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Effects of Acute Nicotine on Risk Taking in Individuals with Attention-Deficit/Hyperactivity Disorder and Age-Matched Controls

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EFFECTS OF ACUTE NICOTINE ON RISK TAKING IN INDIVIDUALS WITH
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AGE-MATCHED
CONTROLS

A Dissertation Presented

by

Katherine Ryan

to

The Faculty of the Graduate College

of

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In Partial Fulfillment of the Requirements
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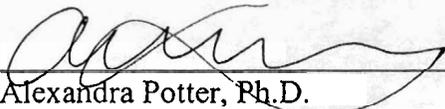
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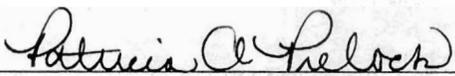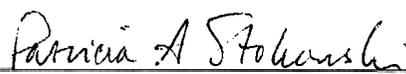Alexandra Potter, Ph.D.
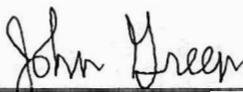
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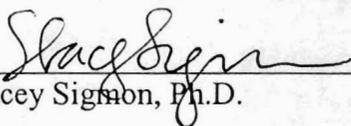
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ABSTRACT

ADHD is one of the most common childhood psychiatric disorders affecting 3-5% of all children. Between 50 and 80% of those diagnosed with ADHD in childhood will show symptoms that persist into adolescence and adulthood. ADHD is characterized by developmentally excessive activity, impulsivity, inattention, and disorganized, off-task behaviors. A high propensity for risk taking is seen in ADHD and is related to negative outcomes such as job failure, accidents and injuries, and substance use. In an attempt to better understand the behavioral and cognitive deficits associated with ADHD, several neuropsychological models have been proposed. We suggest that those models may be used to learn about risk taking propensity in ADHD.

Individuals with ADHD smoke cigarettes at twice the rate of individuals who do not have this diagnosis, and they have greater difficulty quitting. And smokers score higher on a behavioral task of risk taking propensity than non-smokers. 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. Previous work demonstrates that acute nicotine improves behavioral inhibition, working memory, and recognition memory in ADHD. This study examined the acute effects of nicotine on risk taking in non-smoking young adults with ADHD-Combined Type and healthy controls.

This single-dose, acute, double blind study assessed the effects of transdermal nicotine and placebo on 26 non-smoking young adults (15 healthy controls and 11 ADHD-C). Participants received acute nicotine (7 mg patch for 45 minutes) and placebo on separate days. The Balloon Analogue Risk Task (BART) was used to assess risk taking propensity. Behavioral ratings were completed daily by each subject and by the blinded investigator. Vital sign data were collected at 30 minute intervals throughout each study day.

There were no group differences or interaction of drug and group between the ADHD and control group on risk taking propensity. However, using a median split to identify subjects as either high or low in baseline risk taking there was a significant ($p<.05$) Drug by Group interaction with nicotine reducing risk taking in high risk taking subjects and increasing risk taking in the low risk taking subjects.

These findings are consistent with a large body of research demonstrating rate-dependent effects of nicotine on behavior, cognition and mood. Nicotine appears to modulate risk-taking in both high and low risk-taking subjects consistent with cholinergic modulation of behavioral decision making.

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Specific Aims

The purpose of this study is to examine the effects of acute nicotine on risk taking in young adults who are diagnosed with ADHD. High risk taking in individuals with ADHD is related to negative outcomes such as trouble with jobs, high incidence of accidents and injuries, antisocial behavior, difficulty with relationships, and of particular interest high rates of smoking and substance use. Risk taking in adolescence is associated with a pattern of brain immaturity resulting in less developed frontal cognitive control systems, and greater reliance on more mature limbic reward related structures. Recent research demonstrates a developmental delay in brain development in ADHD, with less efficient frontal networks, and more proficient reward related structures. Dopamine dysfunction is implicated in both risk taking and ADHD, and standard treatments for ADHD reduce symptoms via improving dopaminergic tone. One understudied strategy to correct deficits in dopaminergic function is through increased cholinergic transmission. There is a well documented relationship between dopaminergic and cholinergic systems, and research in ADHD-diagnosed populations demonstrates that nicotinic cholinergic agonists can improve impulsivity in ADHD. However, it is unknown if cholinergic stimulation affects risk taking in ADHD. Therefore, this study will examine the effects of acute nicotine administration on risk taking in young adults with ADHD. This proposal is an extension of several years of research in our laboratory into the role of nicotinic receptors on cognition in individuals with ADHD. This proposed study is unique in that it uses acute nicotine administration to specifically assess

risk taking in a clinical population that shows elevated risky behaviors. The research question to be addressed in this study is:

1. Is elevated risk taking (as measured on a standardized test) lessened and/or ameliorated by the administration of nicotine in young adults with ADHD?

The knowledge gained from this study will expand our understanding of the complex neurobiology of ADHD. The cholinergic system has not been well studied in this disorder and may prove to be an important key to advancing treatment. This study may directly inform several areas relevant to improving the lives of children and families with ADHD including: 1) guiding future drug development (e.g., cholinergic-mediated treatments for ADHD), 2) improving understanding of the behavioral and neurochemical deficits associated with ADHD, and 3) facilitating the identification of individuals who may be at high risk for substance abuse. In addition, the proposed study will generate preliminary data for subsequent larger scale investigations into the role of the cholinergic system in risk taking in ADHD using functional neuroimaging, genotyping for cholinergic markers, psychophysiological measures as well as examination of gender and sub-type differences in risk taking.

Section 1: Background and Significance

1.1. Attention Deficit/Hyperactivity Disorder (ADHD)

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood psychological disorders, occurring in as many as 3-5% of children (American Psychological Association (APA), 2000). ADHD is an early-emerging behavioral syndrome where the symptoms must be present before 7 years of age and approximately half of the cases report onset before 4 years of age (APA, 2000). ADHD is characterized by developmentally excessive activity, impulsivity, inattention, and disorganized, off-task behaviors. Hallmark behaviors include going off task with speech or activity, losing things, having trouble staying organized, not seeming to pay attention to what is being said or done, excess activity (in children, running around "as if driven by a motor"), loud, reckless play, and impulsive, even dangerous behavior (e.g., blurting out something that should not be said; darting out into traffic without looking). As a result of these behaviors, children with ADHD are far more likely than their peers to fall behind in school, to be suspended or expelled, to be rejected by peers and have few friends, and to be at risk for accidents and physical injuries (Hinshaw, 2002). This disorder is found more frequently in boys than girls, with ratios between 2:1 and 10:1 reported (APA, 2000).

While ADHD, by definition, has onset in childhood, 50 – 80% of children diagnosed with ADHD will show symptoms that persist into adolescence and adulthood (Barkley, Anastopoulos, Guevremont & Fletcher, 1991). As is seen with children, the symptoms of ADHD in young adults including impulsivity, inattention, and restlessness

(hyperactivity is seen less frequently in young adults) are disruptive and can lead to significant functional deficits (Barkley, 1990; Hechtman, 1991). These deficits can include poor school or work performance, trouble getting along with peers, motor difficulties, increased rates of anxiety and/or depression, marital problems, injuries, as well as antisocial behaviors, alcohol and substance use and dependence, and aggression (Barkley, 1991; Barkley, Murphy, & Kwasnik, 1996a, 1996b; Biederman, Farone, Keenan, Steingard, & Tsuand, 1991).

1.1.2. Risk Taking in ADHD

Avoidable risk taking and poor decision-making in everyday circumstances have been described as key features of ADHD (Barkley, Fischer, Smallish, & Fletcher, 2006; Williams & Taylor, 2006). Risk taking may be defined as the engagement in a behavior that involves the potential for gain balanced by the potential of negative consequences resulting from that behavior (Jessor, 1998; Lejuez et al., 2002). Real-world risk taking behaviors like substance use, unprotected sex, breaking the law, and gambling often have deleterious effects on health and livelihood. Unfortunately, there is much we do not know about risk taking and ADHD such as the neurobiological underpinnings and models of the core cognitive processes underlying this behavior.

1.1.3. Neuropsychological Models of ADHD

In an attempt to better understand behavior associated with ADHD, several neuropsychological models have been proposed. They have focused on the core cognitive deficits that may underlie behavioral symptoms in ADHD. Initial approaches included studies of executive function deficits in ADHD including sustained attention (Posner & Raichle, 1994), working memory (Barkley, 1997), complex organization and planning (Barkley, 1997; Pennington & Ozonoff, 1996), and temporal information processing (Barkley, Edwars, Laneri, Fletcher, & Metevia, 2001; Zakay, 1992). However, executive function represents a broad array of cognitive functions and thus may have limited utility in precisely characterizing core deficits in ADHD. In recent years two particularly promising theoretical models (i.e., Behavioral Inhibition and Delay Aversion) have emerged which identify measurable aspects of cognition disrupted in ADHD, and provide complete theoretical models for how these deficits lead to functional impairments (i.e., symptoms) in ADHD. Behavioral Inhibition emphasizes deficient inhibitory control and Delay Aversion emphasizes impaired signaling of delayed rewards arising from disturbances in motivational processes (Barkley, 1997; Sonuga-Barke, 2002). It has been proposed that there is a dual pathway that underlies the behavior associated with ADHD including both the behavioral inhibition and delay aversion pathways (Sonuga-Barke, 2002, Sonuga-Barke, Dalen, & Remington, 2003). These models, which have been applied to understanding the neurobiology of impulsive behavior in ADHD, may be useful for investigating risk taking.

1.2. The Behavioral Inhibition Model

Barkley (1997) posited that symptoms of ADHD are caused by the disruption of cognitive control systems, resulting in brain– behavior relations that are mediated by deficits in inhibitory processes (Barkley, 1997). Behavioral inhibition refers to three interrelated processes: (a) inhibition of the initial prepotent response to an event; (b) stopping an ongoing response, which thereby permits a delay in the decision to respond; and, (c) the protection of this period of delay and the self-directed responses that occur within it from disruption by competing events and responses (interference control). Barkley (1997) hypothesized that in ADHD the inability to prolong the delay in motor responding hinders the ability to use this delay to process incoming information and to use executive functions as needed to direct behavior. Therefore, without the capacity to delay responses long enough to fully process contextual cues, and compare the current situation to past experiences, individuals with ADHD react in a characteristically impulsive manner. This impulsive behavioral style in those with ADHD leads to behavioral disruptions that impair personal relationships with friends and family, interfere with traditional learning systems in schools, and create difficulties at work.

Behavioral inhibition is measured in the laboratory using the Stop Signal Task (SST). This task is a good measure of "pure" inhibition, or inhibition that is not influenced by reward seeking (Logan & Cowan, 1984). In this task, participants respond to target stimuli as quickly as they can. They are subsequently instructed not to respond when an auditory signal, the stop signal, is present. This stop signal is then introduced on a fixed number of trials at varying latencies from the presentation of the target stimuli. The probability of successfully inhibiting a response is a function of the latency of the

stop signal and the subject's reaction time to the target. By forcing the probability of successfully inhibiting the response to remain at 50 percent, the speed of inhibition, or the stop signal reaction time (SSRT), can be calculated as follows: SSRT = Mean Go Reaction Time – Delay (needed to achieve 50% stopping success).

Several research groups have demonstrated that children and young adults with ADHD are significant slower at inhibiting a response to the target stimulus when the tone is present compared to normal controls, children with pure Conduct Disorder, and anxious children (Schachar & Logan 1990; Schachar, Tannock, Marriott, & Logan, 1995). In a recent meta-analysis, Willcutt, Doyle, Nigg, Faraone, & Pennington (2005) found the most consistent deficit between individuals with and without ADHD occurred on the Stop Signal Reaction Time (SSRT) measure of the Stop Signal Task.

1.2.1. Behavioral Inhibition and Risk Taking

This model may be useful in understanding risk taking in ADHD. Increased risk taking may arise because individuals with ADHD do not fully process contextual cues or create the space to compare past experiences to the current situation in order to predict outcomes, and therefore are more likely to engage in a behavior without a complete assessment of the risk involved. For example, an individual with ADHD may accept an alcoholic beverage without taking the time to examine if they have a designated driver to allow them to get home safely that evening, even though the last time they did this they needed to call a cab. Or an individual with ADHD may be more likely to engage in

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unprotected intercourse because they have not taken the time to process social cues that suggest this is risky.

1.2.2. Neurobiology of Behavioral Inhibition

The Stop Signal Task measures the speed at which an individual inhibits a pre-potent response. In other words, this task creates a race between the "go" and "stop" response. For an individual to be successful, the "go" response, which is initiated first, must be overcome by the "stop" response. The neurobiological processes involved in performance of the Stop Signal Task have been well studied and show consistent and specific activation of the right-lateralized inferior frontal cortex (IFC) (Garavan, Ross, & Stein, 1999; Garavan, Ross, Murphy, Roche, & Stein, 2002; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Konishi, Kawazu, Uchida, Kikyo, Asakura, & Miyashita, 1999; Menon et al., 2001; Rubia et al., 2003). This is supported by a study demonstrating that this region (but not other regions of right or left PFC) was shown to be crucial in a group of patients with unilateral right-PFC damage (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003a).

The underlying processes involved in the stop signal task have been further characterized and the circuitry involved in both the "go" and "stop" processes have been delineated. Motor activity is modulated by a series of control loops or pathways involving cortical and subcortical structures that alter the activity of the output nuclei of the basal ganglia (Aron & Poldrack, 2006). Recently, functional imaging studies have demonstrated the importance of the subthalamic nucleus (STN) and the hyperdirect

pathway in playing a critical role in the "stop" process in the stop signal reaction-time task (Aron & Poldrack, 2005). Aron and Poldrack (2006) using functional magnetic resonance imaging (fMRI) demonstrated that stop signal response inhibition operates by activating the STN to suppress an initiated Go response. The Go process activated motor areas contralateral to the response hand including primary motor cortex, supplementary motor area (SMA), thalamus, and pallidum as well as putamen, consistent with the direct frontostriatal pathway, whereas the Stop process activated predominantly ipsilateral IFC, pre-supplementary motor area, globus pallidus and STN. Furthermore, activation was significantly greater in IFC and STN for fast inhibitors than slow ones, was significantly correlated across subjects, and was significantly greater in the right than left hemisphere. A second high-resolution experiment verified significant stopping activation in the immediate vicinity of right STN.

1.2.3. Dopamine, ADHD, and Behavioral Inhibition

Dopamine and norepinephrine have been the most well-studied neurotransmitters in ADHD (Pliszka, McCracken, & Maas, 1996; Solanto, 2002). Current treatment for the symptoms of ADHD consists mainly of psychostimulants (e.g., methylphenidate) that are thought to exert their effects by increasing both dopaminergic and noradrenergic neurotransmission (Solanto, 2002). The prevalence of stimulant medication use is high, with 93% of all children medicated for ADHD taking stimulant medications (Rowland, Umbach, Stallone, Naftel, Bohlig, & Sandler, 2002). Stimulant medications significantly reduce ADHD symptoms measured by both parent and teacher ratings, including

reductions on ratings of activity levels, hyperactivity/impulsivity and inattention (MTA research group, 1999; Spencer et al., 1996; Spencer et al., 2001; Swanson et al., 1998). In addition, psychostimulant treatment has been shown to improve "non-ADHD" symptoms such as teacher reported social skills (MTA research group, 1999), and aggressive behavior in the school setting (Swanson et al., 1998) contributing to improvements in classroom performance (MTA research group, 1999, Spencer et al., 1996; Spencer et al., 2001). Importantly, research has demonstrated that acute doses of methylphenidate significantly improve performance on the stop signal task in persons with ADHD (Aron, Dowson, Sahakian, & Robbins, 2003b; Pliszka et al., 2007; Potter & Newhouse, 2004). These effects are presumably through enhanced dopamine function supporting more efficient processing of the stop signal.

1.3. The Delay Aversion Model

In contrast to the behavioral inhibition model of ADHD, several motivation-based models have been proposed to explain ADHD. These models swing the focus from core deficits in inhibitory control to suboptimal reward processing. The delay aversion model (Sonuga-Barke, 2002) posits that individuals with ADHD are unwilling to delay their need for gratification and therefore they make rational choices to avoid delay. In this model, the motivation to escape or avoid delay surpasses the motivation for good performance and task related reward. Sonuga-Barke and colleagues (1992) showed that, when given a choice between a small immediate reward and a large delayed reward, children with ADHD chose the immediate reward, but only when this led to shorter total task duration irrespective of the amount of reward available. Therefore, in this model,

ADHD is conceptualized as the outcome of impairment in the power and efficiency with which the contingency between present action and future rewards is signaled. This impairment leads to a reduction in the control exerted by future rewards on current behavior, a dilution in their "value," and an increase in the extent to which they are discounted (i.e., a steeper delay of reward gradient) (Sonuga-Barke et al., 1992). This account is supported by the consistent finding that children with ADHD often display hypersensitivity to delay and consequent difficulties in waiting for motivationally salient outcomes, as well as in working effectively over extended periods of time (Kuntsi, Oosterlaan, & Stevenson, 2001; Neef, Bicard, & Endo, 2001; Schweitzer & Sulzer-Azaroff, 1995; Sonuga-Barke, Williams, Hall, & Saxton, 1996; Tripp & Alsop, 2001).

The delay aversion hypothesis has been experimentally tested using the Choice Delay Task (CDT) in which the subject repeatedly chooses between a smaller-sooner and a larger-later reward. This 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 show significantly greater smaller-sooner reward choices than control children (Solanto et al. 2001; Sonuga-Barke et al. 2003).

Delay aversion shares conceptual overlap with the construct delay discounting. Discounting of delayed reinforcers refers to the observation that the value of a delayed reinforcer is discounted (reduced in value or considered to be worth less) compared to the value of an immediate reinforcer (Bickel & Marsch, 2001). Indeed, to the extent that most individuals would prefer a reinforcer now rather than that same reward later, the discounting of delayed reinforcers is intuitive. The notion of discounting of delayed

rewards provides an explanation of impulsivity, here defined as the selection of a smaller more immediate reward over a larger more delayed reward. Delay discounting tasks have been widely used in the substance abuse field and have repeatedly shown that drug users behave more impulsively (greater discounting of delayed reward) than non-users (Bickel et al., 2007). However, delay discounting has not been studied in individuals with ADHD, whereas delay aversion has been extensively studied in ADHD. And, the two constructs, delay aversion and delay discounting, have an important methodological difference. In the delay aversion task, choosing a smaller reward allows the individual to complete the task faster. Sonuga-Barke, and colleagues (1992) showed, that when the smaller reward did not allow individuals with ADHD to escape the task sooner, they performed no differently than controls.

1.3.1. Reward Processing in ADHD

The delay aversion model has arisen from the literature demonstrating abnormal sensitivity to reinforcement, including reward, punishment, and reinforcement schedules in ADHD (Johansen, Aase, Meyer, & Sagvolden, 2002; Luman, Oosterlaan, & Sergeant, 2005; Sagvolden, Johansen, Aase, & Russell, 2005). An extensive literature documents abnormalities in the ability of children with ADHD to adapt their behavior in response to rewards and punishments (see Luman et al., 2005 for review). According to Sagvolden et al. (2005), children with ADHD have a shorter and steeper delay-of-reinforcement gradient. The delay gradient describes the time interval between the response and reinforcer and its relation to the impact of a reinforcer. The reinforcing effect is largest,

when the reinforcer is delivered immediately after the response. In children with ADHD,

unlike normally developing peers, only responses in close proximity to a reinforcer will

be conditioned (Johansen et al., 2002; Sagvolden et al., 2005). In addition, relatively few

correct responses between the delivery of two consecutive reinforcers will be maintained.

As a result, the association between response and reinforcer is less consistent in

individuals with ADHD. Behavioral observations demonstrate that individuals with

ADHD require stronger and more salient reinforcers to control their behavior and are less

sensitive to changes in reinforcement contingencies (Johansen et al., 2002). Further,

excessive responding is observed during extinction in children with ADHD and in an

animal model of ADHD (Sagvolden, Aase, Zeiner, & Berger, 1998; Sagvolden, 2000).

1.3.2. Reward Processing and Risk Taking

This model can be useful in understanding risk taking in ADHD. Increased risk

taking may arise because individuals with ADHD have an increased sensitivity to

immediate, powerful rewards, as well as a decreased sensitivity to lack of

reward/punishment leading to an increased propensity towards risk taking. For example,

an individual with ADHD may be particularly sensitive to the immediate and strong

effects of alcohol or drug use, to the physiological arousal of gambling money or

speeding on the highway, or to the immediate satisfaction of having sex without taking

time to find a condom so is likely to engage in these behaviors at high rates. Or, an

individual with ADHD may be particularly insensitive to long term health costs of drug

use, money lost during gambling, the ticket earned from speeding, or the risks of sexually

transmitted disease or pregnancy during unprotected sex, and therefore, continues to engage in these risky behaviors.

1.3.3. Neurobiology of the Reward Processing Model

The dopamine system is composed of the three branches of the dopamine system, the mesocortical circuit associated with attention and behavioral organization, the mesolimbic circuit associated with reinforcement and extinction processes, and the nigrostriatal circuit associated with motor functions (Sagvolden et al., 2005; Spanagel &Weiss, 1999). Starting in the midbrain, dopaminergic projections that originate in the ventral tegmental area (VTA) project to the structures closely associated with the limbic system, most prominently the nucleus accumbens (NAcc) shell region and the prefrontal cortex. Synaptic dopamine-mediated transmission in the NACcc shell region is increased preferentially not only by natural rewards such as food, water and sex, but also by a variety of drugs abused by humans including nicotine (Spanagel &Weiss, 1999). Sagvolden and colleagues (2005) argued that the two main behavioral processes causing ADHD are altered reinforcement of novel behaviors and deficient extinction of previously reinforced behavior. Extending this model, the behavioral deficits seen in ADHD may be related to dysfunction in the mesolimbic circuit of the dopamine system, which likely interacts with the mesocortical circuit associated with deficient attention and poor behavioral organization and perhaps the nigrostriatal circuit associated with motor function (Figure 1).

Figure 1. Dopamine System
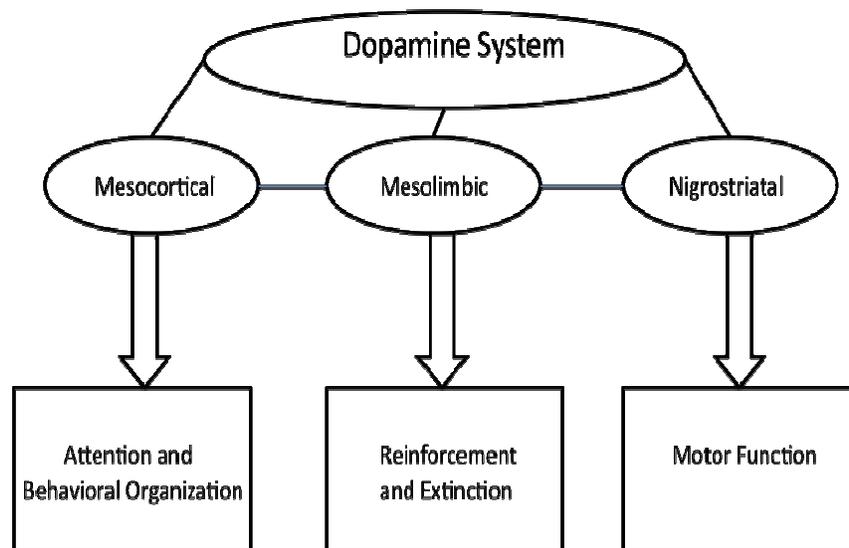
Extracellular dopamine levels are characterized by low, tonic background activity and short-lasting phasic activity (Schultz, 1998). During reinforcement phasic dopamine release occurs in the nucleus accumbans shell (Schultz, 1998). When a specific behavior is followed with reward, a process called acquisition, phasic dopamine release occurs as the primary reward is presented. Dopamine activation is associated with reinforcer unpredictability, reinforcer value, and timing of the reinforcer (earlier presentation elicits greater activation) (Johansen et al., 2002). As the individual learns to reliably predict the reinforcer, the dopamine signaling transfers from the primary reward to the earliest stimulus that predicts future reinforcement. For example, if an individual is rewarded for coming to the dinner table when called, initially dopamine activation will occur as the reward is presented. As the individual learns that the behavior, coming to the dinner table when called, is followed by reinforcement, the dopamine activation will transfer to the earliest stimulus that predicts this reinforcement, hearing the parent call out "dinner is ready." Therefore, dopamine activation may be seen as a teaching signal working according to a prediction rule (Schultz, 1998). When a reward is greater than expected or occurs earlier than expected there is phasic dopamine activation following that reward. Omission of predicted reinforcers (extinction) and reinforcers with a lower than predicted reinforcer value are signaled by a phasic decrease in tonic dopamine activity (Schultz, 1998).

Numerous researchers have argued that the symptoms of ADHD are caused by a deficit in reinforcement processes, in part, due to a hypoefficient central nervous

dopaminergic system (Johansen, et al., 2002; Sagvolgen, et al., 1998; Sagvolden &

Sergeant, 1998; Sagvolden et al., 2005). This model primarily implicates dysfunction of

the mesolimbic dopamine branch that produces the altered reinforcement and extinction

processes as the underlying mechanism for the symptoms of ADHD (Johansen et al.,

2002). Johansen and colleagues (2002) argued that the delay-of-reinforcement gradient is

shorter in ADHD than in healthy individuals, which suggests that only the behaviors

followed closely by the delivery of a reinforcer will be effectively reinforced. The

shorter delay-of-reinforcement gradient observed in individuals with ADHD suggests

they experience dopamine dysfunction that may lead to a reduced tonic dopamine level.

Assuming the same phasic extracellular dopamine level is needed in individuals with

ADHD as in healthy controls for reinforcement to take place, individuals with ADHD

will require an increased release of dopamine following reward to affect a sufficient

number of dopamine receptor associated ion channels for reinforcement to take place.

This argument is in agreement with behavioral observations where individuals with

ADHD require stronger and more salient reinforcers to control their behavior (Johansen

et al., 2002; Schultz, 1998).

The reduced tonic dopamine level would also influence the extinction process

(Johansen et al., 2002). Omission of a predicted reinforcer (extinction) is normally

signaled by a depression in tonic dopamine activity. If an individual has a low baseline

level of tonic dopamine already, the extinction signal may fail to produce change due to a

floor effect. This view is consistent with behavioral observations that individuals with

ADHD are less sensitive to changes in reinforcement contingencies and with studies

finding excessive responding during extinction in children with ADHD and in an animal model of ADHD (Sagvolden et al., 1998; Sagvolden, 2000).

In summary, a propensity to take risks contributes to undesirable outcomes in ADHD including trouble with jobs, high incidence of accidents and injuries, and difficulty with relationships. However, the propensity to engage in risk taking is understudied in this population. The leading neuropsychological models of ADHD have only been used to study impulsive behavior to date. Our understanding of the heightened propensity for risk taking among individuals with ADHD may be informed by both the behavioral inhibition and reward processing models of ADHD. Therefore, in this study, risk taking in ADHD will be studied using the behavioral inhibition and delay aversion models.

1.4. Risk Taking and ADHD

1.4.1. Developmental Neurobiology of Reward

Onset of risk taking behavior typically occurs during adolescence (Spear, 2000). By definition, developmental changes in behavior and cognition coincide with changes in the brain. In order to better understand the developmental shift towards risky behavior during adolescence, research has begun to examine the link between neuroanatomical and neurocircuitry development and behavioral or cognitive changes. Research in adolescents indicate that an underdeveloped prefrontal network coupled with an over-reliance on reward systems during the decision making process creates a propensity towards risk taking (Galvan et al., 2006).

Adolescence is characterized by continued structural and functional development of frontostriatal circuitry implicated in behavioral regulation and reward processing. Human imaging studies show developmental frontostriatal region changes that seem to parallel increased cognitive control (Casey et al., 1997; Rubia et al., 2000). These changes suggest there is an activation shift of prefrontal regions from diffuse to more focal recruitment across development (Casey et al., 1997). Casey and colleagues (1997) observed a greater volume of activity in the prefrontal cortex in children during performance of a Go/No-Go task relative to adults suggesting they are less efficient at using neural resources to inhibit compelling responses. The authors argue that the findings may be attributed to specific developmental differences in the cognitive processes required when performing the task. Specifically, they suggest that the diffuse recruitment of the prefrontal cortex may reflect children having to activate more of this brain region to maintain the representation of task-relevant information. Interestingly, the four best performers of the children (i.e., least number of false alarms) had the most middle frontal activation (Casey et al., 1997). The authors suggest that the decrease in the volume of activation seen with adults may correspond to an increase in neural selectivity as an individual becomes more efficient at representing contextual information with age, especially within the context of conflicting information. The behavioral implication of this developmental process is greater impulsive responding leading to risk taking behaviors during adolescence.

In animal models, periadolescent rats have shown increases in reward-related dopamine transmission in the striatum (Laviola, Adriani, Terranova, & Gerra, 1999), and

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nonhuman primates have shown increased dopaminergic innervation in the prefrontal cortex (PFC) (Rosenberg & Lewis, 1994). Recent human neuroimaging studies have examined reward-related processing in adolescents and shown nucleus accumbens (NAcc) activation similar to that in adults. Galvan and colleagues (2006) used fMRI to examine behavioral and neural responses to reward value manipulations across development. This research suggested that adolescents differ from both children and adults in the patterns of brain activation in response to reward, appearing more like children in the frontal networks and more like adults in reward regions during reward processing (Galvan et al., 2006). Taken together, the developmental neuroimaging data suggest there is a slower maturation of frontal control systems relative to reward regions implicated in appetitive behaviors. This likely contributes to increased risk taking in adolescents as they are driven more by reward systems than frontal systems. Further, immature prefrontal activity in adolescence might hinder appraisal of the potential costs and benefits of risky choices, and therefore frontal networks may be less influential in evaluating outcome than the reward driven NAcc.

1.4.2. ADHD Brain Development

There is consistent empirical evidence suggesting that the brains of children with ADHD are significantly smaller, on average, than the brains of healthy control children throughout childhood and adolescence (Castellanos et al., 2002; Durston et al., 2001, 2004). For example, Castellanos and colleagues (2002) found that children with ADHD showed overall cerebral volumes that were 3.2% smaller than controls. The prefrontal

cortex (PFC) has consistently been shown to be significantly smaller in ADHD children than controls (Castellanos et al., 1996; Durston et al., 2004; Filipek et al., 1997; Kates et al., 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002) and in their unaffected siblings (Durston et al., 2004).

Neuroimaging studies have also revealed anatomical alterations of dopamine-enriched brain areas. These investigations have reported smaller and less active striatal neural networks and reduced dopamine metabolism in the cortex of patients with ADHD (Castellanos et al., 1996; Ernst, Zametkin, Matochik, Jons, & Cohen, 1998). Both volumetric and asymmetry differences have been documented in the caudate between ADHD and control groups (Aylward et al., 1996; Castellanos et al., 2002; Hill et al., 2003), but these findings have not been consistent across studies with some groups finding no differences (Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002; Pineda et al., 2002). Studies of the putamen have yielded equally ambiguous results. Some groups investigating putamen volume have found no significant differences (Aylward et al, 1996; Castellanos et al., 1996). However, a preliminary functional imaging study found decreased blood flow in the putamen of objectively hyperactive boys with ADHD compared to boys whose activity level resembled that of controls (Teicher et al., 2000). Further, it has been found that the globus pallidus, which receives input from caudate and putamen, is significantly smaller in boys with ADHD (Aylward et al., 1996; Castellanos et al., 1996), but the data are mixed as to whether the size reduction was greater in the left or right side. Children with head trauma and damage to the basal ganglia have a high incidence of secondary ADHD (S-ADHD) (Krain & Castellanos, 2006). One study of 99

children who suffered closed head injury found the odds of developing S-ADHD were

3.6 times higher among children with thalamus injury and 3.2 times higher in children

with basal ganglia injury (Gerring et al., 2000). In addition, volumetric MRI studies of

the cerebellum in ADHD have detected smaller cerebellar hemispheric volumes (up to

6%), which are sustained through adolescence (Berquin et al., 1998; Durston et al., 2004;

Hill et al., 2003).

1.4.3. Neurobiology of Risk Taking in ADHD

ADHD has been conceptualized as a disorder of developmental delay where

prefrontal networks mature at a slower rate and therefore a higher reliance on the reward

networks develops. This developmental process likely contributes to exaggerated risk

taking in ADHD. Studies of the neuropharmacolgy, genetics, and neuropsychology of

ADHD show considerable evidence that the neurobiological underpinnings of ADHD lie,

at least to a major degree, with dysregulation of brain catecholaminergic systems in the

prefrontal cortex (PFC) and its connections to striatal areas (Durston, 2003; Arnsten &

Dudley, 2005), which are the same systems implicated in risk taking (Galvan et al.,

2006). Therefore, the developmental delay in frontal control systems may be implicated

in the high incidence of risk taking behaviors observed in young adults with ADHD.

1.5. Cholinergic System and ADHD

The role of dopamine in both risk taking and ADHD is well established.

Manipulations of dopamine function are associated with clinical improvements as well as

normalization of impulsivity in ADHD (Aron et al., 2003b; MTA research group, 1999; Pliszka et al., 2007; Potter & Newhouse, 2004). However, this explanation is insufficient to fully explain either risk taking or ADHD dysfunction. In recent years an interest in the cholinergic system has developed based on the association of ADHD and smoking (Pomerleau, Downey, Stelson, & Pomerleau, 1995), clinical studies of nicotine and nicotinic agonists in ADHD (Levin et al., 1996; Wilens et al, 1999), and the beneficial effects of nicotine on specific cognitive deficits in ADHD (Potter & Newhouse, 2004; 2008).

1.5.1. ADHD and Smoking

In 2006, an estimated 72.9 million Americans aged 12 or older were current (past month) users of a tobacco product (U.S. Department of Health & Human Services, 2006). Young adults aged 18 to 25 had the highest rate of current use of a tobacco product (43.9 percent) (U.S. Department of Health & Human Services, 2006). Most new smokers in 2006 were under age 18 when they first smoked cigarettes (61.2 percent) (.S. Department of Health & Human Services, 2006). While there are four widely recognized risk factors for smoking (socio-demographic, environmental, behavioral, and personal) (U.S. Department of Health & Human Services 1994), it may be the case that certain brain disorders of childhood, namely ADHD, are an additional risk factor and place children at higher risk of becoming cigarette smokers (Potter, Newhouse, & Bucci, 2006).

A recent meta-analysis (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003) reported a significant co-occurrence of ADHD (as well as CD and ODD) and substance

abuse. Although it is possible that comorbid CD may explain part of the association between ADHD and substance abuse, carefully controlled studies indicate that nicotine dependence is affected by ADHD independent of CD (Disney, Elkins, McGue, & Iacono, 1999; Milberger et al., 1997).

Adults and adolescents who are diagnosed with ADHD smoke at significantly higher rates than comparable people in a community sample, and have lower quit ratios than the general population (23% versus 51.6%; (Pomerleau et al., 1995). Pomerleau and colleagues (1995) found 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 and substance dependence (Lambert & Hartsough, 1998) found that by age 17, 46% of adolescents with ADHD were smoking cigarettes daily compared with 24% of age-matched controls. This finding continued into adulthood where 35% of adult subjects with ADHD were smokers as compared to 16% of age-matched controls. The strength of these findings provides a solid theoretical basis for the notion that individuals with ADHD may use smoking as a form of nicotinic self-medication to reduce ADHD symptoms.

1.5.2. Clinical Effects of Nicotine in ADHD

Recent investigations of nicotinic agents in ADHD have shown promising symptomatic improvement in both adolescents and adults with ADHD (Levin et al., 1996; Wilens et al., 1999; Wilens, Verlinden, Adler, Woznia, & West, 2006). Acute

transdermal nicotine has been shown to produce significant improvements in self-rated vigor and concentration, and observer rated illness severity (Levin et al., 1996). In a second study (Levin, 2002), 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 novel cholinergic channel activators (nicotinic agonists) and found significant improvements in subjective ratings of attentiveness and observer-rated illness severity on a clinical global impressions scale (Wilens et al.,1999) and improvements in symptom scores, ADHD index hyperactive/impulsive ratings, and clinical global impression (Wilens et al., 2006). 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.

1.5.3. Nicotine and Behavioral Inhibition in ADHD

Recently the effects of acute nicotine administration on behavioral inhibition in both nonsmoking adolescents and young adults with ADHD have been examined (Potter & Newhouse, 2004; 2008). 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 Stop Signal Reaction Times (SSRTs). Data from a second study extended the finding of a

positive effect of nicotine on behavioral inhibition to young adults with ADHD.

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. These data may suggest cholinergic modulation of this behavioral deficit in people

with ADHD.

1.5.4. Nicotine and Dopamine

There are a variety of mechanisms and anatomical loci where dopaminergic and

cholinergic systems may interact, possibly mediating the positive effects of nicotine on

individuals with ADHD. Nicotine has been shown to increase the release of a number of

neurotransmitters, including dopamine (Rapier, Lunt, & Wonnacott, 1990; Wonnacott,

Irons, Rapier, Thorne, & Lunt, 1989). Nicotinic receptors may serve to regulate

dopamine release in both striatal and mesolimbic pathways (Rapier et al., 1990, Clarke &

Pert, 1985). Levin and colleagues 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

(Levin et al., 1990). Nicotinic blockade appears to impair working memory in the rat,

(Levin et al., 1990), and in humans (Newhouse, Potter, Corwin, 1996). 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. 1990). Nicotinic receptors modulate catecholaminergic transmission, particularly dopaminergic release (Grady, Marks, Wonnacott, & Collins, 1992), suggesting a tight relationship between the two systems.

1.6. Risk Taking and the Balloon Analogue Risk Task

To prevent or ameliorate potential negative outcomes associated with risk taking researchers have attempted to better understand this behavioral phenomenon (Lejuez et al., 2002). Reliable and accurate assessment of these patterns of risk behavior is crucial to facilitate early identification and intervention for individuals with a high probability of engagement in such behaviors.

The assessment of risk taking has traditionally relied on self-report measures of constructs like impulsivity (Barratt & Patton, 1983), sensation seeking (Zuckerman, 1994, Zuckerman, Eysenck & Eysenck, 1978), and venturesomeness (Eysenck, 1983). Self-report measures are limited for various reasons including limited construct validity, bias in responding, and, limited response options leading to decreased variability on these measures. The utility of using laboratory tasks rather than self-report forms to measure impulsivity is two-fold. First, a laboratory task provides an objective measure of a behavior that is linked to an underlying theory. Second, through research the underlying neurobiology of the behavioral output from laboratory tasks can be understood. Further, laboratory measures can be manipulated in experiments allowing further research into the underlying neurobiology of the behavior.

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In the laboratory, risk taking can be measured using the Balloon Analogue Risk Task (BART) developed by Lejuez and colleagues (2002). In this task, participants accumulate money in a temporary bank by pressing a button that inflates a simulated balloon. Each balloon has an explosion point, which if reached, results in the loss of all money in the temporary bank. After each pump that does not result in an explosion, participants have the option of pressing a collect button that will transfer their money to a permanent bank. There is a set number of balloons, and regardless of whether the balloon explodes or money is collected, the participant moves on to the next balloon. Therefore, in deciding whether to make each pump, the participant must balance the potential gain of accruing more money against the potential risk of losing all money accrued for that balloon. The BART involves a variable number of choices in a context of increasing risk (i.e., the amount of money accrued and the probability of losing that money increase with each pump of the balloon). In BART trials, a subject can either (1) perform repeatedly a risk-taking behavior that usually is reinforced with gains of money but sometimes (and unpredictably) is punished with loss of money or (2) perform a conservative behavior that terminates further risk taking, saving currently accumulated money.

Lejuez and colleagues (2003a) compared smokers and nonsmokers on the BART, the Bechara Gambling Task (BGT) (Bechara, Damasio, Damasio, & Lee, 1999), and self-report measures of impulsivity and sensation seeking. The participants performed each behavioral task three times. The data showed that smokers scored higher than nonsmokers, indicating greater risk taking propensity, across all administrations of the

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BART. Logistic regression analyses indicated that the BART and the Sensation Seeking

Scale were predictors of smoking status. This data demonstrates that the BART reliably

discriminates between smokers and nonsmokers suggesting a role for the cholinergic

system in risk taking.

Nicotine self-administration is associated with increased responsiveness to

reward, whereas nicotine withdrawal is associated with refractoriness to reward (Epping-

Jordan, Watkins, Koob, & Markou, 1998). As noted earlier, phasic dopamine release

occurs during presentation of reward and modulates the salience attribution of reward

(Schultz, 1998). Nicotine may increase appetitive responding for reward via activation of

presynaptic nicotinic receptors (nAChRs) on mesocorticolimbic dopaminergic neurons

(Dani & Harris, 2005; Kenny & Markou, 2006). Consistent with this hypothesis, nicotine

enhances the incentive value of monetary reward in smokers following overnight

abstinence. Barr, Pizzagalli, Culhane, Goff, & Evins (2008) manipulated response bias

during a laboratory task to demonstrate the effects of acute nicotine on reward

responsiveness. A signal detection task, designed to measure shift in responding toward

a differentially (more) rewarded stimulus, was administered twice, in two separate

sessions, 3 hours after nicotine patch and after placebo patch application as an objective

measure of reward responsiveness (Pizzagalli, Jahn, & O'Shea, 2005, Tripp & Alsop,

1999; 2001). For each trial, participants were asked to choose which of two stimuli

(short or long mouth) was presented on a previously mouthless cartoon face by making a

corresponding response on a keyboard. Critically, the difference between mouth sizes

(11.5 mm vs. 13 mm) and the stimulus exposure time (100 msec) is small, making the

participants' choice difficult and thus allowing the development of a response bias. Correct identification of one stimulus was rewarded ("Correct!! You won 5 cents") three times more frequently ("rich stimulus") compared with correct identification of the other stimulus ("lean stimulus"). To expose each subject to the intended 3:1 reward ratio, only 40 correct trials (30 rich, 10 lean) were rewarded in each block. Choice of rich stimuli (long vs. short mouth) was counterbalanced between participants and across visits (e.g., if the long mouth was the rich stimulus at the first visit, the short mouth would be the rich stimulus at the second). Before the task, participants were instructed to try to win as much money as possible and told that the money they won would be given to them to keep. They were specifically instructed that not all correct responses would receive a reward feedback, that lack of feedback did not indicate inaccuracy, and that they receive no feedback for errors. The results demonstrate that nicotine increased the responding to the reward which suggests that nicotine may enhance the saliency of reward in the environment. This data suggests that cholinergic stimulation from acute nicotine administration may affect risk taking propensity by increasing the saliency of the rewarding stimuli (monetary gain). According to the reward processing model of ADHD, the delay-of-reinforcement gradient is shorter for individuals with ADHD than in healthy individuals which alters the dopamine release (Johansen et al., 2002). Therefore, nicotine may affect risk taking in individuals with ADHD by correcting dopamine function in the brain reward system.

1.6.1 BART Studies in Clinical Populations

Crowley and colleagues (2006) used the BART to assess risk taking in a sample

of adolescents 14-18 years old with serious conduct and substance use problems

compared to age-matched controls. The adolescents in the clinical group were recruited

from a university residential and day-treatment program and nearly all met DSM-IV-TR

criteria for substance use disorders and most met DSM-IV-TR criteria for conduct

disorder. The clinical group made significantly more total presses, popped significantly

more balloons and earned more money than the control group. The data demonstrated

that the clinical group was significantly more risky than the control group from the start

of the task and this difference persisted throughout the duration of the task, suggesting

that the participants did not learn to respond differently as the task progressed.

Interestingly, the data from the inter-trial intervals showed that the clinical group made

pumping presses more slowly than the controls. And, similarly, the clinical group made

"collect" responses more slowly than controls. This data is important for the current

study as it demonstrates that the BART is able to differentiate a clinical group with

conduct disorder, a disorder characterizezd by impulsivity and frequently co-morbid with

ADHD, from a non-clinical group**.**

Bornovalova and colleagues (2005) used the BART and a behavioral measure of

impulsivity (the Delay Discounting Task [DDT]) to examine whether high levels of risk

taking and impulsivity are evident even in the absence of intoxication. The participants

were primary crack cocaine users with minimal heroin use and primary heroin users with

minimal crack cocaine use. The data showed that crack cocaine users exhibited

significantly higher levels of risk taking on the BART than heroin users. Similarly, the

results of the DDT showed that crack cocaine users discounted the value of delayed rewards more than heroin users. When age and gender were used as covariates the BART score was no longer significant though the DDT score remained significant.

Hopko and colleagues (2006) assessed the construct validity of the BART by examining the relationship between MDMA (3,4-methylenedioxymethamphetamine, also known as ecstasy) use and performance on the BART task. The authors determined that construct validity of the BART would be supported if the BART scores were predictive of MDMA use after controlling for demographic variables, polysubstance use, and theoretically relevant constructs like impulsivity and sensation seeking. The data showed that the BART provided incremental validity in predicting the MDMA use group.

Taken together, these data suggest that the BART reliably differentiates drug users (from a variety of drug domains) from non-users. Further, the data show that the BART can differentiate a highly risky subgroup of drug users from a less risky subgroup. This suggests that the BART may be used as a prevention tool for early identification of individuals at high risk for substance use.

1.6.2. Acute Drug Studies with Adult Healthy Volunteers

Studies examining the effects of an acute drug in healthy volunteers on the performance of the BART have generally yielded no significant findings. The results of an acute drug study with low doses of the prototypic benzodiazepine, diazepam, in healthy volunteers showed that diazepam did not affect performance on any of the behavioral measures, including the BART (Reynolds, Richards, Dassinger, & deWit,

2004). The results of an acute alcohol study with healthy social drinkers indicated that alcohol did not affect performance on the BART (Reynolds, Richards, & deWit, 2006). The data from an acute drug study examining the effects of acute doses of pramipexole (a DA agonist) in healthy volunteers age 18-45 indicated that pramipexole did not significantly impact performance on the BART (Hamidovic, Kang, & deWit, 2008).

However, White, Lejuez, and de Wit (2007) examined the effects of d-amphetamine on risk-taking behavior in healthy volunteers between the ages of 18 and 35 years, with a focus on the influence of personality variables and gender. For male participants, positive correlations between the personality trait of reward sensitivity (Agentic Positive Emotionality factor [AgPEM]) and amphetamine-induced increases in risk taking at all reward levels of the BART. Thus as males' trait reward sensitivity increased, so did their behavioral approach of risky rewards after the consumption of d-amphetamine. The authors postulated that the personality trait AgPEM may comprise a pre-existing risk factor for acute increases in risk taking after consumption of moderately high doses of stimulant drugs in males. Second, when analyzed from a categorical perspective (4-way ANOVA), 20 mg d-amphetamine significantly decreased risk behavior in men with scores in the lower half of the distribution for AgPEM, significantly increased risk behaviors in men with scores in the upper half of the distribution on AgPEM, and had minimal drug effects on behavior in women. The authors suggested this result indicated a systematic variation in behavioral responses to stimulants that could have ramifications for prescribing and dosing amphetamines.

The results suggest that performance on the BART may be affected by acute drug dose in certain clinical populations suggesting the BART may be a useful tool for studying ADHD.   It may be that the studies which found no effect of acute drugs on the BART in adult healthy volunteers may be related to floor effects in healthy populations.

1.6.3. Real-World Implications of the BART

Lejuez and colleagues (2003b) administered the BART to a sample of high-school-aged adolescents to test the utility of the BART as a behavioral measure of risk taking. The data demonstrated that the scores on the BART were correlated with engagement in real-world risk behaviors. Building on this research, Aklin and colleagues (2005) examined the utility of the BART in the assessment of self-reported real-world risk taking behaviors in a sample of high-school-aged inner-city adolescents. The authors used principal components analysis to determine which risk behaviors could be combined into a composite score. A 2-factor model best fit the data. The first factor (delinquency/safety) included fighting, gambling, not wearing a helmet when riding a bike, not wearing a seatbelt when riding in a car, and carrying a weapon. The second factor (substance use) included alcohol, cigarette, and illegal drug use. The data showed that the BART score was a significant predictor of the delinquency/safety factor and the substance use factor. This demonstrates that the BART can identify individuals who engage in actual risky behaviors establishing that the BART has real-word validity. Importantly, the BART was predictive of both delinquency/safety risk behaviors and substance use. As individuals with ADHD are known to engage in unsafe behaviors as

well as substance use this data suggests the BART is a good tool to use in the study of ADHD.

1.6.4. Measurement Properties of the BART

Test-retest reliability on the BART has been shown to be adequately stable. Lejuez and colleagues (2003a) assessed risk behavior on the BART in undergraduate smokers (n=26) and nonsmokers (n=34), by administering the test three times on a single test day. They found that risk behavior on the BART (adjusted average pumps) was correlated 0.62 to 0.82 across the three administrations within the single day, with small but significant increases in risk behavior between administrations (Lejuez et al., 2003a).

However, this data cannot not speak to test-retest reliability across days. White, Lejuez and de Wit (2008) assessed test-retest reliability on the BART across days as a part of a larger, multisession repeated measures study (White, Lejuez, & de Wit, 2007). The data demonstrated that risk behavior on the BART did not differ across sessions. The average behavior on the task assessed in the same participants on two separate study days did not differ despite intervening time and cumulative experience on the task (some participants performed the task 2 times and others 4 times). This finding is important because it indicates that the BART risk task could be relatively resilient to novelty effects, learning effects, and habituation. Risk behavior on the BART showed adequate test– retest reliability (r= .77) over a period of approximately 2 weeks. This finding extends the time window on which test– retest reliability of the BART is known (see Lejuez et al., 2003a). The magnitude of the test-retest estimate compares favorably with

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other tasks, such as delay discounting and probability discounting, which have test-retest correlations of 0.52 to 0.62 (p<.01; k-values), and .76 to .94 (p<.001; h-values), respectively over a shorter time period (i.e., 2–5 days). Spearman rank-order correlations were acceptably high, indicating that between-subjects differences in rank-ordering of risky behavior on the task are likely to be stable over the time period studied. Other behavioral tasks relevant to risk-taking, such as probability and delay discounting, also show stability of individual differences over time periods both shorter (2–5 days). These data suggest that BART responding is fairly stable across repeated performance, and therefore any significant effects between study days in the current study may not be attributed learning effects.

Many of the risk taking dependent measures on the BART are highly interrelated. For example, given that each pump was worth 1 cent, money earned is directly a result of the adjusted number of total pumps made. Therefore, in thinking about statistical analyses, consideration of variable overlap was necessary to avoid an increased possibility of type 1 error.

In the initial evaluation of the BART, Lejuez and colleagues (2002) reported significant gender differences on BART performance with more risky responding for males (greater number of average adjusted pumps) than females. Therefore, gender differences may be expected in the current analyses, and may be used as a covariate in the statistical analyses.

In summary, the existing literature on the BART demonstrates that the task is widely used in the field and has well established reliability and validity as well as real

world relevance. The BART is consistently correlated with real-world risk taking behaviors indicating that the laboratory task assesses processes that occur outside the laboratory. The neurobiology of risk taking can be examined using the BART by measuring the brain output that occurs during performance of the task. Together this suggests that the BART may be a useful tool for the measurement of risk taking behaviors generally and to the further understanding of the neurobiology of risk taking in ADHD. While the acute drug studies suggest that we may see floor or ceiling effects in healthy volunteers, studies in clinical populations have found acute drug modulation of BART performance.

1.6.5. Neurobiological Underpinnings of the BART

Though the neurobiological underpinnings of the BART are not well studied, the two pathways suggested in the literature are the frontal inhibition and reward systems, both innervated by dopamine systems. It has been proposed that disinhibition is a biologically based factor related to risk taking (Markon et al., 2005). Crowley et al. (2006) hypothesized that the clinical group in the study (adolescents with conduct and substance use disorders) who exhibited greater risk taking propensity had a frontal disinhibition syndrome where frontal lobe structural abnormalities impair behavior stopping as ratios of (potential loss)/(potential reward) increase. Bornolova et al. (2005) hypothesized that risk taking propensity in chronic crack cocaine users may be related to deficits in the frontal lobe area, which is generally found to mediate inhibitory processes.

Alternatively, White et al. (2007) propose that trait reward and punishment sensitivity underlies risk taking. Reward and punishment sensitivity is thought to reflect stable between-person variation in the function of an incentive motivational circuit that receives ascending input from dopamine cells of the midbrain VTA. The between-person variation in sensitivity to punishment could provide a brake on risky behavior through its ability to enhance the "stop" response (White et al., 2007).

Models of decision making suggest that individuals only perform a choice once the "evidence" in favor of that choice crosses a certain threshold (Frank, Samanta, Moustafa, & Sherman, 2007). Frank (2006) posited that at the neurobiological level, the subthalamic nucleus (STN) actively modulates the decision threshold to enable an individual to include reinforcement and conflict parameters in the decision making process. In effect, this model posits that when faced with seemingly good options, the STN allows an individual to adaptively wait, buying more time to settle on the best behavioral response (Frank et al., 2007). Frank and colleagues (2007) administered a computerized decision-making task to two groups of patients with Parkinson's disease (PD), and age-matched controls. One group of patients was tested in different sessions on and off deep brain stimulation (DBS) of the STN. To examine conflict effects, reaction times for test pairs having similar reinforcement values were measured and compared to low conflict pairs where the reinforcement values were more easily discernible. It is during these high conflict pairs where it is adaptive to wait or buy more time in order to make the optimal choice. The results demonstrated that DBS induced impulsive responding for the high-conflict decision pairs. In contrast to the other

subjects, patients on DBS failed to slow down with increased decision conflict and even responded moderately faster on the high- compared to low-conflict pairs. This data is consistent with STN models and the animal literature demonstrating that animals with STN dysfunction engage in premature responding that is associated with suboptimal choices (Baunez & Trevor, 1997; Baunez,, Anastasia, Yogita, Claude, & Trevor, 2007; Frank, 2006). This data suggests that the STN plays a crucial role in impulsive decision making that is a part of risk taking. Cholinergic neurons project to the STN suggesting that cholinergic stimulation via acute nicotine administration may directly affect risk taking.

Laboratory experiments with EEG recordings have described an electrophysiological marker of error processing, the error-related negativity (ERN) potential that occurs during error processing. An extensive literature demonstrates that the right dorsal anterior cingulate cortex (dACC) is involved in executive function, inhibitory control, and error processing (Garavan et al., 2002; Liddle, Kiehl, & Smith, 2001; Liotti, & Mayberg, 2001). Holroyd and Coles (2002) reinforcement learning theory and error-processing model proposes that the ERN reflects a negative reinforcement signal that occurs when the system realizes that ongoing events are worse than expected. The anterior cingulated cortex (ACC) then uses this signal to determine the most suitable behavior for the task at hand (Holroyd & Coles, 2002). Alternatively, Botvinick and colleagues (2001) posited that the ERN represents the activation of a conflict-monitoring system after an error is committed that calls for behavioral changes.

In either model, evidence suggests that normal ERN responses are central to processing of negative events and therefore crucial to effective decision-making.

Fein and Chang (2008) recorded EEGs during performance of the BART and found that the ERN wave was elicited in response to a balloon burst. In addition, Liotti and colleagues (2005) demonstrated that individuals with ADHD have abnormally reduced amplitudes of the ERN relative to healthy individuals during performance of the stop signal task suggesting that individuals with ADHD may have a functional deficit in error processing. The scalp topography of the ERP effect suggests that the deficit may arise from midline frontal structures and the dACC in particular (Liotti, Pliszka, Perex, Kothmann, & Woldorff, 2005). Taken together, this data suggests that greater risk taking in ADHD may be related to a functional deficit in error processing and/or impaired dACC function.

1.7. Summary and Hypotheses

1.7.1 Summary

Existing data suggest that risk taking and poor decision making in everyday situations is a key feature of ADHD. The reward processing model of ADHD suggests that a deficit in reward and extinction processes related to reduced dopaminergic functioning in the mesolimbic dopamine circuit and the interaction of this circuit with the mesocortical dopamine branch and the nigrostriatal dopamine branch, underlie risk taking in ADHD. The behavioral inhibition model suggests that in ADHD immature frontal cortical development as well as inefficient STN processes are related to risk taking.

Interestingly, the cholinergic system, which has known effects on dopamine regulation has been understudied in both risk taking and ADHD. Studies have demonstrated that nicotine administration has measurable positive effects on cognition in ADHD which may be mediated through effects of nicotine on cholinergic and/or dopaminergic systems. The BART is a well-established valid measure of risk taking propensity. Numerous studies have demonstrated its ability to differentiate drug users from non-users, including smokers from non-smokers. Research has shown that the BART is sensitive to acute drug manipulation in a clinical population and electrophysiological data show that performance on the BART taps into the mesolimbic and mesocortical circuits. Thus the specific aim of this study is to examine the effects of acute nicotine on risk taking (BART performance) on young adults with ADHD and matched controls.

1.7.2. Hypotheses

This study proposes that the behavioral inhibition model and the reward/extinction model may be useful in examining risk taking propensity in ADHD. The behavioral inhibition model suggests that increased risk taking may arise because individuals with ADHD do not fully process contextual cues or create the space to compare past experiences to the current situation in order to predict outcomes, and therefore are more likely to engage in a behavior without a complete assessment of the risk. The reward/extinction model suggests that increased risk taking may arise because individuals with ADHD have an increased sensitivity to immediate, powerful rewards, as well as a decreased sensitivity to lack of reward/punishment leading to an increased

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propensity towards risk taking. The aim of this study is to assess the effects of acute nicotine on risk taking propensity:

Hypothesis 1: For individuals with ADHD, nicotine will reduce the average number of pumps used on BART task compared to placebo.

Hypothesis 2: For individuals with ADHD, nicotine will lengthen the inter-trial intervals (creating time to process contextual cues and integrate this information with past information before responding) on the BART task compared to placebo.

Hypothesis 3: For individuals with ADHD, nicotine will shift responding post-balloon explosion to be less risky (fewer pumps, longer inter-trial interval). This shift will not occur with the placebo condition.

Hypothesis 4: For healthy controls, nicotine will have no effect on performance of the BART as stated in any of the above hypotheses.

Section 2: Experimental Design and Methods

2.1. Overview

This study is one piece of a larger project that was completed in March of 2008. This was an acute, single dose, within-subjects, double blind study with the following drug conditions: (1) Nicotine Transdermal Patch, (2) Placebo Transdermal Patch. Each subject participated in two separate study days (one with each of the two randomly assigned drug conditions); all sessions were conducted at the General Clinical Research Center (GCRC) of The University of Vermont. The primary outcome measure is a test of risk taking propensity that has been validated in previous studies of risk behavior.

2.1.2. Participants

Twenty-six (11 male, 15 female) non-smoking young adults, eleven (3 male, 8 female) of whom were diagnosed with ADHD, completed the study. Young adults with the combined DSM-IV sub-type (mixed inattentive and impulsive/hyperactive symptoms) of ADHD were considered for participation in this study. Participants were screened for medical illnesses and concurrent psychological diagnoses following standard procedures developed for our laboratory (see screening procedures). Participants were allowed to be on stimulant medication for treatment of ADHD at the time of study (though al participants abstained from taking their stimulant medication at least three half-lives prior to each drug study day) and weighed at least 100 lbs.

Forty-three non-smoking young adults (age 18 – 25) participated in this study. Sixteen were excluded during the screening visit (7 screened out on SSRT, 2 did not meet

DSM-IV-TR ADHD criteria, 2 screened out due to history of Major Depressive Episode, and 5 decided the time commitment was too great) and one was excluded because of missing data.

2.1.3. Drug Administration

All drugs were administered in double blind manner. The order of treatments was randomized across participants. The two study days were separated by at least 48 hours. Participants were not taking any medications other than the study drug during their study days. The drugs consisted of a 7 mg nicotine transdermal patch and a matched placebo patch. The nicotine or matched placebo transdermal patch (NicoDerm CQ) was placed on a clean, dry site of the participant's upper back. The transdermal placebo patch was of identical size and appearance to active patches but delivered no nicotine. After blinding, there was no indication that any volunteer tampered with the patches.

The likely side effects of nicotine include nausea, dizziness, and skin irritation. Patches were removed if these side effects occurred to more than a mild degree. No participants were dropped from the study due to side effects. Based on the available data (Potter & Newhouse, 2004, 2008), we used a 7 mg transdermal nicotine patch administered for 45 minutes. With the data available to date, we believe it is safe to administer 7 mg transdermal nicotine patches to young adults with ADHD.

2.2. Procedure

Participants were involved in a telephone screen, screening visit, computer training session, and two study days during this protocol. The specific procedures involved for each part of the study are detailed below.

2.2.1. Participant Recruitment

Participants were recruited through newspaper advertisement, referrals from primary care physicians, psychiatrists and fliers at local Universities and Colleges. When a potential subject contacted the research lab, they underwent a telephone screening. This provided them with an overview of the study and detailed the procedures and estimated time commitment of the study. The researcher conducted a brief screening to see if the potential participant met initial screening criteria (e.g., age, weight, non-smoking status, currently on stimulus medication). Non-smoking status was defined using the guidelines developed by the Society for Research on Nicotine and Tobacco: less than 100 cigarettes smoked in a lifetime and no cigarettes smoked in the past 3 months.

2.2.2. Screening Visit

To ensure that participants were physically healthy and had no cardiovascular disease a medical screening was completed at the screening visit and consisted of the following: 1) The subject completed a written medical history; 2) Vital signs, height and weight was recorded by a GCRC nurse; 3) An ecg was taken and sent to the GCRC

cardiologist to be read prior to the first study day; and, 4) A history and physical exam was performed by the GCRC nurse practitioner.

Specific criteria for exclusion included current use of barbiturates, rifampin, insulin, carbamezepine, oral hypoglycemics, antidepressants, or lipid-lowering drugs; known diabetes; untreated thyroid disease; significant cardiovascular disease, asthma, active peptic ulcer, hyperthyroidism, pyloric stenosis, narrow angle glaucoma, epilepsy, or pregnancy, past or current Axis I psychiatric disorders (except ADHD) delineated by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Participants with major concomitant illnesses were excluded on the basis of history and physical exam. All participants were taking no centrally active drugs other than methylphenidate and no drugs with cholinergic properties. Smokers were excluded from the study and a confirmatory carbon monoxide measure was taken to ensure non-smoking status prior to each study day (<10 ppm).

Diagnosis of ADHD was confirmed by completion of the *Kiddie-Sads-Present and Lifetime Version* (K-SADS-PL) (Kaufman, Birhaher, & Brent, 1997). This structured interview was completed with the participant to assess current ADHD as well as to rule out comorbid psychological diagnoses. Additional characterization of subjects included the *Young Adult Self Report* (Achenbach, Bernstein, & Dumenci, 2005), and the *Wender Utah Rating Scale* (Ward, Wender, & Reimherr, 1993). All participants were screened for impairments in behavioral inhibition as defined by performance that is at least two standard deviations below average (for their age group) on the *Stop Signal task*

taken from published norms (Williams, Ponesse, Schacher, Logan, & Tannock, 1999). Participants without a deficit on this task were excluded from the protocol.

Overall IQ was measured with the *Weschler Abbreviated Scales of Intelligence* (WASI) (Wechsler, 1999). All subjects were found to have a Full Scale Intelligence Quotient >80. The *Wide Range Achievement Test – III* (WRAT-III) (Wilkinson, 1993) was administered to screen for learning impairments. No learning impairments were documented.

2.2.3. Study Days

Subjects were asked to abstain from eating and/or drinking anything but water from midnight the night before a study day. The timeline for procedures and assessments during the study day is presented in Figure 2. Subjects were admitted to an outpatient facility at the General Clinical Research Center at approximately 8:00 am. Participants were not permitted to smoke tobacco cigarettes for the duration of the study so a confirmatory carbon monoxide measure was taken to ensure non-smoking status. Compliance was excellent and it was never necessary to cancel a session due to smoking. Vital signs (including blood pressure, pulse, temperature and respiration rate) were measured at baseline and 30 minute intervals throughout the study day. The patch (nicotine or placebo) was applied at approximately 8:30 am; this was the 0 hr. time point for the study day. At + 45 minutes (9:15 AM) the patch was removed and the cognitive testing began. The timing of drug dosing ensured that the cognitive testing occurred during the peak effect of the active drug. This consisted of a battery of standardized

laboratory tests including a test of risk taking propensity (detailed below). This took an estimated 50 minutes. A battery of behavioral measures (detailed below) was also completed to assess drug effects on behavior and physical comfort. At +125 minutes (10:05 AM), vital signs were measured. After 1 further hour the subject was provided with lunch and then assessed and discharged if they were free of any adverse symptoms.

2.2.4. Subject Compensation

Subjects received monetary compensation ($300 total) for the time commitment involved in this study as follows: they received $50 at the completion of the first study day, $100 at the completion of the second study day, and $150 at the completion of the final study day. Subjects were not compensated for the screening or training visits.

2.3. Laboratory Assessment and Behavioral Ratings

2.3.1. Primary Outcome Measure

Balloon Analogue Risk Task (BART; Lejuez et al., 2002). The BART was used to measure risk-taking propensity. At the start of the BART, the computer screen displayed four items: a small balloon accompanied by a balloon pump, a reset button labeled "Collect $ $ $," a "Total Earned" display, and a second display labeled "Last Balloon" that listed the money earned on the last balloon. Each click on the pump inflated the balloon incrementally (about 0.3 cm in all directions). With each pump, money was accumulated in a *temporary bank*, the holdings of which were never indicated to the participant. This (BART) program feature allowed for money to accumulate at a rate of 1

Figure 2. Study Day Timeline

Within subjects, double-blind design for 2 drug conditions:
- Placebo
- Transdermal Nicotine (7 mg for 45 minutes)

2 Separate Study Days

Time point A: Nicotine Patch/Placebo Applied
Time point B: Patch Removed
Time point C: Cognitive Battery Assessment
Time Point D: Discharged from GCRC

cent per pump. A *permanent bank* was displayed on screen for participants to view and

consisted of a square box with a dollar figure (beginning with $0.00). When a balloon

was pumped past its individual explosion point, the computer generated a "pop" sound

effect. When a balloon exploded, all money in the temporary bank was lost, no money

was transferred to the permanent bank, 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. Clicking this button transferred all money

from the temporary bank to the permanent bank. So the total earned would be

incrementally updated, 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 that a balloon would

explode was fixed at 1/128 for the first pump. If the balloon did not explode after the

first pump, the probability that the balloon would explode was 1/127 on the second pump,

1/126 on the third pump, and so on up until the 128th pump at which point the probability

of an explosion was 1/1 (i.e., 100%). According to this algorithm, the average breakpoint

was 64 pumps. Modeling real-world situations in which excessive risk often produces

diminishing returns and increases threats to one's health and safety, each successive

pump on any particular balloon trial (a) increased the amount to be lost due to an

explosion and (b) decreased the relative gain of any additional pump. For example, after

the first pump the next pump risked only the 1 cent accrued in the temporary bank and

would increase the possible earnings on that balloon by 100%, yet after the 30th pump,

the next pump risked $0.30 accrued in the temporary bank and increased possible

earnings on that balloon trial only by 3.3%. Detailed instructions provided to the participant were based on those provided by Lejuez et al. (2002), yet it is important to note that participants were given no precise information about the probability of explosion.

2.3.2. Behavioral Measures

Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1971). The POMS is a self-report measure of mood and/or physical well-being. Participants are presented with a list of adjectives, and asked to indicate the severity of each item for that day only. Dependent variables from the POMS include cluster scores for vigor, tension, depression, anger, fatigue and difficulty concentrating.

Physical Symptom Checklist (PSCL) (van Kammen & Murphy, 1975). In the PSCL participants were presented with a list of 22 symptoms and were instructed to rate each as none, slight, moderate, or much, basing their ratings on how they had felt since arriving at the GCRC that morning. This measure has been used extensively in acute drug studies to assess physical symptoms in response to acute drug challenges.

Visual Analogue Battery (subject rating). This is a paper-and-pencil measure in which participants are presented with a series of 100 mm lines, each representing a dimension of functioning. Descriptive anchors are provided (i.e., sleepiness ranges from alert to about to fall asleep). Participants are asked to indicate (by placing a mark on the line) how they feel on each domain using "this morning" as the reference time range.

This scale measures: anxiety, mood, alertness, physical comfort, fear, irritability, hunger, and sense of interest. This scale has been used in many studies and is sensitive to acute drug manipulations in ADHD (i.e., Potter & Newhouse, 2004, 2008).

Visual Analogue Battery (observer rating). This is a paper-and-pencil measure in which the blind investigator indicates on a series of 100 mm lines, each representing a dimension of functioning, how the participant is functioning on different domains. The items measured are: drowsy, motoric restlessness, disoriented, impaired speech, euphoria, irritability, sweating, incoordination, fatigue, depression, anxiety, and alertness. This scale has been used in many studies and is sensitive to acute drug manipulations in ADHD (i.e., Potter & Newhouse, 2004, 2008).

2.4. Data Analysis Plan

The overall data analysis strategy for this study was to use t-tests to examine differences related to drug condition for each diagnostic group. The second step used analysis of variance (ANOVA) to examine the drug treatment by diagnostic group interaction to understand any differential effects of drug treatment.

For hypothesis 1, 2 and 4, a t-test computed drug related changes on the dependent variable of interest (average number of pumps for Hypothesis 1 and 4, average inter-trial interval for hypothesis 2 and 4). The 3rd hypothesis states that for individuals with ADHD, nicotine, but not placebo, will shift responding post-balloon explosion to be less risky (fewer pumps, longer inter-trial interval). To test the 3rd hypothesis a

comparison of the average number of pumps used on balloon trials immediately following an exploded balloon with the average number of pumps used on balloon trials following money banked was made using a t-test. An ANOVA was used to examine the effect of trial type (trial after a balloon explosion versus trial after money banked) and drug condition.

2.5. Sample Size Estimation

The sample size needed for this study was calculated based on the results of a study by White and colleagues (2007). In this study, acute administration of d-amphetamine was associated with reduced risk taking on the BART in individuals with high baseline impulsivity. In that study, the average number of pumps declined by approximately 15 ±6 pumps following d-amphetamine administration. In our current study, we expected a similar reduction of pumps on the BART in our ADHD sample. Using GPOWER, we determined that to find a reduction of 15±6 pumps on the BART with an alpha level of .05, and 80% confidence would require 8 subjects. Thus, we ran 11 ADHD participants and 15 control participants in this study.

Section 3: Results

3.1.1. Data Analysis

The basic approach to data analysis was to perform repeated measures mixed model ANOVA's to determine differences related to drug condition and group on the dependent variables. To examine the effects of block (1st 10 balloons, 2nd 10 balloons, and final 10 balloons) and trial type (trial post-balloon bank versus post-balloon explosion), repeated measures mixed model ANOVA's with drug condition and block or trial type as within subject factors were run to determine the combined effects of drug treatment and block or trial type on performance.

3.1.2. Demographics

The demographics are presented in Table 1. There were no significant differences between the groups on estimated IQ or age. The control group had more males than the ADHD group. Within the ADHD group, 9 were currently taking stimulant medications (Six participants were taking Adderall and of those six, two were also taking Ritalin, two participants were taking Concerta, and one participant was taking Stratera). All participants abstained from taking their stimulant medication at least three half-lives prior to each drug study day.

3.1.3. Hypothesis 1

The first goal of the present study was to explore the effects of nicotine on risk taking, measured by the adjusted average number of pumps made per balloon on the

Table 1. Demographics for the ADHD Group and Healthy Control Group

	ADHD Mean (SE)	Control Mean (SE)	p-value
Estimated IQ	116.1 (12.2)	114.5 (8.1)	Ns
Age	19.64 (2.1)	20.07 (1.5)	Ns
Gender (M/F)	3/8	8/7	--
Wender Utah	37.82 (17.3)	7.0 (5.8)	<.0001

BART task, in individuals with ADHD and age-matched controls. We hypothesized that for individuals with ADHD, nicotine would reduce the average number of pumps compared to placebo. The LS-means (standard errors) are presented in Table 2. There were no significant effects of drug, group, or a drug by group interaction for the adjusted average number of pumps used per balloon on the BART. Analyses of the other dependent variables, adjusted total number of pumps per balloon (also a measure of the amount of money earned on the task because each pump was worth 1 penny) and number of balloons exploded, was completed. Again, there were no significant effects of drug, group, or a drug by group interaction for either adjusted total pumps or explosions.

The 30 balloons may be divided into 3 blocks consisting of the 1st ten balloons, the 2nd ten balloons, and the final 10 balloons. There was a significant [$F_{(2, 48)}=5.02$, $p<.05$] effect of block for the adjusted total number of pumps used per balloon, where a greater number of pumps were used on block 2 ($p=.09$) and block 3 ($p<.01$) than block 1, suggesting that both groups engaged in increasingly risky behavior across the task, and earned greater reward (made more money). There was a significant [$F_{(2, 48)}=3.27$, $p<.05$] block by group interaction, where individuals with ADHD used a greater number of pumps than controls for block 3 ($p<.05$) and there was a trend for more pumps in block 1 ($p=.09$). There was a trend [$F_{(2, 48)}=2.84$, $p=.06$] effect of block for the number of explosions, with fewer explosions in block 3 than block 1 ($p<.05$), indicating that both groups exploded fewer balloons over time.

Given that Lejuez and colleagues (2002) reported significant gender differences on BART performance with males having increased risk taking (greater number of

Table 2. Risk Taking Propensity: No Effects for ADHD vs. Control

	ADHD		Control		Drug		Group		Drug x Gp	
	Nicotine Mean (SE)	Placebo Mean (SE)	Nicotine Mean (SE)	Placebo Mean (SE)	F	p-value	F	p-value	F	p-value
Average Pumps	41.17 (2.7)	42.89 (2.7)	39.11 (2.3)	39.90 (2.3)	1.49	ns	0.54	ns	0.20	ns
Total Pumps	855.12 (37.2)	858.09 (35.7)	789.39 (30.9)	807.93 (30.9)	0.20	ns	1.96	ns	0.11	ns
Balloons Explode	8.79 (1.08)	9.36 (1.05)	9.03 (0.87)	9.0 (0.87)	0.29	ns	0.00	ns	0.35	ns
Average IPI	0.249 (0.029)	0.264 (0.029)	0.288 (0.024)	0.279 (0.024)	0.02	ns	0.68	ns	0.40	ns
Average Pre-IPI	1.064 (0.181)	1.166 (0.175)	1.196 (0.15)	1.402 (0.15)	2.05	ns	0.79	ns	0.24	ns
Average Post-IPI	1.413 (0.096)	1.411 (0.093)	1.231 (0.079)	1.274 (0.079)	0.11	ns	2.28	ns	0.12	ns

average adjusted pumps) than females, exploratory analyses examining gender

differences were conducted. The demographics of these two groups are presented

in Table 3. There was a significant $[F(1, 24)=7.64, p<.05]$ main effect of gender on

adjusted average pumps, such that males had higher average pumps than females, and

there was a trend $[F(2, 48)=2.46, p=.09]$ effect of block, such that greater pumps were

used in block 2 than block 1. For the adjusted total number of pumps there was also a

significant $[F(1, 24)=5.31\ p<.05]$ effect of gender, with males having higher total pumps

than females (and therefore earned more money). There was a significant $[F(2,$

$48)=4.03, p<.05]$ effect of block, such that greater pumps were used in block 2 than block

1 and greater pumps were used in block 3 than block 2. For the total number of balloons

exploded on the BART task, there was a trend $[F(2, 48)=2.66, p=.08]$ block by gender

interaction, such that females decreased the number of balloons exploded over time and

males increased the number of balloons exploded over time. There were no significant

effects of drug or a drug by gender interaction.

3.1.4. Baseline Dependent Effects

The hypotheses in the current study about the effects of nicotine on risk taking in

individuals with ADHD were based on prior research demonstrating that individuals with

ADHD had higher baseline levels of risk taking behavior than individuals without

ADHD. However, this was not the case in our study. In the current study, there were no

significant main effects on the risk taking measures. There is evidence that the effects of

nicotine on cognition and behavior are baseline dependent. The term, 'baseline-

Table 3. Demographics for Males and Females

	Males Mean (SE)	Females Mean (SE)	p-value
Estimated IQ	117.5 (8.9)	113.3 (10.1)	ns
Age	19.45 (1.0)	20.2 (2.1)	ns
ADHD/Control	3/8	8/7	--

dependency' refers to the notion that response to a drug will vary depending upon baseline levels of responding under non-drug control conditions (Dews & Wenger, 1977). Therefore, a median split based on total pumps used on the BART task during the placebo condition (baseline level of risk taking propensity) was used to identify a low risk taking group and high risk taking group. The demographics of these two groups are presented in Table 4. Mixed model ANOVA's were run to determine differences related to drug condition and group on the dependent variables.

For the adjusted average number of pumps, there was a significant $[F_{(1, 23)}=14.74, p<.001]$ drug by group interaction, where individuals in the high risk taking group had significantly fewer pumps per balloon in the nicotine condition compared to the placebo condition ($p<.01$), and individuals in the low risk-taking group had a trend for greater pumps per balloon in the nicotine condition compared to the placebo condition ($p=.08$) (Table 5, Figure 3). There was a trend $[F_{(2, 48)}=2.52, p=.09]$ effect of block, where both groups had fewer pumps in block 1 than block 2 ($p<.05$) and block 3 ($p=.07$). And, there was a significant $[F_{(2, 46)}=4.11, p<.05]$ drug by block by group interaction. For block 1 individuals in the high risk taking group had fewer pumps per balloon in the nicotine condition compared to the placebo condition ($p<.001$), and individuals in the low risk taking group had more pumps per balloon in the nicotine condition compared to the placebo condition ($p<.05$). There were no significant drug differences at any other block for either group.

For the number of balloons exploded on the BART task, there was a significant $[F_{(1, 24)}=7.11, p<.05]$ effect of group, where individuals in the high risk taking group

Table 4. Demographics for the Low Risk Taking and High Risk Taking Groups

	Low Risk Taking Mean (SE)	High Risk Taking Mean (SE)	p-value
Estimated IQ	114.3 (11.7)	116.2 (6.6)	ns
Age	19.54 (1.5)	20.23 (1.0)	ns
ADHD/Control	6/7	5/8	ns
Gender (M/F)	4/9	7/6	--

Table 5. Rate Dependent Nicotine Effects on Risk Taking

| | Low Risk Taking | | High Risk Taking | | | | | |
	Nicotine Mean (SE)	Placebo Mean (SE)	Nicotine Mean (SE)	Placebo Mean (SE)	Drug F-value	Group F-value	Drug x Gp F-value	Drug x Gp x Block F-value
Average Pumps	36.60 (2.01)	34.26 (2.01)	43.21 (2.05)	48.07 (2.01)	1.80	14.29**	14.74**	4.11*
Balloons Explode	7.98 (0.86)	7.149 (0.86)	9.914 (0.88)	11.15 (0.86)	0.16	7.11*	4.00#	0.18

*=p<.05, **=p<.001, #=p=.05

Figure 3. BART: Adjusted Average Pumps

BART Task: Adjusted Average Pumps per Balloon

* = p<.05
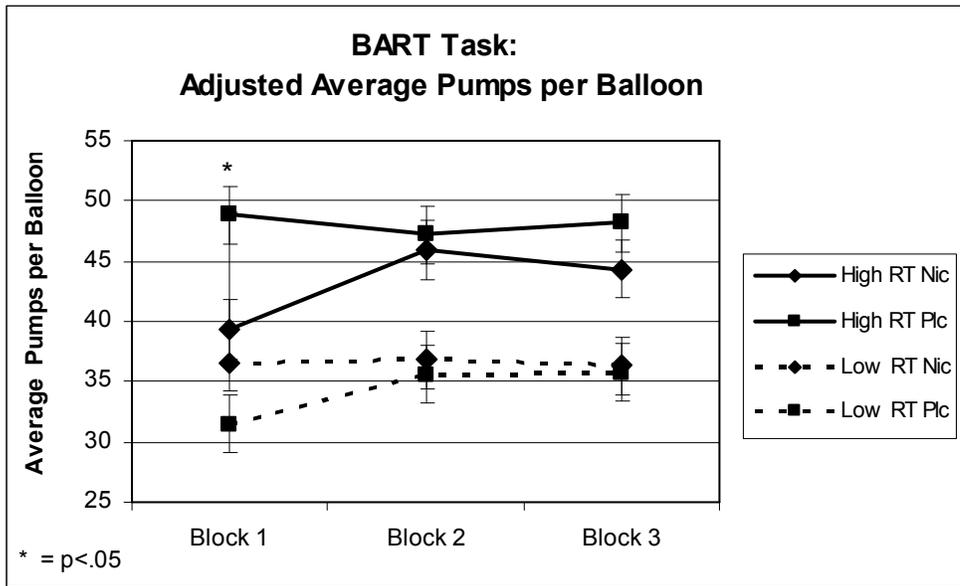
exploded more balloons than the low risk taking group (Figure 4). There was a trend [F(1, 23)=4.00, p=.057] for a drug by group interaction, where individuals in the high risk taking group exploded fewer balloons in the nicotine condition compared to the placebo condition (p=.10), and individuals in the low risk-taking group exploded more balloons in the nicotine condition compared to the placebo condition (p=.26) (Figure 4).

A main effect of gender was found for adjusted average pumps, so follow-up analyses with gender as a covariate were completed. Gender did not significantly affect the results so those results are not reported separately. Analyses examining order effects for the nicotine dose were also completed, but there were no significant findings so those results are not reported separately.

3.1.5. Hypothesis 2

The second goal of the present study was an exploratory analysis of the effects of nicotine on the behavioral response to the task feedback during the BART. We hypothesized that for individuals with ADHD, nicotine would lengthen the inter-trial interval (creating time to process contextual cues and integrate this information with past information before responding) on the BART task compared to placebo. There were no significant effects of drug or group for average inter-pump-interval (IPI) on the BART task, and no drug by group interaction. There were also no significant effects of drug or group or drug by group interactions for average pre-inter-pump-interval (pre-IPI), the time from the start of a trial to the first pump, on the BART task, and no drug by group

Figure 4. BART: Explosions

BART Task: Explosions

+ = p=0.10
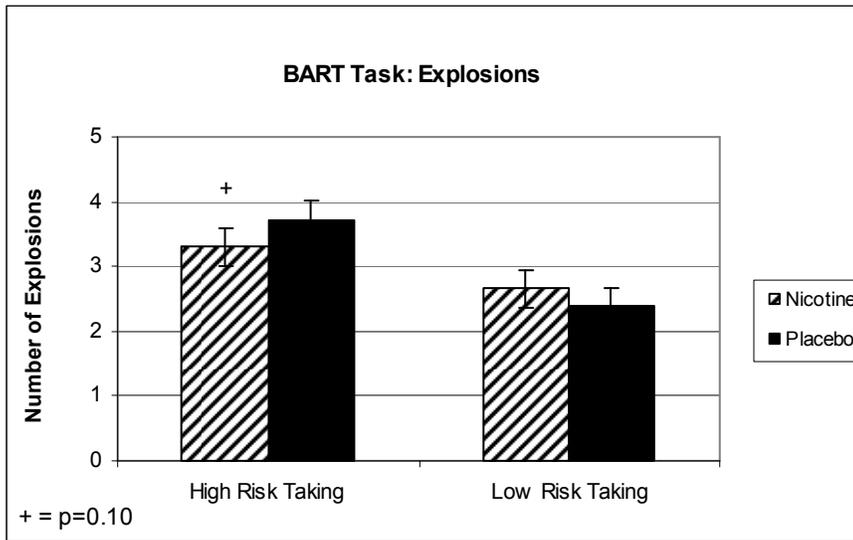
interaction, or average post-inter-pump-interval (post-IPI), the time from the last pump to pressing the bank money button (this only included balloons that were banked) (Table 2).

Exploratory analyses of gender were again conducted. There were no significant effects of drug or gender for average IPI, pre-IPI, or post-IPI and no drug by gender interactions. Exploratory analyses of rate dependent effects were conducted with no significant effects of drug for average IPI, pre-IPI or post-IPI found. For average IPI, there was a trend [F(1, 24)=4.01, p=.056] effect of group, where individuals in the high risk taking group had a faster IPI than the low risk taking group. There was no significant drug by group interaction on this measure.

3.1.6. Hypothesis 3

The third goal of the present study was an exploratory analysis of the effects of nicotine on BART performance on different trial types (post-balloon bank versus post-balloon explosion). We hypothesized that for individuals with ADHD, nicotine would shift responding post-balloon explosion to be less risky (fewer pumps, longer inter-trial interval). There were no significant effects of drug, group, or drug by trial type interactions for average adjusted pumps. For the ADHD group only, there was a trend [F(1, 10)=3.90, p=.077] drug by trial type interaction for average IPI, with nicotine associated with shorter average IPI on trials post-balloon explosion (Figure 5). And, there was a significant [F(1, 10)=6.51, p<.05] effect of nicotine for average pre-IPI, where individuals with ADHD had a shorter average pre-IPI in the nicotine condition than the placebo condition. There were significant effects of trial type. For average

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adjusted pumps there was a significant $[F(1, 24)=16.30, p<.001]$ effect of trial type, where both groups had greater average pumps on trials post-balloon bank than post-balloon explosion. And, there was a significant $[F(1, 24)=70.80, p<.001]$ effect of trial type for average pre-IPI, where both groups had a longer average pre-IPI on trials post-balloon bank than post-balloon explosion. In follow-up analyses for trials post-balloon bank only, there was a trend $[F(1, 23) =3.02, p=.09]$ effect of drug for adjusted average pumps, where both groups used fewer average pumps in the nicotine condition than the placebo condition. There was not a drug by group interaction. In follow-up analyses for trials post-balloon explosion only, no significant effects were found.

Exploratory analyses of gender were conducted. For average adjusted pumps, there were no significant effects of drug or a drug by gender interaction. There was a significant $[F(1, 24)=7.85, p<.01]$ effect of gender, a significant $[F(1, 24)=14.05, p<.01]$ effect of trial type, and a significant $[F(1, 24)=7.11, p<.05]$ gender by trial type interaction. There were no significant effects of drug, gender, or a drug by gender interaction for average IPI. For average pre-IPI, there was no significant effect of gender or a drug by gender interaction, but there was a trend $[F(1, 24)=3.28, p=.08]$ effect of drug, where all participants had a faster average pre-IPI on nicotine than placebo. There was also a significant $[F(1, 24)=70.42, p<.0001]$ effect of trial type, where both groups had a longer average pre-IPI on trials post-balloon bank than post-balloon explosion.

Exploratory analyses of rate dependent effects were conducted. There were no significant drug effects for average adjusted pumps, average IPI, or average pre-IPI. For

Figure 5. ADHD Only: IPI Differences by Trial Type

68
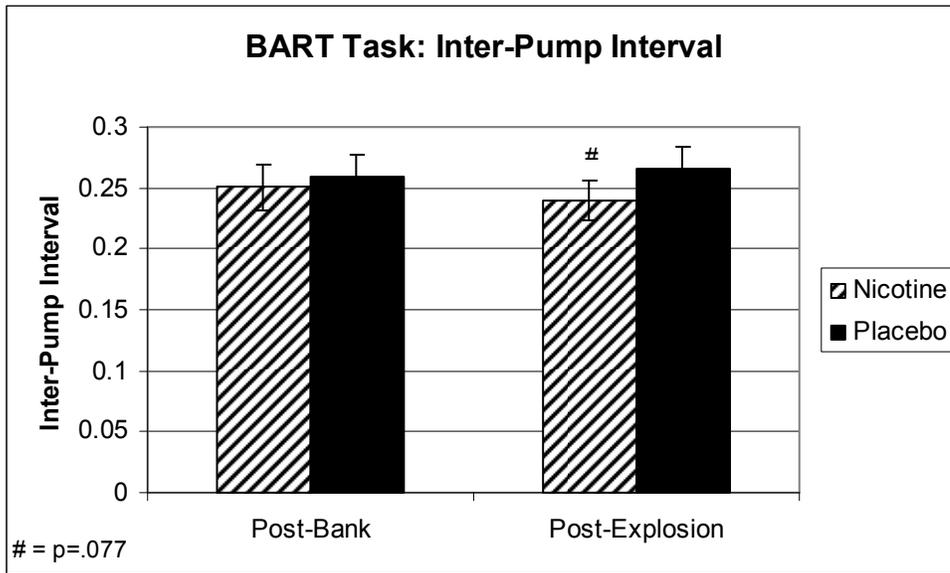
average adjusted pumps there was a significant [F(1, 24)=14.77, p<.001] effect of trial type, where more average pumps per balloon were used on trials post-balloon bank than post-balloon explosion suggesting a decrease in risky behavior for both groups post-balloon explosion. For average pre-IPI there was also a significant [F(1, 24)=73.26, p<.0001] effect of trial type, where average pre-IPI was longer for trials post-balloon bank than post-balloon explosion for both groups.

3.1.7. Behavioral Measures: ADHD vs. Control

Subjective Visual Analogue Scale. There was a significant [F(1, 24)=12.97, p<.01] effect of nicotine on self-rated alertness (Table 6). Participants rated themselves significantly more alert following a dose of nicotine than placebo (Figure 6). And, there was a significant [F(1, 24)=12.21, p<.01] effect of nicotine on self-rated interest. Participants rated themselves significantly more interested following a dose of nicotine than placebo. There was a trend [F(1, 24)=3.012, p=.09] effect of nicotine on self-rated fear. Participants rated themselves less fearful following a dose of nicotine than placebo. There was a trend [F(1, 24))=4.11, p=.054] drug by group interaction, where ADHD participants rated themselves less alert than healthy controls following a dose of placebo but the groups rated themselves alike on nicotine.

Objective Visual Analogue Scale. There was a significant [F(1, 24)=8.29, p<.01] effect of nicotine on clinician-rated drowsiness (Table 6). The clinician rated the

Figure 6. Behavioral Effects of Nicotine: Subjective Ratings
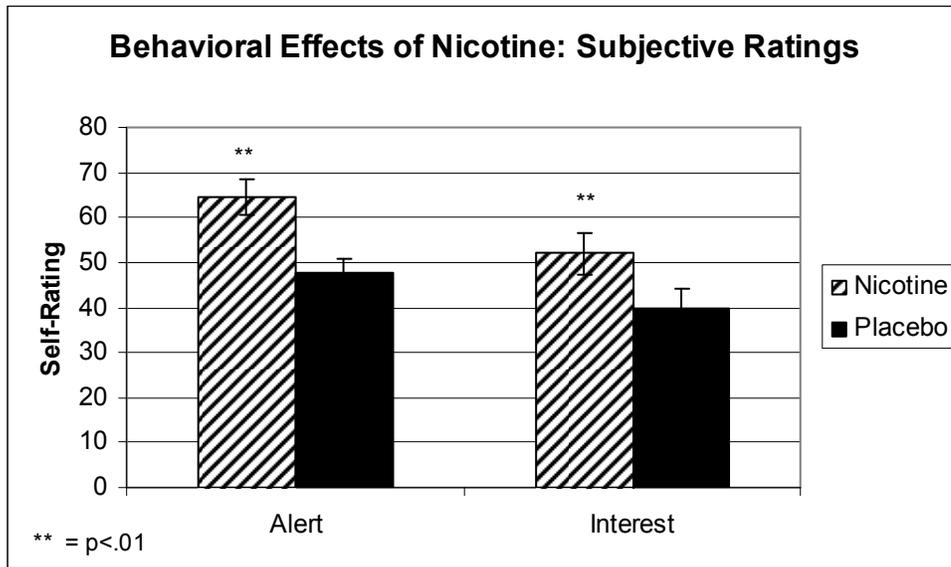
participants as significantly less drowsy following a dose of nicotine than placebo (Figure 7). There was a significant [F(1, 24)=6.41, p<.05] effect of nicotine on clinician-rated fatigue, where the clinician rated participants as significantly less fatigued following a dose of nicotine than placebo. And, there was a significant [F(1, 24)=15.77, p<.01] effect of nicotine on clinician-rated alertness, where the clinician rated participants as significantly more alert on nicotine than placebo. There was a trend [F(1, 24)=3.00, p=.096] drug by group interaction, where the clinician rated ADHD participants more drowsy than healthy controls following a dose of placebo but the clinician rated the groups alike on nicotine. And, there was a trend [F(1, 24)=3.65, p=.068] drug by group interaction for clinician-rated sweatiness, where the clinician rated the ADHD participants as less sweaty on nicotine than placebo and rated the control participants as slightly more sweaty on nicotine than placebo. There was a significant [(F1, 24)=10.37, p<.01] effect of group on clinician-rated restlessness, where the clinician rated the ADHD participants as significantly more restless than the control participants. There was a trend [F(1, 24)=3.96, p=.058] effect of group on clinician-rated euphoria, where the clinician rated the ADHD participants as more euphoric than the control participants. And, there was a trend [(F1, 24)=3.43, p=.076] effect of group for clinician-rated incoordination where the clinician rated the ADHD participants as more incoordinated than the control participants.

     Profile of Mood States. There was a significant [F(1, 24)=4.55, p<.05] effect of nicotine on self-rated fatigue (Table 6). Participants rated themselves as significantly less fatigued following a dose of nicotine than placebo. There was a significant [F(1,

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24)=5.57, p<.05] effect of nicotine on self-rated vigor. Participants rated themselves as experiencing significantly greater vigor following a dose of nicotine than placebo. There was a significant [F(1, 24)=10.71, p<.01] effect of group on self-rated confusion, where participants with ADHD rated themselves as significantly more confused than control participants. And, there was a trend [F(1, 24)=3.29, p=.082] effect of group on total mood disturbance, where participants with ADHD rated themselves as having a greater mood disturbance than control participants.

Physical Symptom Checklist. There were no significant effects of nicotine or group on the physical symptom checklist (total score or individual items).

Vital Signs. Vital sign data (systolic and diastolic blood pressure and pulse) were analyzed using mixed-model repeated measures ANOVAs examining the changes (change score) in vital signs from pre-drug baseline (each day) to 145-minutes post drug (estimated time for maximal physiological effects). For systolic blood pressure, there was a trend [F(1, 23)=3.32, p=.08] effect of drug such that a greater change in systolic blood pressure occurred following a dose of nicotine than placebo. There was a significant [F(1, 23)=7.36, p<.05] effect of group, where individuals with ADHD had a greater change in systolic blood pressure than control participants. There were no significant effects of drug or group for diastolic blood pressure or pulse.

Table 6. Behavioral Ratings: ADHD Group vs. Control Group

	ADHD		Control		Drug			Group			Drug x Gp	
	Nicotine Mean (SE)	Placebo Mean (SE)	Nicotine Mean (SE)	Placebo Mean (SE)	F	p-value		F	p-value		F	p-value
Subjective Ratings												
Alert	64.4 (16.9)	37.9 (17.3)	64.7 (20.9)	57.3 (15.7)	12.97	<.01		--	ns		4.11	.054
Fear	8.4 (11.6)	12.4 (16.9)	8.3 (9.3)	9.3 (11.3)	3.01	.09		--	ns		--	ns
Interest	46.0 (27.2)	32.5 (26.2)	58.1 (20.2)	47.4 (17.5)	12.21	<.01		--	ns		--	ns
Objective Ratings												
Drowsy	8.0 (14.4)	23.8 (21.1)	10.7 (12.6)	14.6 (13.6)	8.29	<.01		--	ns		3.00	.096
Restless	4.8 (10.7)	10.2 (13.3)	0.0 (0.0)	0.0 (0.0)	--	ns		10.37	<.01		--	ns
Euphoria	2.6 (6.4)	0.6 (2.1)	0.0 (0.0)	0.0 (0.0)	--	ns		3.96	.058		--	ns
Sweat	0.7 (2.4)	3.4 (7.6)	0.09(3.6)	0.0 (0.0)	--	ns		--	ns		3.65	.068
Incoord-ination	4.1 (7.2)	1.7 (3.9)	0.0 (0.0)	0.8 (3.4)	--	ns		3.43	.076		--	ns
Fatigue	5.5 (8.6)	16.8 (18.2)	10.7 (12.9)	12.9 (9.5)	6.41	<.05		--	ns		--	ns
Alert	90.9 (17.8)	73.3 (20.6)	94.5 (11.1)	85.1 (16.1)	15.77	<.01		--	ns		--	ns
Profile of Mood States												
Fatigue	4.7 (3.9)	9.5 (7.8)	5.0 (3.3)	5.5 (5.5)	4.55	<.05		--	ns		--	ns
Confusion	7.1 (5.2)	7.9 (4.6)	3.5 (2.1)	3.3 (1.4)	--	ns		10.71	<.01		--	ns
Vigor	10.7 (6.1)	8.3 (8.8)	9.5 (5.6)	7.7 (3.6)	5.57	<.05		--	ns		--	ns
TMD	8.7 (15.4)	18.0 (20.3)	4.3 (11.4)	5.1 (9.8)	--	ns		3.29	.082		--	ns

3.1.8. Behavioral Measures: Low Risk Taking vs. High Risk Taking

Subjective Visual Analogue Scale. There was a trend [F(1, 24)=3.08, p=.092] drug by group interaction for comfort, where participants in the low risk taking group rated themselves as slightly less comfortable in the nicotine condition than placebo and participants in the high risk taking group rated themselves as more comfortable in the nicotine condition than placebo (Table 7, Figure 6). There was also a significant [F(1, 24)=6.38 ,p<.05] effect of group on self-rated interest, where participants in the high risk taking group rated themselves as more interested than the low risk taking group.

Objective Visual Analogue Scale. There was a trend [F(1, 24)=3.15, p=.088] drug by group interaction on clinician-rated sweatiness, where the clinician rated participants in the low risk taking group as less sweaty on nicotine than placebo and the participants in the high risk taking group as more sweaty on nicotine than placebo (Table 7, Figure 7).

Profile of Mood States. There was a significant [F(1, 24)=4.61, p<.05] drug by group interaction on self-rated tension. Participants in the low risk taking group rated themselves as less tense following a dose of nicotine than placebo, and participants in the high risk taking group rated themselves as more tense following a dose of nicotine than placebo (Table 7).

Physical Symptom Checklist. There were no significant effects of nicotine or group on the physical symptom checklist (total score or individual items).

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Figure 7. Behavioral Effects of Nicotine: Objective Ratings
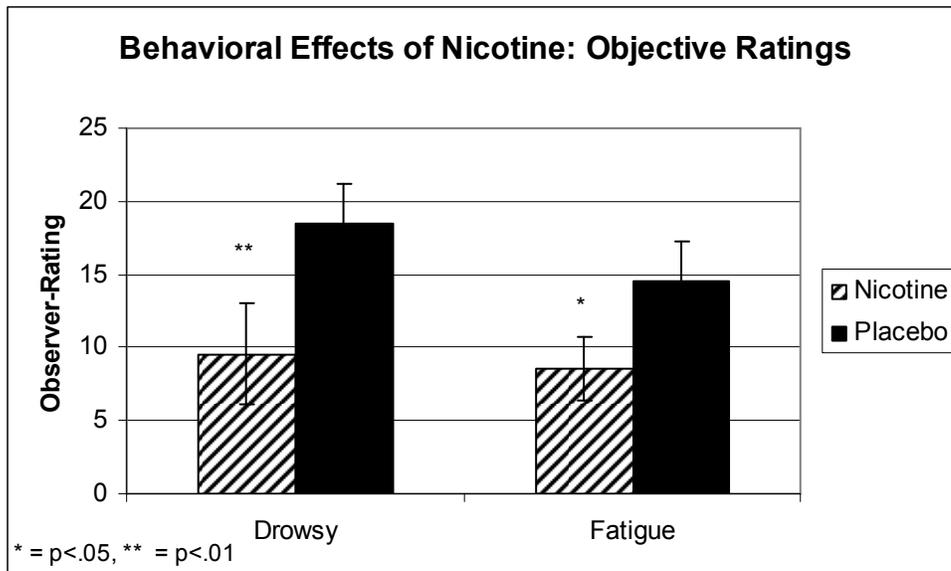
Behavioral Effects of Nicotine: Objective Ratings

Vital Signs. Vital sign data (systolic and diastolic blood pressure and pulse) were analyzed using mixed-model repeated measures ANOVAs examining the changes (change score) in vital signs from pre-drug baseline (each day) to 145-minutes post drug (estimated time for maximal physiological effects). For systolic blood pressure there was a significant [$F(1, 23)=5.90$, $p<.05$) effect of group, where individuals in the low risk taking group had a greater change in systolic blood pressure than individuals in the high risk taking group. There were no significant effects of drug or group for diastolic blood pressure or pulse.

Table 7. Behavioral Ratings: Low Risk Taking vs. High Risk Taking

	ADHD		Control		Drug		Group		Drug x Gp	
	Nicotine Mean (SE)	Placebo Mean (SE)	Nicotine Mean (SE)	Placebo Mean (SE)	F	p-value	F	p-value	F	p-value
Subjective Ratings										
Alert	59.9 (20.6)	44.7 (15.8)	69.2 (16.7)	53.5 (21.1)	9.47	<.01	--	ns	--	ns
Comfort	29.9 (22.4)	32.5 (27.4)	38.1 (26.1)	26.4 (19.9)	--	ns	--	ns	3.08	.092
Interest	42.3 (23.4)	32.5 (18.6)	63.6 (19.4)	49.7 (23.3)	12.15	<.01	6.38	<.05	--	ns
Objective Ratings										
Drowsy	10.5 (15.9)	21.5 (15.4)	8.6 (10.4)	15.6 (18.5)	6.29	<.05	--	ns	--	ns
Sweat	0.6 (2.2)	2.8 (7.0)	1.1 (3.9)	0.0 (0.0)	--	ns	--	ns	3.15	.088
Fatigue	11.8 (13.7)	14.2 (15.0)	5.3 (7.7)	14.9 (12.8)	5.01	<.05	--	ns	--	ns
Alert	89.2 (18.3)	79.2 (20.6)	97.0 (6.3)	80.6 (17.5)	14.79	<.01	--	ns	--	ns
Profile of Mood States										
Tension	3.6 (2.9)	4.8 (3.8)	4.8 (4.2)	2.8 (2.4)	--	ns	--	ns	4.61	<.05
Fatigue	5.8 (3.4)	6.7 (6.4)	3.9 (3.5)	7.7 (7.3)	3.38	.078	--	ns	--	ns
Vigor	10.6 (6.2)	7.6 (5.4)	9.5 (5.7)	8.2 (7.1)	5.67	<.05	--	ns	--	ns

Section 4: Discussion

This study found measurable baseline dependent effects of nicotine on risk-taking propensity as measured by the Balloon Analogue Risk Task. For individuals with a high baseline level of risk taking propensity, nicotine reduced risk-taking propensity, and for individuals with a low baseline level of risk taking propensity, nicotine increased risk-taking propensity. A vast literature exists documenting the rate dependent effects of nicotine on tasks of attention and decision-making (see Perkins, 1999 for review). The term, 'rate-dependency or baseline-dependency' refers to the notion that response to a drug will vary depending upon baseline levels of responding under non-drug control conditions (Dews & Wenger, 1977). Perkins (1999) argued that baseline dependency may account for some between group differences in nicotine effects, and asserted that the effects of the same dose of nicotine on the same dependent measure may differ as a function of baseline response level. The current findings are consistent with the effects of acute nicotine in animal and human studies on tasks of sustained attention, recognition memory, short-term memory, complex reaction time, visual perception, rapid information processing, refined motor movements, and mood (reviewed by Perkins, 1999). The results of this study are consistent with the work of White and colleagues (2007) who found baseline dependent effects of d-amphetamine on BART performance in males. They reported that 20 mg d-amphetamine significantly decreased risk behavior in men with scores in the lower half of the distribution for the personality trait of reward sensitivity (Agentic Positive Emotionality factor [AgPEM]), and significantly increased

risk behaviors in men with scores in the upper half of the distribution on AgPEM (White et al., 2007).

The goal of the study was to examine the effects of nicotine on BART performance for individuals with ADHD and age-matched controls. However, there were no group differences on BART performance between the ADHD group and control group, and no drug by group interaction. Further, there were no order effects of nicotine dose on BART performance. An interesting finding of the current study was that there were no group differences between participants with ADHD and age-matched controls on any of the dependent measures of the BART. One possible reason for this null finding is related to the gender breakdown within each group given that the control group was well balanced (8 males, 7 females), but the ADHD group had only 3 males and 8 females. Lejuez and colleagues (2002) reported gender differences on performance of the BART with males engaging in greater risk taking behavior than females, and similar gender differences were found on BART performance in the current study. Perhaps, the limited number of males with ADHD lessened the level of risk taking behavior on the BART by this group and therefore variability between the two groups did not occur. Unfortunately, with a small sample size we do not have the power to test this hypothesis. Another possibility is that the control group, which consisted of college students from a large state university, was a population that engaged in a higher baseline of risky behaviors, which reduced the variability in performance between the two groups. It is interesting to note that the ADHD participants were recruited to have a baseline deficit on stop signal reaction time on the stop signal task, a measure of behavioral inhibition. Therefore

within the same sample of participants, significant group differences were found on behavioral inhibition as well as working memory. This would suggest that deficits in behavioral inhibition do not necessarily co-occur with risk taking propensity as measured by the BART in individuals with ADHD. Another possibility is that using the categorical DSM-IV-TR diagnosis of ADHD rather than baseline performance on a certain behavior is not the most useful way to examine nicotine effects on that behavior. ADHD combined type is a complex diagnosis that requires an individual to meet 6 out of 9 possible symptoms of inattention and hyperactivity/impulsivity. The difference between someone diagnosed with ADHD and someone considered a healthy control participant could be just 1 or 2 symptoms. This data suggests that baseline performance may be a more informative way to measure drug-related changes.

As this study is the first to examine the effects of nicotine on BART performance in individuals with ADHD and age-matched controls it may be that we had insufficient power to detect the full range of effects of nicotine in this study. However, this is unlikely as the sample size was selected based on prior work with nicotine in this population (Potter & Newhouse, 2004, 2008), and significant nicotinic rate dependent effects on BART performance were shown. Another possible interpretation of the negative drug findings for individuals with ADHD is that the dose-response curve for risk taking propensity may be different than the one for behavioral inhibition, as this was designed based on prior work with nicotine in this population (Potter & Newhouse, 2004, 2008).

In acute drug challenge studies, it is important to consider the effect of repeated cognitive testing across the study days. To minimize practice effects in this study, the order of drug administration was randomized and counterbalanced. The order effects were examined and it was determined that order of drug administration did not affect BART performance.

A final caveat to be considered is that the ADHD participants in this study had different histories of taking stimulant medication. The effect of this on the BART performance in our study cannot be determined. In trying to understand the effect of medication history on cognition and neural function Rubia, Smith, Brammer, Toone, & Taylor (2005) examined brain activation during behavioral inhibition in adolescents with ADHD who were treatment naïve. They found patterns of brain activation that were consistent with prior findings in adolescents who had a history of medication use. The authors concluded that the abnormal brain activation was related to the disorder since it is found in ADHD adolescents both with and without a history of stimulant medication use (Rubia et al., 2005). However, a study by Pliszka, Lancaster, Liotti, & Semrud-Clikeman (2006) found volumetric differences in the anterior cingulated cortex (ACC) related to stimulant medication history in children with ADHD, with smaller right ACC in medication naïve children. However, this study did not look at performance differences related to these volumetric differences, and did not report the dosages of medication in the treatment group. It is also unknown if these volumetric differences change over time and development, and, specifically, if they persist into adulthood.

Exploratory analyses examining the effects of nicotine on inter-trial interval (IPI) were conducted. There were no significant effects of nicotine on IPI, pre-IPI (the time from the start of a trial to the first pump), or post-IPI (for banked balloons only, the time from the last pump to the money is banked) for any group (ADHD vs. Control or Low vs. High risk taking). There were no differences between participants with ADHD and controls on IPI, pre-IPI, or post-IPI. There was a difference for IPI between low risk taking and high risk taking participants, where high risk taking participants had a faster IPI. This was not modified by nicotine. One possible reason for no drug findings is that learning did not occur from trial to trial and therefore participants did not alter the speed at which they completed the task. Another possibility is that the task is not sensitive enough to measure IPI and capture such learning. In order to inflate the balloon participants click a computer mouse, which allows for very rapid pumping. It may be that this design reduces IPI variability and renders the task insensitive to small changes in speed.

Exploratory analyses examining the effects of nicotine on the primary dependent variables for the different trial types (post-balloon bank versus post-balloon explosion) were conducted. There were significant differences by trial type, where all participants (ADHD vs. Control and Low vs. High risk taking) used more average pumps per balloon and had longer average IPI and pre-IPI on trials post-balloon bank than post-balloon explosion. These data demonstrate that after a balloon explodes participants use fewer pumps, which suggests a modification towards less risky behavior after negative feedback. However, contrary to what was hypothesized, nicotine sped up average IPI for

trials post-balloon explosion and sped up average pre-IPI for both trial types for the

ADHD group only. On trials post-balloon explosion following a dose of nicotine

individuals with ADHD pump faster, but there is no drug related change in the number of

pumps. This increase in speed may represent a global improvement from nicotine on

attention and speed, but no effect of nicotine on risk taking. This is consistent with recent

investigations into nicotinic effects in ADHD demonstrating significant improvements in

speed of responding and self-rated vigor and concentration (Levin et al., 1996).

Given that Lejuez and colleagues (2002) reported significant gender differences

on BART performance with males responding more risky (greater number of average

adjusted pumps) than females, exploratory analyses examining gender differences were

conducted on the primary variables. There was an effect of gender, but no drug effects or

drug by gender interactions, for the number of adjusted average pumps used per balloon,

for the adjusted total pumps used per balloon, or the number of explosions, where males

performed more risky than females. This is in contrast to the median split data where

drug effects were observed when the groups differed on baseline performance. It is

possible that due to the small number of males in the study (11 males versus 15 females),

there was not enough power to detect drug differences. There were no effects of drug on

average IPI and post-IPI. There was a significant block by gender interaction for average

IPI, indicating that males sped up in block 2 of the task. These results are consistent with

previous research demonstrating increased risk taking on the BART by males (Lejuez et

al., 2002).   There was a trend effect of nicotine for average pre-IPI indicating that both

males and females had a shorter pre-IPI on nicotine. Again, this increase in speed may

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represent a global improvement from nicotine on attention and speed consistent with recent investigations into nicotinic effects in ADHD demonstrating significant improvements in speed of responding and self-rated vigor and concentration (Levin et al., 1996).

Taken together this study demonstrates that there are measurable rate dependent effects of nicotine on BART performance. For individuals with high baseline levels of risk taking, nicotine reduced risk taking behavior, and for individuals with low baseline levels of risk taking, nicotine increased risk taking behavior. These effects are consistent with a large literature demonstrating baseline-dependent effects of nicotine on measures of cognition, behavior, and mood.

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