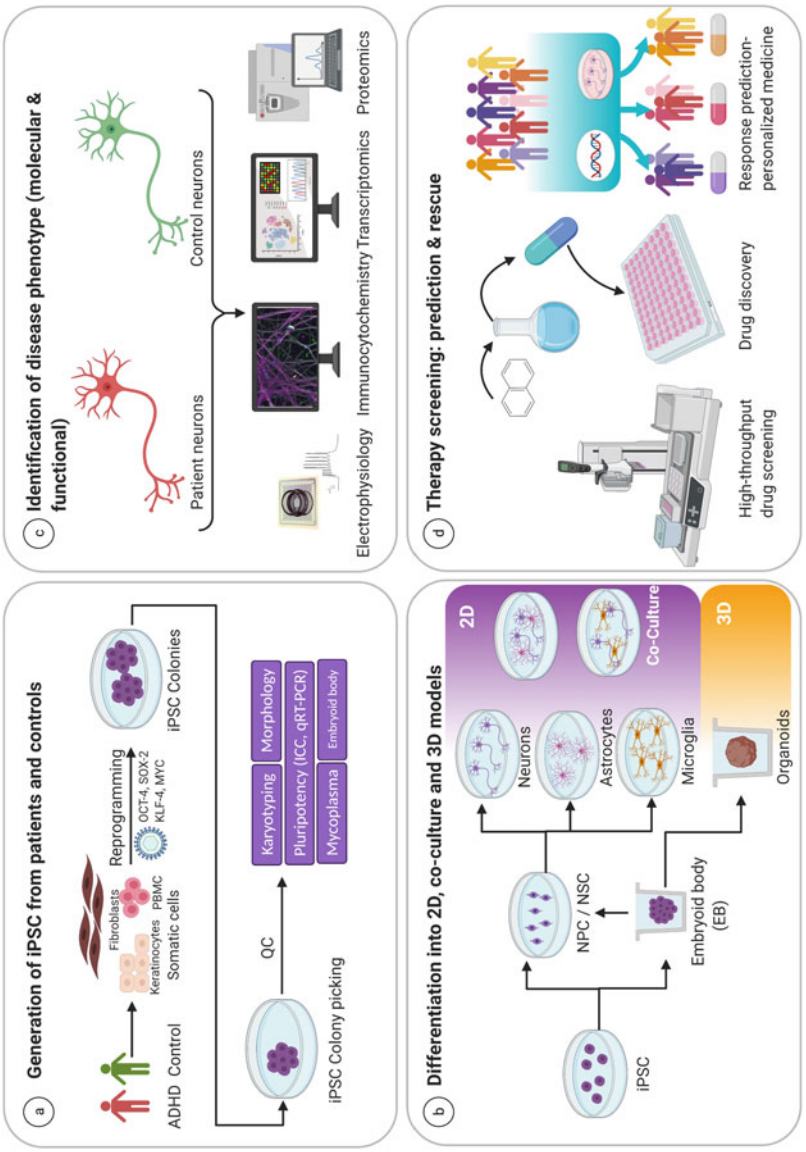

Fig. 1 Overview of possible iPSC workflow and its potential applications for modelling ADHD. (**a**) Generation of iPSC from individuals with and without ADHD from various somatic cells, followed by their quality control processes; (**b**) Potential differentiation paths of iPSC into 2-dimensional (2D) and 3-dimensional (3D) models; (**c**) Potential cellular, molecular and functional analyses for identifying disease phenotypes; (**d**) Potential use of iPSC modelling in drug therapy screening. (The figure was created by BioRender.com)

they cannot fully recapitulate the human genotype and neurobiological phenotypes that occur within the human CNS at the cellular and molecular level (Russell 2011). Genetically-altered mice have also been used as a tool for studying other neuropsychiatric disorders, such as autism spectrum disorder (ASD) and schizophrenia, and the findings compared with those from human induced pluripotent stem cell (iPSC)-derived models (discussed below). The former are more suitable for behavioural, neuroanatomical and systemic investigation. However, even though major ADHD endophenotypes can be reproduced in animal models, recapitulating the entire complex ADHD symptomatology (impulsivity, hyperactivity and inattentiveness), covering the underlying molecular mechanisms involved in ADHD and finding predictive patterns for possible treatments in one single ideal model is still a challenge (Russell 2011; Gainetdinov 2010; Leo and Gainetdinov 2013). Furthermore, in a heterogeneous disorder such as ADHD, other behavioural features that are present in humans with ADHD (e.g., distractibility, carelessness and avoiding organizing and doing tasks) cannot be easily assessed using in vivo animal models (Alsop 2007). By contrast, the latter offer broader and unique advantages in terms of neurophysiological and pharmacological molecular analysis (Falk et al. 2016).

Post-mortem brain tissue is a valuable research resource for exploring possible structural and molecular changes related to a disease aetiopathology by enabling the isolation of CNS cells (Mizee et al. 2017) or genetic material (Hess et al. 2018; Brookes et al. 2007). Nonetheless, many cellular structures and proteins are highly sensitive to processes during and after death (i.e., hypoxia, post-mortem delay intervals and the type of cryopreservation solutions, respectively), and it is therefore necessary to consider these factors in the interpretation of the results (Ferrer et al. 2008). In addition, despite the existence of brain banks designated to neuropsychiatric studies, the scarce availability of donors is a limiting factor that prevents researchers from obtaining large samples and, as a consequence, robust findings (de Lange 2017; Dean 2004). Additional disadvantages of using post-mortem brain tissue are that fixed cells do not fully reflect biological events occurring in functional living cells, and that donors are typically of advanced age; therefore, the brain no longer demonstrates neurodevelopmental processes, which are of particular interest for ADHD research.

A schematic representation of current research approaches with their pros and cons is shown below (Fig. 2), starting with functional brain imaging and post-mortem brain studies, progressing to peripheral biomarkers and iPSC-derived models.

Given the limitations of currently available models, the possibility of using a personalized system in a dish, which preserves the genetic background of a patient, has provided an exciting alternative by enabling research of ADHD in 2D and 3D functional cell cultures, as will be discussed in the next sections.

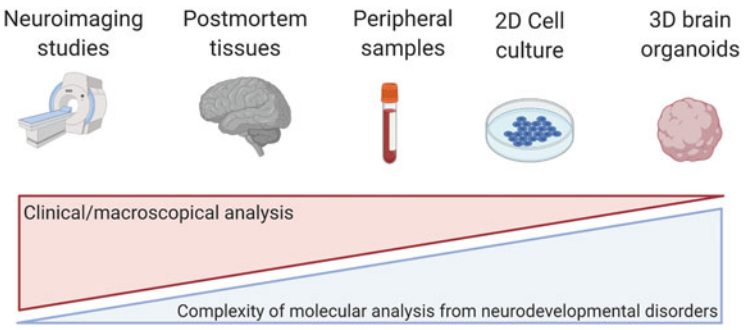

Fig. 2 Current research approaches for ADHD and their respective complexity regarding analysis at the molecular level. (The figure was created by BioRender.com)

3 Induced Pluripotent Stem Cells (iPSC): Potential Applications and Limitations

3.1 History and Evolution of Reprogramming Methods

Induced pluripotent stem cells (iPSCs) from mouse fibroblast cells were first developed in 2006 by Takahashi and Yamanaka. Using a combination of only four transcription factors (Myc, Sox2, Klf4 and Oct3/4; also termed 'Yamanaka factors'), fibroblasts could be transduced using a retrovirus and forced back into a stem cell-like phenotype. These cells were capable of differentiating into the three embryonic germ layers and therefore presented a pluripotent status (Takahashi and Yamanaka 2006), meaning these cells have the potential to differentiate similarly to embryonic stem cells. Soon afterwards, the same group also successfully demonstrated reprogramming using human fibroblasts (Takahashi et al. 2007). However, the main limitation of these original approaches was the difficulty with integration of viral genes into the host genome, and potential mutagenicity. To address this limitation, alternatives were developed, using non-integrating adenovirus and Sendai virus (Hochedlinger 2008). However, the efficiency of successful reprogramming using adenovirus was extremely low (Stadtfeld et al. 2008; Zhou et al. 2009), whereas the Sendai virus reprogramming appeared more efficient (Ban et al. 2011; Fusaki et al. 2009). Further strategies to increase efficiency have included use of additional encoding factors and the optimization of the biochemical microenvironment (Mali et al. 2010; Lin et al. 2009; Huangfu et al. 2008).

Plasmids are extrachromosomal deoxyribonucleic acid (DNA) rings found in bacteria that can be designed to include genes of interest and used as vectors. In this case, episomal plasmids were used to transfer the Yamanaka factors. For example, the PiggyBac mobile genomic element has been used to transfer the Yamanaka factors without leaving a footprint; however, reprogramming efficiency was relatively low (Yu et al. 2009; Kaji et al. 2009; Woltjen et al. 2009). Avoiding the use of viruses altogether, another approach is the transfection of messenger RNA

(mRNA) encoding the Yamanaka factors, which reprograms fibroblasts with a high efficiency (Warren et al. 2010). Less frequently used methods for reprogramming include using small molecules, such as valproic acid, glycogen synthase kinase 3-β (GSK3-β) inhibitors or tranylcypromine, or microRNA (Anokye-Danso et al. 2011; Kim et al. 2009; Li et al. 2009; Shi et al. 2008; Hou et al. 2013). These approaches guarantee a lack of viral residues, which means that they open up the possibility of using generated iPSCs, and their differentiated progeny for medical translation, in transplantation experiments or tissue engineering (reviewed by: Schlaeger et al. 2015).

3.2 The Use of Different Somatic Cells

In addition to fibroblasts, reprogramming of other cell types has been successful, including keratinocytes, lymphocytes and renal epithelial cells (Lowry et al. 2008; Saxena et al. 2008; Loh et al. 2009; Wang et al. 2013; Aasen and Izpisua Belmonte 2010). The primary tissue or cell source is chosen, based on considerations regarding availability, cultivation costs, reprogramming efficiency, long-term viability and genetic stability. In comparison with fibroblasts, cultivation of lymphocytes from peripheral blood is challenging and reprogramming appears to be less efficient. Approaches using urothelial cells or keratinocytes isolated from hair follicles are far less invasive, which is an important consideration in iPSC-based modelling of diseases of childhood and adolescence. Reprogramming from keratinocytes, which has been developed in recent years, has been demonstrated as fast and highly efficient. Nevertheless, due to relatively low cost and high stability, fibroblasts currently remain the cells most frequently selected for induction of iPSC (reviewed by: Raab et al. 2014).

Reprogrammed iPSCs are typically co-cultured with feeder-cells, such as murine fibroblasts, in a medium containing bovine serum, in order to sustain pluripotency. As these conditions can vary widely from culture to culture, feeder-free approaches have been developed, utilizing a serum-free, defined culture environment in order to standardize the generation of stable iPSC lines (Hamada et al. 2020; Yamasaki et al. 2016). When protocols for the generation of iPSCs are performed, it is essential that standardized testing be performed to confirm complete reprogramming to pluripotent status. The characterization of newly reprogrammed lines should always include the following quality control checks (Sullivan et al. 2018; Shibamiya et al. 2020; Kim et al. 2017) (Details see Box 1).

Box 1 Minimal Requirements for iPSC Quality Control

- Ability of iPSCs to differentiate into the three germ layers in culture: ectodermal, mesodermal and endodermal differentiation should be demonstrated by gene and protein expression analysis
- Analysis of genomic expression of pluripotency markers, as well as evidence that the virus is no longer present after the iPSCs are fully cultured for >10 passages.
- Characterization of stem cell morphology, including high nucleus to cytoplasm ratio, round shape and high mitotic activity, growth in sharp 2D colonies, surface markers of pluripotency
- Demonstration of high proliferation rates and telomerase activity
- Verification of genetic stability via (molecular) karyotyping to exclude genetic variations and aberrations due to high cloning numbers
- Verification that cells are free of mycoplasma and other viruses, such HIV and hepatitis

Optional Quality Control

- Single-cell genome sequencing (Rohani et al. 2018)
- Characterization of mitochondrial DNA (Rohani et al. 2018; Prigione et al. 2011)
- Epigenetic characterization (Takikawa et al. 2013; Rohani et al. 2018)

4 Personalized Modelling of ADHD Genetic Subtypes for Molecular and Treatment-Response Studies

Recent genome-wide association studies (GWAS) have revealed several common genetic variants associated with ADHD (Demontis et al. 2019) (see details: chapter "Genetics of Attention-Deficit Hyperactivity Disorder"). However, each common risk-gene variant (usually a single nucleotide polymorphism (SNP)) only marginally increases the risk of developing ADHD. Therefore, the concept of polygenic risk scores (PRS) was introduced. PRS combine the most significantly associated risk-gene variants of a disorder. A PRS is usually calculated by taking the sum of risk-alleles that an individual has and weighing that against the risk-allele effect-sizes, as estimated by a GWAS on the disorder or phenotype. This process can consider either genome-wide significant risk-alleles, only, or all uncorrected significant risk-alleles (Choi et al. 2020). The use of PRS may help to identify people at a high risk of developing a certain disorder, as well as helping to elucidate the most prominent disease pathomechanisms for larger groups of affected individuals.

However, it is also widely recognized that rare genetic variants, such as mutations and copy number variants (CNV), are associated with ADHD (See also chapter "Genetics of Attention-Deficit Hyperactivity Disorder" and "Epigenetics and ADHD"). Genetic syndromes, such as 22q11 deletion syndrome, can lead to ADHD-like phenotypes and, in families with a high burden of ADHD, CNVs in several genes have been found that contribute to a higher risk of developing this disorder than is evident with common variants (Martin et al. 2015; Ramos-Quiroga et al. 2014; Lesch et al. 2011). Therefore, developing patient-derived cellular models of common genetic variants, high-load PRS individuals and rare genetic variants will be important for investigating ADHD aetiology.

To investigate the effect of a genetic variant on cellular and molecular disease mechanisms, comparisons with healthy controls are essential. These controls are often age- and sex-matched healthy controls from a general population, who express the wildtype genetic variant/more common genetic variant, but they can also be unaffected siblings, carrying the wildtype gene variant. However, it might be more promising to generate the so-called isogenic controls, particularly when investigating common gene variants with a suggested small effect. Isogenic control means using the cells derived from the respective patient or individual with a certain risk-gene variant and then 'repairing' this risk variant to the wildtype or protective variant using gene modifying techniques. This can be accomplished using genome editing via technology using Clustered Regularly Interspaced Short Palindromic Repeats-D/CRISPR-associated protein 9 (CRISPR-cas9), which was developed by Doudna and Charpentier (2014). Applying this technology to iPSC clones from an affected individual enables a risk SNP to be changed into a non-risk SNP, by exchanging the nucleotide. This ensures that any resulting difference in the cellular or molecular phenotypes can be attributed to the risk genetic variant of interest, because the remaining genome remains the same. As yet, no results from studies using this approach in ADHD research have been published.

So far, isogenic controls using CRISPR/cas9 have been generated from carriers of single, common SNPs. However, it is technically not yet possible, or at least extremely challenging, to modify several or even hundreds of SNPs, such as all those that might be included in a PRS. Here, it could prove fruitful to compare high-load PRS carriers versus low-load PRS carriers, with or without the disorder phenotype. Another limitation is that CNVs are often too large to be removed (in case of duplications) or added (in case of deletions) to generate isogenic controls, but developments in advanced technologies might overcome this issue in the future.

Furthermore, as with other neuropsychiatric disorders, ADHD is thought to be caused by gene–environment–development interactions. Environmental stressors can be easily added to such iPSC-based models in vitro to gain further insight into potential interactions, and this could also be informative regarding potential prevention strategies or novel therapeutic options.

5 2D and 3D iPSC-Based Models

The development of iPSC technology has revolutionized the way we study neuropsychiatric disorders, such as ADHD, and facilitated the development of a wide range of both two-dimensional (2D) and three-dimensional (3D) models. 2D models are monolayer cell cultures, which can consist of either a single cell type or two or more different cell types (termed a 'co-culture') (Logan et al. 2019). For neuropsychiatric research, iPSCs can be differentiated into a disease-relevant cell type of interest and functionally investigated. For example, dopaminergic signalling has been implicated in ADHD pathogenesis (Li et al. 2006), and therefore researchers have differentiated iPSCs into dopaminergic neurons using 2D cultures for further investigation (Palladino et al. 2020).

In addition, co-cultures can be used to support neuronal maturation and functionality, for example by the inclusion of glial cells, such as astrocytes (Logan et al. 2019). The inclusion of multiple cell types is not only more similar to an in vivo environment, where there are heterogeneous cell populations (Emery and Barres 2008), but has also been shown to be essential for the development of synaptic activity (Klapper et al. 2019). However, few studies have so far attempted the differentiation of iPSCs into ADHD-relevant neuronal cells, or carried out subsequent functional assessment (McNeill et al. 2020). To date, there has only been one published study which differentiated iPSCs from ADHD patients into dopaminergic neurons. These cells additionally carried CNVs in the *PARK2* gene, which have been associated with ADHD development (Jarick et al. 2014). Phenotypic assessment of these cells revealed impaired adenosine triphosphate (ATP) production and altered basal oxygen consumption rate compared to healthy controls, suggesting that metabolic dysfunction may play a role in the development of ADHD (Palladino et al. 2020).

3D models consist of scaffold-based or scaffold-free cell cultures and can be used to generate 'organoids', which are defined as 'a 3D structure derived from either pluripotent stem cells (embryonic stem cells (ESCs) or iPSCs), neonatal or adult stem/progenitor cells, in which cells spontaneously self-organize into properly differentiated functional cell types, and which recapitulates at least some function of the organ' (Huch et al. 2017, p. 938). For ADHD research this technology could be utilized to develop brain organoids, which are thought to resemble early embryonic development, and consist of both glial cells and functionally active neurons (Lancaster and Knoblich 2014). iPSCs can be used to generate brain organoids either via 'undirected' or 'directed' differentiation. Undirected differentiation lacks inductive cues (no chemical stimulation to become a specific cell type) and therefore cells spontaneously give rise to multiple brain regions, whereas directed differentiation requires the application of defined combinations of signalling molecules at specific times to guide neurodevelopment into specified brain regions (Amin and Pasca 2018). However, there is again a lack of published articles using this technology for the investigation of ADHD (McNeill et al. 2020).

Future researchers could aim to develop brain organoids with a forebrain identity, such as the prefrontal cortex, which has been repeatedly implicated in ADHD neurobiology (Arnsten 2009). Moreover, there is now the possibility to create fused brain organoids, whereby different brain regions are generated and then combined in vitro (also known as 'assembloids') (Bagley et al. 2017). For ADHD research, it could be of interest to generate assembloids consisting of forebrain and midbrain identities, such as the prefrontal cortex and midbrain ventral tegmentum, respectively. The development of this mesocortical pathway would require the formation of dopaminergic projections because, as discussed previously, dysregulation of dopaminergic pathways is thought to play a key role in ADHD pathogenesis (Li et al. 2006) (see chapter "New Drugs to Treat ADHD - Opportunities and Challenges in Research and Development"). Despite the promise of 2D and 3D iPSC-based culture models, both have their limitations, which must be taken into consideration when planning an experimental approach. A summary of the main advantages and disadvantages of both models is given in Table 1.

Table 1 Advantages and disadvantages of 2D vs 3D iPSC-derived models. Adapted from Logan et al. (2019)

	Advantages	Disadvantages
2D	• More reproducible	• Less reflective of in vivo environment
	• Cheaper	• Reduced intercellular communication (low cell density compared to tissue)
	• Simpler	• Lack of cell–ECM interactions
	• More homogeneous	• Altered cell morphology (flattening)
	• Easier analysis	• Lack of tissue architecture (potential loss of pathological features)
	• More established technique	–
	• Quicker	–
3D	• More reflective of in vivo environment	• Lack of reproducibility
	• More complex intercellular interactions	• Expensive
	• Allows cell–ECM interactions	• Complex protocols
	• Retention of cellular morphology	• High heterogeneity
	• Retention of tissue architecture	• Difficult to analyse
	• Specific chemical and physical cues can be modelled using scaffolds	• Less established technique
	• Allows faster neuronal maturation	• Time-consuming
	–	• Potential ethical concerns (privacy, consciousness)
	–	• Material properties must be considered for scaffold-based systems
	–	• Specialist equipment required
	–	• Risk of necrosis/cell death/loss of differentiation due to inadequate supply of oxygen/nutrients

6 iPSC Technology in ADHD Research

The development of iPSC technology has not only opened doors for disease modelling but has also revolutionized methodology in many fields of medicine, such as pharmaceutical, embryological and transplantation research (Grskovic et al. 2011; Takebe et al. 2013). However, it is important to note that iPSC research remains at an early stage for many diseases, particularly for neuropsychiatric disorders. This is not least because mental disorders, such as ADHD, are usually characterized by a multitude of symptoms that are complex to measure objectively. Their clinical profiles can be highly heterogeneous with significant inter-patient variability. ADHD research using iPSC-based models is further complicated by its polygenic inheritance pattern, with most genes contributing only a small proportion to the overall genetic background of ADHD (Faraone and Larsson 2019).

Nevertheless, several groups have succeeded in the generation of personalized iPSC cultures derived from ADHD patients. All existing ADHD-derived iPSCs have been reprogrammed using a Sendai virus technique, with somatic cell samples originating from urine epithelial cells (Sochacki et al. 2016), fibroblasts (Jansch et al. 2018), hair follicle keratinocytes (Re et al. 2018; Grossmann et al. 2021; Yde Ohki et al. 2021) or peripheral blood mononuclear cells (Tong et al. 2019; Grossmann et al. 2021). An additional study used dental pulp stem cells from ADHD patients and differentiated those stem cells into dopaminergic neuronal cells, which resulted in the detection of a cellular pathophenotype: dopaminergic neurons derived from patient iPSC lines exhibited an impaired neurite outgrowth and branching, a decreased mitochondrial mass and altered intracellular ATP levels (Nguyen Nguyen et al. 2019). These effects were observed under the condition of absent exogenous brain-derived neurotrophic factor (BDNF) and could be improved by BDNF supplementation, which indicates an implication for BDNF in the pathogenesis of ADHD.

Unfortunately, this study remains one of the few examples for reports about neural differentiation of iPSC cultures derived from ADHD patients thus far. Surely, the generation of the different ADHD iPSC lines presented above marks a milestone in the field of ADHD modelling, but should be considered only as preliminary work, as further differentiation and functional characterization will constitute the next logical steps of investigation. This promises major insights, particularly in the pathophysiology of ADHD as a neurodevelopmental disorder, as the differentiation process is capable of mimicking developmental key processes (Lancaster et al. 2013; Eiraku et al. 2008; Tian et al. 2020), which will help elucidate dysfunction at a cellular and molecular level on a defined genetic basis.

Regarding exactly this genetic background of the ADHD iPSC models mentioned above, one of these cell lines was created from cells carrying a duplication of *SLC2A3* encoding for glucose transporter-3 (GLUT3), which has been identified as a risk gene for ADHD (Lesch et al. 2011). For another ADHD modelling study, PRS data from ADHD patients and respective controls are available as a tool to stratify the two groups, considering their genetic predisposition to develop ADHD.

In other words, following PRS analysis, iPSC lines from patients and controls with high and low genetic risk/PRS, respectively, have been generated from blood cells or hair-derived keratinocytes (Grossmann et al. 2021; Yde Ohki et al. 2021). A pilot study on fibroblast and iPSC-derived dopaminergic neuronal cells of ADHD patients carrying CNV in the *PARK2* gene showed a cellular pathophenotype of disturbed energy metabolism: *PARK2* CNV deletion and duplication carriers showed alterations in gene and protein expression, ATP production and basal oxygen consumption rates (Palladino et al. 2020). Applying common stress paradigms, such as nutrient deprivation, even enhanced some of the effects when compared to healthy and ADHD wildtype control lines. The disturbed energy metabolism found for *PARK2* CNVs in this study could hint at a role in mitochondrial function, which has become a more and more studied target for possible pathological mechanisms in ADHD over recent years. However, genetic data for the other ADHD-derived iPSC lines mentioned above is lacking.

In vitro and in vivo gene expression experiments using non-iPSC-based ADHD models have previously focused on monoaminergic (particularly dopaminergic) or glutamatergic systems (Leo et al. 2003; Roman et al. 2004; Palladino et al. 2019). Therefore, an attempt to replicate these results could be an obvious first step in the characterization of the new models. In addition to the differential analysis of ADHD models, the investigations proposed above should further include analyses of the effect of psychostimulant and non-psychostimulant treatment.

Aside from genetic factors, environmental influences also seem to contribute significantly to the aetiology of ADHD. Environmental factors such as maternal prenatal stress, increased exposure to toxins or emotional and physical abuse might influence the risk of developing ADHD by epigenetic mechanisms, such as DNA methylation, as a means of gene silencing (reviewed in: Palladino et al. 2019). Starting to investigate these gene–environment interactions using iPSC-based ADHD models, e.g., by nicotine exposure mimicking maternal smoking or by starvation mimicking low birthweight, will eventually help contribute to understanding of the complex aetiology and response to treatment of this disease.

7 Summary

iPSC-based ADHD modelling is able to overcome some of the main disadvantages that previously established systems such as in vivo or standard in vitro models face. However, present iPSC technology is not the Holy Grail, as it comes with its own limitations, which are discussed in detail above. Nevertheless, this novel technology offers a valuable and unique way to help understand some of the genetic factors and neurodevelopmental processes underlying ADHD aetiology and pharmacotherapy. Much has been learned from the study of iPSC-derived models of ADHD, but the immense translational potential of this technology has yet to be fully exploited.

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