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Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder

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Abstract

Objective: The strong association between ADHD and cigarette smoking and the known effects of nicotine on cognition has lead to interest in the role of cholinergic function in ADHD cognitive deficits. We have previously demonstrated that acute nicotine improves behavioral inhibition in adolescents with ADHD. This study examined acute nicotine in young adults with ADHD-Combined type on cognitive domains including behavioral inhibition, delay aversion, and recognition memory.
Methods: 15 non-smoking young adults (20±1.7 years) diagnosed with ADHD-C received acute nicotine (7 mg patch for 45 min) and placebo on separate days. Cognitive tasks included the Stop Signal Task, Choice Delay task, and the High–Low Imagery Task (a verbal recognition memory task). Three subjects experienced side effects and their data was excluded from analysis of cognitive measures.
Results: There was a significant ($p<.05$) positive effect of nicotine on the Stop Signal Reaction Time measure of the Stop Signal Task. The SSRT was improved without changes in GO reaction time or accuracy. There was a trend ($p=.09$) for nicotine to increase tolerance for delay and a strong trend ($p=.06$) for nicotine to improve recognition memory.
Conclusions: Non-smoking young adults with ADHD-C showed improvements in cognitive performance following nicotine administration in several domains that are central to ADHD. The results from this study support the hypothesis that cholinergic system activity may be important in the cognitive deficits of ADHD and may be a useful therapeutic target.

Keywords: Nicotine; Cholinergic; ADHD; Cognition; Behavioral inhibition; Delay aversion; Methylphenidate; Stop Signal Task; Impulsivity

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood psychological disorders, occurring in as many as 3–5% of children (APA, 1994). While ADHD is a disorder that appears in childhood, up to 80% of children diagnosed with ADHD show symptoms that persist into adolescence (Barkley et al., 1991, 1990) and adulthood (Biederman et al., 2000; Hervey et al., 2004).

The clinical diagnosis of ADHD includes symptom onset prior to age 7, chronicity of symptoms of at least 6 months, and significant functional impairment across at least 2 domains of functioning (APA, 1994). Symptoms are categorized into a cluster of inattention (i.e. easily distracted, trouble sustaining attention), and a cluster of hyperactivity/impulsivity (i.e. trouble sitting still or feelings of restlessness, difficulty waiting, frequently interrupting). ADHD diagnosis is made on the basis of the number and types of symptoms that are present. The diagnosis of ADHD is further characterized by sub-type. There are three sub-types as described in the DSM-IV-TR; ADHD-primarily inattentive type (ADHD-I; 6 or more symptoms of inattention and less than 6 symptoms of hyperactivity/impulsivity), primarily hyperactive/impulsive type (ADHD-HI; 6 or more symptoms of hyperactivity/impulsivity and less than 6 symptoms of inattention), and combined type (ADHD-C; 6 or more symptoms of each cluster) (APA, 1994). Many researchers have questioned whether the ADHD-I subtype is a

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distinct disorder from the ADHD-C subtype (for example Barkley, 2001; Chhabildas et al., 2001; Milich et al., 2001; Hinshaw, 2001) with differing underlying neurobiology. Adolescents with ADHD have increased vulnerability to becoming cigarette smokers (Milberger et al., 1997; Lambert and Hartsough, 1998) and begin smoking at a younger age than controls (Riggs et al., 1999). Kollins and colleagues' (2005) analysis of the National Longitudinal Study of Adolescent Health (an epidemiological study of 15, 197 adolescents) found a significant relationship between reported (retrospective) ADHD symptoms and lifetime cigarette smoking after controlling for demographic variables and conduct disorder symptoms. This relationship was largely linear with each additional symptoms of ADHD conferring additional risk of smoking, and with hyperactivity/impulsivity symptoms being a better predictor of lifetime smoking than inattentive symptoms (Kollins et al., 2005). A prospective study of tobacco smoking and substance dependence found that by age 17, 46% of adolescents with ADHD were smoking cigarettes daily compared with 24% of age–mate controls (Lambert and Hartsough, 1998). This pattern continued into adulthood where 35% of adult subjects with ADHD were smokers as compared to 16% of age-matched controls. In addition to earlier smoking initiation, smokers with ADHD have lower quit ratios than the general population (Pomerleau et al., 1995).

Studies have found beneficial effects of nicotine (Conners et al., 1996; Levin et al., 2001a,b; Shytle et al., 2002) and a novel nicotinic agonist (Wilens et al., 1999) on ADHD symptoms. In addition, acute nicotine administration has positive effects on behavioral inhibition (a specific cognitive deficit) in adolescents with ADHD-C (Potter and Newhouse, 2004). However the cholinergic system has been understudied in ADHD and the neurobiological mechanism(s) by which nicotine exerts effects in ADHD are not understood (Potter et al., 2006).

In recent years there has been increased focus on identifying the specific neuropsychological characteristics of ADHD including poor planning, deficits in working memory and lack of cognitive flexibility (Cepeda et al., 2000; Clark et al., 2000). Of the many cognitive domains that have been examined, two primary deficits in ADHD appear to be behavioral inhibition (Barkley, 1997a,b) and delay aversion (Sonuga-Barke et al., 1992). Deficits in behavioral inhibition and delay aversion are both hypothesized to result in impulsive behavior in ADHD, and these deficits have been shown to contribute independently to ADHD symptoms (Solanto et al., 2001; Sonuga-Barke et al., 2003).

Behavioral inhibition (BI) refers to the ability to delay or refrain from responding due to environmental cues. In the Stop Signal Task, which measures BI, the primary outcome measure is an estimate of the speed of inhibition (the stop signal reaction time or SSRT). Abnormally slow SSRTs have been robustly associated with ADHD diagnosis (see Castellanos and Tannock, 2002 for review) and current theories of ADHD indicate that deficits in behavioral inhibition, while not the unitary deficit in ADHD, are a reliable and central cognitive dysfunction of this disorder (Nigg, 2005; Aron and Poldrac, 2005). Meta-analytic studies of Stop Signal Task performance have shown ADHD diagnosis to be associated with both longer reaction time to the go signal (GORT) and longer stop signal reaction time (SSRT) (Oosterlaan et al., 1998; Willcutt et al., 2005). PET and fMRI studies during response inhibition have shown a more diffuse pattern of brain activation in subjects with ADHD than controls (Bush et al., 1999; Rubia et al., 1999; Schweitzer et al., 2003). Methylphenidate (Tannock et al., 1995) and nicotine (Potter and Newhouse, 2004) have been shown to reduce SSRT in ADHD.

The delay aversion model (Sonuga-Barke et al., 1992) characterizes impulsive behavior in ADHD as the expression of a motivational state in which people with ADHD choose to avoid delay. In this model, the motivation to escape or avoid delay over-rides the motivation for high performance and task related rewards (Sonuga-Barke, 2002). Delay aversion has been experimentally examined using the Choice Delay Task (CDT). Children with ADHD show significantly greater aversion to experimental delay than controls (Solanto et al., 2001; Sonuga-Barke et al., 2003). Sergeant and colleagues (1999) have proposed that delay aversion is related to motivational processes involving the meso-limbic dopamine branch associated with reward circuits.

Deficits in sustained attention are among the strongest finding in studies of the cognitive deficits in ADHD (Willcutt et al., 2005), although they may be secondary to deficits in inhibition (Nigg, 2001). Regardless, it is possible that persons with ADHD use cigarettes to improve sustained attention. Nicotine has well described effects on improving sustained attention in humans as assessed by the Continuous Performance Task. These include positive findings in normal young adults as well as non-abstinent smokers (Levin et al., 1998). Studies of the effects of nicotine on persons with ADHD have found that nicotine improves accuracy (d') on this task (Shytle et al., 2002). Other studies have revealed nicotine-induced reductions in errors of omission and reductions in the variability of response times (Levin et al., 1996) demonstrating a beneficial effect of nicotine on sustained attention in patients with ADHD.

Abundant research demonstrates that the cognitive deficits that characterize ADHD in childhood are present in adolescents and adults with the disorder (Seidman, 2006; Gualtieri and Johnson, 2006). A recent review found that studies comparing ADHD subjects to control subjects found clear deficits in executive function associated with ADHD across all ages examined (Seidman, 2006). A large cross-sectional study found deficits in set shifting and Stroop performance in ADHD subjects compared to controls (ages 10–29; Gualtieri and Johnson, 2006). This study found an interesting developmental shift in performance with age. Normal adults had both faster reaction times and greater accuracy than normal adolescents. In contrast, adults with ADHD had greater accuracy but not faster reaction times compared to ADHD adolescents (Gualtieri and Johnson, 2006). This along with significant deficits in set-shifting in ADHD was interpreted as demonstrating that young adults with ADHD have difficulty with the allocation of attentional resources (Gualtieri and Johnson, 2006). The finding that ADHD is associated with persistent deficits in the efficient allocation of attention supports the notion that regulation of the cholinergic system may improve these cognitive deficits in

ADHD. It has been suggested that the effects of nicotine are most pronounced on tasks that demand effortful processing (Rusted and Warburton, 1994). In addition, a recent theory proposes that the cholinergic system allocates additional attentional resources during tasks that are demanding (i.e. sustained attention, set shifting, etc; Sarter and Bruno, 1997). Thus it may be that in ADHD, cholinergic systems are under-responsive or under-developed and thus stimulation of nicotinic receptors via nicotine results in improved cognitive performance particularly on tests requiring effortful processing.

Nicotine has well-documented effects on improving attention and memory in normal and diseased populations (i.e. Wesnes and Warburton, 1983; Newhouse et al., 1991; Levin et al., 1996; White and Levin, 2004). Nicotine reduces the Stroop effect (a measure of cognitive inhibition) in normal smokers (Wesnes and Warburton, 1983), non-smokers (Provost and Woodward, 1991), and adolescents with ADHD (Potter and Newhouse, 2004) suggesting that nicotine enhances inhibitory attentional mechanisms. Sarter and Bruno (1997) propose that cholinergic activity regulates signal-detection processes via both sensory (bottom–up) and higher order cognitive (top–down) processes. According to this model tasks that require more attentional effort, i.e. sustained attention, shifting of attention, or ignoring irrelevant stimuli, recruit basal forebrain cholinergic projections to the cortex resulting in responses that are modulated by top–down cognitive processes.

Nicotine increases the release of dopamine in both striatal and mesolimbic dopaminergic pathways (Rapier et al., 1990; Wonnacott et al., 1989; Clarke and Pert, 1985) and mecamylamine (a nicotinic antagonist) decreases dopamine activity in mesolimbic and nigrostriatal systems (Levin et al., 1990a). Thus, nicotine may also have positive effects on cognition in ADHD through interactions between the cholinergic and catecholaminergic systems (Newhouse et al., 2004).

This study extended a previous examination of nicotine and cognition in ADHD in two ways. First, the cognitive domains studied were extended to include both behavioral inhibition and delay aversion, two central deficits in ADHD, with proposed mechanisms for cholinergic modulation of task performance. Second, this study examined young adults with ADHD-C allowing for examination of the consistency of the effects of nicotine from adolescence into adulthood. We hypothesized that a single acute dose of nicotine would improve behavioral inhibition and increase tolerance for delay in non-smoking young adults with ADHD.

2. Materials and methods

2.1. Design overview

This study was approved by the Institutional Review Board at the University of Vermont. The design was an acute, single dose, within subjects, double blind study with the following drug conditions: 1) 7 mg Nicotine administered by transdermal patch for 45 min and 2) placebo. Transdermal nicotine (Nicoderm CQ) and placebo were purchased from 1-800-PATCHES. Each drug was administered on a separate study day (randomly assigned), separated by at least 48 h, at the General Clinical Research Center (GCRC) of the University of Vermont. Primary outcome measures were tests of behavioral inhibition, delay aversion, and recognition memory.

2.2. Subjects

Fifteen (9 male and 6 female) non-smoking young adults (age 18–24) diagnosed with DSM-IV ADHD-Combined type (ADHD-C) and weighing at least 45.5 kg (100 lb) participated in this study. Non-smoking status was defined as never being a regular user of tobacco products and not using any tobacco products in the last 6 months. Smoking was assessed by self-report and confirmed with expired carbon monoxide at screening and the morning of each study visit. All subjects were screened for psychological disorders using the SCID (First et al., 2002) modified to include the K-SADS-PL structured interview behavior disorder supplement (Kaufman et al., 1997). Subjects did not currently meet DSM-IV criteria for any Axis I psychiatric disorder other than ADHD-C. Given the nature of this small pilot study we decided to limit our subjects to those having ADHD-C. Subjects were allowed to have a past history of Oppositional Defiant Disorder and/or Conduct Disorder, but had to have a lifetime absence of other Axis I disorders. Subjects were administered the Wechsler Abbreviated Scales of Intelligence (WASI) and were required to have a Full Scale Intelligence Quotient (FSIQ) of at least 80. In addition, subjects were screened for inhibition deficits using the SSRT measure of the Stop Signal Task and were required to perform at least 1.5 standard deviations below the mean for controls in the reference age range on this measure. Norms for this task were taken from published data (Williams et al., 1999) conducted on a random sample of volunteers. Subjects were additionally characterized on the Wender–Utah Rating scale, a retrospective self-report of childhood ADHD symptoms. A summary of the demographic characteristics of the subjects is presented in Table 1.

Subjects were excluded if they were on any psychotropic medications other than standard treatments for ADHD (psychostimulants or Strattera). The status of current (past 6 months) medication treatment for ADHD symptoms was collected during the clinical interview at screening. Six (6) subjects were not taking any medications for ADHD. Four (4) subjects reported taking prescribed medication sporadically (less than 4 days a week). Doses reported are total daily dose of each medication. Adderall 10 mg 2 subjects, Ritalin 10 mg 1 subject, Strattera 20 mg 1 subject. Five (5) subjects reported followed a

Table 1
Demographic characteristics of subjects ($n=15$)

	Age (years)	WASI (FSIQ)	Wender–Utah total score	SSRT at screening (ms)
Mean	20.0	117.64	46.30	347.3
SD	1.7	13.19	15.30	61.8
Min	18.0	97.00	21.00	313.0
Max	24.0	136.00	63.00	524.5

FSIQ = Full Scale Intelligence Quotient, SSRT = Stop Signal Reaction Time.

stable medication regime at least 4 days a week as follows: Adderall 10 mg 1 subject, Adderall 20 mg 1 subject, Adderall 90 mg 1 subject, Strattera 40 mg 1 subject. All subjects who reported taking any medications for ADHD abstained from treatment for at least 3 half-lives before each study day. This was verified by subject's report of their last dose of medication at the beginning of each study day.

Following the screening visit, each subject completed a computer training session. This was done to minimize learning effects on the cognitive tasks used in this study. Subjects were trained to stable asymptotic performance on the SST, and completed the Choice Delay task one time.

2.3. Study day procedures

Study days were scheduled to be at least 48 h and no more than 10 days apart. Subjects abstained from eating and/or drinking anything but water after midnight the night before a study day. Subjects were admitted to the outpatient facility at the General Clinical Research Center (GCRC) at approximately 8:00 am. Confirmation of non-smoking status was obtained by an expired carbon monoxide level of <10 ppm. Female subjects were required to have a negative urine pregnancy test prior to drug administration each morning. Drug was administered double-blind in patches containing either nicotine or placebo. 45 min following patch application, the patch was removed and the cognitive testing session began. The cognitive testing session lasted approximately 45 min/subject. After the cognitive testing session, subjects were served lunch, and were discharged 60 min after the conclusion of the cognitive testing session. Vital signs (blood pressure and pulse) were monitored at 30 minute intervals throughout the study session.

2.4. Assessment battery

Cognitive tests were administered immediately following patch removal in a fixed order as follows: Stop Signal Task, Stroop task, immediate recognition trials of the High–Low Imagery Task (trials 1 and 2), choice delay task, delayed recognition trial of the High–Low Imagery Task (trial 3). Immediately following these assessments (approximately 35 min later), subjects completed the self report questionnaires (physical symptom checklist, visual analog scales, and Profile of Moods States (POMS). Subjects were instructed to endorse any item that they had experienced "this morning including now". Subjects were further instructed to report the maximal intensity of any item that they had experienced.

2.4.1. Cognitive outcome measures

1. Stop Signal Task (Logan et al., 1984): This is a computer-administered test of behavioral inhibition. Subjects are asked to respond to two equally probable "go" signals (the letters X and O) by pressing corresponding keys on a computer keyboard. Subjects are instructed not to respond to the target stimulus if an auditory signal (the stop signal) is present. The version of this task used here begins using a 250 ms stop signal delay (the interval between the onset of the go signal and the stop signal). This delay is adjusted after every trial according to the subject's performance to achieve a 50% inhibition success rate. With the probability of inhibition, the stop signal reaction time (a measure of the speed of inhibiting) is calculated (Williams et al., 1999). Other dependant variables include GORT, accuracy, and the probability of successfully inhibiting to the stop signal. This task has been shown to discriminate ADHD from control subjects (i.e. Nigg, 1999; Willcutt et al., 2005; Willcutt et al., 2001).
2. The Stroop Task (Stroop, 1935): This computer-administered version of the Stroop task assesses the speed of word reading, color naming, and interference. In the word reading condition, subjects respond on a keyboard to 100 words presented one at a time on the monitor. The words are all color names; red, green or blue. In the color naming condition, subjects respond to 100 blocks of color presented on the screen (red, green, or blue). On the interference condition, subjects are instructed to respond to the color of the font for words that are color names (i.e. the word blue printed in a red font where the correct response is red). The Stroop effect is the expected longer reaction times in the interference condition compared to the color naming condition. Dependant measures for this task include number of errors and correct responses, and reaction times for the different stimulus conditions (word reading, color naming and interference). Several review articles have concluded that ADHD subjects show a deficit in Stroop interference (i.e. Sergeant et al., 2002; Pennington and Ozonoff, 1996).
3. The Choice Delay Task (Dougherty et al., 2005): In this task subjects are presented with a circle and a square on a computer monitor. They are instructed to choose (using a mouse click) either the circle or the square to earn points. Choosing the circle always gives 5 points following a 5 second delay. Choosing the square gives 15 points following a variable delay. The delay begins at 15 s and increases 2 s for each consecutive choice, but the delay for the 15 points decreases by 2 s for each choice of the circle. Subjects complete 40 choices in this task. In this version of the task, points were not exchanged for money or any other tangible reward. The preference for immediate choices (and thus smaller overall reward) has been shown to reliably distinguish ADHD from control subjects (Solanto et al., 2001; Sonuga-Barke et al., 2003).
4. High–Low Imagery Task: This is a computer-administered recognition memory test in which subjects are presented (on a computer screen) 14 target words. 7 of the words are high imagery ("cat") and 7 are low imagery ("idea") (Snodgrass and Corwin, 1988). Next, subjects are tested on 28 words, the 14 original plus 14 distractors (7 high imagery, and 7 low imagery). Subjects are asked to indicate which words are old (from the original 14) and which words are new. Two learning trials and a delayed trial are completed. Dependant variables from this task include number of hits (correct yes responses), and false alarms (incorrect yes responses). This task was administered because it has been shown to be sensitive to acute doses of nicotinic agents in young adults (Newhouse et al., 1992, 1996a,b; Potter et al., 1999).

2.5. Behavioral assessments

Behavioral assessments were administered immediately following the cognitive testing session (approximately 60 min after patch removal). Subjects were instructed to complete the ratings to reflect their entire experience during the morning. They were further instructed to report the maximal severity of any item they noticed during the morning (for example on the Physical Symptom Checklist for the item rating hunger subjects were instructed to "rate your hunger during the entire morning, reflecting the hungriest you have been this morning including now").

1. Clinical Global Impression (NIMH, 1985): This is a paper and pencil form which is completed by the investigator. This form measures several global domains of functioning.
2. Profile of Mood States (POMS) (McNair et al., 1971): The POMS is a self-report measure of mood and/or physical well being. Subjects are presented with a list of adjectives, and asked to indicate the severity of each item for that day only. Dependant variables from the POMS include the total score, and cluster scores for vigor, tension, depression, anger, fatigue and difficulty concentrating.
3. Visual Analog Battery (subject rating): This is a paper and pencil measure in which subjects are presented with a series of 100 mm lines, each representing a dimension of functioning (sleepiness, mood, ability to concentrate etc.). Descriptive anchors are provided (i.e. sleepiness ranges from alert to about to fall asleep). Subjects are asked to indicate (by placing a mark on the line) how they feel today on each domain.
4. Visual Analog Battery (observer rating): This is a paper and pencil measure in which the blind investigator indicates on a series of 100 mm how the subject is functioning on different domains (sleepiness, mood, compliance, agitation, concentration, etc.).
5. Physical Symptom Checklist (Van Kammen and Murphy, 1975): This is a paper and pencil checklist of 22 physical symptoms. Subjects rate each symptom as none, slight, moderate, or much, which are scored from 0–3. Physical symptoms include items such as hunger, headache, nausea and drowsiness. Dependant measures include scores on individual items as well as a total score (the sum of the individual items).

2.6. Data collection and storage

Computer generated data were down-loaded into Microsoft Excel workbooks. Scores of paper and pencil tests were calculated and entered into the Excel spreadsheets by study personnel. All data was double entered (by two different individuals) into spreadsheets which were then compared via computer. All data entry discrepancies were resolved using source data. All study data were archived on the computer information system of the University of Vermont GCRC.

2.7. Data analysis

The basic approach to data analysis was to perform two-tailed paired *t*-tests to determine differences related to drug treatment on the dependant variables. For tasks that included blocks of trials (the Stop Signal Task) or different trial types (immediate and delayed recognition memory trials), a series of mixed model ANOVA's with drug condition and trial type as within subject factors were run to determine the combined effects of drug treatment and task condition on performance.

Vital sign data was analyzed using mixed-model repeated measures ANOVAs comparing the 2 drug conditions across the 9 time points. Data was collected on systolic and diastolic blood pressure and pulse. Secondary analyses examined changes in vital signs from pre-drug baseline (each day) to 150 minute post-drug (estimated time for maximal physiological effects).

3. Results

Three subjects reported side effects (nausea and dizziness) from the medication approximately 40 min after the patch was applied. Data from these subjects was therefore excluded from all cognitive analyses. Data from all 15 subjects is presented for the behavioral assessments. Thus, the cognitive data presented below reflect the results of the 12 subjects who did not experience significant side effects.

3.1. Cognitive measures

3.1.1. Stop Signal Task

Examination of the probability of responding to a stop signal indicated that the task parameters and tracking algorithm were successful in approximating a 50% inhibitory success for all subjects, supporting the validity of the resultant Stop Signal Reaction Time (SSRT) as an estimate of the speed of inhibition. There was a significant [$t(11)=2.07$, $p<.05$] effect of drug on SSRT with performance during nicotine treatment significantly faster than during placebo treatment (Fig. 1a). Analysis of GO-RT (time to respond to the go signal) and accuracy found that nicotine did not significantly affect these measures of performance [$t(11)=.24$, $p=.6$] and [$t(11)=.62$, $p=.4$] respectively (Fig. 1b).

3.1.2. The Stroop Task

Analysis of reaction time data across all task conditions (word reading, color naming, and conflict) showed a significant main effect of drug [$F(1,11)=12.69$, $p<.05$] but no Drug × Condition interaction on median reaction time. Nicotine was associated with slower reaction times in all task conditions. The Stroop effect was calculated by subtracting the median reaction time in the color naming condition from the median reaction time in the conflict condition. There was no significant effect of nicotine on this measure.

3.1.3. 2 Choice Task

Due to a computer failure, data from the first 5 subjects on this task were unavailable for analysis. Data from 2 of the remaining subjects were excluded from the analysis because of failure to correctly complete the task. Data from the remaining 8 subjects were analyzed.

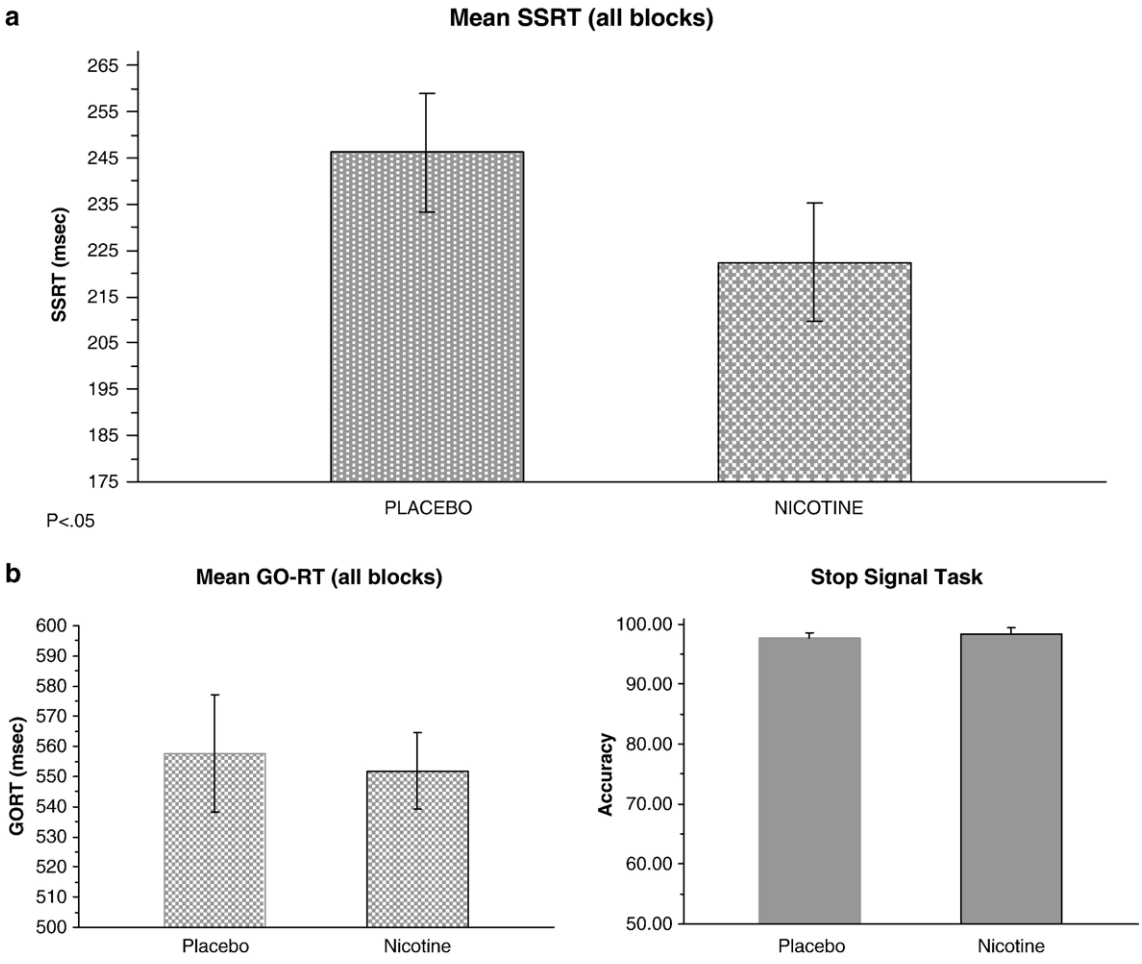

Fig. 1. a. Effect of nicotine on SSRT; b. Effect of nicotine on GO-RT and accuracy.

Analysis of the number of delayed choices made during each 10-trial block of the task found a trend [$F(3,21)=2.43$, $p=.09$] for an interaction of drug and task block (Fig. 2). Nicotine was associated with a greater number of delayed choices during the second ($t(7)=2.25$, $p<.05$ block and there was a trend for nicotine to be associated with greater delayed choices in the third $t(7)=1.64$, $p=.10$ task blocks.

3.2. High–Low Imagery Task

There was no main effect of drug or drug × trial interaction on the total number of hits or false alarms during this task. This was found in each imagery condition (high versus low imagery words) separately as well as on the total word list. Analysis of the change in the number of words correctly recognized between trials 1 and 2 was conducted to assess the effect of nicotine on learning, and the change between trial 2 and the delay trial was conducted to assess the effect of nicotine on the amount forgotten during the delay. Analysis of the amount of learning revealed a strong trend [$t(10)=4.45$, $p=.06$] for an effect of drug on this measure, with nicotine associated with an increase in the number of words correctly recognized between trials 1 and 2 (increase of .5 words on placebo and 2.667 words on nicotine). This trend finding was present but weaker in both imagery conditions high imagery [$t(10)=.1.76$, $p=.10$], low imagery [$t(10)=.1.83$, $p=.09$] separately. There was no effect of drug on the difference between trials 2 and 3 on either imagery condition separately or on the total word list on this task.

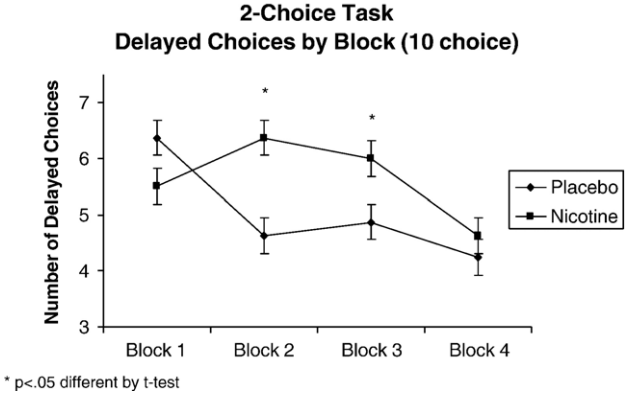

Fig. 2. Effect of nicotine on 2-choice task: delayed choices.

3.3. Behavioral measures

The Physical Symptom Checklist total score showed that nicotine produced significantly more side effects than placebo [$t(11)=48.91$, $p<.05$]. This increase in the side-effect total score was not however, reflected in a consistent increase in the score of any single item (such as nausea, dizziness, etc) but was revealed only on the sum of all items. Furthermore, the total score represented a slight increase in scores which were not clinically significant (mean score on nicotine=6.9, on placebo 4.0; possible scores range from 0–66).

There were no significant drug-related changes on the Subjective Visual Analog Scale, or the Profile of Mood States (POMS). Analysis of investigator rated behavioral effects of nicotine revealed that there were no significant drug-related changes on any of these measures including Clinical Global Impressions Scale and the Observer Visual Analog Battery.

3.4. Vital signs

Analysis of systolic blood pressure, diastolic blood pressure and temperature showed no effect of nicotine. Analysis of pulse indicated that there was a significant ($p<.05$) effect of drug with nicotine associated with higher pulse. Analysis of the change in pulse from pre-drug baseline to the 150 minute time-point revealed a significant [$t(13)=2.32$, $p<.05$) effect of nicotine on this change score. Pulse rate during the nicotine condition rose by 6 bpm (from 65 to 71 bpm) and fell by 3 bpm (from 68 to 65 bpm) in the placebo condition.

4. Discussion

The results from this study demonstrate that a single low dose of acute nicotine robustly improves stop signal reaction time in young adults with ADHD. The finding that there was no change in GO-RT or errors on this task supports the specificity of enhanced behavioral inhibition and not merely non-specific benefits to performance or an overall improvement in speed. This finding is consistent with our prior study in adolescents with ADHD which found improvements in SSRT without improvements in GO-RT or Accuracy (Potter and Newhouse, 2004). The finding that both adolescents and young adults with ADHD are responsive to nicotine may indicate that the beneficial effect of nicotine on inhibition is not a developmental effect. This is consistent with research demonstrating that methylphenidate has positive effects in children, adolescents and young adults with ADHD (i.e. Greydanus et al., 2002; Zito et al., 2003; Ingram et al., 1999). Deficits in behavioral inhibition remain sensitive to nicotinic stimulation arguing for the importance of the cholinergic system in understanding the neurobiology of these deficits in ADHD.

There has been considerable interest in determining the neurobiological mechanisms that might underlie the cognitive/behavioral inhibition deficits in ADHD. van Boxtel et al. (2001) and Overtoom et al. (2002) have both reported distinct frontal brain wave patterns (abnormal n200) associated with inhibitional failure on the Stop Signal Task. Functional MRI studies have shown reduced striatal activation in children (Vaidya et al., 1998) and adolescents (Rubia et al., 1999) with ADHD during performance of the Stop Signal Task. Nicotine promotes dopamine release in the striatum (Rapier et al., 1990) and has been shown to increase dopamine release from the substantia nigra (Clarke and Pert, 1985). This may result in increased dopaminergic tone in the striatum that may improve motor performance on this task. In a review of performance on the Stop Signal Task, Nigg (2001) concluded that performance on this task is linked to activity in the prefrontal cortex. Nicotine administration increases dopamine release from the ventral tegmental area (Meru et al., 1987) which has direct projections to the prefrontal cortex (Kramer et al., 2001). In addition, an in vivo microdialysis study in rats showed that presynaptic nicotine was associated with dose-related increases in dopamine release in the striatum, the nucleus accumbens, and to a smaller degree the frontal cortex (Marshall et al., 1997).

Nicotinic receptors may serve to regulate dopamine release in both striatal and mesocortical pathways (Rapier et al., 1990; Clarke and Pert, 1985). Levin and colleagues (1990b) have performed an extensive series of studies suggesting complex interactions with several possible anatomical loci for the site(s) of interaction including both limbic and hippocampal areas as well as descending projections to dopamine containing areas of the mesencephalon via the medial habenula. Nicotinic blockade impairs working memory in the rat (Levin et al., 1990a,b) and this effect is reversed by nicotine administration. The nicotinic blocker mecamylamine decreases dopamine activity in mesolimbic and nigrostriatal systems, suggesting a mechanism for its effect (Levin et al., 1990b). Nicotinic receptors modulate catecholaminergic transmission, particularly dopaminergic release (Grady et al., 1992), suggesting a tight relationship between the two systems.

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 and thereby modulate motor activity. One particularly important pathway is the so-called “hyperdirect pathway” which appears to involve the subthalamic nucleus, apparently under glutamatergic and GABAergic control, in modulating the output of basal ganglia output structures such as the globus pallidus (Nambu et al., 2002). Recently, functional imaging studies have demonstrated the importance of the subthalamic nucleus and the hyperdirect pathway in playing a critical role in the “stop” process in the Stop Signal Reaction Time task (Aron and Poldrack, 2006). As the subthalamic nucleus appears to contain $\alpha4\beta2$-type and perhaps other nicotinic receptors (Schulz et al., 1991; Quik et al., 2000; Kulak et al., 2002), the action of nicotine may be to improve throughput through the subthalamic nucleus, thereby 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 alterations in other pathways within the motor control system or within the cortical impulse generators themselves that produce impairments in this task and in other types of impairments of control or impulsive responding.

This finding is also consistent with studies demonstrating a positive effect of nicotine and a novel nicotinic agonist on the

behavioral symptoms of ADHD (Conners et al., 1996; Levin et al., 2001a,b; Shytle et al., 2002; Wilens et al., 1999). Reductions in impulsivity related to nicotine may have contributed to the overall improvements seen in clinical symptoms in these studies.

In a previous study (Potter and Newhouse, 2004) we found that nicotine reduced the Stroop effect in adolescents with ADHD. This finding was not replicated in our current study. The Stroop task, which measures cognitive interference control, has been examined extensively in ADHD and a recent meta-analysis (Van Mourik et al., 2005) found that evidence for a deficit in interference control in ADHD was weak using this task. In comparing the results of this study to our previous study in adolescents (Potter and Newhouse, 2004), we found a large baseline difference in reaction time between the adolescents we studied and the young adults in the current study. The adolescents had a mean word reading reaction time of 852 ms and a mean color naming reaction time of 867 ms in contrast the young adult subjects had a mean word reading of 648 ms and color naming of 667 ms Thus it is possible that the known rate dependency effects of nicotine (Perkins, 1999) explain why the young adults did not experience a benefit from nicotine.

This study found a trend for nicotine to increase tolerance for delay in our subjects. This finding was based on a partial sample of only 8 subjects due to a computer malfunction. It may be that with additional subjects this finding would have reached statistical significance. Thus this study provides some evidence for nicotinic modulation of this deficit. It has been demonstrated that children with ADHD show impairment on the delay aversion task (e.g. Solanto et al., 2001; Sonuga-Barke et al., 2003) in that they prefer smaller-sooner over larger-later reward choices when the smaller-sooner choices reduce the total amount of time spent completing the task. Delay aversion is believed to be related to motivational processes involving the mesolimbic dopamine system (Sergeant et al., 1999; Sonuga-Barke, 2002). 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 (Quik et al., 2000; Chiba et al., 1995). Evidence that nicotine may affect the tolerance for delay in ADHD is intriguing and needs replication and further investigation.

On the recognition memory task, nicotine was associated with a trend for a significant increase in words recognized between trials 1 and 2. These results compare with our previous experimental evidence showing that nicotine produces positive effects on recognition memory in adolescents with ADHD (Potter and Newhouse, 2004), and patients with Alzheimer's disease (Newhouse et al., 1991). The results found here suggest possible improvements in encoding or acquisition following acute nicotine administration.

4.1. Limitations and future directions

The subjects in this study had carefully characterized ADHD-Combined type with pre-existing deficits in behavioral inhibition. We have not examined the effects of acute nicotine in other ADHD subtypes, or in subjects without a pre-existing deficit in SSRT. Therefore it is unknown whether nicotine would have the same beneficial effect to other sub-types of ADHD or to those without a pre-existing deficit in inhibitory function.

Subjects in this study had a varied history of treatment with stimulant medication for ADHD symptoms. All subjects were required to be off their treatment regime for 3 half lives before a study session to minimize acute effects of stimulant medications in this study. However, it is unknown how chronic treatment with stimulants may affect nicotinic receptor expression and function. This study did control for smoking history (all subjects were never-smokers) which has known effects on nicotinic cholinergic receptors.

In order to minimize side effects of nicotine in non-smokers, the nicotine patch was administered for 45 min and then removed at the beginning of the cognitive testing session. Thus over the course of the testing session it is likely that there were variations in the plasma concentration of nicotine. The cognitive testing battery was administered in a fixed order as indicated in the methods section. Thus nicotine levels were presumably higher during the stop signal and Stroop tasks than during the delay aversion task. However, it is unclear how declining drug levels would specifically affect cognitive operations. There is no strong evidence to suggest that the nicotine plasma level is linearly related to the cognitive effects of nicotine. Indeed previous studies of the effects of nicotine have demonstrated a non-linear relationship between nicotine plasma levels and physiological measures (Newhouse et al., 1991). Further studies aimed at understanding the relationship between nicotine plasma level and the cognitive effects of acute nicotine in non-smoking subjects may be useful to advance nicotinic therapeutic interventions in clinical populations such as ADHD and schizophrenia.

This study used a single, acute dose of transdermal nicotine. Thus it is unclear whether these effects would persist during chronic treatment with nicotine. In addition, we did not conduct dose ranging in this study and therefore we do not know the size of the therapeutic window for the positive effect of nicotine on cognition in ADHD. Future studies to address these important issues will be critical in determining the therapeutic implications of this study.

There was a loss of data for the two-choice (delay aversion) data in this study. Thus the trend towards significance in this task must be interpreted with caution. Further studies that are fully powered are necessary to understand the effects of nicotine on this task.

Finally, this study was not powered to detect gender differences in response to acute nicotine in young adults with ADHD. There is evidence that women may respond differently to nicotine than men, and these differences will be important to examine in future studies.

5. Summary

This study demonstrated that a single acute dose of nicotine can reduce cognitive deficits in non-smoking young adults with ADHD. Specifically, improvements were seen on tests of behavioral inhibition, delay aversion and recognition memory. Behavioral inhibition and delay aversion are two of the central

deficits in ADHD, believed to underlie much of the higher order symptoms including poor planning and executive function, and difficulty with goal setting and attainment (Barkley, 1997a,b, Sonuga-Barke, 2002). The study provides evidence for the importance of the nicotinic cholinergic system in these deficits in ADHD. Future studies that combine functional brain imaging with drug administration may help to determine the specific underpinnings of these important behavioral findings.

In addition, this study demonstrated that the cognitive effects of nicotine are detectable in young adults with ADHD. The cognitive deficits in ADHD persist from adolescence to adulthood, and nicotine corrects these deficits in both age groups. This may indicate that the neurochemical abnormalities that underlie cognitive deficits in ADHD do not merely represent immature brain development, but persist into adulthood for those with ADHD. In addition, the finding that acute nicotine improves cognition in adolescents and young adults supports the hypothesis that cholinergic function may contribute to the cognitive deficits in ADHD and that stimulation of this system may have therapeutic benefit.

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