

Section II  
Chapter

5a

Disorders

Attention deficit hyperactivity disorder  
in children and adolescents

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ADHD Phenomenology

Attention deficit hyperactivity disorder (ADHD) is a complex psychiatric syndrome characterized by developmentally excessive manifestations of inattention, hyperactivity, and impulsivity which have their onset prior to age 7 and are associated with impairments in at least two domains of psychosocial functioning (e.g. scholastic achievement, family interactions, peer relations) [1]. Widely considered to be the most common psychiatric disorder of childhood, ADHD affects approximately 5% of school-aged children worldwide [2], with diagnostic rates in males exceeding those of females by 4:1 in non-referred investigations and 9:1 in clinically referred samples [3].

Comorbidity profiles in children with ADHD

Upwards of two-thirds of children and adolescents with the disorder meet criteria for one or more comorbid psychiatric conditions. In particular, approximately 50–60% meet criteria for oppositional defiant disorder (ODD), 30–50% meet criteria for conduct disorder (CD), 25% meet criteria for one or more anxiety disorders, and 15–25% have a comorbid mood disorder [4]. Relative to same-aged peers, children with ADHD are also at heightened risk for tic disorders, learning disabilities, and substance use disorders [4]. The high prevalence of psychiatric comorbidity among youth with ADHD may reflect common etiological mechanisms and/or temperamental features (e.g. impulsivity), as well as associated psychosocial consequences of the disorder (e.g. demoralization stemming from impaired social functioning). ADHD is also considered a significant risk factor for adverse outcomes during adolescence and adulthood [5]; however, the relative contributions of ADHD vs. psychiatric comorbidity to subsequent outcomes have been difficult to isolate.

Chapter premise and objectives

Since its inception as a diagnostic entity, efforts have been undertaken to identify the underlying etiological

mechanisms associated with ADHD, based on the assumption that deficient neuropsychological processes underlie the heterogeneous array of behavioral difficulties associated with the disorder. Although technological and methodological advances have ushered in a flurry of scientific exploration and helped to resolve numerous ambiguities, such investigations have also raised additional questions, and, with a few exceptions, have neglected to approach the search for constituent deficiencies from a developmental perspective.

In the current chapter, specific emphasis has been placed on reviewing: (i) neuropsychological profiles of ADHD in children and adolescents; (ii) the stability of neuropsychological functioning across the aforementioned developmental periods in youth with ADHD (including relationships between the stability of neuropsychological functioning and the continuity/persistence of ADHD symptoms); (iii) potential moderators of neuropsychological functioning; (iv) patterns of structural and functional neuroimaging; and (v) pharmacological, psychosocial, and neurocognitive remediation strategies for children with ADHD.

Neuropsychology of pediatric  
ADHD across development

Initially conceptualized as a condition largely confined to boys who were hyperactive or hyperkinetic, the role of attentional dysfunction in ADHD was introduced by Douglas in 1972 [6], who examined vigilance deficits in these children. Research characterizing the precise nature of attentional dysfunction, as well as cognitive correlates of hyperactivity and impulsivity, has since increased. Neuropsychological research of ADHD has informed modern clinical practice and contemporary models of underlying pathophysiology, and guided neuroimaging approaches. However, only recently have investigators begun to appreciate the limitations of time-locked snapshots of neuropsychological functioning in ADHD and the importance of developmental factors (e.g. age, symptom stability,

Section II Adolescents

Dis-

environmental changes) that have the potential to confound concurrent estimates of neurocognitive dysfunction in youth with ADHD. As such, current knowledge about the developmental trajectory of neurocognitive dysfunction in ADHD largely comes from *cross-sectional* interpretations of a vast literature, which are highlighted in the forthcoming sections.

## Neuropsychological characterization of ADHD

Neuropsychological research studies of pediatric ADHD frequently dichotomize cognitive performance into "higher-order executive functions" and "lower-order non-executive functions". Other terms used to describe this dichotomy include "top-down" vs. "bottom-up", and "effortful" vs. "automatic". Higher-order executive functions broadly encompass attentional control, working memory, response inhibition, cognitive flexibility, planning, organization, and set-shifting. In contrast, lower-order functions include state regulation, activation/arousal, processing speed, and basic language processing, as well as long-term memory and basic sensory and motor functions. As detailed below, recent findings have cast doubt on whether ADHD constitutes a pure disorder of executive function given that many children with ADHD perform poorly on both higher-order and lower-order measures [7].

### Neuropsychological profiles of preschool children with ADHD

Despite the fact that the symptoms of ADHD frequently have their onset during the preschool period [8], the preponderance of studies examining neuropsychological correlates of ADHD have been conducted using school-age children. The limited literature examining preschoolers with ADHD has yielded inconsistent results regarding the presence of neurocognitive impairments. Sonuga-Barke et al. examined planning, working memory, and inhibition in preschoolers with and without high ADHD symptom counts and found that only inhibition was associated with ADHD symptoms [9]. In a later study, these investigators observed that, while both executive dysfunction (working memory, set shifting, planning) and delay aversion (reward sensitivity) factors made significant and independent contributions to predictions of ADHD symptoms, only the executive dysfunction factor correlated significantly with age, suggesting that, while executive dysfunction may emerge

during early childhood, delay aversion may be more developmentally independent [10]. Others have found preschoolers with ADHD to perform more poorly than controls on tests of vigilance, motor control, and working memory [11], as well as measures of early academic skills [12].

More recently, investigators have suggested that lower-order regulatory deficits are most prominent during the preschool period. For example, Marks et al. demonstrated that, despite overall weaker performance of preschoolers at risk for ADHD on measures of working memory and inhibitory control, such weaknesses could not be attributed to executive function impairments after accounting for groupwise disparities in lower-level processes [13]. Similarly, Berwid and colleagues showed that at-risk preschoolers do not exhibit specific deficits in either inhibitory control or sustained attention; rather, the most consistent effect related to risk status across tasks was the greater number of errors, and longer, more variable reaction times of at-risk preschoolers [14]. These findings suggest that ADHD-associated decrements in performance on executive function tasks in preschool children are probably related to state regulatory impairments rather than insufficiently developed executive function systems.

### Neuropsychological profiles of school-age children with ADHD

Relative to their typically developing counterparts, school-age ADHD cohorts have been shown to exhibit weaknesses on higher-order executive measures as well as lower-order, nonexecutive indices, with effect sizes generally falling within the moderate range [15]. In a recent meta-analysis of 123 studies, ADHD probands scored significantly lower than controls on measures of general intellectual functioning and academic achievement, as well as on an array of executive and non-executive indices [16]. Among youth with ADHD, effect sizes for FSIQ were larger than those for several executive function measures, while effect sizes for measures of academic achievement and computerized indices of vigilance were significantly larger than those for FSIQ.

A number of other meta-analyses have examined specific neuropsychological domains and measures relevant to pediatric ADHD. For example, a meta-analysis of working memory performance revealed strong effects for *spatial* storage and central executive domains and relatively weaker effects for *verbal* storage and central executive measures [17]. Recently, several meta-analyses

have reviewed ADHD, as [e.g. 16, 18-20] while of ADHD meta-analysis index of ADHD ex times to pri as slower S moderate st 22]. Finally, Performance with ADHD ity (RTSD) trols [23], a slower or fa above studi strongest ef

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have reviewed the literature on interference control in ADHD, as assessed via the Stroop Color-Word Test [e.g. 16, 18–20]. Some have reported minimal interference effects across different developmental periods [18, 20] while others have shown more pronounced interference deficits in ADHD [16, 19]. In addition, two recent meta-analyses applied to the Stop-Signal Task as an index of response inhibition found that children with ADHD exhibited slower and more variable reaction times to primary task stimuli (i.e. go-stimuli), as well as slower Stop-Signal reaction times; effects sizes of moderate strength were observed across analyses [21, 22]. Finally, in a review of 18 studies of Continuous Performance Tests (CPTs) in both children and adults with ADHD, 16 found significantly greater RT variability (RTSD) in patients with ADHD compared to controls [23], a pattern that was not attributable to overall slower or faster responding. Across virtually all of the above studies, measures of RTSD yielded among the strongest effect sizes [23].

#### Neuropsychological profiles of adolescents with ADHD

Relative to the plethora of neuropsychological research in school-age children with ADHD, comparatively little research has examined neuropsychological profiles of adolescents with the disorder. Small to moderate executive function weaknesses have been reported in this age group and have been linked to symptoms of inattention but not hyperactivity-impulsivity [24]. Recent findings from a large Finnish cohort indicated that adolescents with ADHD performed more poorly on measures of reading fluency, working memory, inhibition, response variability, and set-shifting relative to those with sub-threshold ADHD and typically developing controls [25]. Approximately half of the ADHD cohort was classified as having a categorically derived executive function deficit relative to 29% of the subthreshold ADHD group and 10% of the control group [25].

#### Potential moderators of group differences in neuropsychological functioning

Attempting to reconcile disparities across studies, several investigators have looked to potential moderators of group differences in studies completed to date. Beyond differences in age, inclusion/exclusion criteria, comorbidity, treatment status, etc., one such factor has involved the practice of statistical covariance for overall IQ. This issue has been somewhat controversial, with some investigators arguing that removing the

effect of IQ is necessary to isolate groupwise EF discrepancies [26] and others [27] suggesting that doing so may obfuscate any detectable EF disparities. Ultimately, reconciliation of such issues (e.g. reporting findings with and without IQ covariation) will be critical for leveling the interpretive playing field across investigations.

#### Stability of neuropsychological functions across development

Although some symptoms of ADHD typically diminish with age [28], limited data exist regarding the stability of neuropsychological functioning over development and the extent to which neuropsychological functions covary with or predict symptom stability over time. In light of the fact that such issues are addressed in Chapter 5b by Semrud-Clikeman and Fine, we provide only a cursory discussion below.

#### Neuropsychological stability relative to symptom stability

To date, few studies have investigated the extent to which neuropsychological functioning has paralleled ADHD symptom stability or remission over development. Such analyses are critical to understanding the centrality (or lack thereof) of neuropsychological dysfunction to ADHD. Kalf et al. examined the neurocognitive profiles of 5- and 6-year-old children who were diagnosed as either having ADHD or subthreshold ADHD 18 months later, as well as typically developing children without ADHD symptoms [29]. Poorer performance on measures of visuomotor integration, verbal working memory, and visual attention at baseline were predictive of ADHD 18 months later. Further, the performance of subthreshold ADHD children 18 months prior generally fell between that of ADHD children and controls [29].

Recently, our group found that executive and nonexecutive skills correlated with the presence or absence of childhood ADHD at early adult follow-up [30]. Specifically, when divided into subgroups of ADHD persisters and remitters, performance on putative measures of executive or effortful processes closely paralleled adolescent/young adult clinical status, with remitters performing more similarly to controls than persisters. In contrast, measures of less effortful, bottom-up, processes generally differentiated those with childhood ADHD from controls irrespective of adolescent/young adult clinical status. Overall, elements of the

neurocognitive profile of ADHD (e.g. lower-order processes) appear to reflect stable traits that heighten diagnostic liability, while others (e.g. higher-order executive processes) may constitute state-like and/or compensatory epiphenomena.

### Diagnostic utility of neuropsychological measures

Although clearly beneficial for elucidating neurocognitive substrates, approximately 50% of pediatric ADHD cohorts perform in the "normal" range on any given neurocognitive measure, suggesting poor sensitivity [31]. Further, the absence of an "impaired" score on neuropsychological tasks seldom rules out the presence of ADHD, contributing to reduced specificity [31]. Despite these limitations, neuropsychological assessment in pediatric ADHD remains important, particularly with respect to issues of differential diagnosis and/or psychiatric comorbidity (e.g. learning disabilities, language and/or pervasive developmental disorders), identification of individual learning styles (e.g. reconciliation of speed vs. accuracy), and establishment of home- and/or school-based interventions

### Etiological mechanisms in ADHD

Data from numerous studies indicate that both genetic and environmental factors interact to produce the diverse constellation of behavioral characteristics that define ADHD. However, results from family, twin, and adoption studies have shown that ADHD tends to cluster in families and that genetic factors alone reportedly explain up to 80% of the variance in the ADHD phenotype [32]. Beyond general heritability, molecular genetic studies have focused primarily on genetic alterations that may interfere with proper functioning of brain catecholamines dopamine and norepinephrine. Dopamine and norepinephrine neurons are functionally expressed in many interconnected brain pathways involved in top-down (e.g. prefrontal cortex) and bottom-up (e.g. locus coeruleus) cognitive control, respectively. Further, the majority of effective pharmacological treatments for ADHD (e.g. stimulants and nonstimulants) interact with dopamine and norepinephrine systems to dramatically improve the core symptoms of inattention and hyperactivity/impulsivity. Indeed, association (i.e. case-control analysis) and linkage (i.e. family pedigree analysis) approaches have shown that polymorphisms in a variety of dopaminergic and noradrenergic genes are preferentially associated with ADHD. For example, a

recent meta-analysis of molecular genetic studies of ADHD identified four dopamine genes as being significantly associated with ADHD [32]. A more recent large-scale study examining children with ADHD Combined Type and their affected siblings confirmed the association of several dopamine-related genes to ADHD [33].

An emerging line of research involves the study of molecular genetic influences on neuropsychological functioning in ADHD. For instance, Swanson and colleagues demonstrated that, contrary to expectations, the absence of the 7-repeat allele of the dopamine D4 receptor (DRD4-7R) in ADHD children was associated with impaired performance on measures of attention and inhibitory control; those with the DRD4-7R allele performed similarly to controls [34]. Thus, genetic factors, particularly those associated with both normal cognitive functions and ADHD (e.g. dopaminergic and noradrenergic system genes), may help identify subgroups of ADHD children with a partial syndrome characterized by behavioral excesses without neurocognitive deficits.

### Neuroimaging in pediatric ADHD

Prior to the availability of modern imaging data, frontal lobe dysfunction was presumed to be the neural substrate for ADHD based on the resemblance between patients with frontal lobe lesions and the ADHD phenotype (e.g. poor impulse control and inattention). While neuroimaging research has supported frontal lobe pathology in ADHD, support has also been provided for diffuse and dynamic neurologic dysfunction.

### Structural magnetic resonance imaging

#### Cerebral cortex

Studies conducted to date have demonstrated overall reductions in total cortical volume in children with ADHD relative to age- and sex-matched controls through age 19 by approximately 3% overall and 3–5% in the right hemisphere [35]. Abnormal morphology (bilateral volumetric reduction) has been documented in virtually all areas of the frontal cortex. In contrast, prominent increases in grey matter have been reported in the posterior temporal and inferior parietal cortices bilaterally in ADHD [36]. In limbic regions, larger bilateral hippocampus as well as reduced bilateral amygdala over the area of the basolateral complex have been reported in ADHD [37].

#### Basal Ganglia

The basal ganglia play a key role in motor physiology and are also a mediator of executive functions. Studies have shown that dysfunction in these structures is associated with ADHD, particularly in the context of attention and inhibitory control.

#### Corpus callosum

The corpus callosum is a major white matter tract connecting the two cerebral hemispheres. Research has shown that children with ADHD have a smaller corpus callosum, particularly in the anterior and middle sections. This finding has been associated with ADHD symptoms, particularly in the context of attention and executive functions.

#### Cerebellum

The cerebellum is involved in motor coordination and cognitive functions. Studies have shown that children with ADHD have a smaller cerebellum, particularly in the vermal regions. This finding has been associated with ADHD symptoms, particularly in the context of attention and executive functions.

#### Functional MRI

Functional MRI (fMRI) studies have shown that children with ADHD have altered brain activation patterns, particularly in the frontal cortex and basal ganglia. This finding has been associated with ADHD symptoms, particularly in the context of attention and executive functions.

#### Prefrontal cortex

The prefrontal cortex is involved in executive functions and decision-making. Studies have shown that children with ADHD have altered brain activation patterns in this region, particularly in the context of attention and executive functions.

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### Basal Ganglia

The basal ganglia have been implicated in the pathophysiology of ADHD due to their input-output role as a mediator of frontal-subcortical communication and catecholamine modulation of motor and cognitive functions. Subtle caudate nucleus volume and symmetry differences have been reported in ADHD in childhood; however, caudate normalization in ADHD typically occurs by adolescence [38].

### Corpus callosum

The corpus callosum is the largest interhemispheric commissure connecting the right and left cerebral hemispheres, and reductions in size may lead to a decrease in the amount of fibers that normally traverse the hemispheres. Reduced area of the corpus callosum in ADHD has been reported in the anterior (rostrum, genu, rostral body) and posterior (splenium) portions (see [35] for review). In contrast, a comparison of the corpus callosum of children diagnosed with ADHD to that of their non-affected siblings demonstrated no differences in corpus callosum morphometry between the two groups, either in local anatomy or total structure, suggesting corpus callosum abnormalities may be more environmentally sensitive than genetically mediated in ADHD [39].

### Cerebellum

Differentiation in cerebellar morphometry between children with ADHD and typically developing controls is arguably among the most consistent structural imaging finding to date [35]. An early quantitative examination of the cerebellum in general and the cerebellar vermis in particular reported that overall volumes were significantly reduced in boys with ADHD [40]. The decrease was localized to the posterior-inferior lobule, but not to the posterior-superior lobule, and remained significant after adjusting for total cerebral volume and IQ.

### Functional magnetic resonance imaging

Functional MRI studies have consistently implicated connectivity among the prefrontal cortex, basal ganglia, thalamus, and cerebellum in the pathophysiology of pediatric ADHD. Yet specific neural substrates have not been identified, as both hypoactivation and hyperactivation within this connectivity have been observed.

### Prefrontal-subcortical connectivity

A series of studies have examined response inhibition in ADHD with mixed results. Schulz et al. prospectively

examined response inhibition in adolescents diagnosed with ADHD during childhood compared to adolescents with no history of ADHD [41]. Adolescents with childhood ADHD exhibited markedly greater activation of frontal regions, while controls activated a distinct neural network including temporal, cerebellar, and hippocampal regions. Activation of the anterior cingulate gyrus was inversely related to performance, with greater activation in individuals who had more difficulty inhibiting the prepotent response [41]. Rubia et al. examined inhibition and error-processing in adolescents with ADHD and controls [42]. In controls, successful inhibition was characterized by increased neural activation in a fronto-cerebellar network, while adolescents with ADHD showed no significant activations within this network. Activation patterns during error-processing were similar in ADHD and control adolescents overall; however, controls showed significantly increased activation of the posterior cingulate and precuneus relative to ADHD participants [42]. Finally, recent work by Durston and colleagues [43] has suggested that inhibitory deficits in ADHD appear to be genetically mediated and may involve compromised activation of the inferior frontal gyrus and anterior cingulate gyrus.

To help better determine whether hypo- or hyperactivation is more indicative of ADHD, Dickstein et al. employed the recently developed activation likelihood estimation (ALE) technique to carry out a quantitative meta-analysis of published fMRI studies of ADHD [44]. When the individual ALE maps for the two groups (ADHD and controls) were compared statistically, controls demonstrated significantly greater probability of activation in a variety of regions relative to individuals with ADHD, including the left ventral and dorsolateral prefrontal cortex, anterior cingulate cortex, bilateral parietal lobe, right thalamus, left middle occipital gyrus, and an area centered at the right claustrum extending from insula to the striatum. In contrast, greater probability of activation in ADHD vs. controls included the left frontal lobe, insular cortex and portions of middle frontal gyrus, left thalamus and the right paracentral lobule.

### Developing vs. mature neural systems

Recent longitudinal MRI studies have demonstrated substantial neuroanatomic differences in pediatric ADHD that fluctuate dynamically. The first study to examine neural changes over time followed a large sample of individuals with ADHD and age-matched healthy controls (age range 4.5-19 years) using a mixture of longitudinal and cross-sectional MRI analytical methods [38].

At baseline, healthy controls had significantly greater total cerebral volume than ADHD patients, as well as larger frontal grey and white matter. However, after adjustment for total cerebral volume, no significant difference in frontal volume remained between the two groups. Further, analysis of a subset of follow-up scans 2–3 years later demonstrated no disparity in frontal morphometry in ADHD; rather, the frontal lobes had the smallest effect sizes of any anatomical region. Baseline differences in cerebellar volume persisted, with a non-significant tendency for this difference to increase over time [38]. Longitudinal cerebellar growth has been linked recently to different clinical outcomes in ADHD: the growth trajectory of total cerebellar volume in children with ADHD with better clinical outcomes parallels that of normally developing controls, whereas cerebellar growth in those with poorer outcomes is characterized by a progressive decrease in total cerebellar volume that falls further away from the normal trajectory over time [45].

Automated measures of cortical thickness across the entire cortex have recently demonstrated an association between rates of cortical thinning and symptom improvement in ADHD [46]. As a group, children with ADHD had significantly reduced cortical thickness; however, such observations were most prominent in prefrontal and anterior temporal regions. On baseline scans examined retrospectively, ADHD probands with poor clinical outcomes displayed relative thinning in medial and superior prefrontal regions and cingulate cortex bilaterally relative to those with better clinical outcomes, even after adjustment for IQ and overall cortical thickness. Probands with favorable outcomes differed minimally in cortical thickness from controls except for a small region of thinning in the left dorsolateral PFC, and showed normalization of right parietal cortical thickness over time.

Most recently, work by Shaw and colleagues has suggested that ADHD is characterized by a delay rather than deficiency in regional cortical maturation [47]. Cortical maturation progressed in a similar manner regionally in both children with and those without ADHD, with primary sensory areas attaining peak cortical thickness before higher-order association areas. However, there was a marked delay in attaining peak thickness throughout most of the cortex in ADHD: the median age by which 50% of the cortical points attained peak thickness for this group was 10.5 years, which was significantly later than the median age of 7.5 years for typically developing controls. The delay was most prominent in the lateral prefrontal cortex and in the posterior portions of the middle/superior temporal gyrus bilaterally [47].

## Evidence-based interventions

The following section is devoted to a discussion of what is considered to be the two most empirically well-supported interventions to date: behavioral interventions and psychopharmacological treatment. In addition, we will also briefly review two large-scale intervention studies for ADHD – the Multimodal Treatment of ADHD (MTA) Study as well as the Preschool ADHD Treatment Study (PATS) – that have been instrumental in developing practice guidelines for the treatment of ADHD in youth.

## Behavioral interventions

### Behavioral parent training

Behavioral parent training (BPT) has been a well-studied intervention for various childhood mental health disorders including ADHD [48]. BPT is a treatment approach wherein parents are taught how to manipulate antecedents (e.g. rules, commands) and consequences (e.g. rewards, time out) of their child's behavior (e.g. aggression, noncompliance) in order to improve behavior. Although effects of BPT on core ADHD symptoms have been reported [49], it appears that the primary evidence for BPT as an intervention for ADHD is founded on the effects of BPT on co-occurring oppositional problems and impairment in children versus improvements in the core symptoms of ADHD *per se* [50]. Given that children with ADHD often present with comorbid ODD, the effect of BPT on ODD is noteworthy. Lastly, BPT for families of children with ADHD has also demonstrated improvements in parental functioning [49]. Thus, the evidence for BPT for ADHD suggests that BPT improves co-occurring oppositional/defiant behavior, impairment, parental functioning, and, to a lesser extent, core ADHD symptoms. Collectively, the evidence is substantial that BPT improves the functioning of children with ADHD and their families; however, further empirical investigation is necessary to determine for whom BPT works best as well as how best to maximize BPT for traditionally difficult-to-engage and difficult-to-treat ADHD populations [48].

### Classroom behavior management

Given the notable difficulties that children with ADHD have within the school setting, it is not surprising that a primary emphasis for treatment is to target classroom behavior and academic productivity. In fact, interventions implemented in the classroom, primarily in the

form of behavior management, such as greater external structure, consistent consequences for ADHD, positive reinforcement, and direct communication, are essential to understand and manage the behavior of children with ADHD. Peer and teacher feedback, and teaching/instruction of praise and positive reinforcement, are essential to classroom management. Time-out from the classroom, daily report cards, and behavior interventions for ADHD are essential. Direct observation in the classroom is essential. Analysis of classroom behavior has reported a number of designs, approaches, and approximations. Clearly, classroom management can result in successful outcomes for children with ADHD [52]. Focusing on the next-generation effects of classroom management comes in the form of behavior management in the classroom.

### Summer Treatment

The Summer Treatment Program for children with ADHD is a comprehensive, multi-component program that includes daily report cards, problem-solving training, and group therapy for the entire school year. The program offers children with ADHD appropriate relationships with their counselors. The STP [54], large-scale designs [56]

form of behavioral interventions, have been studied to a greater extent relative to other psychosocial interventions for ADHD, including BPT [51]. Classroom behavior management often takes the form of psychoeducation and direct consultation with the teacher to better understand and manage the child's difficulties across academic, peer, and teacher-child contexts. This often requires educating/instructing the teacher on the appropriate application of praise, planned ignoring, effective commands, classroom rules, use of contingent rewards/reinforcers, time-out from positive reinforcement, and the use of a daily report card. Studies on classroom behavioral interventions for ADHD demonstrate that this form of intervention is highly effective, with significant effects on direct observation and teacher ratings of child behavior in the classroom [3]. Effect size data from one meta-analysis of classroom behavior management for ADHD reported a mean effect size of 0.60 for between-subject designs, approximately 1.00 for within-subject designs, and approximately 1.40 for single-case designs [52]. Clearly, classroom behavior management procedures result in substantial improvements in the behavior of children with ADHD. Although meta-analyses indicate the benefits of academically focused interventions for ADHD [52], these are relatively few compared to studies focusing on behavior management in the classroom. Next-generation studies should further explore the specific effects of academic interventions on academic outcomes in children with ADHD and how best to combine behavior management and academic interventions in the classroom for youth with ADHD.

### Summer Treatment Program

The Summer Treatment Program (STP) for children with ADHD is an intensive psychosocial program that seamlessly integrates multiple evidence-based treatment components for school-age children, including BPT, praise, effective commands, point systems, time-out, daily report cards, social skills training, and problem-solving training (see ref. 53 for details). Children are grouped according to developmental level and spend the entire day together with highly trained and supervised counselors and an experienced lead counselor. This offers children the opportunity to learn how to develop appropriate social skills, problem-solving skills, and peer relationships under the support and encouragement of their counselors. Over the past decade, the effectiveness of the STP has been evaluated in large between-group [54], large crossover [55] and several single-subject designs [56], indicating the acute benefits of the STP

for youth with ADHD. It is clear that intensive interventions, such as the STP, are an important aspect of comprehensive care for youth with ADHD; however, data are sorely needed regarding the longer-term benefits of this intensive intervention when children return to school. How best to maximize and sustain the often dramatic treatment gains found in the STP to post-STP settings remains an essential empirical question.

### Pharmacological interventions

Stimulant medications are the first-line pharmacological intervention for ADHD [57] and include short- and long-acting preparations of methylphenidate and amphetamine salts. The literature on stimulant medication for ADHD has demonstrated acute benefits on multiple behavioral outcomes (see ref. 58 for reviews), including improvements in core symptoms of ADHD, compliance, aggression, and academic productivity. Although a dose-dependent response to stimulant medication has been cited in the literature [59], such increases may also be accompanied by the emergence and/or exacerbation of adverse events. In addition, several studies have noted that the dose of stimulant medication can be reduced substantially if a combined approach is taken whereby both stimulant medication and behavioral interventions are in place [60]. The opposite is also true; that is, the intensity of behavioral interventions can be substantially reduced if concurrent stimulant medication is provided. Given the noted side effects associated with stimulant medication and that many parents prefer nonpharmacological approaches to treating ADHD [61], the use of behavioral interventions alone or at least in combination with stimulant medication may be a more palatable treatment regimen for most families. Within the past several years, non-stimulant alternatives (e.g. atomoxetine) have come to market and may constitute a viable option for individuals for whom stimulants are either ineffective or poorly tolerated. Given that as many as 30% of youth do not respond to or have an adverse response to stimulant medication [62], the development of alternative pharmacological interventions is clearly necessary.

### Key clinical trials

#### Multimodal Treatment Study of Children with ADHD (MTA)

The MTA Study constitutes the largest clinical trial of a childhood mental health disorder funded by the NIMH to date and included 579 children between the ages of 7 and 9

who were diagnosed with ADHD, Combined type [63]. The study was developed to compare the most evidence-based interventions for ADHD on multiple outcomes over a 14-month period and to gauge the extent to which the intensive interventions provided through the study fared better than treatments received in the community. Children were randomized to one of four treatment conditions: (1) behavioral treatment (BPT, STP, classroom behavior management); (2) medication management (primarily stimulant medication); (3) combined behavioral and medication management; or (4) a community comparison condition. The immediate 14-month post-treatment data indicated that medication management alone was as effective as the combined treatment condition in reducing ADHD symptoms, suggesting that there was no incremental benefit of behavioral interventions [64]. However, compared to the medication management condition, the combined treatment condition resulted in greater improvement in key domains of functioning, including children's social skills and parent-child relationships [65]. Moreover, normalization of functioning was more likely to occur from participation in the combined treatment condition [66]. Although many accolades have been showered upon the MTA study, and practice guidelines have been guided by its outcomes, data regarding normalization of functioning in key domains over the long term have been sobering. Swanson and colleagues found that between 32 and 64% of children continued to exhibit clinically significant levels of ADHD despite the intensive MTA stimulant medication and behavioral treatment regimens [67]. Moreover, children continued to have significant difficulties in peer relationships – a key domain of functioning related to children's long-term positive outcomes [68]. It therefore appears that while stimulant medication and/or behavioral interventions appear to help to reduce the breadth and severity of ADHD symptoms, many remain deviant relative to their peers in key areas of functioning.

### Preschool ADHD Treatment Study (PATS)

Despite the fact that symptoms of ADHD typically have their onset during the preschool period [8] there has been a relative dearth of studies examining the efficacy and safety of stimulant medication in young children. Although several investigations have highlighted the potential benefits of stimulant treatment for young children with ADHD (e.g. ref. 60), it was clear that a large, representative stimulant medication trial of preschool children with ADHD using well-validated and broad-based measures assessing multiple outcomes, including

safety and tolerability, was needed. The Preschool ADHD Treatment Study (PATS; see ref. 69) was conducted as a 6-site, 8-phase, 70-week clinical trial of stimulant medication for preschool-aged children with ADHD. An initial, intense screening phase followed by a 10-week BPT program was conducted to exclude children who responded well to the psychosocial intervention from the subsequent pharmacological trial, thereby retaining more severe ADHD cases. Following this, an open-label safety lead-in was conducted to determine whether children could tolerate the doses of stimulant medication that were to be used in the study (i.e. 1.25 mg TID, 2.5 mg TID, 5 mg TID, and 7.5 mg TID). This was followed by a 5-week, double-blind, placebo-controlled, crossover titration to determine optimal dosing and then a 4-week, double-blind, placebo-controlled parallel study of best-dose or placebo. The last two phases of the study involved an open-label maintenance phase and a discontinuation phase to determine safety and relative long-term effectiveness of stimulant medication. Results indicated that all but the smallest dose was effective in reducing ADHD symptoms [70]; however, even the lowest dose was effective in improving functioning in some settings (i.e. classroom). Similar to other studies, there were notable increases in side effects (e.g. emotional lability), particularly at higher dosages. Compared to school-age children enrolled in the MTA Study, effect size data were smaller for preschool-age children enrolled in the PATS study, indicating that stimulant medication may be less effective for younger children. Moreover, the fact that stimulant medication did not normalize ADHD symptoms in a majority of children suggests that alternative and adjunctive interventions may be necessary to maximize outcomes for preschoolers with more severe manifestations of ADHD.

### Cognitive remediation strategies for children with ADHD

Although both pharmacological and psychosocial interventions provide acute benefits with respect to symptom reduction and impairment (e.g. parent-child relationships), these interventions seldom result in sustained benefits once the intervention has been discontinued [48] nor do they yield long-term improvements in psychosocial functioning [71]. Limitations of these "evidence-based" interventions have consequently spurred the development of alternative interventions for ADHD, particularly those that target either attention [72, 73] or working memory [74, 75].

### Remediation

Two studies have been conducted that are focused on improving attention through intensive, targeted programs. Kerns et al. (2001) conducted a study titled "Attention!, which aimed to enhance sustained attention through a computer-based program. Results indicated that children who were engaged in computer-based activities (e.g. puzzles), ADHD symptoms decreased. The "Attention!" program improved neurocognitive functioning and achievement. However, it did not improve attention. There was a trend toward improvement in attention and in the Pay Attention!

Recently, a study by the Center for the Study of Children's Attention (CPA) was conducted. The study was designed to address the need for attention, orientation, and memory training [73]. Relative to children who did not participate in the program, children who participated in the program showed improved performance on computer-based tests and a reduction in ADHD symptoms.

Collective research has been focused on improving attention through several different modalities and reports of effectiveness. However, reports of effectiveness are often based on focused interventions in a laboratory setting. A notable limitation of these studies is that they do not provide a naturalistic setting in which these interventions are used. Therefore, more studies of the effectiveness of these interventions in a naturalistic setting are needed.

### Remediation

In addition to the need for attention training, there is a need for training programs for enhancing attention and working memory symptoms of ADHD.

## Remediation of attentional functioning

Two studies have been conducted that focus on improving attention in children with ADHD through *intensive, targeted attention-focused training programs*. Kerns et al. [72] evaluated the program, Pay Attention!, which includes materials designed to enhance sustained, selective, alternating, and divided attention through both visual and auditory activities. Results indicated that, compared to those who were engaged in computer-based activities (e.g. games and puzzles), ADHD probands who participated in Pay Attention! improved their performance on several neurocognitive tests as well as measures of academic achievement. Parent reports of ADHD symptoms did not improve as a function of treatment; however, a trend toward improvement in teacher-reported inattention and impulsivity was reported for children in the Pay Attention! condition.

Recently, a computerized progressive attentional training (CPAT) program was evaluated in a sample of children with ADHD; it includes four training tasks designed to activate sustained attention, selective attention, orienting of attention, and executive attention [73]. Relative to children with ADHD who took part in computer games and paper-and-pencil activities, participation in the 8-week CPAT program resulted in improved performance on non-standardized academic tests as well as a reduction in parent-reported ADHD symptoms.

Collectively, programs that have focused on improving attention have resulted in improvements on several neurocognitive tests, academic achievement, and reports of children's behavior. Clearly, attention-focused interventions hold promise as a therapeutic modality for children with ADHD; however, there are notable limitations that will necessitate further empirical investigation (e.g. lack of comparison with empirically supported interventions). Further, the extent to which these programs can be implemented under "real-world" conditions is critical. Consequently, such interventions, while promising, warrant additional studies of both efficacy and generalizability.

## Remediation of working memory

In addition to interventions that have focused on directly *targeting attention*, the Cogmed Working Memory Training Program (Cogmed) has demonstrated evidence for enhancing working memory and reducing behavioral symptoms of inattention and hyperactivity/impulsivity

in children with ADHD [74, 75]. This software-based training program was developed to improve working memory abilities, particularly in children with ADHD or severe attention problems. The training is implemented with a software product (RoboMemo® from Cogmed Cognitive Medical Systems AB, Stockholm, Sweden) and includes a set of computerized visual-spatial and auditory-verbal working memory tasks. All tasks involve: (a) maintenance of simultaneous mental representations of multiple stimuli; (b) unique sequencing of stimulus order in each trial; and (c) progressive adaptation of difficulty level as a function of individual performance. Training plans are individualized and are modified according to performance; however, the typical plan includes 13 tasks, with 15 trials of eight tasks each day.

In two clinical trials, the Cogmed intervention was compared to an identical computer program using low working memory load tasks that were *not adjusted based on child performance*. In the initial, double-blind, controlled study, the Cogmed intervention, relative to the low working memory load condition, yielded significantly greater improvements on measures of working memory, nonverbal complex reasoning, response inhibition, and motor activity [74]. In a larger, multi-site clinical trial similar beneficial effects of Cogmed were reported, with significant intervention effects observed for measures of verbal and nonverbal working memory, nonverbal complex reasoning, and response inhibition relative to participants in the low memory load condition [75]. However, contrary to the initial investigation, no treatment effects were observed for measures of motor activity. *Importantly, the above gains in neurocognitive functioning were maintained at 3-month follow-up for those receiving the Cogmed intervention* [58]. Although behavioral ratings obtained at post-intervention did not reveal changes in teacher reports of ADHD severity, significant treatment effects were observed using standardized and nonstandardized parent ratings of ADHD severity, many of which were maintained at follow-up.

Although promising, the results of the above working memory interventions must be considered in the context of high rates of treatment noncompliance (approximately one-third) and restrictive inclusion and exclusion (e.g. required computer access, exclusion of ODD participants) The lack of significant improvement in teacher-rated ADHD behaviors is also a significant concern, as one would expect improvements in working memory to translate into improvements within settings in which these abilities are most taxed

and/or impaired (i.e. at school). The absence of teacher-identified behavioral changes may reflect an expectancy bias on the part of parents who may have not been as blind to the nature of the interventions in question. Ultimately, closer examination of treatment effects across multiple outcomes coupled with prospective investigations of long-term efficacy will be key steps in future studies of this intervention.

### Enhancement of executive function development

As we close this section on cognitive interventions, one recent study is worth noting. Although it is not directly aimed at children with ADHD, Diamond and colleagues [76] evaluated "Tools of the Mind", a comprehensive preschool curriculum designed to enhance executive function development, which is particularly relevant to ADHD given reported impairments in time management and organizational skills in children with ADHD [15]. Tools of the Mind is grounded in established developmental theory and was developed based on Luria's [77] and Vygotsky's [78] theory of development and includes 40 activities interwoven into classroom activities that promote executive functioning throughout the preschool day, including the use of self-regulatory (internalized) speech, dramatic play, and aids to support memory and attention. In a sample of children from low-income, urban preschools, Tools of the Mind was compared to the school district's existing literacy program, which focused on similar academic content but did not address executive functioning development. Results indicated that children randomized to Tools of the Mind classrooms demonstrated significant improvements in inhibitory control, working memory, and cognitive flexibility relative to those assigned to the conventional literacy program.

Importantly, the Tools of the Mind program includes several design elements that may inform interventions in general, and cognitive interventions in particular. First, the intervention emphasizes early childhood, a time when executive functioning skills are coming on line developmentally. Efforts to target executive functioning when skills are emerging may be preferable to remediation that occurs past the point of typical skill acquisition/development [79]. Second, rather than solely relying on the involvement of professionals, familiar and potentially transformative adult figures (i.e. teachers) implement the intervention within a setting in which these children live and learn (i.e. school), thereby intensifying the potency and

palatability of the intervention. Moreover, the fact that the intervention is seamlessly woven into the existing curriculum and relies on activities that children find to be enjoyable and that teachers can readily support bolsters the sustainability of the intervention and resulting improvement(s).

Thus, while the aforementioned studies have notable limitations, considerable progress has been made on how to ameliorate patterns of neurocognitive dysfunction of children with ADHD. Contrary to existing methods, such techniques may improve both the acute difficulties children with ADHD experience as well as the long-term outcomes for these children. Although many questions remain, several clear directions exist for future work in this area (e.g. comparison and/or augmentation with well-validated treatments) that may ultimately help to reduce the severity of ADHD symptoms and breadth of psychosocial impairment.

### Summary and future directions

ADHD is a heterogeneous psychiatric disorder characterized by clinically significant manifestations of inattention, hyperactivity, and impulsivity, which persist in a significant subset of affected individuals and portend risk for a number of adverse psychosocial outcomes. Within the past several decades, a variety of models have been proposed identifying various "core" cognitive deficits in children with ADHD, based on the suspicion that deficient neuropsychological functioning underlies the diverse array of behavioral difficulties associated with the disorder. Although numerous theoretical models have emphasized frontally-mediated executive functions with regard to the underlying pathophysiology and resulting symptomatic expression [80], recent reviews and meta-analyses [15] have suggested that executive function deficiencies do not account for most of the variance in ADHD symptoms, discounting the clinical utility of such measures in diagnostic assessment. Yet the apparent schism between executive function development on the one hand, and the presence of ADHD symptoms on the other, suggests that alternative models may be required to account for the emergence of early externalizing behaviors. One recent model [28] has proposed that distinct mechanisms underlie the etiology of, and recovery from, ADHD, with the former posited to result from noncortical dysfunction that remains static through development, and the latter a byproduct of cortically mediated, effortful control. Consequently, targeted efforts to augment

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top-down processes, which have already demonstrated acute benefits with respect to both neurocognitive and behavioral functioning [78], may hold promise in altering the long-term trajectories of children with ADHD. In addition to emphasizing ecologically sensitive measures, remedial strategies would be well-served to examine the role of psychiatric comorbidity in remediation techniques and whether developmental status impacts responsivity to such methods.

#### ADHD phenomenology

- ADHD is a highly prevalent, often chronic psychiatric disorder that, by definition, is associated with impairment in multiple spheres of psychosocial functioning.
- Co-occurrence with other psychiatric disorders, particularly other disruptive behavior disorders, is clearly the rule rather than the exception; however, the contributions of ADHD vs. psychiatric comorbidity to later outcomes have been difficult to isolate.

#### Neuropsychological profiles

- During both childhood and adolescence, many individuals with ADHD display impairment(s) in one or more domains of neuropsychological functioning; however, such deficits are neither necessary nor sufficient to make the diagnosis and may vary as a function of several moderating factors (e.g. inclusion criteria, IQ covariation, etc.)
- Although distinctions between lower-order and higher-order functions may not have discriminative utility during childhood, this dichotomy may hold promise for distinguishing between persisters and remitters.

#### Etiological mechanisms

- Catecholaminergic systems (i.e. dopamine and norepinephrine) have been most consistently implicated in the pathophysiology of ADHD and are targeted neurochemical systems for treatment
- ADHD is considered among the most heritable psychiatric disorders and has been linked to allelic variations in the dopamine D4 receptor (DRD4) and transporter (DAT).

#### Structural and functional neuroimaging

- Findings from structural and functional neuroimaging studies have consistently implicated

perturbations in fronto-thalamo-striatal regions; however, support has also been provided for diffuse and dynamic neurological dysfunction.

- Recent investigations have suggested that ADHD is characterized by a delay rather than deficiency in regional cortical maturation (i.e. attainment of peak cortical thickness).

#### Psychosocial and psychopharmacological intervention

- First-line pharmacological interventions for ADHD include both psychostimulants (e.g. methylphenidate and amphetamine salts) as well as non-stimulants (e.g. atomoxetine; bupropion); however, the jury is out as to which preparation works most effectively for which children or symptom cluster.
- Evidence-based psychosocial treatments include parent management training; teacher consultations; summer treatment programs; social skills interventions; and paraprofessional programs; and have been shown to produce reductions in ADHD symptoms and associated patterns of psychiatric comorbidity.
- Recently developed methods of cognitive remediation have targeted attention and/or working memory and may hold promise vis-à-vis acute manifestations of ADHD as well as the long-term outcomes for affected individuals.

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