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Effects of smoking abstinence on smoking-reinforced responding, withdrawal, and cognition in adults with and without attention deficit hyperactivity disorder

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Abstract

Rationale—Individuals with attention deficit hyperactivity disorder (ADHD) have a more difficult time quitting smoking compared to their non-ADHD peers. Little is known about the underlying behavioral mechanisms associated with this increased risk.

Objectives—This study aims to assess the effects of 24-h smoking abstinence in adult smokers with and without ADHD on the following outcomes: smoking-reinforced responding, withdrawal, and cognitive function.

Methods—Thirty-three ($n=16$ with ADHD, 17 without ADHD) adult smokers (more than or equal to ten cigarettes/day) were enrolled. Each participant completed two experimental sessions:

one following smoking as usual and one following biochemically verified 24-h smoking abstinence. Smoking-reinforced responding measured via a progressive ratio task, smoking withdrawal measured via questionnaire, and cognition measured via a continuous performance test (CPT) were assessed at each session.

Results—Smoking abstinence robustly increased responding for cigarette puffs in both groups, and ADHD smokers responded more for puffs regardless of condition. Males in both groups worked more for cigarette puffs and made more commission errors on the CPT than females, regardless of condition. Smoking abstinence also increased ratings of withdrawal symptoms in both groups and smokers with ADHD, regardless of condition, reported greater symptoms of arousal, habit withdrawal, and somatic complaints. Across groups, smoking abstinence decreased inhibitory control and increased reaction time variability on the CPT. Abstinence-induced changes in inhibitory control and negative affect significantly predicted smoking-reinforced responding across groups.

Conclusions—Smokers with ADHD reported higher levels of withdrawal symptoms and worked more for cigarette puffs, regardless of condition, which could help explain higher levels of nicotine dependence and poorer cessation outcomes in this population. Abstinence-induced changes in smoking-reinforced responding are associated with changes in inhibitory control and negative affect regardless of ADHD status, a finding that may lead to novel prevention and treatment programs.

Keywords

ADHD; Nicotine; Reinforcement; Self-administration

Introduction

Attention deficit hyperactivity disorder (ADHD) affects millions of children and adults in the USA and is a significant independent risk factor for smoking (Kessler et al. 2006; Lambert and Hartsough 1998; Milberger et al. 1997a, b; Molina and Pelham 2003a; Pomerleau et al. 1995). Individuals with ADHD or high levels of ADHD symptoms also start smoking at an earlier age, become more nicotine-dependent, and are more likely to progress from smoking experimentation to regular use (Fuemmeler et al. 2007; Kollins et al. 2005; Milberger et al. 1997a; Rohde et al. 2004; Wilens et al. 2008).

Clinical samples of individuals with ADHD and non-diagnosed individuals with high levels of ADHD symptoms may also have worse smoking outcomes. For example, in a sample of adults, the ratio of those reporting ever-regular smoking to those reporting not being a current smoker was significantly lower for individuals with ADHD, suggesting a lower likelihood of ever quitting (Pomerleau et al. 1995). A history of childhood ADHD also predicted significantly worse smoking cessation outcomes in a sample of adult smokers engaged in a quit attempt (Humfleet et al. 2005). Finally, in a large sample of adult smokers being treated with bupropion and nicotine patch, those reporting higher levels of ADHD symptoms, particularly hyperactive-impulsive symptoms, had significantly lower rates of continuous abstinence than individuals with low levels of symptoms (Covey et al. 2008).

The behavioral mechanisms underlying increased risk for smoking, generally, and poor cessation outcomes, specifically, have not been systematically examined among smokers with ADHD. Several studies have reported that smokers with ADHD report greater withdrawal severity following abstinence. For example, adult regular smokers with ADHD exhibited comparatively greater abstinence-induced disruptions in both inhibitory control and attention, measured with a continuous performance task (CPT) and following overnight abstinence (McClernon et al. 2008). Another study reported that smokers with ADHD who

were undergoing a contingency-managed 12-day quit attempt reported significantly higher levels of negative affect and craving compared to non-ADHD smokers (McClernon et al. 2011). It is possible that individuals with ADHD lapse sooner during cessation attempts due to relatively greater increases in withdrawal severity. Alternatively, observed differences in both cognitive function and self-reported withdrawal symptoms following acute smoking abstinence may be associated with abstinence-induced changes in ADHD symptoms, since some studies have reported that these constructs are significantly correlated (Berlin et al. 2012). At least one study, however, has reported that increased withdrawal severity among smokers with ADHD is independent of changes in ADHD symptoms (McClernon et al. 2011).

Smoking-reinforced responding, or the extent to which individuals will emit responses to receive cigarette puffs, may provide additional insight into the behavioral mechanisms responsible for higher rates of smoking in individuals with ADHD, as well as why these individuals report worse cessation outcomes. ADHD has been consistently characterized as a disorder involving altered reinforcement processes (Johansen et al. 2009; Luman et al. 2005), and studies of the neurobiological bases of ADHD provide support for these behavioral theories of the disorder by highlighting alterations in dopamine and other catecholamine function in relevant brain regions (Brennan and Arnsten 2008; Brocki et al. 2008; Prince 2008; Tripp and Wickens 2008; Wilens 2008). Importantly, similar brain regions and neuro-transmitter systems are modulated by both chronic and acute nicotine administration (De Biasi and Dani 2011). It stands to reason, therefore, that differences in smoking-reinforced responding among individuals with ADHD may be related to differential rates of smoking and cessation outcomes in those with the disorder.

A number of studies have evaluated the reinforcing effects of smoking in human subjects, as well as the impact of several variables that can impact smoking-reinforced responding (Bickel et al. 1995, 1997; Perkins et al. 1994; Tidey et al. 1999). For example, access to cigarette puffs has been shown to reliably maintain responding in adult smokers, and increasing response requirements (i.e., number of button presses) and availability of non-contingent puffs have both been shown to decrease responding for contingent puffs (Bickel et al. 1997). Several factors have been examined as moderators of smoking-reinforced responding. One of the more widely studied manipulations has been to examine the effects of smoking abstinence on subsequent smoking-reinforced responding. Smoking abstinence has been consistently shown to increase smoking-reinforced responding. Using varying response requirements (e.g., button pressing, riding an exercise bike), studies have shown that the duration of smoking abstinence preceding an opportunity to work for puffs increases the probability and rate of responding (Epstein et al. 1991; Griffiths et al. 1982). The influence of abstinence on smoking-reinforced responding has also been shown to be affected by other manipulations, such as the availability of alternative reinforcers, the presence of visual smoking cues, or other contingencies (Epstein et al. 1991; Griffiths et al. 1982; Lussier et al. 2005; Perkins et al. 1994). Overall, there is considerable evidence that smoking-reinforced responding is a valid approach for understanding the behavioral mechanisms underlying smoking behavior across a range of environmental conditions.

To date, only one published study has examined the effects of abstinence on smoking-reinforced responding in a psychiatrically comorbid sample of smokers—those with schizophrenia. Like ADHD, schizophrenia is often associated with smoking/nicotine dependence, and it has been proposed that smoking serves to self-medicate aspects of the illness (Lavin et al. 1996). Heavy-smoking (>25 cigarettes/day) individuals diagnosed with schizophrenia completed more ratios under a *progressive ratio* (PR) task following a 5–6-h period of abstinence than when not abstinent (Tidey et al. 1999). Neither this study nor others of which we are aware have directly compared the reinforcing effects of smoking in

clinical and non-clinical samples, thus leaving unanswered the question of whether there may be important group differences in abstinence-induced smoking-reinforced responding. Such data may help explain differential risk for smoking among those with psychiatric illness generally and ADHD specifically. The current study was designed to examine the effects of 24-h abstinence on the relative reinforcing effects of cigarette smoking in adults with and without ADHD, while controlling for a number of other important factors (e.g., sex, age, race, nicotine dependence). Given previous studies that have reported increases in withdrawal severity in those with ADHD, we also examined both executive functioning and self-reported withdrawal symptoms across groups and the association of these constructs with self-reported ADHD symptoms. We hypothesized that the reinforcing effects of cigarette smoking would be greater in smokers with ADHD (a main effect) and that this effect would be most pronounced under conditions of abstinence (group $\times$ condition interaction). Moreover, we hypothesized that abstinence-induced disruptions in inhibitory control and negative affect, both of which have been shown to be more pronounced in smokers with ADHD (McClemon et al. 2008, 2011), would predict abstinence-induced smoking-reinforced responding to a greater extent in smokers with ADHD. Finally, we examined whether abstinence-induced changes in executive functioning and self-reported withdrawal symptoms would be independent of self-reported ADHD symptoms.

Methods

Participants

Participants for the study were 33 male and female adult regular smokers between the ages of 18–50 years recruited from the community. Sixteen of the participants were diagnosed with ADHD by a licensed clinician, and the remaining 17 participants were free from any psychiatric diagnosis, except for nicotine dependence. Diagnostic status of all participants was determined using the Structured Clinical Interview for DSM (SCID; First et al. 1997), the Conners Adult ADHD Diagnostic Interview for DSM (CAADID; Epstein et al. 2000), and the Conners Adult ADHD Rating Scale (CAARS; Conners et al. 1998). Other inclusion criteria included self-reported current smoking of at least ten cigarettes/day, afternoon expired air CO levels of ≥ 10 ppm, and, for the ADHD group, age- and sex-adjusted T-scores on relevant CAARS subscales that were ≥ 65 . Exclusion criteria included estimated IQ scores of <80 measured using the Kaufman Brief Intelligence Test (Kaufman and Kaufman 2004), positive urine drug screen for illicit drugs, breath alcohol level >0.00 , any significant medical condition (i.e., neurological or CNS-related disorder such as epilepsy, diabetes, coronary disease, renal function, or other conditions that, in the judgment of the study physician, would influence study participation or warrant more immediate medical care), and, for the control group, T-scores on relevant CAARS scales >55 . Individuals in the ADHD group who were currently treated pharmacologically for their ADHD ($n=3$) were allowed to participate, provided they washed out of their medication for a duration of at least five half-lives prior to the baseline and experimental sessions. Subjects in either group taking other kinds of psychotropic medication were excluded from participation. All participants provided informed consent, and the study was reviewed and approved by the local Institutional Review Board.

Design and procedures

Following screening, all participants completed a *baseline* visit and two *experimental* visits. Participants were compensated \$50 for each of the four visits, plus a completion bonus of \$100 for completing the study. In addition, participants could earn up to an additional \$11 depending on their performance on the progressive ratio task (see below), for a total study compensation of \$311. During the baseline visit, participants were familiarized with all procedures and measures to be used in the experimental visits. The two experimental visits

were identical except that one was conducted following biochemically verified 24-h abstinence and the other was conducted following typical smoking behavior. Participants were randomly assigned to the order of experimental visits during the baseline visit and were given instructions about the *abstinence* session. In general, they were instructed not to smoke cigarettes or use any tobacco products beginning 24 h prior to their scheduled visit. Participants were also reminded via email, phone call, or text message a day in advance of each experimental visit and were reminded about the smoking requirements for each session. During the abstinence session, participants provided an expired air CO level that had to be 5 ppm in order to proceed with the session. During the *satiated* session, all participants were provided several scheduled smoke breaks to control for the time since the last cigarette.

Experimental visits lasted approximately 5 h. Participants arrived at the lab, and alcohol and drug use was assessed via breathalyzer and urine drug screen, respectively. Participants had to have a breath alcohol level of 0.0 and a negative drug screen to continue with the session. Vital signs were measured, a smoking diary was completed to record smoking since the last visit, and the subjective and executive functioning measures (see below) were completed. Approximately 90 min into the session, the progressive ratio task was completed for 90 min. Following this, additional subjective effect measures and vital signs were collected, followed by an additional 90 min of leisure time. This was included to provide a delay from the end of the PR task to the opportunity to smoke during the abstinent condition. Participants were then dismissed from the laboratory and either debriefed (following the second experimental visit) or scheduled for the next session.

Measures

Smoking-reinforced responding—The primary outcome measure for the study was the number of responses completed for cigarette puffs during a 90-min PR task. During the task, subjects were positioned in front of a computer screen and keyboard and instructed that they would have the opportunity to press the buttons on the keyboard to earn either standardized puffs of a cigarette (two puffs/opportunity) or a fixed amount of money (\$0.50). The PR task session was 90 min in duration. Similar to other PR studies conducted with human subjects, participants were instructed that they could choose not to press the buttons, but that the duration of the session would be 90 min regardless of whether they completed none or all of the ratios for smoking opportunities or money (Sigmon et al. 2003; Tidey et al. 1999).

Ratios for cigarette puffs and money operated independently such that subjects could respond exclusively for one consequence or the other, alternate their responses for each of the consequences, or not respond at all. For each consequence, the first ratio required 75 responses, and each successive ratio required 1.75 times the previous ratio such that the response requirements for each reinforcer were 75, 131, 229, 401, 702, 1,229, 2,151, 3,764, and so on (Kollins et al. 2009). Subjects were required to remain in the testing room for the 90-min duration of the task, regardless of whether they chose to work for puffs or money. Following the completion of each ratio, which was signaled by a message that appeared on the computer screen and an audible signal, there was a 2-min time-out period. During this period, participants received either two standardized puffs of their preferred brand of cigarette delivered via a controlled puff volume apparatus (Levin et al. 1989), or \$0.50 in cash. Puff volume was measured at 30 mL. Following the time-out period, subjects were allowed to resume responding on the PR task.

Executive functioning—The Conners' CPT (Conners 2000) was used to assess inhibitory control and attentional control. During the task, participants were required to press a button whenever a letter appeared on the screen unless that letter was an "X". Measures of inhibitory control (errors of commission—pressing the button on X trials) and

attentional control (errors of omission, reaction time standard error) served as primary measures from this task. These outcomes from the CPT have been shown in previous studies to be sensitive to the effects of smoking abstinence in smokers with and without ADHD (McClernon et al. 2008).

Smoking withdrawal—A modified version of the Shiffman–Jarvik Withdrawal Questionnaire (SJWQ; Rose and Levin 1990; Shiffman and Jarvik 1976) was used. This is a 32-item measure of craving (e.g., Are you thinking of cigarettes?), arousal (e.g., Do you feel wide awake?), negative affect (e.g., Do you feel irritable?), somatic symptoms (e.g., Is your heart beating faster than usual?), habit withdrawal (e.g., Do you miss having something to do with your hands?), and appetite disturbance/hunger (e.g., Do you feel hungrier than usual?). Previous studies have shown that this instrument is sensitive to the effects of smoking abstinence in adult smokers with and without ADHD (McClernon et al. 2011).

Data analyses

The primary analysis to examine the effects of smoking abstinence on smoking-reinforced responding was conducted using a 2 (group: ADHD vs. control) × 2 (sex: male vs. female) × 2 (condition: abstinent vs. satiated) mixed model ANOVA. We included sex in the ANOVA model since a previous work has suggested sex by ADHD status interactions on smoking abstinence outcomes (McClernon et al. 2008, 2011; Van Voorhees et al. 2012). Smoking-reinforced responding was examined in two ways. First, the number of completed ratios for puffs was calculated for each group and sex under each condition. Second, the total number of responses for cigarette puffs during the 90-min PR task was calculated for the groups under each condition. For the total responses made for puffs, initial examination of the data revealed significant departures from normality, so the data were log-transformed prior to analysis. Using the same ANOVA model, we also examined the number of completed ratios for cash, the number of cash responses made under each condition, and the proportion of ratios completed for puffs/ratios completed for cash in each condition. The effects of smoking abstinence on inhibitory control and attention were examined using commission errors and reaction time standard error from the CPT and a similar mixed model ANOVA. Each of the six subscales of the SJWQ was also examined using the same mixed model ANOVA.

Since we were also interested in the effects of abstinence-induced disruptions in cognition and affect on smoking-reinforced responding, a series of linear regression models were used to predict the change in smoking-reinforced responding across conditions, using completed ratios for puffs on the abstinent day minus completed ratios made for puffs on the satiated day. Difference scores (i.e., abstinent condition *minus* satiated condition) for the two CPT measures (commission errors and reaction time standard error) and the six SJWQ subscales were used as predictors. We also examined the effects of group status, sex, cigarettes/day, Fagerstrom Test for Nicotine Dependence (FTND) score, and responses for puffs under satiated conditions. All analyses were conducted in SPSS (v.19.0).

Results

Participant characteristics

A total of 197 subjects were initially telephone-screened for the study, resulting in 101 in-person screens. Of these, 54 passed all inclusion and exclusion criteria and enrolled in the study. A total of 33 subjects ($n=16$ ADHD and $n=17$ control) completed all sessions and provided useable data for the main outcome measures. Of the subjects who were not included in the analysis, eight ($n=4$ ADHD, $n=4$ control) were lost to follow-up or moved; five ($n=3$ ADHD, $n=2$ control) had repeated scheduling difficulties; four ($n=3$ ADHD, $n=1$

control) did not provide useable data from the CPT; two ($n=1$ ADHD, $n=1$ Control) had a positive urine drug screen at baseline; one (ADHD) initiated pharmacotherapy for ADHD; and one (ADHD) stopped smoking after the screening session. The rate of attrition did not differ across the ADHD and control groups. Also, there were no significant differences between completers and non-completers with respect to age, sex, race, screening CO, or number of cigarettes smoked/day. Table 1 shows demographic and smoking characteristics of the final analyzed sample at screening.

Effects of abstinence on smoking-reinforced responding

CO levels obtained during both abstinence and satiated experimental sessions indicate that participants were compliant with study requirements. Mean CO levels for the abstinence session were 3.6 and 2.7 ppm for the ADHD and control groups, respectively. For the satiated session, mean CO levels were 17.8 and 17.9 ppm for ADHD and control groups, respectively.

Figure 1a illustrates the effects of smoking abstinence on completed ratios for cigarette puffs in ADHD and non-ADHD smokers. Smokers with and without ADHD completed a mean of 2.2 ($SD=2.1$) and 1.2 (1.3) ratios for cigarette puffs during the abstinence condition, respectively. In the satiated condition, smokers with and without ADHD completed a total of 0.8 (1.0) and 0.3 (0.7) ratios for cigarette puffs, respectively. There was a significant main effect of condition ($F(1, 29)= 16.0, p<0.001$) indicating that, across groups, participants completed significantly more ratios in the abstinence condition. There was also a trend toward a main effect of group, suggesting that, regardless of condition, smokers with ADHD tended to complete more ratios for cigarette puffs ($F(1, 29)= 3.50, p=0.07$). There was also a main effect of sex, indicating that regardless of condition, males completed more ratios for cigarette puffs compared to females ($F(1, 29)=6.4, p=0.02$). There were no significant two- or three-way interactions. For total responses made for puffs, results of the ANOVA with the log-transformed data revealed a similar pattern of results, with a significant main effect of condition ($F(1, 29)=7.7, p=0.01$). Significant main effects of group ($F(1, 29)=4.3, p=0.05$) and sex ($F(1, 29)=9.4, p=0.005$) were also observed, indicating that smokers with ADHD and males emitted more responses for cigarette puffs across conditions. Again, no interactions were observed. For ease of interpretation, Fig. 1b illustrates the actual non-transformed puff response data.

We also examined group and condition effects on responding for cash. Smokers with and without ADHD completed a mean of 8.5 ($SD=0.89$) and 8.4 (0.51) ratios for cash during the abstinence condition, respectively. In the satiated condition, smokers with and without ADHD completed a total of 8.7 (0.70) and 8.8 (0.39) ratios for cash, respectively. There were main effects of condition for both completed ratios for cash and log-transformed responses for cash ($F(1, 29)>7.0, p's<0.02$). There were no significant main effects for group or sex and no significant two- or three-way interactions.

Since participants had continuous access to response options for both cigarette puffs and money, the final way in which we examined the relative reinforcing effects of smoking was by comparing the proportion of ratios completed for cigarette puffs to ratios completed for money, under both abstinent and satiated conditions (Fig. 2). There was a significant main effect of condition in that the ratio of completed ratios for puffs/completed ratios for cash was significantly higher during the abstinent condition ($F(1, 29)=16.87, p<0.001$). There was a significant main effect of sex in that the puff/money ratio was higher for males in both groups ($F(1, 29)=7.06, p<0.05$). There was also a trend for the puff/money ratio to be greater for ADHD smokers under both conditions ($F(1, 29)=3.54, p=0.07$). There were no two- or three-way interactions.

Effects of abstinence on executive functioning and withdrawal

Figures 3a, b illustrate the effects of smoking abstinence on inhibitory control and attention, respectively, as measured by the CPT. For commission errors, there was a significant main effect of sex ($F(1, 29)=5.1, p=0.03$) that was characterized by males making significantly more commission errors than females regardless of condition. There were also trends toward significant effects of both condition ($F(1, 29)=3.4, p=0.08$) and group ($F(1, 29)=3.1, p=0.09$) characterized by increased commission errors on the abstinent day and in the ADHD group. There were no significant two- or three-way interactions for commission errors. There was a significant effect of condition on reaction time standard error ($F(1, 29)=9.5, p=0.004$). There were no main effects of group or sex and no significant interactions for reaction time standard error.

Table 2 depicts means and standard deviations for each of the six Shiffman–Jarvik Withdrawal Questionnaire subscales. Since there were no significant main effects of sex and was the only one interaction involving sex; data are shown only for condition and group. There were significant main effects of condition in the expected direction for all six subscales, indicating greater self-reported withdrawal during the abstinence condition. There were also significant main effects of group (ADHD vs. control) for the somatic symptoms, arousal, and habit withdrawal subscales, indicating that regardless of condition, smokers with ADHD reported more withdrawal symptoms in these domains, compared to non-ADHD smokers. For the somatic symptoms subscale, a condition $\times$ group $\times$ sex interaction was observed ($F(1, 29)=9.04, p=0.005$) and characterized by increases in self-reported somatic symptoms during abstinence for ADHD males (mean score during abstinence=2.3 [SD=0.86], mean score during satiated=1.51 [SD=0.53]) and control females (mean score during abstinence=1.4 [SD=0.52], mean score during satiated=1.19 [SD=0.20]). Changes in somatic symptoms were relatively unchanged across conditions for ADHD females (mean score during abstinence=1.47 [SD=0.58], mean score during satiated=1.53 [SD=0.68]) and control males (mean score during abstinence=1.31 [SD=0.44], mean score during satiated=1.38 [SD=0.57]). Since some studies have suggested that ADHD symptoms and self-reported smoking withdrawal symptoms are confounded, we examined the correlation between self-reported ADHD symptoms at screening and SJWQ subscale scores for each of the conditions (abstinent and satiated). Four of the SJWQ subscale scores (negative affect, arousal, somatic symptoms, and habit withdrawal) from the abstinent condition were significantly correlated with total ADHD symptom ratings from screening (p 's < 0.05). There were no significant correlations between screening ADHD symptoms and SJWQ subscale scores from the satiated condition.

Effects of abstinence-induced changes in executive functioning/withdrawal on smoking-reinforced responding

The effects of abstinence-induced changes in cognition and withdrawal on abstinence-induced changes in smoking-reinforced responding (measured using completed ratios for puffs) were evaluated using a series of stepwise linear regression models. In the first model, three blocks of predictor variables were entered. Block 1 consisted of group (ADHD vs. control), sex, cigarettes/day, FTND total score, and total responses for puffs on the satiated day. Block 2 consisted of change scores for measures of cognition (abstinence session–satiated session): CPT commission errors and reaction time standard error. Block 3 consisted of change scores for measures of smoking withdrawal using each of the six SJWQ subscales. Results of this model suggested that only two of the variables across blocks were retained as significant predictors of smoking-reinforced responding: change scores for CPT commission errors (standardized $\beta=0.42, t=2.95, p<0.01$) and change scores for the negative affect subscale of the SJWQ (standardized $\beta=0.43, t=3.04, p<0.01$). We subsequently tested a model including both of these variables, along with interaction terms that included ADHD

group status and each of the two significant predictors (commission errors and negative affect). In this model, change in commission errors and change in negative affect were retained as significant predictors, while neither of the interaction terms was significant, suggesting that abstinence-induced changes in commission errors and negative affect predict smoking-reinforced responding in a similar manner across groups.

Discussion

The present study examined smoking-reinforced responding using a standardized PR task under abstinent and satiated conditions in adult regular smokers with and without ADHD. Several findings are noteworthy. First, compared to smokers without ADHD, smokers with ADHD tended to produce greater response output for cigarette puffs, regardless of condition. Our prediction that smoking-reinforced responding would be greater under abstinent conditions for the ADHD smokers (an interaction) was not supported statistically. There was also a significant main effect of sex on smoking-reinforced responding in that males in both groups worked harder for cigarette puffs across conditions. There were no differences between the groups for responding for money under either condition. Second, inhibitory and attentional control tended to be disrupted during smoking abstinence in both groups, and there was a trend for decreased inhibitory control regardless of condition for the smokers with ADHD. This finding was consistent with our predictions. Third, there were expected main effects of abstinence on self-reported withdrawal symptoms, and smokers with ADHD reported significantly greater levels of withdrawal on several of the subscales of the SJWQ, regardless of condition. Moreover, there was a complex condition $\times$ group $\times$ sex interaction for one of the SJWQ sub-scales (somatic symptoms). Finally, findings from the present study showed that abstinence-induced changes in inhibitory control and negative affect significantly predicted smoking-reinforced responding across both ADHD and non-ADHD smokers, again partially supporting our hypotheses that these constructs would predict smoking-reinforced responding, although (unexpectedly) not to a greater degree in the ADHD smokers.

It is well established that smoking abstinence increases the reinforcing effects of smoking (Lussier et al. 2005; Tidey et al. 1999). However, as noted previously, only one study of which we are aware has examined the effects of abstinence on smoking-reinforced responding in a psychiatric sample of smokers and reported that even brief abstinence (5–6 h) increased responding for smoking opportunities in adult smokers with schizophrenia (Tidey et al. 1999). Other studies have compared samples of smokers with and without psychiatric disorders and have generally shown that smokers with psychiatric illness (e.g., depression, schizophrenia) smoked more or valued cigarette smoking more than non-psychiatric controls (MacKillop and Tidey 2011; Spring et al. 2003; Tidey et al. 2005, 2008; Weinberger et al. 2007). The present study is the first to directly compare smoking-reinforced responding in smokers with and without psychiatric comorbidity using a PR task. The use of a behaviorally based measure of smoking-reinforced responding and the use of responses for cash as a control are important methodological features of the current study design. Differences in smoking-reinforced responding were observed despite a lack of group differences on other potentially confounding factors including FTND score and cigarettes/day. This finding is important since it may provide a mechanism for why individuals with ADHD and high levels of ADHD symptoms have poorer smoking cessation outcomes (Covey et al. 2008; Humfleet et al. 2005; Pomerleau et al. 1995, 2003). It would be useful for future studies to determine the extent to which smoking-reinforced responding in laboratory settings predicts cessation outcomes. Given the relative consistency with other studies comparing psychiatric to non-psychiatric control smokers, the present results also suggest that investigating common genetic or neurobiological processes that underlie group differences cutting across psychiatric disorders may prove informative.

Findings from the current study suggest greater abstinence-induced increases in smoking-reinforced responding in males versus females. In the present study, cigarette puffs were administered via a puff delivery device with a measured dose and through which participants were not able to hold and manipulate a cigarette as they would do with normal smoking. As such, the finding of greater abstinence-induced smoking-reinforced responding for males is consistent with research that has shown that maintenance of smoking behavior in females may be less strongly associated with nicotine dose and more related to sensory or other non-pharmacological factors (Perkins et al. 1999, 2002, 2006).

Consistent with previous studies (Bekker et al. 2005; Hatsukami et al. 1989; Powell et al. 2002; Zack et al. 2001), the present experiment found that smoking abstinence precipitated disruptions in inhibitory control and reaction time standard error—a putative measure of attentional control—although the effects on inhibitory control were observed only at the trend level. Inconsistent with previous studies (McClernon et al. 2008), we did not observe a significant ADHD status by condition interaction on these cognitive outcomes. There are several possible explanations for this discrepancy. First, the duration of abstinence in the present study (24 h) was somewhat longer than in the previous study (overnight, specific duration not reported). It is possible that the longer duration of abstinence resulted in an increased magnitude of cognitive disruption in the non-ADHD smokers, thus mitigating the interaction. Another possibility was that there was substantial variability in these outcome measures in both groups of smokers. Even though there was a numeric difference in the expected direction (ADHD>control) for both commission errors and reaction time standard error across conditions, there was not a main effect of group in part due to large standard deviations observed in both groups. It is still important to demonstrate that, independent of psychiatric status, smoking abstinence resulted in disruption in both inhibitory and attentional control.

Also consistent with previous studies, smoking abstinence in the present experiment robustly increased self-reports of withdrawal symptoms on effects of abstinence on withdrawal. Importantly, there were several main effects of group status on SJWQ subscales of somatic symptoms, arousal, and habit withdrawal. Scores on the somatic symptoms and habit withdrawal subscales were increased, and scores on the arousal subscale were decreased in smokers with ADHD, regardless of condition. Importantly, each of these three subscales, as well as the negative affect subscale, was significantly correlated with self-reported ADHD symptoms at screening. As such, these findings are somewhat consistent with others that have reported overlap between smoking withdrawal symptoms and ADHD symptoms (Berlin et al. 2012; Gray et al. 2010), though at least one study reported that self-reported withdrawal symptoms are independent of ADHD symptoms (McClernon et al. 2011).

While a number of studies have reported increases in smoking-reinforced responding following abstinence, the current study is the first to report on specific moderators of this phenomenon. Results suggest that abstinence-induced disruptions in inhibitory control and negative affect are significant predictors of abstinence-induced increases in responding for cigarette puffs, even after controlling for ADHD status, nicotine dependence, cigarettes/day, and responding for puffs during satiated conditions. While it is a widely held belief that individuals smoke more in response to negative affect and that smoking alleviates these unpleasant states, the empirical and theoretical literature highlights that such “direct-effects” explanations are likely to be overly simplistic (Kassel et al. 2003). Drawing on a previous theoretical work (Gilbert and Gilbert 1995) in their comprehensive review of stress, smoking, and negative affect, Kassel et al. (2003) noted that “...the critical question is not whether smoking alleviates stress and [negative affect] but for whom, under what conditions, and for which stress-, and affect-related outcomes...” (p. 290). The same

question could also be raised regarding the effects of smoking on cognitive function (Heishman et al. 2010). Data from the current study begin to address some of these more complex questions about the relationships among smoking-reinforced responding and negative affect/cognition. These results suggest that interventions that target abstinence-induced changes in inhibitory control and negative affect may be useful to reduce the relative reinforcing effects of smoking during a quit attempt.

Our finding that abstinence-induced disruptions in inhibitory control and negative affect predicted smoking-reinforced responding in both ADHD and non-ADHD smokers is consistent with recent empirical and theoretical work on the causal heterogeneity of ADHD. These studies suggest that multiple and distinct neuropsychological subtypes can independently give rise to the clinical diagnosis of ADHD (Nigg et al. 2004, 2005). Moreover, the patterns of neuropsychological heterogeneity within ADHD samples is similar to that observed in typically developing children and differ only in terms of magnitude (Fair et al. 2012). Results from the present study show that individual variation in inhibitory control and/or affective regulation predicts abstinence-induced increases in smoking-reinforced responding, regardless of ADHD status. As such, the tendency for ADHD smokers to exhibit relatively greater smoking-reinforced responding may be related to a relatively greater proportion of individuals with disruption in these processes and/or more significant patterns of disruption.

Findings from the present study are also consistent with neurobiological models of both ADHD pathophysiology and nicotine addiction. Adults with ADHD are hypothesized to exhibit decreased dopaminergic activity in striatal brain regions, and these deficits are correlated with symptom severity and impairment (Volkow et al. 2009, 2011). Preclinical studies have demonstrated that *acute* nicotine administration facilitates dopamine signaling in similar areas of the striatum, including the nucleus accumbens, and these actions underlie the rewarding/reinforcing effects of the drug (De Biasi and Dani 2011). In contrast, *chronic* nicotine exposure and subsequent acute withdrawal both result in substantial reductions in tonic dopamine activity and associated reward-related brain function (Epping-Jordan et al. 1998; Perez et al. 2012; Zhang et al. 2012). Moreover, nicotine withdrawal following chronic exposure results in enhanced sensitivity of DA release to phasic stimulation, such as with acute nicotine administration (Zhang et al. 2012). Inhibitory control processes are also modulated by striatal dopamine activity and influenced by functional variants of dopamine genes (Ghahremani et al. 2012; Hamidovic et al. 2009). Collectively, data from the present study and the extant literature suggest that individuals with ADHD exhibit alterations in striatal dopamine signaling that are potentially further modified following chronic nicotine exposure. Following acute withdrawal, this hypodopaminergic state is further exacerbated, while increasing the sensitivity of the dopamine system to phasic stimulation, such as exposure to cigarette puffs or cues for smoking (i.e., sensory stimuli). This provides some neurobiological explanation for the findings reported here, although clearly additional work is needed to clarify the role of altered dopamine signaling in smoking withdrawal among smokers with ADHD.

Results from the present study should be considered alongside some important limitations. First, we used a relative versus absolute measure of smoking-reinforced responding by using a concurrent PR task. It is possible that, in the absence of other response alternatives, the observed effects would have been different. However, the opportunity to choose between consequences (i.e., smoking versus money) is arguably a more valid model of smoking in the natural environment. Second, we did not examine the potential effects of medication on our outcomes. Previous laboratory studies have reported that stimulant drugs commonly used to treat ADHD (e.g., methylphenidate and amphetamine) increase smoking behavior in both ADHD and presumably non-psychiatric smokers (Rush et al. 2005; Sigmon et al. 2003;

Vansickel et al. 2011). By contrast, at least two controlled smoking cessation clinical trials with smokers with ADHD have reported that stimulant medication did *not* increase smoking behavior, even if these treatments did not result in significantly higher rates of short-term smoking cessation (Kollins et al. 2012; Winhusen et al. 2010). It would be clinically meaningful to examine the effects of stimulant drugs on the abstinence-induced increases in smoking-reinforced responding observed in the present study. Third, we only examined a single magnitude of both our smoking (i.e., two puffs) and money (i.e., \$0.50) consequences. It would be informative to conduct a more comprehensive behavioral economic analysis of smoking-reinforced responding in those with and without ADHD. For example, it would be useful to determine whether increases or decreases in the money alternative attenuated or magnified group differences, respectively. Such analyses could be useful for determining optimal parameters for incentive-based interventions for smokers with ADHD, especially since such approaches have been shown to be relatively successful in reducing smoking in this population (Kollins et al. 2010).

A related observation from the current study was that there were a number of participants in both groups (5/16 ADHD and 7/17 control) who did not complete any ratios for cigarette puffs even during the abstinent condition. This suggests that the relative reinforcing effects of smoking were diminished for some of the subjects, relative to the monetary reinforcer value. Another source of variance may be that, for some subjects, the novel artificial context of the laboratory and experimental setting modified the (perceived) relative value of smoking, as other conditioned reinforcers were absent (e.g., social context). It would be important for future studies to isolate possible individual difference variables that may account for the lack of smoking reinforcement under abstinent conditions. A fourth limitation was that, only 61 % (33/54) of the participants enrolled in the study completed all sessions with useable data. Although there was no differential attrition across groups and no differences in baseline characteristics of completers and non-completers, the manner in which this attrition affected study outcomes is unknown. Finally, given the sample size for our study and the variability across some of the measures, we may have been underpowered to detect significant interaction effects. For example, we hypothesized a group $\times$ condition interaction, and results were in the expected direction (e.g., Fig. 1b). However, the effect size for this interaction was small (partial eta squared= 0.02). As such, with a larger sample, this finding may have reached statistical significance.

Despite these limitations, results from this study add to the relatively sparse literature on the mechanisms underlying adverse smoking outcomes in individuals with psychiatric conditions. It is well established that individuals with psychiatric comorbidity, generally (Lasser et al. 2000), and ADHD, specifically (Milberger et al. 1997b; Molina and Pelham 2003b; Wilens et al. 2008), are more likely to be regular smokers and are at risk for a wide range of other adverse smoking outcomes. Understanding the effects of abstinence on the relative reinforcing effects of smoking, along with other important moderators, can help refine knowledge about why individuals with ADHD (and other psychiatric comorbidities) smoke more or find it harder to quit and may eventually lead to more refined and targeted prevention and intervention programs.

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Fig. 1. Completed ratios for cigarette puffs (**a**) and total responses made for cigarette puffs (**b**) during the PR task in smokers with and without ADHD under satiated and abstinent conditions. *Error bars* indicate SEM. See text for statistical details

Fig. 2. Proportion of completed ratios for cigarette puffs/completed ratios for cash during the PR task in smokers with and without ADHD under satiated and abstinent conditions. *Error bars* indicate SEM. See text for statistical details

Fig. 3.

Commission errors, a measure of inhibitory control (**a**), and reaction time standard error, a measure of attentional control (**b**), across abstinent and satiated conditions for smokers with and without ADHD. *Error bars* indicate SEM. See text for statistical details

Table 1

Subject characteristics at screening

	ADHD	Control	<i>p</i> value
Sex			ns ^a
Female	7	8	
Male	9	9	
Race			ns ^a
White	10	6	
Non-White	6	11	
Age (years) (SD)	30.2 (9.2)	35.6 (10.6)	ns ^b
Marital status (%)			ns ^a
Single	69	76	
Married/divorced/separated	25	24	
Not reported	6	0	
Educational level (%)			ns ^a
High school or less	25	53	
Some college	56	41	
College or professional/graduate	19	6	
CAARS subscale scores (T-scores)			
DSM-IV inattentive (mean, SD)	78.4 (8.6)	41.6 (6.6)	<0.0001 ^b
DSM-IV hyperactive-impulsive (mean, SD)	64.7 (12.1)	42.6 (9.1)	<0.0001 ^b
DSM-IV total symptoms (mean, SD)	76.1 (10.0)	41.2 (8.0)	<0.0001 ^b
ADHD subtype (%)			
Predominantly inattentive	63		
Predominantly hyperactive-impulsive	0		
Combined	37		
Cigarettes/day (SD)	13.6 (3.8)	15.4 (3.9)	ns ^b
FTND total score (SD)	4.6 (1.7)	4.9 (1.1)	ns ^b
CO level (SD)	21.9 (9.4)	21.9 (8.9)	ns ^b
Years regular smoking (SD)	11.9 (7.6)	17.2 (11.4)	ns ^b

^aChi-square test^b*t* test

Table 2

Mean (SD) from Shiffman–Jarvik questionnaire subscales as a function of group and condition

Subscale	Satiated		Abstinent		F values (df=1, 29)		
	ADHD	Control	ADHD	Control	Condition	Group	Condition × group
Craving	2.5 (1.1)	2.0 (0.8)	5.7 (1.0)	5.2 (1.6)	99.27*	3.00	0.02
Negative affect	2.8 (1.1)	2.8 (0.5)	4.3 (1.3)	3.7 (0.9)	30.97*	1.56	0.98
Appetite disturbance	1.8 (0.9)	1.5 (1.2)	2.8 (2.3)	2.3 (1.5)	20.62*	0.89	0.00
Somatic symptoms	1.5 (0.6)	1.3 (0.4)	1.9 (0.84)	1.4 (0.5)	5.50**	4.58**	2.49
Arousal	4.9 (1.4)	5.6 (0.8)	4.5 (0.8)	5.2 (1.0)	4.94**	4.76**	0.02
Habit withdrawal	1.9 (1.0)	1.4 (0.6)	4.0 (1.4)	3.1 (1.5)	67.37*	4.11**	0.66

* $p < 0.05$;

** $p < 0.01$