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Review

Central nicotinic cholinergic systems: A role in the cognitive dysfunction in Attention-Deficit/Hyperactivity Disorder?

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Abstract

Theories of the neurobiological basis of Attention-Deficit/Hyperactivity Disorder (ADHD) have largely focused on dysregulation of central dopaminergic function. However, other neurotransmitter systems may be implicated in specific cognitive deficits in ADHD. Interest in the potential involvement of nicotinic cholinergic systems in ADHD has arisen in part from the observation that adolescents and adults with ADHD smoke cigarettes at significantly higher rates than people without this disorder. In addition, several studies report that nicotine alleviates ADHD symptoms, and recent neuro-genetics studies indicate that cholinergic systems may be altered in persons with ADHD. In this review, we describe the evidence for a role of central nicotinic cholinergic systems in cognitive deficits in ADHD. We also propose mechanisms by which alterations in cholinergic function may contribute directly and/or indirectly to these deficits. Finally, we identify specific paradigms and models to guide future investigations into the specific involvement of nicotinic cholinergic systems in ADHD, possibly leading to the development of more effective pharmacotherapies for ADHD.

Keywords: ADHD; Cholinergic; Acetylcholine; Nicotine; Smoking; Substance abuse

Contents

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1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common childhood psychological disorder, affecting approximately 3–5% of children and persisting into adolescence and adulthood for an estimated 60–80% of people who are affected [1]. Research on the neurobiological basis of ADHD has traditionally focused on dysregulation of central dopaminergic function, and psychostimulant treatment has been shown to have positive effects on ADHD symptoms [55,96]. However, ADHD is a complex disorder that is characterized by several heterogeneous symptom clusters. Given this complexity it is unlikely that ADHD is related to a single neurotransmitter abnormality (dopamine) and rather more likely that multiple neurotransmitter systems are involved in this disorder. Indeed, it has recently been proposed [28] that non-catecholaminergic neurotransmitter systems may be involved in the cognitive symptoms of ADHD, but there are few reports that go on to identify or address the specific involvement of other transmitter systems.

Here we present evidence for a specific role of central nicotinic cholinergic systems in the cognitive deficits of ADHD. After first reviewing current theories regarding the neurochemistry of ADHD, we describe the precipitous use of use nicotine by persons with ADHD and the effects of nicotine on the behavioral manifestations of the disorder. We then present evidence to support the hypothesis that cholinergic alterations may contribute to several specific cognitive deficits in ADHD including impairments in behavioral inhibition, delay aversion, sustained attention, and working memory. These cognitive deficits are currently thought to give rise to the overt behavioral symptoms (i.e., hyperactivity, inattentiveness, impulsivity) of ADHD as measured using behavior checklists and observations (Barkley [6,7], Sonuga-Barke et al. [99]). We thus further the notion that persons with ADHD may use nicotine to self-medicate and alleviate cognitive deficits that underlie ADHD symptoms by describing how nicotine may exert its beneficial effects. Finally we describe the neural mechanisms that may mediate the effects of nicotine on cognitive impairment in ADHD, as well as therapeutic implications.

2. Neurochemistry of ADHD

Research on the neurochemistry of ADHD indicates that there is not a single neurotransmitter abnormality that is responsible for the symptoms of ADHD [123]. Dopamine and norepinephrine have been the most well studied neurotransmitters, largely due to the positive therapeutic effects of psychostimulants on ADHD symptoms. It has been suggested that the balance between these two systems may be altered and result in the symptoms of ADHD [97]. Recent neuro-imaging studies have revealed anatomical changes in dopamine-rich brain regions such as the globus pallidus and frontal cortex in children with ADHD [19]. Subjects with ADHD have also been shown to have reduced frontal and striatal activity during relevant cognitive tasks [25,27,43], which may be related to reduced dopaminergic tone. Other lines of evidence indicate that reduced noradrenergic activity, altered dopamine re-uptake, and changes in the dopamine D4 receptor are often observed in persons with ADHD [22,44].

Current treatments for ADHD consist mainly of psychostimulants (e.g. methylphenidate), which are thought to exert their effects by increasing both dopaminergic and noradrenergic neurotransmission [63]. Stimulant medications have been well demonstrated to significantly reduce ADHD symptoms measured by both parent and teacher ratings. These effects include reductions on ratings of activity levels, hyperactivity/impulsivity and inattention ([101–103], MTA research group). In addition, psychostimulant treatment has been shown to improve "non-ADHD" symptoms such as teacher reported social skills [68], and aggressive behavior in the school setting [103] contributing to improvements in classroom performance [68,101,102].

The exact mechanisms by which psychostimulants produce improvements in ADHD remain unclear. It is also not entirely certain which dopaminergic system(s) are involved or how they regulate behavior. Moreover, psychostimulants have greater effects on overt behavioral features of the disorder as measured through observer-rated behavior checklists than on cognitive domains measured in the laboratory [101]. The reduction of motor activity associated with administration of psychostimulants also follows a different dose–response curve than the effects on cognition (i.e., sustained attention) [76,97]. Furthermore, studies in normal volunteers indicate that psychostimulants improve performance on a broad array of tasks and that these improvements are not specific to individuals with ADHD [84].

These findings have prompted the proposition that other, non-catecholaminergic, neurotransmitter systems may be involved in the cognitive symptoms of ADHD [27]. A few studies have begun to address specific nicotinic cholinergic abnormalities in ADHD. In addition, converging evidence regarding the propensity for persons with ADHD to use and abuse nicotine-containing products, along with the evidence that nicotine alleviates symptoms and specific cognitive deficits in ADHD, suggests that central nicotinic cholinergic systems may have an important role in the cognitive impairments observed in ADHD.

3. Nicotine and ADHD

3.1. Cigarette smoking and ADHD

A major impetus for improving the understanding of the basis of ADHD involves the precipitous use and abuse of nicotine by

persons with ADHD. Adults and adolescents who are diagnosed with ADHD smoke at significantly higher rates than comparable people in a community sample [75]. In addition, adult males with ADHD also have lower quit ratios (percentage of ever-smokers who are ex-smokers) than the general population (23% versus 51.6%). Pomerleau et al. [75] identified a relationship between current smoking status and retrospective reports of ADHD symptoms, with current smokers recalling a greater number and greater severity of ADHD symptoms in childhood. A prospective study of tobacco smoking [45] found that by age 17, 46% of adolescents with ADHD were smoking cigarettes daily compared with 24% of age-mate controls. This finding continued into adulthood where 35% of adult subjects with ADHD were smokers as compared to 16% of age-mate controls. Likewise, a recent longitudinal study of predictors of adolescent smoking found a diagnosis of ADHD to be associated with earlier first use of cigarettes, earlier progression to daily smoking, and earlier use of illicit drugs [56].

ADHD has high rates of comorbidity with Conduct Disorder (CD), Oppositional Defiant Disorder, anxiety disorders, and depression [2,3,12,13,104], making it difficult to discern the true relationship between ADHD and substance abuse. However, Disney et al. [24] reported that while ADHD itself has little effect on most substance use outcomes independent of the effects of CD, nicotine dependence is an exception. Thus, ADHD may have a direction relationship with nicotine dependence. This notion is supported by Milberger et al. [66] who found a prospective relationship between ADHD and cigarette smoking in boys after controlling for the effects of CD. In addition, Molina and Pelham [67] and Burke et al. [17] both found that child inattention symptoms prospectively predicted substance use outcomes when CD was controlled for. Together, these findings indicate that persons with ADHD may be particularly susceptible to nicotine abuse and support the notion that nicotine may be used to alleviate specific symptoms of ADHD [51,116].

3.2. Effects of nicotine on overt behavioral symptoms of ADHD

Recent investigations of nicotinic agents in ADHD have shown promising symptomatic improvement in both adolescents and adults with ADHD [53,77,78,95,116,118]. Levin et al. [53] examined the acute effects of transdermal nicotine in adults with ADHD (both smokers and non-smokers) and found significant improvements in self-rated vigor, concentration, and observer-rated illness severity (CGI) in both subject groups. In addition, there were improvements on speed of responding for both the smokers and non-smokers and a reduction in variability of reaction time for the smokers [53]. In a second study [49], the effects of chronic (4 weeks) nicotine administration were compared to treatment with methylphenidate, placebo, and a combination of nicotine and methylphenidate in adults with ADHD. Nicotine significantly reduced clinician ratings of severity of symptoms and decreased self-reported symptoms of depression as well as variability of reaction times on a continuous performance task.

Other studies have examined a novel cholinergic channel activator (nicotinic agonist) ABT-418 in adults with ADHD using a cross-over design with each subject receiving 2 double-blind 3-week treatment periods with placebo and ABT-418 [116]. Significant improvements in subjective ratings of attentiveness and observer-rated illness severity on a clinical global impressions scale were reported following treatment with ABT-418. A newer, more selective agonist acting at the $\alpha 4\beta 2$ nicotinic receptor subtype has also recently been tested in adults with ADHD [118]. ABT-089 was administered to adults for 2 weeks in a multidose randomized, double-blind, placebo-controlled trial and was superior to placebo based on improvements in symptom scores, ADHD index hyperactive/impulsive ratings, and clinical global impression. Studies such as these provide evidence that stimulation of nicotinic cholinergic systems can alleviate some of the overt behavioral symptoms of ADHD as measured through self-report and observer ratings. However, they do not specifically address the cognitive domains through which nicotine may affect persons with ADHD.

4. Involvement of cholinergic systems in the cognitive impairments in ADHD

There are several means by which stimulation of central cholinergic systems may produce beneficial effects on the cognitive deficits associated with ADHD. For example, it is now widely accepted that processes such as sustained attention and working memory are regulated by central cholinergic systems [87,88]. Indeed, ADHD has historically been understood in terms of the overt clinical symptoms of inattention and hyperactivity as defined by the DSM and measured on parent and teacher-completed rating scales of behavior. More recently, many ADHD theorists have highlighted the need for improved and testable theoretical frameworks for elucidating the biological abnormalities associated with this disorder [6,7,72,81]. This has lead to an increased focus on the cognitive deficits in ADHD using methodology and theoretical approaches from cognitive psychology.

It is now believed that the attention problems in ADHD are not manifest in information processing or perception per se [90,110]; instead, the current literature on the neuro-cognitive profile of ADHD emphasizes impairments in laboratory tasks of behavioral inhibition, delay aversion, sustained attention, and executive function [73,93]. In particular, laboratory measures of behavioral inhibition (e.g., Stop Signal Task) and delay aversion (e.g., the 2-Choice Task) have good discriminant validity separately and excellent discriminant validity together in distinguishing persons with ADHD from normal control subjects [98,100]. The involvement of cholinergic systems in behavioral inhibition and delay aversion are quite understudied, and only recently have the effects of nicotinic cholinergic manipulations been examined in these domains.

4.1. Behavioral inhibition

Deficits in behavioral inhibition are among the most well documented cognitive deficits in ADHD. A recent meta-analysis

found that the strongest and most consistent group differences between ADHD and control subjects were on the Stop Signal Task [119]. The Stop Signal Task is a measure of behavioral inhibition that is not influenced by reward seeking [56] and involves two concurrent tasks for subjects, a "go task" and a "stop task," from which a stop signal reaction time (SSRT) can be calculated. The SSRT provides an estimate of the speed of inhibiting a response, thus reflecting activation of inhibitory systems. Neuroimaging studies reveal that subjects with ADHD have reduced frontal and striatal activation during performance of inhibition tasks [25,27,43] and several studies provide evidence that SSRT is improved by acute administration of psychostimulants [5,15]. However, psychostimulants also have a non-specific effect on reaction times (faster) in all phases of the task [11,104,105]. Thus, it is difficult to interpret the effects of psychostimulants on inhibitory processes when more global processes such as reaction time are enhanced.

Our laboratory has recently examined the effects of acute nicotine administration on behavioral inhibition in both non-smoking adolescents and young adults with ADHD [77,78]. In one study, adolescents were acutely administered either nicotine or methylphenidate (subjects' usual morning dose). Nicotine (as well as methylphenidate) improved behavioral inhibition as reflected in significantly faster SSRTs (Fig. 1). Data from a second study extended the finding of a positive effect of nicotine on behavioral inhibition to young adults with ADHD (Fig. 1). Importantly, the effects of nicotine in the Stop Signal Task were not due to global improvements in performance as there were no significant differences found on go-reaction time or accuracy (which was above 90% for all doses on all blocks) in either study (Fig. 2).

An additional study in humans examined the effect of nicotine on inhibition using the Stroop Task, which measures cognitive interference control. Subjects must inhibit a faster cognitive process (word reading) to respond with a slower cognitive process (color naming). The primary outcome variable on the

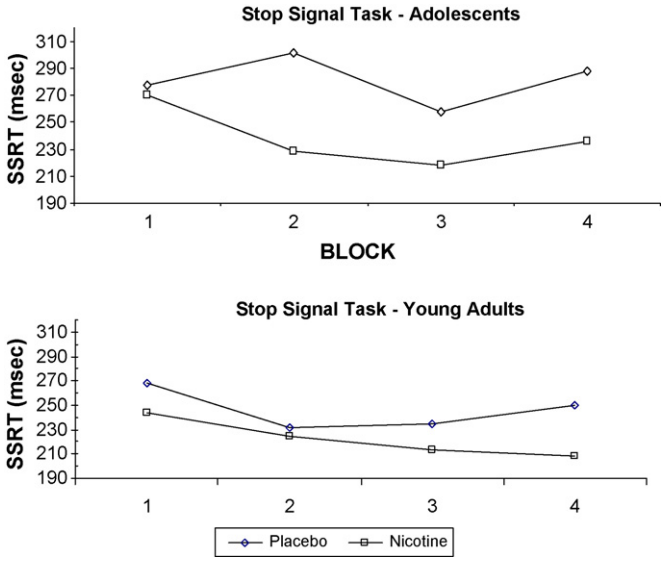

Fig. 1. Stop signal reaction time was improved by nicotine treatment in both adolescents (top panel) and young adults (lower panel) with ADHD.

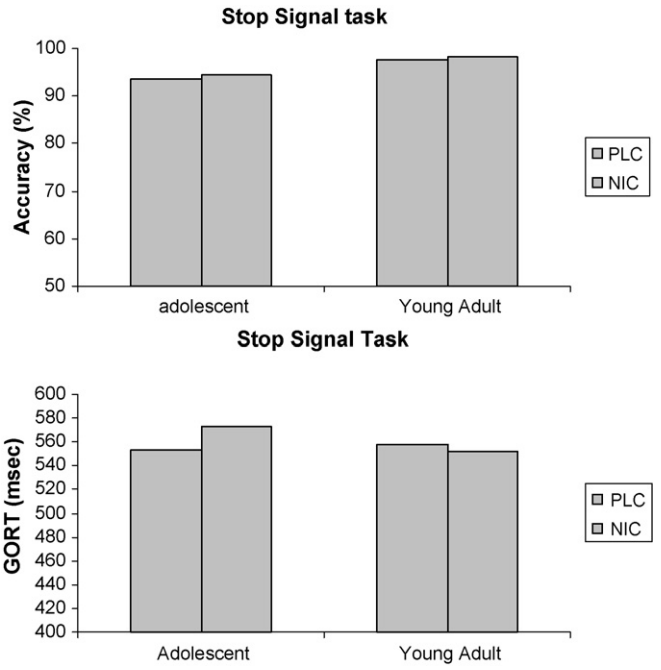

Fig. 2. The effect of nicotine on "go" reaction time (top panel) and accuracy (lower panel) on the Stop Signal Task in adolescents and young adults with ADHD. There were no statistically significant effects of nicotine on either of these parameters.

Stroop Task is the Stroop Effect, a measurement of the cost of inhibiting the automatic process (word reading) and responding with a slower process (color naming). Studies have found that children and adolescents with ADHD have a larger Stroop Effect compared to normal controls [57,59,74]. Nicotine, but not methylphenidate, produced an improvement on the Stroop Task in adolescents with ADHD, reflecting improvement in inhibitory function (Fig. 3).

We have recently examined the effects of nicotine on conditioned inhibition in rats using a serial feature negative discrimination task [60]. In this paradigm, a stimulus Y is followed by food reward on some trials, but on other trials Y is preceded by another stimulus, X. On those trials food is not delivered after presentation of Y. Although there are limitations in directly comparing this task to the Stop Signal Task in humans, it is noteworthy that inhibition was enhanced in rats treated with nicotine, as evidenced by a greater discrimination between the two trial types. Notably, nicotine decreased responding on the

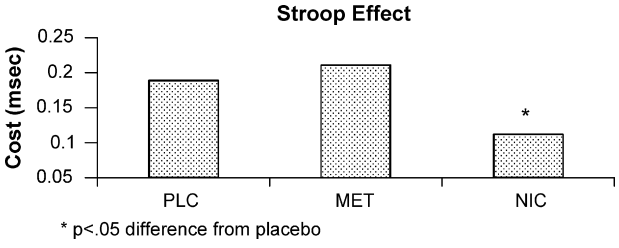

Fig. 3. Nicotine enhanced the performance of adolescents with ADHD in the Stroop Task.

non-reinforced trials but did not affect responding on reinforced trials, as observed with humans in the Stop Signal Task.

4.2. Delay aversion

In addition to behavioral inhibition, another cognitive process that is believed to contribute to overt behavioral symptoms in ADHD is delay aversion. The delay aversion hypothesis characterizes impulsive behavior as the expression of a motivational state in which the person makes a rational choice to avoid delay [99]. This hypothesis has been experimentally tested using the Choice Delay Task in which the subject repeatedly chooses between a smaller-sooner and a larger-later reward. The Choice Delay Task is administered with a fixed number of trials so that smaller-sooner choices are associated with a shorter testing session but less overall reward. Children with ADHD exhibit significantly fewer larger-later reward choices than non-ADHD children [98,99].

We have recently conducted a small scale study examining the effects of acute nicotine administration on delay aversion in young adults with ADHD. Nicotine was administered transdermally (7 mg patch) for 45 min and delay aversion was measured with the Choice Delay Task. There was evidence of an increase in the number of delayed choices made during the nicotine condition (Fig. 4), indicative in a change in the ability of persons with ADHD to refrain from responding and choose to wait for larger rewards ($p < 0.08$).

4.3. Sustained attention

Deficits in sustained attention are among the strongest finding in studies of the cognitive deficits in ADHD [119], although they may be secondary to deficits in inhibition [72]. Regardless, it is possible that persons with ADHD use nicotine to improve sustained attention. Nicotine has well described effects on improving sustained attention in humans as assessed in the Continuous Performance Task. These include positive findings in normal young adults as well as non-abstinent smokers [54]. Studies of the effects of nicotine on persons with ADHD have found that nicotine improves accuracy (d') on this task [95]. Other studies have revealed nicotine-induced reductions in errors of omission and reductions in the variability of response times [53] demonstrating a beneficial effect of nicotine on sustained attention in patients with ADHD.

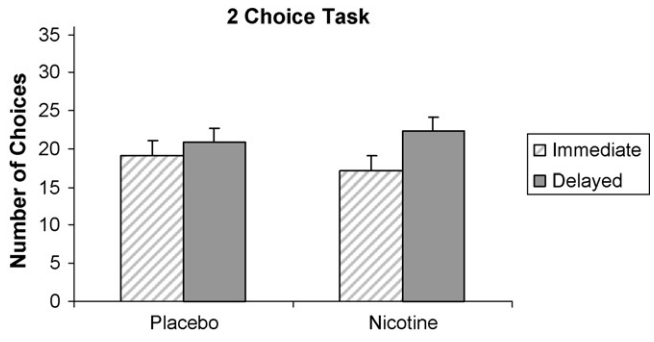

Fig. 4. The effect of nicotine on delay aversion in young adults with ADHD ($n = 9$). There was a trend ($p < 0.08$) for increased tolerance for delay (more delayed choices) following nicotine administration.

In laboratory animals, sustained attention has been examined using the 5-choice serial reaction-time (5-CSR) task. Nicotine administration improves performance on this task generally only when the baseline performance is deficient, i.e., in studies using brain lesioned rats or rats that have existing deficits on this task [37,38,69]. In addition, recent studies in mice using the 5-choice serial reaction time task found that nicotine improved sustained attention and that α7 knockout mice had higher errors of omission on a modified version of the task [121,122]. These data are consistent with the notion that nicotinic acetylcholine receptors play a significant role in sustained attention and suggest an additional mechanism by which persons with ADHD may use nicotine to alleviate cognitive dysfunction.

4.4. Working memory

Cholinergic systems are also thought to play a key role in working memory [35,71], another aspect of cognitive dysfunction associated with ADHD. Nicotine has been shown to enhance working memory in deprived healthy smokers [31] and in various studies with laboratory animals. For example, both α4β2 and α7 nicotinic agonists improve working memory and nicotinic antagonists disrupt working memory [49]. Hippocampal infusion of the centrally-acting nicotinic antagonists produces spatial working memory deficits in the radial arm maze [29]. In contrast, nicotine does not appear to have an effect on reference memory [50,51,54].

To our knowledge, there has yet to be a comprehensive investigation of the effects of nicotine on working memory in persons with ADHD. Nonetheless, it is noteworthy that the working memory deficit in ADHD is thought by some researchers to reflect an inability to suppress irrelevant information [23]. Studies by Buccafusco and others suggest that nicotinic receptor stimulation may improve working memory in rats and non-human primates by reducing distractibility [79,80,107]. For example, nicotine as well as the nicotinic agonists ABT-418 and ABT-089 improved performance in a delayed-recall task by increasing accuracy particularly when a distracter was present [79]. Thus, nicotinic stimulation may improve working memory by enhancing the ability to inhibit irrelevant (distracting) information in ADHD.

5. Neural mechanisms mediating the effects of nicotine on cognitive impairment in ADHD

There are several neural mechanisms by which stimulation of central cholinergic systems may affect cognition in persons with ADHD. Administration of nicotine may produce a “direct” effect by enhancing cholinergic-mediated cognitive functions per se. An alternate, “indirect” mechanism by which cholinergic manipulations may influence cognitive performance in persons with ADHD is through cholinergic modulation of dopaminergic systems and dopamine-mediated functions.

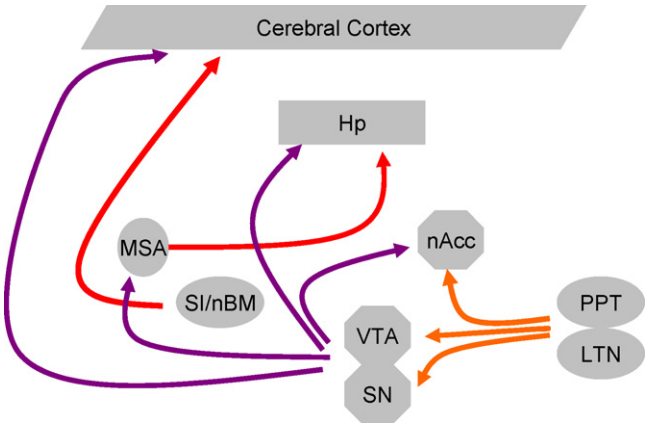

Fig. 5. Major cholinergic pathways in the CNS and sites of potential interaction between cholinergic and dopaminergic systems. Magnocellular neurons in the MSA and SI/nBM provide the major cholinergic innervation of the hippocampus and neocortex, respectively (red arrows). Neurons located in the PPT and LTN provide cholinergic input to dopaminergic cell groups in the SN, VTA, and nAcc (orange arrows). Dopaminergic neurons in the SN and VTA project to areas including the hippocampus, MSA, cerebral cortex, and nAcc (purple arrows). *Abbreviations*: Hp, hippocampus; MSA, medial septal area; SI/nBM, substantia innominata/nucleus basalis magnocellularis; PPT, pedunclopontine tegmental nucleus; LTN, laterodorsal tegmental nucleus; VTA, ventral tegmental area; nAcc, nucleus accumbens; SN, substantia nigra.

5.1. Central cholinergic systems

The beneficial effects of nicotine on cognition in ADHD could arise from direct effects on cognitive functions known to be mediated by central cholinergic systems such as the basal forebrain cholinergic system (BFCS). The BFCS is composed of a continuum of several different nuclei including the medial septum (MS), the vertical and horizontal limbs of the nucleus of the diagonal band of Broca (VDB/HDB), globus pallidus (GP), ventral pallidum (VP), magnocellular preoptic area (MgPO), and substantia innominata (SI)/nucleus basalis magnocellularis (nBM; referred to in primates as the nucleus basalis of Meynert). Magnocellular neurons located in these nuclei provide the major cholinergic innervation of the cortex and hippocampus [114] as shown in Fig. 5. The BFCS has often been divided into two main projection pathways, a medial and a lateral pathway [46,58,85,86]. The vast majority of neurons that constitute the medial pathway are located more rostrally (MS, VDB), and primarily innervate the hippocampus, and also the cingulate and retrosplenial cortex. In contrast, most neurons comprising the lateral pathway are located in the caudal extent of the basal forebrain (SI/nBM, GP, VP), and provide widespread innervation of the neocortical mantle (see Fig. 5).

These components of the BFCS are critically involved in various aspects of attentional function, including sustained attention, selective attention, and the ability to increase and decrease attention to stimuli [8,9,16,18,20,39,62,88,89]. Indeed, it has been suggested that dysregulation of cholinergic systems may contribute to attentional deficits in some forms of ADHD [10]. The cholinergic system supports the detection of external signals (bottom-up information processing) as well as supporting processing of task relevant and knowledge based detection processes (top-down information processing; [89]). Recruitment of the system appears to increase with increasing cognitive demands and may reflect effortful processing. Impairments in cholinergic system functioning are likely to result in impairments on tasks the have high attentional demands such as tasks that are difficult, require task or context switching, or require searching for targets [26].

5.2. Cholinergic–dopaminergic interactions

Stimulation of cholinergic receptors located on dopaminergic neurons results in increased activation of central dopaminergic systems and may lead to enhancement of dopaminergic-mediated functions [21,83,120]. There are several major dopaminergic systems in the brain that have been implicated in the pathophysiology of ADHD. These systems originate in the substantia nigra (SN) or ventral tegmental area (VTA; [106]). The mesostriatal dopaminergic system originates in the SN and projects primarily to the neostriatum, specifically the caudate and putamen. The mesolimbic system originates in the VTA, providing dopaminergic innervation of the limbic system (e.g., amygdala, nucleus accumbens, and hippocampus) as well as frontal cortical areas. In turn, the VTA receives feedback connections from frontal cortex and nucleus accumbens, and serves to regulate reward and certain motivational processes [110]. Indeed, behavioral inhibition is thought to be associated with the mesocortical branch of the dopamine system projecting into the pre-frontal cortex and that delay aversion is related to motivational processes involving the mesolimbic dopamine system [92].

There are a variety of mechanisms and anatomical loci where dopaminergic and cholinergic systems may directly interact, possibly mediating the positive effects of nicotine on individuals with ADHD (Fig. 5). Comprehensive anatomical studies have identified approximately eight different cholinergic projection systems [65,84,113]. At least three of these cholinergic systems, originating in various brainstem nuclei (e.g., pedunculopontine (PPT) and laterodorsal tegmental (LTN) nuclei), provide direct input to dopaminergic cell groups in the SN and VTA [113]. Recent studies confirm a direct synaptic connection between cholinergic terminals and dopaminergic cell bodies in the VTA [34]. Indeed, nicotine has been shown to increase the release of dopamine in both striatal and mesolimbic dopaminergic pathways [21,83,120]; Levin et al. [52] found that activation of nicotinic receptors and dopamine receptors is additive, and possibly synergistic. Conversely, the nicotinic blocker mecamylamine decreases dopamine activity in mesolimbic and nigrostriatal systems [52]. Furthermore, cholinergic neurons in the LDT have been found to modulate dopaminergic activity in the nucleus accumbens [30], and cholinergic stimulation of the VTA activates mesolimbic dopamine systems [36]. Nicotinic acetylcholine receptor activation has recently been shown to increase the expression of dopaminergic biosynthetic enzymes [94].

In addition, there is evidence of a dynamic functional interaction between dopaminergic and cholinergic systems in ADHD. In a study showing that ADHD was associated with elevations in

the dopamine transporter (DAT), further analyses revealed that a subset of subjects smoked cigarettes and that this group actually exhibited significantly lower levels of DAT [43]. These data support the notion that nicotine use may act directly on DAT [43], providing a mechanisms by which nicotine may improve functions regulated by dopaminergic systems. Other data indicate that interactions between brainstem cholinergic systems and dopaminergic pathways may have a significant role in reward mechanisms. Indeed, several recent behavioral studies provide strong support for that notion [40,64].

5.3. Cortical–subcortical interactions

Recent studies have suggested that there are a series of control loops or pathways involving cortical and subcortical structures that alter the activity of the output nuclei of the basal ganglia. One particularly important pathway is the so-called "hyperdirect pathway" which involves the subthalamic nucleus, apparently under glutamatergic and GABA-ergic control, in modulating the output of basal ganglia output structures such as the globus pallidus [70]. Recently, functional imaging studies have demonstrated the importance of the subthalamic nucleus and the hyperdirect pathway and suggest that they play a critical role in the "stop" process in the Stop Signal Task [4]. Since the subthalamic nucleus contains α7-nicotinic cholinergic receptors and perhaps other nicotinic receptors [82,91], nicotine may improve performance on the Stop Signal Task throughput through the subthalamic nucleus, improving its ability to modulate or interrupt "go" signals when a stop signal is generated cortically. Conversely, individuals with ADHD may either have deficits in this pathway or within the cortical impulse generators themselves that produce impairments in this task and in other types of impairments of control or impulsive responding.

6. Therapeutic implications

A more thorough understanding of cholinergic contributions to the cognitive deficits in ADHD may lead to new and improved therapies for this disorder. Indeed, cognitive deficits are currently thought to give rise to the overt behavioral symptoms of ADHD (Barkley [6,7], Sonuga-Barke et al. [99]) thus alleviating cognitive dysfunction may reduce ADHD behavioral symptoms.

Although psychostimulants are effective for many patients with ADHD, their use has several limitations. For example, only 70% of patients will achieve a therapeutic response to a psychostimulant [14], and the effects of long term of stimulant treatment during child development are only now being explored with some results suggestive of long-lasting negative effects [112]. One recent study indicates that stimulants increase smoking behavior by increasing the relative reinforcing effects of cigarette smoking [108]. This suggests that stimulant medication, while exhibiting clinical efficacy may actually increase the risk of these individuals becoming regular smokers over and above the risks associated with the disorder itself.

The prospect of developing specific cholinergic therapeutic approaches in ADHD has been a subject of increasing interest over the last several years. With the advent of well tolerated, orally available cholinergic agents, the potential for utilizing cholinergic treatment as either a primary or secondary approach to treating ADHD has become a more realistic possibility. Currently available agents include non-specific oral anti-cholinesterases, including donepezil, galantamine, and rivastigmine. Both donepezil and galantamine have both been reported to be helpful as an adjunctive treatment in childhood ADHD [47,117] with positive clinical benefits reported. Reportedly, galantamine significantly improved both clinical ratings and measures of executive function while donepezil produced smaller, non-significant improvements. It is notable that a major difference between these two agents is that galantamine, in addition to its anticholinesterase effects, which are relatively weak, also has positive allosteric effects at α4β2 nicotinic receptors.

Despite these positive preliminary findings, there are significant obstacles to the widespread or long-term use of anticholinesterase medication in ADHD, particularly in childhood. The effect of long-term administration of centrally and peripherally active anti-cholinesterase agents to children, adolescents, and young adults is unknown. For example, the ovary is known to contain muscarinic receptors which may have a variety of regulatory roles on ovarian function [33,61], and concerns could be raised about whether alterations to ovarian function could be produced. Furthermore, oral cholinesterase inhibitors have a relatively narrow therapeutic index even in adults and therefore the tolerability of these agents, particularly in children, is open to some question.

Potentially more practical may be the development of novel nicotinic agonists for ADHD either as an adjunctive treatment or a primary treatment. While nicotine itself has a very narrow therapeutic index, novel nicotinic agonists have been developed that appear more likely to be therapeutically acceptable to children and adolescents (e.g., ABT-089). ABT-089 was superior to placebo based on improvements in symptom scores, ADHD index hyperactive/impulsive ratings, and clinical global impression. While ABT-089 and similar compounds target the α4β2 nicotinic receptor, there is also interest in drug development targeting the α7 nicotinic receptor subtype. Abnormalities in the expression of this receptor have been identified as being important in attentional impairments in schizophrenia [32,48].

If nicotinic agents alleviate cognitive impairment in ADHD and produce relevant improvements in the overt symptoms of ADHD, then the clinical role of such agents will need to be determined. It is unclear whether these agents will have the magnitude of effects necessary to adequately treat the clinical symptomatology of ADHD. Whether they are used adjunctively or as a primary therapy, nicotinic stimulation may have the side benefit of lowering the risk of initiation of cigarette smoking by adolescents and young adults with ADHD. This alone may be a strong argument to consider their use, especially as there is evidence that stimulant use may actually increase the reinforcing aspects of cigarette smoking [108,115].

7. Conclusions

The literature described in this review provides important evidence for the potential involvement of central nicotinic cholin-

ergic systems in cognitive dysfunction in ADHD. Persons with ADHD use and abuse nicotine products at a much higher rate than the general public, suggesting that persons may self-medicate with nicotine. Moreover, clinical trials of drugs that stimulate nicotinic receptors have demonstrated clinical benefits in ADHD [51,116,118]. Additional studies indicate that nicotine treatment has specific effects on the cognitive domains that are currently proposed to be central to the disorder, including behavioral inhibition, delay aversion, sustained attention, and working memory [77,78]. In addition, recent neuro-genetics studies provide evidence that cholinergic function may be altered in persons with ADHD via alterations in specific nicotinic cholinergic receptor subtypes [41,42,109].

Nevertheless, the role of cholinergic systems in the cognitive deficits associated ADHD is greatly underappreciated as well as understudied. Despite several advances, it still remains unclear whether cholinergic dysfunction is part of the etiology of ADHD. It is also unclear whether nicotine enhances cholinergic-mediated cognitive functions and/or attenuates symptoms indirectly by stimulating other dysfunctional neurotransmitter systems (e.g., dopamine). Likewise, it is unknown if the effects of nicotine on cognition in ADHD are mediated by cholinergic systems per se, or cholinergic modulation of dopaminergic function. Future studies in laboratory animals could be carried out using combined neurochemical lesion and pharmacological approaches as well as receptor knockout models to address some of these questions. Complementary studies in humans would be useful to examine the effects of subtype-specific cholinergic receptor antagonists on the core cognitive functions currently thought to underlie ADHD, such as behavioral inhibition and delay aversion. Together, these avenues of research may lead to new therapies for ADHD, as well as a better understanding of the etiology of the disorder.

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References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. U.S. Government Printing Office; 1994.
[2] Angold A, Costello EJ. Developmental epidemiology. Epidemiol Rev 1995;17:74–82.
[3] Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry Allied Disciplines 1999;40(1):57–87.
[4] Aron AR, Poldrack RA. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1285–92.
[5] Aron AR, Dowson JH, Sahakian BJ, Robbins TW. Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2003;54:1465–8.
[6] Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65–94.
[7] Barkley RA. Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatrics 1997;18:271–9.
[8] Baxter MG, Holland PC, Gallagher M. Disruption of decrements in conditioned stimulus processing by selective removal of hippocampal cholinergic input. J Neurosci 1997;17:5230–6.
[9] Baxter MG, Bucci DJ, Holland PC, Gallagher M. Impairments in conditioned stimulus processing and conditioned responding after combined selective removal of hippocampal and neocortical cholinergic input. Behav Neurosci 1999;13:486–95.
[10] Beane M, Marrocco RT. Norepinephrine and acetylcholine mediation of the components of reflexive attention: implications for attention deficit disorders. Prog Neurobiol 2004;74:167–81.
[11] Bedard AC, Ickowicz A, Logan GD, Hogg-Johnson S, Schachar R, Tannock R. Selective inhibition in children with attention-deficit hyperactivity disorder off and on stimulant medication. J Abnorm Child Psychol 2003;31:315–27.
[12] Biederman J, Farone SV, Keenan K, Steingard R, Tsuand MT. Familial association between attention deficit disorder (ADD) and anxiety disorder. Am J Psychiatry 1991;8:633–42.
[13] Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993;150:1792–8.
[14] Biederman J, Spencer T, Wilens T. Evidence-based pharmacotherapy for attention-deficit hyperactivity disorder. Int J Neuropsychopharmacol 2004;7:77–97.
[15] Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK. Does methylphenidate improve inhibition and other cognitive abilities in adults with childhood-onset ADHD? J Clin Exp Neuropsychol 2005;27:278–98.
[16] Bucci DJ, Holland PC, Gallagher M. Removal of cholinergic input to rat posterior parietal cortex disrupts incremental processing of conditioned stimuli. J Neurosci 1998;18:8038–46.
[17] Burke JD, Loeber R, Lahey BB. Which aspects of ADHD are associated with tobacco use in early adolescence? J Child Psychol Psychiatry Allied Disciplines 2001;42:493–502.
[18] Butt AE, Bowman TD. Transverse patterning reveals a dissociation of simple and configural association learning abilities in rats with 192 IgG-saporin lesions of the nucleus basalis magnocellularis. Neurobiol Learn Memory 2002;77:211–33.
[19] Castellanos FX. Neuroimaging studies of ADHD. In: Solanto MV, Arnsten AF, Castellanos FX, editors. Stimulant drugs and ADHD: basic and clinical neuroscience. New York: Oxford University Press; 2001. p. 243–58.
[20] Chiba AA, Bucci DJ, Holland PC, Gallagher M. Basal forebrain cholinergic lesions disrupt increments but not decrements in conditioned stimulus processing. J Neurosci 1995;15:7315–22.
[21] Clarke PBS, Pert A. Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. Brain Res 1985;348:355–8.
[22] Cook EH, Stein MA, Krasowski MD, Cox NJ, Olkon DM, Kieffer JE, et al. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet 1995;56:993–8.
[23] Cornoldi C, Marzocchi GM, Belotti M, Caroli MG, Meo T, Braga C. Working memory interference control deficit in children referred by teachers for ADHD symptoms. Child Neuropsychol 2001;7:230–40.
[24] Disney ER, Elkins IJ, McGue M, Iacono WG. Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. Am J Psychiatry 1999;156(10):1515–21.
[25] Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 1999;354:2132–3.
[26] Dumas JA, Saykin AJ, et al. Muscarinic and nicotinic blockade alters working memory performance and brain activation patterns in older women. In: 35th Annual Meeting of the Society for Neuroscience. 2005.
[27] Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, et al. Differential patterns of striatal activation in young children with and without ADHD. Biol Psychiatry 2003;53:817–8.
[28] Durston S. A review of the biological bases of ADHD: what have we learned from imaging studies? Mental Retard Dev Disabilities Res Rev 2003;9:184–95.

[29] Felix R, Levin ED. Nicotinic antagonist administration into the ventral hippocampus and spatial working memory in rats. Neuroscience 1997;81:1009–17.
[30] Forster GL, Blaha CD. Laterodorsal tegmental stimulation elicits dopamine efflux in the rat nucleus accumbens by activation of acetylcholine and glutamate receptors in the ventral tegmental area. Eur J Neurosci 2000;12:3596–604.
[31] Foulds J, Stapleton J, Swettenham J, Bell N, McSorley K, Russell MA. Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. Psychopharmacology 1996;127:31–8.
[32] Freedman R, Coon H, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci 1997;94:587–92.
[33] Fritz SK, Fohr KJ, Boddien S, Berg U, Brucker C, Mayerhofer A. Functional and molecular characterization of a muscarinic receptor type and evidence for expression of choline-acetyltransferase and vesicular acetylcholine transporter in human granulosa-luteal cells. J Clin Endocrinol Metab 1999;84:1744–50.
[34] Garzon M, Vaughan RA, Uhl GR, Kuhar MJ, Pickel VM. Cholinergic axon terminals in the ventral tegmental area target a subpopulation of neurons expressing low levels of the dopamine transporter. J Comp Neurol 1999;410(2):197–210.
[35] Green A, Ellis KA, Ellis J, Bartholomeusz CF, Ilic S, Croft RJ, et al. Muscarinic and Nicotinic receptor modulation of object and spatical n-back working memory in humans. Pharmacol Biochem Behav 2005;81:575–84.
[36] Gronier B, Perry KW, Rasmussen K. Activation of the mesocorticolimbic dopaminergic system by stimulation of muscarinic cholinergic receptors in the ventral tegmental area. Psychopharmacology 2002;147:347–55.
[37] Grottick AJ, Higgins GA. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. Behav Brain Res 2000;117:197–208.
[38] Hahn B, Shoaib M, Stolerman IP. Nicotine-induced enhancement of attention in the five-choice serial reaction time task: the influence of task demands. Psychopharmacology (Berl) 2002;162:129–37.
[39] Holland PC. Brain mechanisms for changes in processing of conditioned stimuli in Pavlovian conditioning: implications for behavior theory. Anim Learn Behav 1997;25:373–99.
[40] Ikemoto S, Wise RA. Rewarding effects of the cholinergic agents carbachol and neostigmine in the posterior ventral tegmental area. J Neurosci 2002;22:895–904.
[41] Kent L, Middle F, Hawi Z, Fitzgerald M, Gill M, Feehan C, et al. Nicotinic acetylcholine receptor alpha4 subunit gene polymorphism and attention deficit hyperactivity disorder. Psychiatr Genet 2001;11:37–40.
[42] Kent L, Green E, Holmes J, Thapar A, Gill M, Hawi Z, et al. No association between CHRNA7 microsatellite markers and attention-deficit hyperactivity disorder. Am J Med Genet 2001;105:686–9.
[43] Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. Neurosci Lett 2000;285:107–10.
[44] LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, et al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry 1996;1:121–4.
[45] Lambert NM. Hartsough CS Prospective study of tobacco smoking and substance dependencies among samples of adhd and non-adhd participants. J Learn Disabilities 1998;31:533–44.
[46] Lamour Y, Dutar P, Jobert A. Topographic organization of basal forebrain neurons projecting to the rat cerebral cortex. Neurosci Lett 1982;34:117–22.
[47] Lehmann C. ADHD symptoms respond to cholinergic drugs. Psychiatric News 2003;38:25–8.
[48] Leonard S, Gault J. DNA variants in the alpha 7 nicotinic recptor gene promoter are associated with schizophrenia. Biol Psychiatry 2001;49:166S.
[49] Levin ED. Nicotinic receptor subtypes and cognitive function. J Neurobiol 2002;53:633–40.
[50] Levin ED, Kaplan S, Boardman A. Acute nicotine interactions with nicotinic and muscarinic antagonists: working and reference memory effects in the 16-arm radial maze. Behav Pharmacol 1997;8:236–42.
[51] Levin E, Wilson W, Rose J, McEvoy J. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Neuropsychopharmacology 1996;15:429–36.
[52] Levin ED, McGurk SR, Rose JE, Butcher LL. Cholinergic-dopaminergic interactions in cognitive performance. Behav Neural Biol 1990;54:271–99.
[53] Levin ED, Conners CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, et al. Nicotine effects on adults with attention-deficit/hyperactivity disorder. Psychopharmacology 1996;123:55–63.
[54] Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J, et al. Transdermal nicotine effects on attention. Psychopharmacology 1998;140:135–41.
[55] Levy F, Swanson JM. Timing, space and ADHD: the dopamine theory revisited. Aust N Z J Psychiatry 2001;35:504–11.
[56] Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychology: Hum Percept Performance 1984;10:276–91.
[57] Lufi D, Cohen A, Parish-Plass J. Identifying attention deficit hyperactive disorder with the WISC-R and the Stroop color and word test. Psychol Schools 1990:28–34.
[58] Luiten PGM, Gaykema RPA, Traber J, Spencer JDG. Cortical projection patterns of magnocellular basal nucleus subdivisions as revealed by anterogradely transported Phaseolus vulagris leucoagglutinin. Brain Res 1987;413:229–50.
[59] MacLeod D, Prior M. Attention deficits in adolescents with ADHD and other clinical groups. Child Neuropsychol 1996;2:1–10.
[60] MacLeod JE, Potter AS, Simoni MK, Bucci DJ. Nicotine administration enhances conditioned inhibition in rats. Eur J Pharmacol 2006;551:76–9.
[61] Mayerhofer AN, Dimitrijevic N, Kunz L. The expression and biological role of the non-neuronal cholinergic system in the ovary. Life Sci 2003;72:2039–45.
[62] McGaughy J, Everitt BJ, Robbins TW, Sarter M. The role of cortical cholinergic afferent projections in cognition: impact of new selective immunotoxins. Behav Brain Res 2000;115:251–63.
[63] Mercugliano M. What is attention-deficit/hyperactivity disorder? Pediatr Clin North Am 1999;46(5):831–43.
[64] Merlo Pich E, Chiamulera C, Carboni L. Molecular mechanisms of the positive reinforcing effect of nicotine. Behav Pharmacol 1999;10(6–7):587–96.
[65] Mesulam M-M, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). Neuroscience 1983;10:1185–201.
[66] Milberger S, Beiderman J, Faraone SV, Chen L, Jones J. ADHD is associated with early initiation of cigarette smoking in children and adolescents. J Am Acad Child Adolescent Psychiatry 1997;36:37–44.
[67] Molina BS, Pelham WE. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J Abnorm Psychol 2003;112:497–507.
[68] MTA Cooperative Group. A 14 month randomized clinical trial of treatment strategies of attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1999;56:1073–86.
[69] Muir JL, Everitt BJ, Robbins TW. Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. Psychopharmacology (Berl) 1995;118:82–92.
[70] Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci Res 2002;43:111–7.
[71] Newhouse PA, Potter A, Kelton M, Corwin J. Nicotinic treatment of Alzheimer's disease. Biol Psychiatry 2001;49:268–78.
[72] Nigg JT. Is ADHD a disinhibitory disorder? Psychol Bull 2001;127:571–98.
[73] Nigg JT. Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the state of the field and salient challenges for the coming decade. Biol Psychiatry 2005;57:1424–35.

[74] Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiatry Allied Disciplines 1996;37:51–87.
[75] Pomerleau OF, Downey KK, Stelson FW, Pomerleau CS. Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. J Subst Abuse 1995;7:373–8.
[76] Porrino LJ, Rapoport JL, Behar D, Ismond DR, Bunney Jr WE. A naturalistic assessment of the motor activity of hyperactive boys. II. Stimulant drug effects. Arch Gen Psychiatry 1983;40:688–93.
[77] Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. Psychopharmacology 2004;176:182–94.
[78] Potter AS, Newhouse PA. Cognitive effects of acute nicotine and ultra low-dose Mecamylamine in attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:69S.
[79] Prendergast MA, Jackson WJ, Terry Jr AV, Decker MW, Arneric SP, Buccafusco JJ. Central nicotinic receptor agonists ABT-418, ABT-089, and (−)-nicotine reduce distractibility in adult monkeys. Psychopharmacology (Berl) 1998;136:50–8.
[80] Prendergast MA, Terry Jr AV, Jackson WJ, Marsh KC, Decker MW, Arneric SP, et al. Improvement in accuracy of delayed recall in aged and non-aged, mature monkeys after intramuscular or transdermal administration of the CNS nicotinic receptor agonist ABT-418. Psychopharmacology (Berl) 1997;130:276–84.
[81] Quay HC. Inhibition and attention deficit hyperactivity disorder. J Abnorm Child Psychol 1997;25:7–13.
[82] Quik M, Polonskaya Y, Gillespie A, Jakowec M, Lloyd GK, Langston JW. Localization of nicotinic receptor subunit mRNAs in monkey brain by in situ hybridization. J Comp Neurol 2000;425:58–69.
[83] Rapier C, Lunt GG, Wonnacott S. Nicotinic modulation of [3h]dopamine release from striatal synaptosomes: pharmacological characterisation. J Neurochem 1990;54:937–45.
[84] Rapoport JL, Buchsbaum MS, Weingartner H, Zahn TP, Ludlow C, Mikkelsen EJ. Dextroamphetamine. Its cognitive and behavioral effects in normal and hyperactive boys and normal men. Arch Gen Psychiatry 1980;37:933–43.
[85] Rye DB, Wainer BH, Mesulam M-M, Mufson EJ, Saper CB. Cortical projections arising from the basal forebrain: a study of cholinergic and noncholinergic components employing combined retrograde tracing and immunohistochemical localization of choline acetyltransferase. Neuroscience 1984;13:627–43.
[86] Saper CB. Organization of cerebral cortical afferent systems in the rat. I. Magnocellular basal nucleus. J Comp Neurol 1984;222:313–42.
[87] Sarter M, Bruno JP. Cognitive functions of cortical acetylcholine: towards a unifying hypothesis. Brain Res Rev 1997;23:28–46.
[88] Sarter M, Bruno JP, Givens B. Attentional functions of cortical cholinergic inputs: what does it mean for learning and memory? Neurobiol Learn Memory 2003;80:245–56.
[89] Sarter M, Hasselmo ME, Bruno JP, Givens B. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res Rev 2005;48:98–111.
[90] Schachar R, Tannock R, Logan G. Inhibitory control, impulsiveness, and attention deficit hyperactivity disorder. Clin Psychol Rev 1993: 721–39.
[91] Schulz DW, Loring RH, Aizenman E, Zigmond RE. Autoradiographic localization of putative nicotinic receptors in the rat brain using 125I-neuronal bungarotoxin. J Neurosci 1991;11:287–97.
[92] Sergeant JA, Oosterlaan J, van der Meere J. Information processing and energetic factors in attention-deficit/hyperactivity disorder. In: Quay H, Hogan A, editors. Handbook of disruptive behavior disorders. New York: Plenum Press; 1999. p. 75–104.
[93] Sergeant JA. Modeling attention-deficit/hyperactivity disorder: a critical appraisal of the cognitive-energetic model. Biol Psychiatry 2005;57: 1248–55.
[94] Serova L, Sabban EL. Involvement of alpha 7 nicotinic acetylcholine receptors in gene expression of dopamine biosynthetic enzymes in rat brain. J Pharmacol Exp Ther 2002;303:896–903.
[95] Shytle DR, Silver AA, Wilkinson BJ, Sanberg P. A pilot controlled trial of transdermal nicotine in the treatment of Attention Deficit Hyperactivity Disorder. World J Biol Psychiatry 2002;3:150–5.
[96] Solanto MV. Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. Behav Brain Res 2002;130(March): 65–71.
[97] Solanto MV, Conners CK. A dose-response and time-action analysis of autonomic and behavioral effects of methylphenidate in attention deficit disorder with hyperactivity. Psychophysiology 1982;19:658–67.
[98] Solanto MV, Abikoff HB, Sonuga-Barke E, Schachar R, Logan G, Wigal T, et al. The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. J Abnorm Child Psychol 2001;29:215–23.
[99] Sonuga-Barke EJ, Taylor E, Sembi S, Smith J. Hyperactivity and delay aversion. I. The effect of delay on choice. J Child Psychol Psychiatry 1992;33:387–98.
[100] Sonuga-Barke E, Dalen L, Remington B. Do executive deficits and delay aversion make independent contributions to preschool attention-deficit/hyperactivity disorder symptoms? J Am Acad Child Adolescent Psychiatry 2003;42:1335–8.
[101] Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolescent Psychiatry 1996;35:409–32.
[102] Spencer T, Biederman J, Wilens T, Faraone S, Prince J, Gerard K, et al. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2001;58: 775–82.
[103] Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJS, Jensen PS, Cantwell DP. Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet 1998;351:429–33.
[104] Tannock R. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry Allied Disciplines 1998;39:65–99.
[105] Tannock R, Schachar RJ, Logan GD. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. J Abnorm Child Psychol 1995;23:253–66.
[106] Taylor JR, Jentsch JD. Repeated intermittent administration of psychomotor stimulant drugs alters the acquisition of Pavlovian approach behavior in rats: differential effects of cocaine, d-amphetamine and 3,4- methylenedioxymethamphetamine ("Ecstasy"). Biol Psychiatry 2001;50(2):137–43.
[107] Terry Jr AV, Risbrough VB, Buccafusco JJ, Menzaghi F. Effects of (+/−)-4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio]phenol hydrochloride (SIB-1553A), a selective ligand for nicotinic acetylcholine receptors, in tests of visual attention and distractibility in rats and monkeys. J Pharmacol Exp Ther 2002;301:284–92.
[108] Tidey JW, O'Neill SC, Higgins ST. D-Amphetamine increases choice of cigarette smoking over monetary reinforcement. Psychopharmacology 2000;153:85–92.
[109] Todd RD, Lobos EA, Sun LW, Neuman RJ. Mutational analysis of the nicotinic acetylcholine receptor alpha 4 subunit gene in attention deficit/hyperactivity disorder: evidence for association of an intronic polymorphism with attention problems. Mol Psychiatry 2003;8: 103–8.
[110] van der Meere J, Wekking E, Sergeant J. Sustained attention and pervasive hyperactivity. J Child Psychol Psychiatry Allied Disciplines 1991;32:275–84.
[112] Volkow ND, Insel TR. What are the long-term effects of methylphenidate treatment? Biol Psychiatry 2003;54:1307–9.
[113] Wainer BH, Mesulam M-M. Ascending cholinergic pathways in the rat brain. In: Steriade S, Biesold D, editors. Brain cholinergic systems. New York: Oxford University Press; 1990. p. 65–119.
[114] Warburton DM, Rusted JM. Cholinergic control of cognitive resources. Neuropsychobiology 1993;28(1–2):43–6.
[115] Whalen CK, Jamner LD, Henker B, Gehricke JG, King PS. Is there a link between adolescent cigarette smoking and pharmacotherapy for ADHD? Psychol Addictive Behav 2003;17(4):332–5.

[116] Wilens TE, Biederman J, Spencer TJ, Bostic J, Prince J, Monuteaux MC, et al. A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder. Am J Psychiatry 1999;156(12):1931–7.

[117] Wilens TE, Biederman J, Wong J, Spencer TJ, Prince JB. Adjunctive donepezil in attention deficit hyperactivity disorder youth: case series. J Child Adolescent Psychopharmacol 2000;10(3):217–22.

[118] Wilens TE, Verlinden MH, Adler LA, Woznia PJ, West SA. ABT-089, a neuronal nicotinic receptor partial agonist, for the treatment of attention-deficit/hyperactivity disorder in adults: results of a pilot study. Biol Psychiatry 2006;59(11):1065–70.

[119] Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry 2005;57(June (11)):1336–46.

[120] Wonnacott S, Irons J, Rapier C, Thorne B, Lunt GG. Presynaptic modulation of transmitter release by nicotinic receptors. Prog Brain Res 1989;79:157–63.

[121] Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C, et al. Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. Eur Neuropsychopharmacol 2006;(April) [Epub ahead of print].

[122] Young JW, Finlayson K, Spratt C, Marston HM, Crawford N, Kelly JS, et al. Nicotine improves sustained attention in mice: evidence for involvement of the alpha7 nicotinic acetylcholine receptor. Neuropsychopharmacology 2004;29(5):891–900.

[123] Zametkin AJ, Rapoport JL. Neurobiology of attention deficit disorder with hyperactivity: where have we come in 50 years? J Am Acad Child Adolescent Psychiatry 1987;26:676–86.