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Rate dependent effects of acute nicotine on risk taking in young adults are not related to ADHD diagnosis

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Abstract

Beneficial effects of nicotine on cognition and behavioral control are hypothesized to relate to the high rates of cigarette smoking in Attention-Deficit/Hyperactivity Disorder (ADHD). Given that ADHD is associated with both impulsivity and elevated risk taking, we hypothesized that nicotine modulates risk taking, as it does impulsivity. 26 non-smoking young adults (15 controls with normal impulsivity and 11 ADHD with high impulsivity) received 7 mg transdermal nicotine, 20 mg oral mecamylamine, and placebo on separate days, followed by the Balloon Analogue Risk Task (BART). Statistical analyses found no group differences in baseline risk taking. Reexamination of the data using a median split on baseline risk taking, to create high (HRT) and low (LRT) risk taking groups, revealed significant effects of nicotinic drugs that differed by group. Nicotine reduced risk taking in HRT and mecamylamine increased risk taking in LRT. This finding supports the hypothesis that nicotinic receptor function modulates risk taking broadly, beyond those with ADHD, and is consistent with rate dependent cholinergic modulation of other cognitive functions. Further, the results demonstrate that high impulsivity is separable from high risk taking in young adults with ADHD, supporting the utility of these differential behavioral phenotypes for neurobiological studies.

Keywords

risk taking; Balloon Analog Risk Task; cholinergic; nicotine; mecamylamine; impulsivity; ADHD; acetylcholine

1. Introduction

Impulsivity is a multifaceted construct that encompasses several aspects of behavior including increased reward seeking, risk taking, difficulty in behavioral inhibition, inability to delay gratification, and impairments in time estimation (Weafer *et al.*, 2011, Whiteside and Lynam, 2001). Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with cognitive deficits on domains including sustained attention (Posner and Dehaene, 1994), working memory (Barkley, 1997), complex organization and planning (Barkley, 1997, Pennington and Ozonoff, 1996), temporal information processing (Barkley, 1997, Barkley *et*

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al., 2001, Zakay, 1992), and most robustly with impulsivity (Willcutt *et al.*, 2005). Specifically, a meta-analysis of cognitive domains affected in ADHD found the largest and most consistent deficits in response inhibition (Willcutt *et al.*, 2005). Deficits in response inhibition have particular importance as they are related to many functional impairments in ADHD including poor work performance, difficulty forming and maintaining relationships, injuries, alcohol and substance abuse and dependence, and aggression (Barkley *et al.*, 1991, Barkley *et al.*, 1996, Biederman *et al.*, 1991).

Interestingly, adolescents and adults with ADHD initiate cigarette smoking earlier, have significantly higher rates of smoking, and have a more difficult time quitting than a comparable community sample (Kollins *et al.*, 2005, Milberger *et al.*, 1997, Pomerleau *et al.*, 1995). It has been suggested that individuals with ADHD may use smoking as a form of self-medication to manage difficulties of attention and impulsivity (Levin *et al.*, 1996, Potter *et al.*, 2006, Wilens *et al.*, 2007). In recent years literature has emerged lending support to this hypothesis, documenting beneficial effects of nicotine and nicotinic agonists on attention, working memory and response inhibition in individuals with ADHD (Wilens *et al.*, 2006). Specific to impulsivity, studies in adolescents and young adults with ADHD have found that acute doses of nicotine improve performance on the Stop Signal Task (SST), a laboratory measure of response inhibition (Potter and Newhouse, 2004, 2008). Interestingly, administration of a nicotinic receptor antagonist, mecamylamine, produced impairments in response inhibition in healthy controls (Potter *et al.*, 2012). These studies demonstrate a role for nicotinic cholinergic system function in modulating response inhibition and support the notion that this system may be important in other aspects of impulsive behavior as well.

While response inhibition is one component of impulse control, other cognitive and behavioral processes are implicated in impulsive behavior in ADHD. For example, the propensity to engage in risk taking behavior in everyday situations is abnormally high in ADHD (Barkley *et al.*, 2006, Williams and Taylor, 2006) and has been linked to the increased rates of substance use, driving without a seat belt, and automobile accidents in adult ADHD (Barkley, 2002, Barkley *et al.*, 2002). In the past several years a new understanding of risk taking which broadens the understanding of this behavior has emerged from the developmental neuroscience literature (Casey *et al.*, 2008, Steinberg, 2008). For example, Steinberg and colleagues (2008) have proposed a model in which risky behavior is the product of the interaction between two facets of impulsivity; poor response inhibition and heightened reward seeking. These components of impulsivity are proposed to have distinct neural underpinnings, with reward seeking related to dopaminergic activity in limbic and paralimbic areas of the brain, and response inhibition functionally related to the lateral prefrontal and parietal cortices and the anterior cingulate cortex (Steinberg, 2010, Steinberg *et al.*, 2008). Consistent with this theory, imaging data suggest that an over-reliance on reward systems and an under-reliance on prefrontal systems may underlie some of the behavioral symptoms observed in individuals with ADHD, including the propensity towards risk taking (Galvan *et al.*, 2007, Galvan *et al.*, 2006).

Much of the research on nicotine and reward processing has been conducted in cigarette smokers, creating confounds including nicotine addiction and withdrawal processes, and making it difficult to draw conclusions about nicotinic receptor function and reward independent of cigarette smoking. However, it has recently been shown that acute transdermal nicotine enhances the salience of rewarding stimuli in healthy non-smokers (Barr *et al.*, 2008). The mechanism for this finding may be related to nicotinic receptors in the ventral tegmental area (VTA) which alter neuronal activity to enhance dopamine release and are necessary for the rewarding effects of nicotine (Mansvelder *et al.*, 2003, Nisell *et al.*, 1994, Schilstrom *et al.*, 1998). Thus, given that deficits in response inhibition are improved with acute nicotine in ADHD (Potter and Newhouse, 2004, 2008) and that nicotine

modulates reward salience (Barr *et al.*, 2008, Paterson, 2009), we propose that high risk taking in ADHD may be related to nicotinic cholinergic receptor function.

Risk taking can be measured in the laboratory with the Balloon Analogue Risk Task (BART; (Lejuez *et al.*, 2002), a well validated task that is highly correlated with real-world risk taking. Studies have demonstrated relationships between BART performance and several behaviors including cigarette smoking, alcohol consumption, illicit drug use, delinquency and risky sexual behavior (Aklin *et al.*, 2005, Bornovaalova *et al.*, 2005, Lejuez *et al.*, 2007, Lejuez *et al.*, 2003a, Lejuez *et al.*, 2003b, Lejuez *et al.*, 2002, Lejuez *et al.*, 2004). In addition, a recent study found BART performance to be modified by participation in a residential treatment for substance abuse (Aklin *et al.*, 2009). While initial acute drug studies using the BART in healthy volunteers did not find significant performance changes (Hamidovic *et al.*, 2008, Reynolds *et al.*, 2004, Reynolds *et al.*, 2006b), a recent study found that d-amphetamine decreased risk behavior on the BART in men with low reward sensitivity and increased risk behaviors in men with high baseline reward sensitivity (White *et al.*, 2007), suggesting that the BART is sensitive enough to detect acute drug effects. To our knowledge, there have been no studies of the effect of cholinergic manipulation on BART performance despite the strong relationship between risk taking and cigarette smoking (Lejuez *et al.*, 2003a).

Therefore, this study was designed to examine the effects of nicotinic cholinergic receptor function manipulations, nicotinic stimulation and antagonism, on both high and normal risk taking young adults. We hypothesized that nicotine would reduce risk taking in individuals who were high risk takers at baseline and have no measurable effect for individuals who were low risk takers at baseline. Conversely, we predicted that mecamylamine would increase risk taking in individuals who were not risky at baseline and have no effect on high risk takers. Several issues arise in the identification of a specifically high risk taking population. First, in the absence of published norms on the BART it is not feasible to screen on this behavioral measure; second many studies have failed to find correlations between laboratory and questionnaire measures of related constructs such as sensation seeking and impulsivity, raising questions about their utility to screen for high risk taking (Lane *et al.*, 2003, Reynolds *et al.*, 2006a, Romer *et al.*, 2009) as measured by the BART. Thus, we chose to recruit individuals with ADHD who had specific deficits in response inhibition, a component of impulsivity related to risk taking.

2. Experimental Design and Methods

2.1 Overview

While the present risk taking data are novel and have not been published previously, other data from this investigation of the effects of cholinergic manipulation on impulsivity in young adults with and without Attention-Deficit/Hyperactivity Disorder (ADHD) have been reported in part elsewhere (Potter *et al.*, 2012). This study was approved by the Institutional Review Board at the University of Vermont and was conducted in compliance with the Declaration of Helsinki and all other relevant regulations. This was an acute, single dose, within-subjects, double blind study with three drug conditions: nicotine, mecamylamine, and placebo. After obtaining informed consent, each subject participated in three study days, separated by at least 48 hours, at the General Clinical Research Center (GCRC) of the University of Vermont.

2.2 Participants

Subjects were recruited via posters on local college campuses. Fifty nine individuals provided consent and completed a screening visit, of which, 27 non-smoking young adults (18–25 years old) entered the study. The 32 screen fails were due to scheduling conflicts,

failure to meet impulsivity criteria, medical contraindication, psychiatric co-morbidity, nicotine use, co-morbid learning disability, recreational use of psychostimulants, and failure to meet ADHD criteria. One subject dropped out of the study for personal reasons resulting in 26 subjects who completed the study.

Eleven (3 male, 8 female) of 26 subjects met DSM-IV criteria for ADHD-Combined type by structured interview and performed at least one and a half standard deviations above published norms on the response inhibition measure (stop signal reaction time, SSRT) of the Stop Signal Task (SST; (Williams *et al.*, 1999). These subjects made up the high impulsive, ADHD group (ADHD). Control (CTRL) subjects were required not to have current or past ADHD and to have normal SSRTs (within 1 standard deviation of the mean). Demographic data for the sample is provided in Table 1.

Participants were screened for psychological disorders using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; (First *et al.*, 1996) modified to include the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL; (Kaufman *et al.*, 1997) behavior disorder supplement to assess for ADHD, Oppositional Defiant Disorder and Conduct Disorder. All subjects were required to have a lifetime absence of Axis I disorders, except ADHD participants who met DSM-IV criteria for ADHD. All subjects had an estimated Full Scale Intelligence Quotient greater than 80 determined using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Additional subject characterization included the Impulsivity-Sensation Seeking Scale (ImpSS) of the Zuckerman-Kuhlman Personality Questionnaire (Zuckerman, 2002).

Non-smoking status - no smoking in the last 3 months and never a period of daily smoking - was assessed by self-report and confirmed with expired carbon monoxide at screening and the morning of each study visit (<10 ppm). Participants with major concomitant illnesses were excluded on the basis of history and physical exam. Female subjects were required to test negative on a urine pregnancy test prior to drug administration on each study day.

No subjects were taking centrally active drugs other than ADHD treatments and no drugs with cholinergic properties. Of the 11 subjects in the ADHD group, 9 were currently receiving pharmacotherapy for ADHD (8 subjects receiving psychostimulants and one atomoxetine). Psychostimulants were washed out for 48 hours (at least 12 half-lives) and atomoxetine for 7 days before study days. The length of washout for psychostimulant medication is consistent with previous literature testing acute effects of drugs on cognition in ADHD (Aron *et al.*, 2003, DeVito *et al.*, 2009, Potter *et al.*, 2012), and the length for atomoxetine exceeds 30 half-lives.

2.3 Drug Administration and Study Procedures

The three drug conditions were: 7 mg transdermal nicotine (NIC), 20 mg oral mecamylamine (MEC), and placebo (PLC). All drugs were administered double blind using a double dummy in which subjects took oral capsules and wore a patch on each study day. Subjects received only one (or no) active drug each day and the order of treatment was randomized across participants by a research pharmacist. The nicotine and placebo transdermal patches (NicoDerm CQ 7 mg or matched placebo from 1-800-PATCHES) were placed on the participants' upper backs. Mecamylamine (Inversine, purchased from Targacept Inc.) and placebo (lactose) were crushed and placed in capsules.

Upon arrival at the GCRC, non-smoking status was confirmed using an expired carbon monoxide measure (<10 ppm), fasting status (only clear liquids after midnight) was confirmed via subject report, and pregnancy was ruled out for female subjects with a urine pregnancy test. Oral medication (mecamylamine or placebo) was administered followed 105

minutes later by application of a transdermal patch (nicotine or placebo). The patch was worn for 45 minutes at which time it was removed by a research nurse and the subject completed the cognitive testing and behavioral ratings. The full cognitive test battery lasted approximately 45 minutes and included the stop signal task and a choice reaction time task, reported previously (Potter *et al.*, 2012). Drug dosing and the timing of testing was determined from previous studies demonstrating that 45 minutes of the 7 mg nicotine patch in healthy non-smoking adults and 150 minutes of 20 mg oral mecamylamine provides measurable behavioral and cognitive effects with minimal side effects (Dumas *et al.*, 2008, Newhouse *et al.*, 1994, Potter *et al.*, 2012). At the conclusion of the testing session, participants were provided lunch, assessed for discharge using a standard field sobriety test, and paid. Participants received \$100 compensation for completing each study day.

2.5 Primary Outcome Measure

The Balloon Analogue Risk Task (BART) was used to measure risk taking as described by Lejuez and colleagues (Lejuez *et al.*, 2002). At the start of the BART, the computer screen displayed four items: a small balloon accompanied by a balloon pump, a button labeled “Collect \$ \$ \$”, and a “Total Earned” box which displayed the amount in the permanent bank. Each click on the pump inflated the balloon and added 1 cent to a temporary bank, the holdings of which were not indicated to the participant. When a balloon was pumped past a random explosion point a sound effect was triggered, all money in the temporary bank was lost, and the next un-inflated balloon appeared on the screen. At any point during each balloon trial, a participant could stop pumping the balloon and click the “Collect \$ \$ \$” button to transfer all money from the temporary bank to the permanent bank during which a slot machine payoff sound played to confirm payment. A new balloon appeared after each balloon explosion or money collection until a total of 30 balloons (i.e. trials) were completed. The probability of exploding on the first pump was set to 1/128 with an average break point of 64 pumps. Participants were given no precise information about the probability of explosion. Dependent variables included average adjusted pumps (AAP; the average number of pumps per balloon that did not explode), and number of balloons exploded (explosions; (Lejuez *et al.*, 2002). AAP is preferable to the average number of pumps because when a balloon explodes the pumps are constrained and thus it is impossible to know how many pumps the subject would have made if the balloon did not explode ((Lejuez *et al.*, 2002).

2.6 Behavioral Measures

Subjects completed behavior ratings (Physical Symptom Checklist and Subjective Visual Analog scale) immediately following the cognitive assessment. The investigator completed an Objective Visual Analog scale at this time as well. These measures were used to assess side effects and mood-related effects of the drugs.

The Physical Symptoms Checklist (PSCL) is a 22 item symptom rating scale in which subjects indicate on a four point scale their rating of each symptom using “this morning” as the reference time frame. This measure includes items measuring nausea, itchiness, headache, etc. and has been used to assess physical symptoms in many acute drug challenge studies (McNair *et al.*, 1971, Potter *et al.*, 2012, Potter and Newhouse, 2008, Van Kammen and Murphy, 1975).

The Subjective Visual Analog scale (SVA) consists of 8 different dimensions of function (anxiety, irritability, comfort, etc.). Subjects indicate on 100 mm lines how much of each item they have felt during the morning. Items are scored on a scale from 0 to 100. The Objective Visual Analog (OVA) was completed by the investigator to measure the same dimensions of functioning. Both of these measures have been used by our laboratory and

others to assess the effects of acute drugs on mood and arousal (Potter and Newhouse, 2004, 2008).

2.7 Data Analysis

Baseline demographic characteristics and performance were compared between groups using student's t-test for continuous and chi square for categorical variables. An a priori alpha level of 0.05 was used. Next, to determine differences related to drug condition and group on BART performance repeated measures mixed model ANOVAs with group as the between factor and drug as the within factor were completed using SAS v.9.0.

3. Results

3.1 Sex Differences in BART Performance

Given the known sex differences in BART performance (Lejuez *et al.*, 2002), initial analyses examined the effects of sex on performance to guide subsequent analyses. There were significant effects of sex on adjusted average pumps (AAP) [$t(24) = 2.96$, $p = .0068$], and explosions [$t(24) = 2.30$, $p = .0305$]. Males scored higher than females on both AAP (46.3 ± 2.26 vs 37.5 ± 1.93) and explosions (10.7 ± 0.85 vs 8.1 ± 0.73) consistent with the literature demonstrating higher risk taking for males than females. Therefore, sex was used as a covariate for all subsequent analyses examining the effects of drugs.

3.2 The Highly Impulsive ADHD Group is not High Risk Taking

There were no significant main effects of group on either AAP [$t(24) = 0.76$, $p = .4546$] or explosions [$t(24) = 0.30$, $p = .7675$] indicating that the highly impulsive ADHD group did not have elevated risk taking compared to the CTRL group. The drug by group interactions were not significant for AAP [$F(2,24) = 0.82$, $p = .3421$] or explosions [$F(2,24) = 0.55$, $p = .5865$]. There was a significant main effect [$F(2,24) = 4.01$, $p = .0313$] of drug on AAP, however neither MEC nor NIC was significantly different from PLC.

3.3 Characteristics of High Risk Takers

Given extant evidence for rate dependent effects of nicotine on cognition (Dews, 1977, Perkins, 1999) and the absence of a group difference on risk taking, we re-examined our sample to characterize baseline risk taking. A median split based on baseline risk taking propensity, AAP during first 10 balloons of PLC, was used to create a low risk taking group (LRT) and high risk taking group (HRT). The first 10 balloons were used based on literature demonstrating that group differences in risk taking are detectable with 10 balloons (Lejuez *et al.* 2003). Of the 12 subjects who were originally members of the highly impulsive ADHD group, 7 subjects were characterized as low risk taking (LRT) and 5 as high risk taking (HRT). Demographic comparisons between the two risk groups, as well as between the original ADHD/CTRL groups are presented in Table 1. The frequency of ADHD between the two risk taking groups was not significantly different and there were no significant differences between the groups on sex, age, estimated IQ, SSRT, or self-reported impulsivity (ImpSSS).

3.4 Rate Dependent Effects of Cholinergic Manipulations on BART Performance

Analysis of performance found a significant [$F(2,24) = 6.63$, $p = .0020$] drug by group interaction on AAP. The HRT group had significantly fewer pumps per balloon in the NIC condition compared to PLC (mean NIC 47.31 ± 1.9 , mean PLC 42.62 ± 2.0 ; [$t(24) = -2.68$, $p = .0134$] (Figure 1a) and the LRT group had fewer pumps per balloon in the PLC condition compared to the MEC (mean PLC 35.75 ± 2.0 , mean MEC 39.41 ± 2.3 , [$t(24) = 2.91$, $p = .0077$] condition (Figure 1b).

There was a significant [$F(2,24) = 6.26, p=.0027$] interaction of drug and group on the number of exploded balloons during the task. The HRT group exploded significantly more balloons than the LRT group during both the PLC [$t(24) = -3.85, p=.0008$] and MEC [$t(24) = -2.57, p=.0167$] conditions but not during the NIC condition (Figure 2).

3.5 Behavioral Measures and Side Effects

Both drug conditions were well tolerated and there were no serious adverse events. Mixed model ANOVAs found no significant differences on the Physical Symptom Check List (PSCL) total score, or on physical discomfort items on the subjective visual analog scale (SVA; i.e. physical comfort, headache) or the investigator completed objective visual analog scale (OVA; i.e. sweating, gastrointestinal distress).

Examination of mood related variables found no interaction of drug and group on any measure of the SVA or OVA. There were significant main effects of drug on the alertness [$F(2,24) = 10.32, p=.0006$] and sense of interest [$F(2,24) = 4.79, p=.0127$] items of the SVA with NIC associated with greater alertness and interest compared to PLC (Supplemental Table 1 contains full results from SVA and OVA). On the OVA there were significant main effects of drug on the drowsy [$F(2,24) = 19.79, p<.0001$] and alertness [$F(2,24) = 20.14, p<.0001$] subscales. Both MEC and NIC were significantly different from PLC on these items (Supplemental Table 1) with NIC associated with less drowsiness and more alertness while MEC was associated with greater drowsiness and lower alertness scores.

4. Discussion

This study found significant effects of single doses of nicotine and mecamylamine on risk taking as measured by the Balloon Analog Risk Task (BART). For individuals with high baseline risk taking propensity nicotine reduced risk taking. For subjects with low baseline risk taking mecamylamine increased risk taking. These findings suggest a broad role for nicotinic receptor functioning in the regulation of risk taking behavior for individuals with both pathological and non-pathological risk taking.

Previous work examining baseline dependent effects of d-amphetamine on BART performance in males (White *et al.*, 2007), found that 20 mg d-amphetamine significantly decreased risk taking in men with low reward sensitivity and increased risk behaviors in men with high reward sensitivity. It is interesting that d-amphetamine influenced risk taking in the opposite direction of the nicotine effects reported in the current study. This suggests that the mechanism for the nicotine effect on risk taking is likely different from the mechanism for the effect of d-amphetamine. Nicotine is known to stimulate the release of dopamine and norepinephrine in the brain (Clarke and Pert, 1985, Levin *et al.*, 1990, Rapier *et al.*, 1990) which has led to the suggestion that nicotinic potentiation of dopamine release may be a primary mechanism for many cognitive and behavioral effects of nicotine. The data from the current study are inconsistent with this notion, and instead fit well with data demonstrating that nicotine and methylphenidate (which blocks the uptake of norepinephrine and dopamine) have separable effects on cognitive function in human and animal models (Potter and Newhouse, 2004, 2008) presumably through separable mechanisms. Methodological differences between the two studies including characteristics of the subjects and the timing of drug dosing may also contribute to the discrepant findings. Future studies directly testing the effects of different neurotransmitter manipulations on risk taking are necessary to address these questions.

The Steinberg 2010 model of risk taking, which proposes that the interaction of impulsive responding and heightened reward sensitivity is related to high levels of risk taking in adolescents, may be useful for understanding the findings from pharmacological studies of

BART performance. We propose that in the current study nicotinic acetylcholine receptor function modulates risk taking both by improving impulsive responding (via cholinergic transients in prefrontal cortex) and by influencing reward processing (via dopaminergic modulation of the mesolimbic reward system). This fits with studies demonstrating that nicotine improves response inhibition in ADHD, an effect that is hypothesized to reflect cholinergic transients related to the occurrence of the stop signal (Potter *et al.*, 2012, Sarter *et al.*, 2009). This proposal is also consistent with the observation that nicotine increases dopaminergic activity in the VTA (Barr *et al.*, 2008) to modulate reward processing (Barr *et al.*, 2008, Mansvelder *et al.*, 2003). A recent study of drugs of abuse on an animal model of risk taking (Mitchell *et al.*, 2011) produced results that are also consistent with this theory. In their study, the probability of punishment was increased on successive task blocks allowing for assessment of risk behavior under punishment conditions that varied from no possibility of punishment to high probability of strong punishment. They found that nicotine reduced risk taking across all punishment conditions, while amphetamine affected risk taking only when punishment was possible and affected behavior to a greater degree as the probability of punishment increased. This may reflect greater effects of nicotine on response inhibition and attention than on reward processes, while amphetamine may affect both response inhibition and reward processes equally.

The results of the current study integrate well with numerous investigations in both humans and animals demonstrating rate dependent effects of nicotine across many cognitive and behavioral domains including impulsivity, sustained attention, recognition memory, short-term memory, complex reaction time, visual perception, rapid information processing, refined motor movements, and mood (reviewed by (Perkins, 1999, Potter *et al.*, 2012). The finding that manipulations of nicotinic acetylcholine receptor function affects both ends of the behavioral continuum (those high and low in risk taking) is intriguing and suggests that cholinergic system function may act to normalize behavior via multiple cognitive mechanisms acting in consort (i.e. impulsivity, risk taking, attention, etc.).

The original aim of this study was to examine the effects of nicotine on BART performance in individuals with ADHD, a population that was assumed to be high risk takers, and healthy controls. However, there were no group differences on BART performance between the ADHD and control groups. In the time between the recruitment of the study and data analysis, research emerged demonstrating that there is not a correlation between performance on the BART and the stop signal task (SST; (Fernie *et al.*, 2010, Reynolds *et al.*, 2006a). Our results are consistent with this literature. This finding likely relates to the complexities within the behavioral constructs of risk taking and impulsivity. The separability of risk taking and response inhibition within individuals with ADHD provides guidance for further studies of the neurobiological underpinnings of risk taking and impulsivity. Careful phenotypic characterization of the specific cognitive or behavioral operation under study is important given the behavioral heterogeneity of diagnoses such as ADHD. As risk taking, like most behavioral characteristics, exists in a continuum, it is reasonable to suggest that baseline performance may be a more informative way to measure drug-related changes to these types of behavioral processes.

Other possible reasons for the finding that the impulsive ADHD subjects were not high risk takers may relate to the gender breakdown within each group given that the control group was well balanced (8 males, 7 females), but the ADHD group was unbalanced (3 males and 8 females). Lejuez and colleagues (Lejuez *et al.*, 2002) first reported sex differences on performance of the BART, with males engaging in greater risk taking behavior than females, and similar sex differences were found on BART performance in the current study. Perhaps, the limited number of males with ADHD lowered the level of risk taking in the ADHD group. Alternatively, the relationship between risk taking and response inhibition may be

different for males and females who have ADHD given that all the ADHD subjects were screened for difficulties on response inhibition. Future research to systematically address these questions is necessary to understand this relationship.

Clinical Implications

The data suggest that there may be a behavioral benefit (regulation of risk taking behavior) gained from self-administration of nicotine in high risk taking individuals. Therefore, targeting nicotinic receptors may be a useful pharmacologic strategy to reduce risk taking behavior in individuals with pathological levels of risk taking. It will be important to move beyond reliance on DSM-IV diagnoses as the sole measure of pathological risk taking as our data and others support a dimensional approach to understanding pharmacological effects on complex behavior such as risk taking. In addition to implication for treating psychopathology, these data also have implications for smoking cessation. Nicotine withdrawal may increase risk taking behavior leading to poor decision making such as smokers placing themselves in situations where they are likely to relapse to smoking.

Future Directions

The separability of risk taking measured on the BART from related constructs such as impulsivity as measured on the SST, supports the use of the BART for further research to understand the neurobiology of risk taking. The finding that nicotinic cholinergic system function modulates risk taking is novel and may help to explain the high rates of smoking among individuals with behavioral dysregulation including high risk taking. Further studies combining pharmacological manipulations and functional brain imaging will help to clarify the neural systems related to different behavioral component processes of risk taking, (i.e. choosing whether or not to continue filling the balloon, experiencing the risk of filling the balloon, processing the feedback, modulating behavior on the next balloon) and to the regulation of neural networks by cholinergic and catecholaminergic neurotransmission.

Summary

Taken together the results of this study demonstrate that acute manipulation of nicotinic cholinergic receptor function has significant effects on risk taking behavior in the BART. These effects are dependent on baseline levels of risk taking such that for individuals with high baseline risk taking nicotine reduced risk taking behavior and for those with low baseline risk taking mecamylamine increased risk taking behavior. These findings cannot be explained by global effects of drugs on physical side effects, mood related variables, or arousal. There is a large literature demonstrating baseline dependent effects of nicotine on measures of cognition, behavior, and mood (Dews, 1977, Perkins, 1999), and results from the current study are consistent with this literature. While the mechanism for these effects on risk taking cannot be fully determined from this study, they are consistent with improved attention and/or impulse control via cholinergic neurotransmission in frontal cortex, likely in combination with regulation of reward processing related to cholinergic modulation of dopaminergic neurotransmission. Finally these results underscore the important distinction between risk taking and impulsivity as subjects who were carefully selected for clinical (ADHD diagnosis) and behavioral (SST performance) indices of impulsivity were not a high risk taking sample.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- This is the first report of the effects of cholinergic agents on the BART.
- ADHD subjects were not in higher risk taking than non-impulsive controls.
- There were rate dependent effects of nicotine and mecamylamine on BART performance.
- This study has implications for disorders characterized by pathological risk taking.

Figure 1.

Average adjusted pumps across drug conditions (LS Means). Abbreviations: HRT, high risk taking; LRT, low risk taking; AAP, adjusted average pumps; PLC, placebo; NIC, nicotine; MEC, mecamylamine. Error bars are SE. * $p < .05$, ** $p < .001$ different from PLC.

Figure 2.

Explosions across drug conditions by group (LS Means). Abbreviations: HRT, high risk taking; LRT, low risk taking; PLC, placebo; NIC, nicotine; MEC, mecamylamine. Error bars are SE. * $p < .05$, ** $p < .001$ different between groups.

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Table 1

Characteristics of 26 subjects at screening, by group. Data presented as Mean±SD unless otherwise specified. Between group p-values are from Chi-Square for categorical and from t-test for quantitative variables. CTRL, control; LRT, low risk taking; HRT, high risk taking; IQ, intelligence quotient; SST, stop signal task; SSRT, stop signal reaction time; BART, balloon analogue risk task; AAP, adjusted average pumps; ImpSSS, impulsivity and sensation seeking subscale.

	CTRL (n=15)	ADHD (n=11)	p-value	LRT (n=13)	HRT (n=13)	p-value
Sex (Female / Male)	7 / 8	8 / 3	0.1839	9 / 4	6 / 7	0.2337
ADHD / No ADHD	0 / 15	11 / 0	---	6 / 7	5 / 8	0.6914
Age	20.07±1.5	19.64±2.1	0.5520	19.69±1.5	20.08±2.0	0.5908
IQ	114.5±8.1	116.1±12.2	0.1822	114.7±12.2	115.6±6.5	0.8168
SST (SSRT; msec)	198.9±28.4	295.2±69.3	0.0009	247.3±73.6	234.7±67.2	0.6604
BART ^a (AAP)	39.47±2.6	41.09±4.3	0.7530	31.23±1.9	49.08±2.4	<0.0001
ImpSSS						
Total	8.07±3.39	9.80±5.16	0.3195	9.25±4.85	8.31±3.59	0.5839
Impulsivity	2.33±1.91	3.40±2.46	0.2353	3.00±2.30	2.54±2.11	0.6051
Sensation Seeking	5.73±2.19	6.40±3.41	0.5555	6.25±3.19	5.77±2.24	0.6703

^aBART was not administered at screening. Data from the first 10 trials on the PLC drug day (used to create the LRT and HRT groups) are reported.