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Cognitive enhancers for the treatment of ADHD

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is associated with multiple cognition-related phenotypic features in both children and adults. This review aims to clarify the role of cognition in ADHD and how prevailing treatments, which are often highly effective at reducing the clinical symptoms of the disorder, fare in modulating ADHD-related cognitive processes. First, we consider how the broad construct of cognition can be conceptualized in the context of ADHD. Second, we review the available evidence for how a range of both pharmacological and non-pharmacological interventions have fared with respect to enhancing cognition in individuals affected by this pervasive disorder. Findings from the literature suggest that the effects across a broad range of pharmacological and non-pharmacological interventions on the characteristic symptoms of ADHD can be distinguished from their effects on cognitive impairments. As such the direct clinical relevance of cognition enhancing effects of different interventions is somewhat limited. Recommendations for future research are discussed, including the identification of cognition-related end ophenotypes, the refinement of the ADHD clinical phenotype, and studying the difference between acute and chronic treatment regimens.

Keywords

ADHD; Cognition; Pharmacological treatment

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders, affecting approximately 8–9% of school-aged children and 4–5% of adults (Froehlich et al., 2007; Kessler et al., 2006; Visser et al., 2007). Although formally the disorder is characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity (APA, 2000), myriad phenotypic features—many of which are related to cognition broadly defined—have been shown to distinguish those with ADHD from those without the disorder. A clearer perspective regarding both the role of cognition in ADHD and how prevailing treatments modulate cognitive function may help provide guidance for future research, as well as clinical practice. To this end, the purpose of this review is twofold. First, we will consider how the broad construct of cognition can be

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conceptualized in the context of ADHD. Second, we will review the available evidence for how a range of both pharmacological and non-pharmacological interventions have fared with respect to enhancing cognition in individuals affected by this pervasive disorder.

2. Defining cognition in ADHD

The past two decades have yielded a voluminous literature on the neuropsychological and cognitive correlates of ADHD across the lifespan. As of August 2010, a PubMed search of the terms ‘ADHD’ and ‘Cognition’ resulted in over 1000 empirical studies published since 1990. This rapid accumulation of new knowledge has demonstrated the great promise of neuropsychological methods for both research and clinical purposes. On the other hand, the complex and sometimes contradictory results that have emerged from these studies also illustrate the complexity and heterogeneity of the neurocognitive dysfunction associated with ADHD.

Until recently, most neurocognitive models of ADHD have implicated a simple linear pathway in which a single causal factor is hypothesized to give rise to a core cognitive deficit that is both necessary and sufficient to account for all cases of ADHD. The most prominent models proposed that ADHD is due to deficits in overall executive functions (EFs) or specific aspects of EF such as response inhibition (Barkley, 1997; Nigg, 2001; Pennington and Ozonoff, 1996), aversion to delay (Sonuga-Barke, 2003; Sonuga-Barke et al., 1992), difficulty modulating behavior in response to reward and punishment cues, (Luman et al., 2005) response inconsistency (Sergeant et al., 2003), and overall slow processing speed (Shanahan et al., 2006).

A comprehensive review of neuropsychological and cognitive theories of ADHD is beyond the scope of this paper. In the following section, we summarize a number of domains that have been implicated in the etiology of ADHD. These domains will serve as a framework to subsequently consider the role of various interventions for addressing some of the identified deficits in those individuals with the disorder.

2.1. Executive functions

One of the most prominent neuropsychological theories of ADHD suggests that ADHD symptoms arise from a primary deficit in executive functions (EF), cognitive processes that help to maintain an appropriate problem-solving set to attain a future goal (Pennington and Ozonoff, 1996). Each day we must continuously evaluate many potential actions and select the option that is most appropriate for that specific set of circumstances. This task is extremely complex because some potential choices are directed toward achieving a positive outcome in the future, whereas alternative actions may maximize initial gains but eliminate the chance for larger long-term benefit (Pennington, 2002).

Several distributed neural networks appear to play a role in executive functions, but the primary neural circuit includes the thalamus, basal ganglia, cerebellum, and prefrontal cortex (Casey et al., 2002; Pennington, 2002). Studies that used structural magnetic resonance imaging (MRI) to measure the volume of different brain regions found that groups with ADHD consistently had smaller volumes in the area of prefrontal cortex (PFC) that is most closely involved in executive functions (Seidman et al., 2005), and several functional MRI studies have reported differences in brain activity in these regions when groups with and without ADHD are completing an EF task (Banich et al., 2009; Ernst et al., 2003; Rubia et al., 1999; Vaidya et al., 1998). Weaknesses in these prefrontal regions are thought to interact with dysfunction in subcortical regions, including striatal regions and the cerebellum, in order produce requisite EF deficits in ADHD patients (Halperin and Schulz, 2006).

Previous theoretical models of ADHD have often invoked the notion of "executive control" as a single unified construct. However, exploratory and confirmatory factor analyses of EF tasks and results from fMRI studies suggest that executive functions may be more accurately described as a collection of related but separable abilities (Collette et al., 2006; Friedman et al., 2006, 2008b; Willcutt et al., 2005). Although the specific dimensions that emerged varied to some extent across studies, separable dimensions of EFs have typically included the ability to inhibit maladaptive behaviors ("response inhibition/inhibitory control"), hold and manipulate information in memory ("working memory"), shift back and forth between two simultaneous tasks ("set shifting"), and suppress attention to extraneous information in the environment to increase focus on a target ("interference control"). Based on these results, some cognitive theories of ADHD have suggested that rather than a global EF deficit, ADHD may be associated with amore focal weakness in a specific domain of EF such as response inhibition (Barkley, 1997, 2010).

2.2. Dysfunctional reward sensitivity

Explanations of ADHD related to reward sensitivity have several variants, but all of these models suggest that ADHD is attributable to a dysfunctional response to reward and punishment contingencies (Hartung et al., 2002; Luman et al., 2005). Delay aversion is a special variant of the dysfunctional reward sensitivity model that suggests that children with ADHD have a motivational style that leads them to find delay extremely aversive (Sonuga-Barke et al., 1992, 2008). A neural circuit that includes ventromedial prefrontal cortex, the amygdala, and other limbic structures plays an essential role in coordinating the interface between motivation and cognition during decision-making processes (Bechara, 2004; Rolls, 2004). Damage to this network often leads to difficulty learning from mistakes, delaying gratification, and monitoring subtle shifts in reward and punishment probabilities to maximize the short- and long-term benefits of a choice. Although few neuroimaging studies of ADHD have examined regions involved in this network, two studies reported a correlation between reduced ventromedial prefrontal cortex volume and ADHD (Carmona et al., 2009; Hesslinger et al., 2002).

2.3. Response variability

The reaction times (RTs) of children, adolescents, and adults with ADHD are significantly more variable than the RTs of individuals without ADHD across a wide range of cognitive tasks (Castellanos et al., 2005; Leth-Steensen et al., 2000; Sergeant et al., 2003). The overall effect size of the group difference is medium to large in magnitude, and is similar to the effects observed for response inhibition and working memory tasks (Willcutt and Bidwell, 2010).

Theoretical models of response variability are less developed than those for reward sensitivity and EFs. An initial parsimonious hypothesis suggested that increased RT variability might simply result from slower overall response speed coupled with measurement error, and many studies have confirmed that measures of intra-subject variability are often moderately correlated with mean RT (Klein et al., 2006). However, the difference in response variability between groups with and without ADHD is not eliminated when mean RT is controlled, and more complex statistical models of RT distributions suggest that increased response variability may be due to a relatively small number of trials with extremely long RTs rather than systematically greater response variability across all trials (Hervey et al., 2006). One theoretical model suggest that these slow trials reflect attentional lapses due to chronic underarousal or inconsistent regulation of arousal during lengthy tasks and that these attentional lapses are related to compromises in the functional connectivity between anterior cingulate and precuneal regions (Castellanos et al., 2008; Johnson et al., 2007; Sergeant, 2005; Sonuga-Barke and Castellanos, 2007). Another

theoretical account of reaction time abnormalities suggests that greater response variability could result from dysfunction in short-duration timing mechanisms that are largely mediated by cerebellar circuits (Castellanos and Tannock, 2002; Toplak and Tannock, 2005).

2.4. Processing speed

Although no theoretical models of ADHD explicitly propose slow cognitive processing speed as the primary neuropsychological weakness in ADHD, deficits in this domain are among the most robust predictors of ADHD symptoms (Rucklidge and Tannock, 2002; Willcutt et al., 2005). Slow processing speed has been reported in groups with ADHD on a range of measures that require both verbal and nonverbal responses (Shanahan et al., 2006), and the overall effect size for processing speed is the largest effect in meta-analyses of studies of both children and adults with ADHD (Willcutt and Bidwell, 2010). The neurophysiology of slow processing speed is not well understood, but generalized low cortical arousal provides one potential explanation.

2.5. Intelligence, academic achievement, and social cognition

The more global cognitive processes of intelligence, academic achievement, and social cognition have also been implicated in ADHD. Although deficits in these broad domains are likely to be impacted by the individual cognitive processes described above, pervasive social and academic deficits are of particular importance to the clinical impact of ADHD.

2.5.1. Intelligence and academic achievement—Intelligence and academic achievement are among the most global measures of cognitive functioning. Group differences in intelligence (i.e. Full Scale IQ) and academic achievement have also been found between individuals without and without ADHD (Bidwell et al., 2007). Some have argued that neuropsychological impairments associated with ADHD can be explained more parsimoniously by group differences on such correlated variables (Lahey et al., 1998; Werry et al., 1987). On the other hand, ADHD symptoms may directly cause an individual to perform poorly on standardized tests of intelligence or reading/(Barkley, 1997).

2.5.2. Social cognition—ADHD is associated in a handful of studies with deficits in social cognition, including face perception, emotional prosody perception, theory of mind, and reduced empathy (Uekermann et al., 2009). Few neuroimaging studies have examined social cognition directly in ADHD patients. However, research in healthy populations has demonstrated that these processes rely on many of the same frontal–striatal regions implicated in ADHD. Further, while patients with ADHD frequently suffer from a range of social and interpersonal problems, it remains unclear whether these difficulties arise from true deficits in social cognition or can be more parsimoniously explained by the behavioral symptoms of ADHD, i.e. lapses in inattention and impulsivity.

2.6. Summary

ADHD is associated with multiple neuropsychological weaknesses, many of which have identifiable neural substrates. Moreover, it is clear that there is considerable clinical and neuropsychological heterogeneity among individuals who meet the criteria for the disorder. These converging results have precipitated a major reconceptualization of theoretical models of ADHD. Rather than attempting to identify a single neuropsychological weakness that is necessary and sufficient to cause ADHD, more recent theoretical models explicitly hypothesize that complex disorders are heterogeneous conditions that arise from the combined effects of weaknesses in multiple cognitive domains (Nigg, 2006; Pennington, 2006; Sonuga-Barke, 2005). The remainder of this review will focus on the extent to which

a range of both pharmacological and non-pharmacological interventions have been shown to be effective in addressing the cognitive deficits described above.

3. Effects of pharmacological treatment on domains of cognition in ADHD

The pharmacological management of ADHD and related problems in children has been studied for nearly 50 years, with the first controlled studies of stimulant treatment published in the early 1960 s (Conners and Eisenberg, 1963; Conners et al., 1964). It is interesting that some of these early studies demonstrated beneficial effects for both amphetamine (AMP) and methylphenidate (MPH) on endpoints associated with cognitive functioning. For example, two studies demonstrated that in children institutionalized for severe problem behaviors, the administration of either MPH or AMP resulted in significant improvements in performance on the Porteus Maze test, a measure of generalized cognitive functioning (Conners and Eisenberg, 1963; Conners et al., 1969).

Consistent with the long history of research on the clinical effects of medications and behavioral interventions for ADHD and related conditions, a large number of studies have documented the effects of these interventions on a range of cognitive processes in clinical samples. In the following section, we review the effects of these interventions as they relate to the broad domains of cognition described in the previous section. We first review stimulant drug formulations (MPH and AMP), followed by non-stimulant formulations (atomoxetine, guanfacine, clonidine), including novel agents that have not yet been approved for use in treating this population (nicotinic agents, ACE inhibitors), and finally, we consider non-pharmacological interventions.

3.1. Stimulants: methylphenidate (MPH) and amphetamine (AMP)

3.1.1. Clinical overview—Stimulant drugs are by far the most widely studied class of drugs for ADHD. Hundreds of randomized controlled trials have consistently demonstrated efficacy of these agents for reducing the requisite symptoms of the disorder in both children and adults (Conners, 2002; Meszaros et al., 2009). MPH and AMP significantly reduce the core symptoms of ADHD in approximately 70% of children (Wilens, 2008). Although response rates in adults are somewhat more variable, stimulants are also very effective clinically in older individuals and one-third of all stimulant prescriptions are now written for adults with the disorder (Okie, 2006; Wilens, 2008).

3.1.2. Mechanism of action—Both MPH and AMP facilitate dopamine neurotransmission in striatal regions, which is believed to play a critical role in the therapeutic effects of these compounds (Levy, 1991; Wilens, 2008). The specific mechanism by which these stimulants enhance dopamine differs—MPH inhibits the reuptake of dopamine via blockade of presynaptic dopamine transporter and AMP stimulates release of vescicular dopamine stores in presynaptic terminals (Volkow et al., 2002a).

PET imaging studies have been instrumental in elucidating the specific ways in which MPH and AMP act in the human brain. Corroborating preclinical studies, a series of experiments have shown that MPH induces significant blockade of the DAT in striatum, with doses as low as 0.25 mg/kg occupying 50% of the DAT (Volkow et al., 1998). Moreover, clinically relevant doses of both MPH and AMP result in significant increases in extracellular dopamine levels (Volkow et al., 2002b; Villemagne et al., 1999). Recent work has also shown that MPH may exert some clinical benefits via blockade of the norepinephrine transporter (NET). Using methylreboxetine as a radiotracer, this study demonstrated that therapeutic doses of MPH resulted in 70–80% occupancy of NET, suggesting even greater affinity for NET than for DAT (Hannestad et al., 2010).

3.1.3. Stimulant effects across domains of cognition—Extensive work has been conducted on the effects of stimulants and cognition and several reviews have been published in recent years that address the effects of MPH on a broad range of cognitive functions implicated in ADHD (Advokat, 2010; Pietrzak et al., 2006; Swanson et al., 2011).

3.1.3.1. Studies in individuals without ADHD: In studies evaluating the effect of stimulants on cognition in non-clinical samples, one of the most established findings is stimulant's effects on improving attention/(Advokat, 2010; Koelega, 1993). This effect is largely achieved by decreasing RTs and improving the 'hit' rate of the target stimuli (an index of improved attention). However, there is often no effect on the number of times a response is made when it should not have been (i.e. "false alarms;" an index of response inhibition and impulsivity). Further, although performance on simple tasks that require sustained attention is enhanced, more demanding tasks, that require selective attention, may be impaired by stimulant drugs. Similarly, stimulants may actually impair performance on executive attention tasks that require set shifting, flexibility, and planning.

3.1.3.2. Studies in individuals with ADHD: Recent reviews of the effects of stimulants on cognitive deficits in individuals with ADHD have concluded that there is no clear evidence of stimulant medications completely correcting any of the cognitive deficits associated with ADHD and have broadly found the effects of stimulants medications vary depending on the dose of medication used and the specific domain of functioning assessed (Advokat, 2010; Pietrzak et al., 2006; Swanson et al., 2011). Across well-controlled studies of individuals with ADHD, stimulant-related cognitive enhancements were more prominent on tasks without an executive function component (complex reaction time, reaction time variability, sustained attention, spatial recognition memory reaction time, and delayed matching-to-sample) than on tasks with an executive function component (inhibition, working memory, planning, and set-shifting) (see Swanson et al., 2011 for a comprehensive review). Dose–response studies of stimulant medications suggest that the optimal dose varies across individuals and depends somewhat on the domain of function, with high doses tending to produce greater enhancement on some (e.g., attention, vigilance, memory, and working memory) but not others (e.g., planning, cognitive flexibility, inhibitory control, naming, and motor speed). Further, recent and preliminary neuroimaging evidence suggests that stimulant medications may exert their effects on cognitive task performance by normalizing the response to salient task-related stimuli (Liddle et al., 2010). In this study of 18 children with ADHD and a matched sample of control children, MPH was found to normalize deactivation of a default or "task negative" brain network and improve engagement of task-relevant brain areas during an inhibitory control task.

In terms of academic achievement, evidence suggests that stimulants improve acute academic performance of children with ADHD, but that long-term effects have not been supported. For example, the Multimodal Treatment study of ADHD(MTA) demonstrated treatment with stimulant medications over the 14-month trial resulted in significant improvement of achievement scores in math and reading on the Wechsler Individual Achievement Test (WIAT) immediately post-treatment (1999). However, these improvements were no longer significant at the 3-year follow up assessment, suggesting that any relative cognitive enhancement may not be sustained (Jensen et al., 2007).

In contrast to the extensive work on the effects of stimulants on attention, executive function, and achievement, the potential influence of stimulants on other types of cognition implicated in ADHD (e.g. social cognition and reward sensitivity) is comparatively unknown. In one study of social cognition using event-related potentials (ERPs), children and adolescents with ADHD were investigated before and 4 weeks after treatment with methylphenidate (Williams et al., 2008). Several ERP abnormalities during emotional

processing could be observed prior to treatment, which were ameliorated with methylphenidate. In addition, medication significantly improved base line deficits in the recognition of anger- and fear-related facial expressions. However, the performance of ADHD patients remained impaired relative to healthy controls. Thus, although methylphenidate normalized neural activity, it was associated with only minimal improvement on emotion recognition. This finding is in line with studies that suggest medication results in improvements of inattention and disruptive behavior in children with ADHD, whereas positive social behavior and peer status remain unchanged (Whalen and Henker, 1991; Whalen et al., 1989).

3.1.4. Summary—Extensive work examining the effects of stimulants on attentional and executive processes has not found consistent evidence that stimulants enhance or ameliorate these ADHD-related deficits. Although reaction times are significantly reduced, performance on tasks with increased attentional or executive demands is not consistently improved by stimulants. Further, while short-term improvements in academic achievement scores have been demonstrated with stimulant treatment, stimulant medications do not normalize academic achievement in children with ADHD. Similarly, although little experimental work has been done, available evidence suggests that deficits in social cognition are not restored with stimulant treatment.

3.2. Atomoxetine

3.2.1. Clinical overview—Atomoxetine (ATX) was approved in 2002 for the treatment of adults and children with ADHD and was the first non-stimulant drug approved for this indication. Since that time a large number of clinical trials have demonstrated the efficacy and tolerability of the compound, although most head-to-head trials that have compared stimulant medication to ATX have generally shown greater efficacy for both MPH and AMP formulations (Gibson et al., 2006). Importantly, however, ATX was still superior to placebo in large-scale registration trials in both adults and children with ADHD (Michelson et al., 2001, 2002, 2003).

3.2.2. Mechanism of action—Atomoxetine is a potent inhibitor of norepinephrine (NE) uptake, which consequently results in increased extracellular concentrations of NE, primarily in regions of the prefrontal cortex (PFC) (Bymaster et al., 2002; Wong et al., 1982). Interestingly, ATX also inhibits binding of both serotonin and dopamine, though much less effectively. Moreover, ATX increased extracellular concentrations of dopamine to a similar degree as NE, though only in PFC regions—not in striatum or nucleus accumbens (Bymaster et al., 2002). This preferential action of ATX in PFC is hypothesized to underlie both the clinical efficacy of the drug, as well as its lower comparable abuse liability (Heil et al., 2002; Wee and Woolverton, 2004).

Though the development of radiotracers for PET imaging of NET has not evolved as much as research on DAT, recent studies have begun to quantify the extent of NET occupancy in humans and nonhuman primates. One of the earliest studies showed that ATX dose-dependently increased NET occupancy in a range of brain regions known to contain high densities of NET (Seneca et al., 2006). More recent work has shown that ATX occupies NET in relevant brain regions in humans, although this study failed to report a dose–response relationship (Logan et al., 2007). This study also found that doses below the therapeutic threshold (e.g. 25 mg) resulted in significant increases in NET occupancy, raising the possibility that the clinical effects of ATX may be mediated by other neuronal actions, possibly cholinergic or histaminergic (Liu et al., 2008; Logan et al., 2007; Tzavara et al., 2006).

3.2.3. Atomoxetine effects across domains of cognition—Relative to the stimulants, ATX has been the subject of experimental work for only a very short time. Still, there is a growing literature on the effects of this drug on cognition in individuals with ADHD and other disorders.

3.2.3.1. Studies in Non-Human Species: Evidence regarding the cognition enhancing effects of ATX in nonhuman species has been mixed. One early study evaluated effects of a range of compounds on two variants of a delayed matching to sample task, a measure of short-term memory and attention. Results showed that a number of test drugs, including nicotine, MPH, and caffeine improved performance on the task, while ATX did not significantly improve performance (Bain et al., 2003). By contrast, another study demonstrated that ATX improved performance on other measures of memory functioning, including an 8-arm radial maze task and an object recognition task, though the effects were not dose-dependent (Tzavara et al., 2006). In a demonstration of the effects of ATX on attentional functioning, Newman and colleagues biochemically lesioned noradrenergic regions of the medial prefrontal cortex in rodents so as to disrupt attentional set-shifting. Administration of ATX reduced the set-shifting impairments resulting from the lesions. However, animals that were not lesioned exhibited disrupted performance of the task following ATX administration, suggesting that the effects of the drug are dependent upon baseline levels of noradrenergic functioning (Newman et al., 2008).

3.2.3.2. Studies in individuals without ADHD: A number of studies have evaluated the cognition altering effects of ATX in clinical and non-clinical samples of human subjects who do not have ADHD. A study of healthy, non-clinical adults demonstrated that ATX (60 mg) successfully improved inhibitory control in a stop-signal reaction time task, but had no effect on a probabilistic learning task (Chamberlain et al., 2006). When the authors followed up these results using functional neuroimaging, results indicated that 40 mg of ATX improved performance and increased activation in the right inferior frontal gyrus when healthy volunteers inhibited their responses during the stop signal task (Chamberlain et al., 2009).

A number of studies have evaluated the effects of ATX on cognitive dysfunction in individuals with other CNS disorders. For example, in patients with Parkinson's Disease, open-label ATX (25–100 mg) improved clinician and patient ratings of executive functioning, though had little effect on measured neuropsychological performance (Marsh et al., 2009). However, other studies have not reported cognitive enhancement resulting from ATX administration in other clinical conditions, including Huntington's Disease and Alzheimer's Disease (Beglinger et al., 2009; Mohs et al., 2009). At least 2 randomized, placebo-controlled studies have studied the effects of ATX on cognitive dysfunction in patients with schizophrenia. Neither of these studies reported any difference between ATX and placebo for improving cognitive deficits associated with schizophrenia (Friedman et al., 2008a; Kelly et al., 2009).

3.2.3.3. Studies in individuals with ADHD: Not surprisingly given its primary indication for ADHD, a number of studies have evaluated the cognition enhancing effects of ATX in individuals with ADHD. At least 4 studies have been conducted in children. A randomized, within subjects, placebo-controlled trial of ATX (1.2 mg/kg) administered for 28 days reported that compared to placebo, the drug significantly improved visuospatial working memory and inhibitory control in children diagnosed with both ADHD and a reading disorder. Those children with ADHD alone or RD alone showed no benefit from the drug (de Jong et al., 2009). Another study reported that ATX treatment (1.0–1.4 mg/kg for 16 weeks) in children with ADHD alone or ADHD + dyslexia resulted in significant improvement in ADHD symptoms, as well as measures of reading and spelling

achievement. Moreover, the two groups also showed unique patterns of additional benefits compared to one another (Sumner et al., 2009). Another open label study in children with ADHD reported that 6 months of ATX treatment significantly improved rating scale measures of cognition and executive functioning. Improvements in neuropsychological test performance were also reported, but similarly observed in a matched group of undiagnosed, untreated control children suggesting that the effects may have been due to practice (Maziade et al., 2009).Most recently, Gau and Shang (2010) reported that 4 or 12 weeks of open label treatment with ATX resulted in significant improvements on a range of executive functioning measures from the Cambridge Neuropsychological Test Automated Battery (CANTAB), including set shifting, spatial short-term memory, sustained attention, inhibitory control, spatial working memory, spatial planning, and problem solving (Gau and Shang, 2010).

A recent study evaluated the effects of ATX on self-reported behaviors associated with executive functioning. In this randomized, double-blind, placebo-controlled trial, adults with ADHD received six months of treatment with ATX (25 mg–100 mg daily) or placebo. Those treated with drug demonstrated significant improvement on all aspects of the self-report scale, including items measuring regulation of alertness, modulation of emotion, and working memory (Brown et al., 2011).

3.2.4. Summary—Considerably more research is needed to clarify the effects of ATX on specific domains of cognitive function. The available evidence suggests that the drug may be beneficial for treating cognitive disruptions, but that these effects may be selective. Most of the studies of ATX effects on cognitive function in clinical groups other than ADHD failed to show robust response and evidence from animal studies suggests that the baseline levels of noradrenergic functioning may be critical in determining the beneficial effects of the drug. Certainly the range of cognition related endpoints pertinent to the ADHD diagnosis has not yet been explored in any depth with ATX.

3.3. Alpha 2 agonists: guanfacine and clonidine

3.3.1. Clinical overview—The alpha 2 (α2) agonists clonidine and guanfacine have held a place among standard ADHD treatments for over twenty-five years, primarily useful as adjunctive or alternative agents to stimulant drugs. Providers have tended to consider this class in patients with pre-existing tic disorders, with tics emerging during stimulant therapy, or those who for other reasons are unable to tolerate psychostimulants. Until recently, however, use of α2 agents represented “off-label” therapy in that no drug in this class had received FDA approval for treatment of ADHD. This has changed with the FDA approval of Intuniv® (guanfacine XR) in 2009, followed by the approval of Kapvay® (long-acting clonidine) in 2010, for treatment of ADHD in children and adolescents. Similar to ATX, clinical trials of both guanfacine and clonidine have demonstrated tolerability and efficacy in terms of superiority to placebo, but have not demonstrated superiority to stimulant medications (Bidwell et al., 2010).

3.3.2. Mechanism of action—The α2 agonists mimic norepinephrine actions in the PFC through the stimulation of α2A receptors on PFC neurons (Ramos et al., 2006). Clonidine has high affinity for all three subtypes of α2 receptors (A, B, and C), as well as for imidazole I1 receptors (Ernsberger et al., 1990; Uhlen and Wikberg, 1991), which mediate many of the hypotensive effects of clonidine in the brainstem (Ernsberger et al., 1987). The sedative effects are probably mediated via all three subtypes, including potent actions at presynatic receptions and actions in the thalamus (Wang et al., 2007). Guanfacine acts more preferentially at postsynaptic norepinephrine α2A receptors strengthening PFC network connectivity (Wang et al., 2007).

3.3.3. Evidence across domains of cognition

3.3.3.1. Studies in non-human species: The α2-adrenoceptor agonists, guanfacine and clonidine, have been shown to improve attention and working memory in rats and monkeys (Rama et al., 1996; Ramos et al., 2006; Sagvolden, 2006). In monkeys, guanfacine improved working memory and attentional functions in a dose-dependent manner; facilitatory effects were more prominent in elderly monkeys with presumed noradrenaline deficiency (Arnsten et al., 1988; Franowicz and Arnsten, 1998). Working memory improvement was accompanied by reduced distractibility (Arnsten and Contant, 1992) and enhanced regional cerebral blood flow in the dorsolateral prefrontal cortex (Avery et al., 2000). Blockade of α2A-adrenoceptors in monkey PFC with yohimbine profoundly impaired spatial working memory (Li and Mei, 1994) and eroded delay-related firing of PFC neurons (Li et al., 1999). Other research suggests that the α2A-receptor subtype likely underlies guanfacine's beneficial effects on PFC function (Arnsten et al., 1998), asα2 agonists lose efficacy in mice with a functional knockout of the α2A-adrenoreceptor subtype, but remain effective in α2C-adrenoreceptor knockout mice (Franowicz et al., 2002; Tanila et al., 1999). Further, the cognitive and hypotensive effects of guanfacine were reversed by idazoxan, an α2A-adrenergic antagonist (Franowicz and Arnsten, 2002; Wang et al., 2004).

3.3.3.2. Studies in individuals without ADHD: There is also evidence for a role for the α2-system in the modulation of attentional functions in humans. Jakala and colleagues examined the effects of clonidine and guanfacine during visual memory, spatial working memory, and planning tasks in healthy individuals and demonstrated that guanfacine and clonidine both improved visual memory performance, but did not affect performance when there was a delay. However, only guanfacine improved planning and working memory performance in a dose dependent fashion, and clonidine disrupted performance on these tasks. Further, clonidine disrupted performance in an attentional task with distracters (Jakala et al., 1999a, 1999b, 1999c). The lower α2A- vs. α2C-adrenoceptor selectivity ratio of clonidine and the affinity for α1-adrenoceptors of clonidine may have been responsible for the different action of these drugs on attention, planning, and working memory (Lee et al., 1998).

Other studies in healthy volunteers found no effects of α2 agents on cognition. One study examine the effects of guanfacine on performance and task-related brain activation as measured by fMRI during a task of visuospatial attention with variably cued choice reactions and found no changes in cognitive function (Coull et al., 2001). Similarly, clonidine had no effect on performance in a planning task (Choi et al., 2006) and Muller et al. (2005) found no effects on tests of memory, planning, motor inhibition, and executive attention after guanfacine administration.

3.3.3.3. Studies in individuals with ADHD: Two studies have directly examined the effects of α2 agents on cognitive performance in individuals with ADHD (Kollins et al., 2011; Scahill et al., 2001). Scahill et al (2001) demonstrated that in a placebo-controlled clinical trial, children who were comorbid for DSM-IV ADHD Combined Type and a tic disorder were treated with guanfacine, which not only improved total ADHD symptoms and tic severity, but also improved their performance on measures of sustained attention and response inhibition on a Continuous Performance Task. In another placebo-controlled clnical trial, Kollins et al. (2011) reported that extended release guanfacine was clinically effective and superior to placebo at doses that did not impair cognitive functioning or increase daytime sleepiness.

3.3.4. Summary—In sum, α2 agonists have been shown in some studies to strengthen cognitive functions in animals and humans. However these findings have not been entirely

consistent across human studies and further research is needed, especially in clinical populations, across the range of cognitive deficits implicated in ADHD. This is especially true given the robust findings in nonhuman studies regarding the effects of this class of drugs on executive functioning and related brain areas (Arnsten and Li, 2005). In addition, research comparing the classes of α2 receptors is needed to draw strong conclusions regarding potential differences among the receptors' functions and various agents.

3.4. Non-FDA approved pharmacological interventions—nicotinic agents

3.4.1. Clinical overview—Nicotinic agonists have recently been explored as possible therapeutic agents for treating cognitive deficits in a wide range of patient populations including ADHD (Wilens and Decker, 2007). This focus on nicotinic compounds has been spurred by two factors. First, nicotine, the primary psychoactive agent in tobacco smoke, has been shown to improve various aspects of cognition in both human laboratory and pre-clinical research studies (Levin et al., 2006). Second, individuals with ADHD are at greater risk for smoking (Lambert and Hartsough, 1998; Pomerleau et al., 1995), begin smoking at an earlier age (Milberger et al., 1997) and have greater difficulty quitting smoking (Humfleet et al., 2005). Together, these findings have led to the hypothesis that individuals with ADHD may smoke in order to alleviate requisite symptoms of the disorder and further suggest nicotine and/or nicotinic agonists can be used to improve aspects of cognitive function in these patients (McClernon and Kollins, 2008). Some support for this hypothesis has been provided by studies which have shown positive effects of nicotine on ADHD symptoms (Gehricke et al., 2009; Shytle et al., 2002) and cognitive performance (Levin et al., 1996; Potter and Newhouse, 2004) in non-smokers with ADHD. Whereas there are currently no FDA-approved nicotinic agonists to treat ADHD, laboratory and small-scale clinical trials have been conducted in recent years, and novel nicotinic pharmacotherapies are on the horizon.

3.4.2. Mechanism of action—Nicotinic acetylcholine receptors are a family of ligand-gated ions channels (Changeux, 1990). Nicotinic receptors are found across nearly all brain regions, though their neuroanatomical distribution varies as a function of subtype. Nicotinic α4β2 receptors, for instance, are abundant in mesolimbic systems areas (Nashmi and Lester, 2006) where they mediate reward and reinforcement (Picciotto et al., 1998). Nicotinic receptors modulate the function of other neurotransmitter systems including dopamine, serotonin, GABA and glutamate. Striatal dopamine signaling, for instance, is strongly influenced by nicotinic modulation of GABA and glutamate neurons that in turn modulate dopamine neuron firing; and by the influence of nicotinic receptors on dopamine neurons themselves (Dani and Bertrand, 2007).

Potentially reflecting anatomic and functional variation, different receptor subtypes have been shown to have differential effects on cognition. Whereas research has been conducted on many of the known receptor subtypes, the best characterized are the α4b2 and the α7 subtypes. Experimental α4b2 specific agonists have been shown to enhance memory (Levin and Christopher, 2002) and attention (Grottick and Higgins, 2000) in laboratory animals. Administration of antagonists that block α4b2 receptors in specific brain regions suggest that the influence of α4b2 receptors on memory are likely mediated in hippocampus (Arthur and Levin, 2002) and amygdala (Addy et al., 2003). Nicotinic α7 receptors have also been shown to be involved in various aspects of cognition. Whereas mice bred to lack the α7 receptor exhibit deficient attention and memory (Young et al., 2004); research on the effects of experimental α7 receptor agonists have been mixed (Grottick and Higgins, 2000; Levin et al., 1999). The role of other receptor subtypes including the α6 containing (Drenan et al., 2008), while less studied than the a4b2 and a7, are under increasing investigation.

3.4.3. Effects of nicotine on cognition—Dozens of studies have assessed the effects of nicotine on cognition in healthy, nicotine-naïve samples including studies of memory (McClernon et al., 2003), attention (Froeliger et al., 2009) and inhibitory control (Potter and Newhouse, 2004). In a recent meta-analysis of 48 studies in which nicotine was administered to non-smokers or only minimally deprived smokers (Heishman et al., 2010), nicotine was shown to have positive effects on multiple domains including attention and working memory. Twenty-nine studies specifically assessed non-smokers and among those, positive effects were observed for reaction time on tests of sustained (or alerting) attention and working memory.

Studies of the effects of nicotine on inhibitory control were not included in the meta-analysis, but a handful of studies suggest potential positive effects of nicotine on this domain. Two small studies have observed acute (Levin et al., 1998) and chronic (McClernon et al., 2006) transdermal nicotine administration to result in trends toward decreases in errors of commission on a CPT task. Moreover, nicotine has been shown to reduce CPT commission errors in nonsmokers with schizophrenia (Barr et al., 2007), non-smokers low in attentiveness (Poltavski and Petros, 2006); and decrease stop signal reaction time in adolescents nonsmokers with ADHD (Potter and Newhouse, 2004). Despite these findings, nicotine was not shown to improve response inhibition in adults with ADHD as measured with a CPT task (Levin et al., 2001).

3.4.4. Effects of nicotinic agonists on cognition and ADHD symptoms—A small number of nicotinic agonists have been approved for administration to humans and tested in samples of individuals with ADHD. ABT-418, which preferentially targets the α4b2 receptor has been shown to improve memory in preclinical studies (Levin et al., 2006). Whereas ABT-418 was found to improve ADHD symptoms in a randomized cross-over trial in adults with ADHD (Wilens et al., 1999), its effects on cognitive performance were not assessed. More recently, another agonist targeting the α4b2 receptor, ABT-089, was evaluated in a small sample of adults with ADHD (Wilens et al., 2006). In that study, ABT-089 resulted in dose-dependent improvements in working memory and response inhibition. Whereas additional other nicotinic agonists have been tested in Alzheimer's and other patient populations, no data on their effects in ADHD patients is currently available.

3.5. Non-FDA approved pharmacological interventions—other agents

A wide range of other medications has been evaluated to treat the core symptoms of ADHD, many of which may have cognition-enhancing effects. Several of these compounds will be briefly reviewed here.

Modafinil is a novel stimulant-like compound that is currently approved for the treatment of narcolepsy, and has been widely studied as a potential treatment for ADHD. Its mechanism of action is complex with evidence of effects across a wide range of neurotransmitter systems, including catecholamines, serotonin, glutamate, GABA, and orexin (Minzenberg and Carter, 2008). Modafinil has been shown to significantly improve core symptoms of ADHD in a number of randomized, placebo-controlled trials (Biederman et al., 2005; Greenhill et al., 2006; Swanson et al., 2006). Moreover, the relative efficacy of modafinil has been shown to be comparable to MPH (Amiri et al., 2008). Concern over the emergence of dermatological adverse events led to the FDA's decision, however, in 2006 to deny approval for the ADHD indication. In addition to its efficacy for treating the core symptoms of ADHD, modafinil has been shown to improve a range of cognitive functions in animals, healthy human subjects, and psychiatrically impaired individuals (Finke et al., 2010; Minzenberg and Carter, 2008; Turner et al., 2004a, 2004b). In children, adolescents, and adults with ADHD, modafinil has been shown to improve performance on tasks measuring

attentional control, response inhibition, and several aspects of memory functioning (Rugino and Copley, 2001; Turner et al., 2004a). Interestingly, though not evaluated in individuals with ADHD, the stereo-isomer of modafilnil, R-modafinil did not improve cognitive functioning in a sample of patients with schizophrenia (Kane et al., 2010).

Although considerable controversy continues to circulate around the use of modafinil and other comparable drugs with wake-promoting or cognitive enhancing effects (including psychostimulants like MPH and AMP) (Cakic, 2009; Sahakian and Morein-Zamir, 2010), it is unlikely to be used as an approved product for the treatment of ADHD.

Cholinesterase inhibitors are a class of drugs including donezepil and galantamine widely used to treat cognitive deficits associated with Alzheimer's Disease, dementia, and related conditions (Hansen et al., 2008). These compounds have also been studied for their cognition enhancing effects in healthy individuals as well, though the results are less compelling (Repantis et al., 2010). Two of these cholinesterase inhibitors have been evaluated in small-scale studies of patients with ADHD. A chart review of 5 pediatric patients who were treated with donezepil reported improvement in ADHD symptoms and executive functioning, although all of the patients exhibited comorbid psychopathology and were concurrently treated with a range of other medications (Wilens et al., 2000). A subsequent prospective open label trial evaluated ADHD children and adults who did not respond optimally to stimulant treatment and who did not have other Axis I comorbidity. Donezepil was used adjunctively with stabilized stimulants and results showed no improvements in either ADHD symptomatology or scores on an executive functioning rating scale (Wilens et al., 2005). Two other studies with donepezil reported that the drug improved functioning in children with ADHD or ADHD-like symptoms and pervasive developmental disabilities or tics (Cubo et al., 2008; Doyle et al., 2006). One double-blind, placebo-controlled trial of galantamine was conducted in adults diagnosed with ADHD. In this 12-week study, there was no effect of the drug compared to placebo on any of the relevant outcome measures (Biederman et al., 2006).

Memantine is another compound often used in the treatment of Alzheimer's Disease and related conditions, though its mechanism of action is different from the cholinesterase inhibitors in that it is an NMDA antagonist (McKeage, 2009). At least one study has evaluated the effects of this drug in pediatric patients with ADHD and reported that children treated with 20 mg/d memantine exhibited improvements in ADHD symptoms relative to a group who received 10 mg/d (Findling et al., 2007).

Collectively, the evidence suggests that cognitive enhancers used for treatment of Alzheimer's disease and other related conditions are of limited utility in treating ADHD. The specific effects of these drugs on domains of cognition in ADHD have not been systematically evaluated. Treatment of individuals with ADHD and certain comorbidities (i.e., tics, developmental disabilities) or treatment with NMDA-antagonists may result in comparatively better outcomes.

3.5.1. Antidepressant-like drugs (Bupropion, MAO-inhibitors, tricyclic antidepressants)—A number of drugs widely used in the treatment of depression and related mood problems have been evaluated for both the treatment of ADHD and their effects on cognition-related endpoints (Verbeeck et al., 2009).

Although not superior to stimulants, bupropion does have demonstrated efficacy in the treatment of ADHD (Pliszka, 2007). No studies have directly examined the effects of bupropion on cognition in ADHD patients. However, a few studies have found effects on cognitive measures in other clinical populations. Evins et al. (2005) found that bupropion

improved reaction time variability and set-shifting in patients with schizophrenia. In addition, another study reported some improvement on measures of learning and memory, but not on executive tasks, after bupropion treatment in patients with major depressive disorder (Herrera-Guzman et al., 2008).

Monoamine oxidase inhibitors (MAOIs) are another class of drugs used to treat mood problems that have been evaluated for the treatment of ADHD. Several studies suggest efficacy of MAOIs for the treatment of ADHD, in some cases to a comparable degree as stimulant drugs (Akhondzadeh et al., 2003; Mohammadi et al., 2004; Rubinstein et al., 2006). This class of drugs has also been shown to impact cognition related endpoints in patients with ADHD (Rubinstein et al., 2006), although effects have not been that robust in other patient populations(Birks and Flicker, 2003). It is important to note that the use of MAOIs for the treatment of ADHD, especially in children has generally been limited by the relatively unfavorable safety profile of this class of drugs (Spencer et al., 2004).

Similar to the MAOIs, tricyclic antidepressants have been evaluated for efficacy in ADHD patients and have been shown in some studies to have beneficial effects on cognitive outcomes in other patient populations (Doraiswamy et al., 2003; Prince et al., 2000). However, also like MAOIs, safety issues have precluded widespread use of the TCAs for the treatment of ADHD (Spencer et al., 2004).

While some of the antidepressant drugs may reduce ADHD symptoms and/or improve cognition related endpoints, their use with ADHD is generally not widespread, mainly for safety reasons. Additional research is needed to determine whether these drugs specifically target the kinds of cognitive outcomes known to be most disrupted among those with ADHD.

3.6. Non-pharmacological interventions to improve cognition in ADHD

In addition to the myriad pharmacological compounds that have been used to enhance cognition and subsequently improve ADHD-related impairment, a number of relatively recent studies have assessed the efficacy of non-pharmacological approaches for improving various aspects of cognition (Toplak et al., 2008). Though a wide range of such approaches have been available commercially for a number of years, only a handful of interventions have been rigorously evaluated. We will discuss the evidence for two such approaches: computer-based working memory training and neurofeedback.

3.6.1. Working memory training—One of the first studies in this area examined the effects of several weeks of computer-based working memory training in a small sample of children with ADHD (Klingberg et al., 2002). The training involved repeated performance of working memory tasks, with feedback and rewards based on the accuracy for every trial. This study showed that the intervention improved not only performance on the specific working memory tasks that were part of the training, but also measures of untrained visuospatial working memory and scores on Raven's Progressive Matrices, a putative measure of generalized nonverbal cognitive functioning (Klingberg et al., 2002). A follow-up study included a larger sample and a control condition (Klingberg et al., 2005). The effective training time for the intervention was 30–40 min per day, 5 days a week for 5 weeks (totaling approx. 15 h). The difficulty of the tasks is adjusted during the WM training on a trial-by-trial basis by changing the amount of information to be remembered so that it is close to the capacity of the subject. The comparison condition, used the same tasks, but the WM load was low and participants did not experience increasing difficulty of the task, presumably not “exercising” working memory processes. Subjects in the active intervention condition demonstrated improvements on trained and untrained measures of working memory, and also showed improved response inhibition and reductions in parent-rated

inattentive symptoms of ADHD that were durable at follow-up assessments (Klingberg et al., 2005). This same training protocol was shown to produce increases in brain activation (Olesen et al., 2004) and changes in the density of prefrontal and parietal dopamine D1 receptor binding potential, indicating neural plasticity that arises as a result of the training (McNab et al., 2009).

This approach to training working memory or related processes has shown promise in enhancing cognitive deficits among patients with ADHD with concomitant beneficial effects on the core symptoms of the disorder. Although still nascent, this research area is likely to grow quickly with at least 5 separate active trials ongoing (clinicaltrials.gov; search terms ADHD cognitive training).

3.6.2. Neurofeedback—Although the specific methods and intervention protocols vary considerably, neurofeedback generally refers to a variant of biofeedback wherein subjects are given real time feedback about their neural activity via EEG recordings that are filtered through a computerized video game format (Toplak et al., 2008). Since brain functioning of individuals with ADHD is thought to be characterized by excess slow wave activity relative to non-diagnosed individuals, the goals of neurofeedback in this population focus on increasing fast wave activity by providing positive feedback for the individual consciously altering brain wave patterns (Butnik, 2005).

A number of studies have been published examining the effects of neurofeedback on a range of outcome measures in individuals with ADHD. These studies have, in general, produced large effects on parent and teacher-rated ADHD symptoms (Toplak et al., 2008). With respect to cognitive outcomes, neurofeedback across studies has shown more variable effects. Effect sizes of neurofeedback on continuous performance tests, which tap sustained attention, inhibitory control, and vigilance, range from 0.02 to 0.87. Another study of neurofeedback on verbal working memory reported an effect size of 0.87, while effects on general measures of intellectual functioning have been small, ranging from 0.09 to 0.26. All of the foregoing reported effect sizes from neurofeedback studies were reported in a meta-analysis using between-group effect sizes (Glass's Δ) (Toplak et al., 2008).

Though controversial, the literature on neurofeedback continues to grow and more recent studies have begun to address some of the methodological problems raised in earlier work (Heinrich et al., 2007). Ongoing work continues with several active trials listed in clinicaltrials.gov. Similar to computer based attention or working memory training, neurofeedback should continue to be viewed as an experimental treatment for both core symptoms of ADHD and different domains of cognitive function.

3.7. Summary and conclusions

As evidenced from the foregoing review, a large literature has examined either directly or indirectly the effects of a range of interventions on cognition-related outcomes relevant to ADHD. Several classes of drugs have uniformly shown evidence of acute cognitive enhancement and improvement in the core symptoms of the disorder (i.e., stimulants, alpha-2 adrenergic agonists), and have thus received regulatory approval for clinical use. ATX has shown cognition-enhancing effects primarily in ADHD samples and has also shown symptom improvement. Other classes of agents have shown robust effects on cognition-related endpoints, but have not shown as large an impact on clinically relevant outcomes, or have been shown to have suboptimal tolerability (e.g., nicotinic agents, modafinil). Still other drugs that have shown cognition enhancement in other populations have failed to demonstrate clinical efficacy in individuals with ADHD (e.g., cholinesterase inhibitors).

3.7.1. Relevance of cognition-related endpoints in clinical syndrome of ADHD—Throughout this review, we have generally distinguished between treatment effects on the core symptoms of ADHD and the effects across a range of related, but conceptually and empirically distinct cognitive constructs. Inmost studies the core symptoms are measured by parent, teacher, self, or clinician ratings of a checklist of the DSM-IV ADHD symptoms, whereas measurement approaches for the cognition related endpoints vary widely. This method variance raises the important question of how relevant the cognition related endpoints are in understanding and interpreting the effects of various treatments.

This issue has been addressed previously by a number of authors. In one early review of the literature, Barkley concluded that the ecological validity of laboratory tasks to measure clinically relevant features of inattention, impulsivity, and overactivity was low to moderate (Barkley, 1991). Empirical support for this disconnect between measures of cognition and clinical outcomes has also been reported. In one study, 53 children with ADHD were randomized to receive either MPH, clonidine, or placebo for 7 weeks. Performance on an inhibitory control task was assessed at baseline and following treatment. Results showed that 53% of children in the MPH condition, 47% of children in the clonidine condition, and 11% of children in the placebo condition demonstrated clinically significant improvements, but that there were only marginal effects on inhibitory control. Moreover, performance on the laboratory task was not predictive of clinical response (van der Meere et al., 1999). More recently, Coghill and colleagues evaluated the effects of sustained treatment (12 weeks) with 2 doses of MPH and placebo on neuropsychological and clinical outcomes in 75 boys with ADHD. Chronic MPH improved performance on a recognition memory component of functioning and inhibitory control, but failed to exert beneficial effects on other tasks of executive functioning. Performance across the cognitive domains showed only moderate utility in predicting clinical response (Coghill et al., 2007).

Findings suggesting a lack of isomorphism between cognitive and clinically relevant endpoints are reminiscent of the classic study by Sprague and Sleator demonstrating that the optimal stimulant dose for improving social behavior resulted in decrements in cognitively oriented tasks. These learning tasks showed optimal improvements on stimulant doses that had minimal effects on more overt disruptive behavior (Sprague and Sleator, 1977). Collectively these studies and the broader literature highlight the heterogeneity inherent in the ADHD diagnosis. To the extent that specific cognitive endpoints are strongly associated with the clinical features that define the disorder (e.g., link between inhibitory control and DSM-IV impulsivity symptoms), assessing the effects of interventions on these endpoints may be useful. However, as many studies have shown, the acute effects of a range of interventions on cognitive endpoints that are less strongly correlated with ADHD clinical features may be less meaningful from a clinical perspective.

As noted in the introduction, these discrepancies have led, in part, to an emphasis on the identification of endophenotypes (Castellanos and Tannock, 2002), which mediate the link between neurobiology/neuropsychopharmacology and clinical presentation. By definition these endophenotypes are also predictive of the clinical outcomes and should therefore provide more ecologically valid targets for intervention development. Alternatively, refinement of the clinical phenotype of ADHD may elucidate which cognitive deficits are most strongly associated with different aspects of clinical presentation. Latent class analyses and related approaches have been useful to identify symptom classes that vary with respect to severity (Lubke et al., 2007, 2009). Such approaches may be useful to examine with respect to predicting different patterns of cognitive dysfunction and response to treatment.

3.7.2. Acute versus chronic cognitive enhancement—The vast majority of studies that have examined the effects of putative cognitive enhancers for ADHD have limited the

time course of investigation to acute effects. Several studies described above examined sub-chronic (7–12 weeks) treatment with modest changes in cognition-related endpoints (Coghill et al., 2007; van der Meere et al., 1999). Several studies have examined longer term impact of medication treatment on cognition related outcomes. As note previously the MTA study did not find significant effects of randomized treatment assignment at 3-year follow up on academic achievement (Jensen et al., 2007). By contrast, another study reported that children receiving MPH demonstrated durable improvements in academic achievement and related outcomes across a 2-year period (Hechtman et al., 2004). There is considerable need for more sustained and systematic assessment of how cognition-enhancing interventions impact longer term functioning in those with ADHD. For example, it would be theoretically plausible that interventions such as working memory training or neurofeedback might have substantial chronic advantages since there is an element of learning involved in these interventions.

4. Concluding remarks

The foregoing review highlights a number of potential areas for continued investigation. Certainly, the continued exploration of novel pharmacological agents that may be useful to improve cognition-related deficits in ADHD is warranted. However, as our review has highlighted, it will be important to take a bidirectional, translational approach to identify both the more specific and basic processes that underlie the clinical impairment observed in ADHD, but also the most promising neuropharmacological targets to alter those processes. Such an approach is likely to involve the full range of translational methods, from preclinical work to basic human laboratory work to clinical trials. Considering the number of new agents that have been approved for use in ADHD in the last 8 years alone, it is likely that continued growth in this area will flourish both in terms of understanding the basic pathophysiology of ADHD and treatments to improve the lives of those with the condition.

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