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Abstinence-Induced Withdrawal Severity among Adolescent Smokers With and Without ADHD: Disentangling Effects of Nicotine and Smoking Reinstatement

L. Cinnamon Bidwell^{1,2}, Sara G. Balestrieri², Suzanne M. Colby^{2,3,4}, Valerie S. Knopik^{6,3,5}, and Jennifer W. Tidey^{3,4}

¹Institute of Cognitive Science, University of Colorado, UCB 344, Boulder, CO 80309-0345, USA

²Center for Alcohol and Addiction Studies, Brown University, Providence, RI

³Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI

⁴Department of Behavioral and Social Health Sciences, School of Public Health, Brown University, Providence, RI

⁵Division of Behavioral Genetics, Rhode Island Hospital, Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, Providence, RI

⁶Department of Human Development and Family Studies, Purdue University

Abstract

Rationale—Individuals with attention deficit hyperactivity disorder (ADHD) start smoking earlier, are more likely to progress to nicotine dependence, and 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, particularly at the adolescent stage.

Objective—This study aimed to assess the effects of overnight nicotine abstinence and smoking reinstatement on subjective withdrawal states in adolescent smokers with and without ADHD.

Methods—Adolescent daily smokers (27 with ADHD and 17 without ADHD) completed three experimental sessions: 1) a placebo patch followed by smoking a nicotine cigarette, 2) placebo patch followed by smoking a nicotine-free cigarette, and 3) nicotine patch followed by smoking a nicotine-free cigarette. Subjects abstained overnight before each session, and patches were administered 45 min before smoking. The primary outcome measure was a smoking withdrawal symptom questionnaire.

Results—ADHD smokers experienced greater difficulty concentrating and impatience/restlessness during abstinence than non-ADHD smokers. Smoking a cigarette improved abstinence-induced difficulty concentrating and restlessness, regardless of its nicotine content, and regardless of whether transdermal nicotine was received or not.

*Corresponding author: L. Cinnamon Bidwell, Institute of Cognitive Science, University of Colorado Boulder, 344 UCB, Boulder, CO 80309-0345, USA. Tel: 781-608-3711, lcb@colorado.edu.

Conclusions—Thus, sensorimotor aspects of smoking, rather than nicotine itself, appeared to relieve withdrawal. Although ADHD smokers report greater withdrawal symptoms than non-ADHD smokers, they responded strongly to the sensorimotor aspects of smoking during withdrawal. These findings suggest that even lighter, adolescent smokers with ADHD are vulnerable to smoking progression through altered smoking abstinence and withdrawal relief processes.

Keywords

Adolescents; ADHD; NRT; sensorimotor replacement; attention; denicotinized cigarette

Introduction

Despite recent declines in cigarette smoking, tobacco use continues to be one of the most widespread preventable causes of death in the United States (DHHS 2014) and remains a key public health concern, particularly among adolescents as 9 out of 10 cigarette smokers began smoking cigarettes prior to age 18 (Singh et al. 2016). Neurobiologically, adolescents may be more sensitive to the reinforcing effects of nicotine when compared to their adult counterparts, which in turn increases adolescent susceptibility to nicotine dependence (NCCDP 2012). Furthermore, adolescent smokers experience nicotine withdrawal symptoms during periods of smoking abstinence, suggesting that, although adolescents tend to be relatively lighter smokers with briefer smoking histories, withdrawal severity and negative reinforcement processes associated with smoking reinstatement are already engaged at this early stage of nicotine dependence (Bidwell et al. 2013; Colby et al. 2010).

Further, specific groups of adolescents may have additional risk factors that increase likelihood of initiation and vulnerability to continued tobacco use. It has been well documented that attention deficit hyperactivity disorder (ADHD) symptomology is a prospective risk factor for earlier smoking initiation, progression from occasional to regular smoking, developing more severe nicotine dependence, and having more failed quit attempts (Clark and Cornelius 2004; Pomerleau et al. 1995; Rohde et al. 2004; Tercyak et al. 2002; Upadhyaya et al. 2002; Wilens et al. 2008). These associations hold true for both an ADHD diagnosis and for continuous measures of ADHD symptoms that may not meet diagnostic thresholds. Although the ADHD-smoking link has been established in the literature, the mechanisms underlying this association have not been systematically examined, particularly in adolescents with ADHD.

One established predictor of smoking maintenance and relapse is withdrawal severity during abstinence from smoking (Shiffman et al. 2006). This process appears to be augmented in smokers with ADHD, contributing to more severe dependence and greater risk for relapse. For example, studies in adult smokers with ADHD have reported greater overall withdrawal severity during smoking abstinence compared to those without ADHD (Bidwell et al. 2014; Kollins et al. 2013; McClernon et al. 2008). More specifically, adult ADHD smokers have reported greater irritability and difficulty concentrating during smoking abstinence (Bidwell et al. 2014; Pomerleau et al. 2003), and greater disruptions in response inhibition (McClernon et al. 2008). It has been argued that ADHD is associated with certain smoking

withdrawal symptoms (e.g., concentration problems) due to an exacerbation of baseline disturbances associated with the ADHD syndrome rather than withdrawal effects per se. However, laboratory studies that directly contrast abstinence vs. non-abstinence states suggest that, although particular withdrawal symptoms may be elevated in ADHD smokers regardless of abstinence status, ADHD smokers also experience greater increases in those symptoms during abstinence states relative to non-ADHD smokers (Bidwell et al. 2014; Kollins et al. 2013). Further, laboratory studies suggest that withdrawal severity and the desire to relieve it, especially after a period of abstinence, heightens the reinforcing effects of smoking in ADHD smokers more so than in non-ADHD smokers (Kollins et al. 2013). Thus, the subjective state of withdrawal is a critical process that likely contributes to greater difficulty abstaining from smoking during quit attempts in smokers with ADHD. Although these withdrawal and smoking reinstatement processes are gaining traction in theories of smoking risk and relapse in adult smokers with ADHD, the impact of laboratory-controlled abstinence on subjective withdrawal symptoms has yet to be examined in adolescent smokers with ADHD.

Should the finding that smokers with ADHD show more severe withdrawal symptoms after abstinence be replicated in adolescents, the question of whether smoking reinstatement and/or nicotine replacement ameliorates these effects is crucial to understanding risk for smoking reuptake and the progression to nicotine dependence in this population. Studies of the neurobiological bases of ADHD provide support for the possibility that individuals with ADHD have increased sensitivity to nicotine, in part by highlighting alterations in dopamine and other catecholamine function in brain regions and neuro-transmitter systems (Brennan and Arnsten 2008) that are also modulated by both chronic and acute nicotine administration (De Biasi and Dani 2011). Thus, the neurobiology of ADHD may increase risk for smoking progression by conferring heightened vulnerability to the reinforcing effects of nicotine (Kollins et al. 2013; McClernon and Kollins 2008), especially during withdrawal.

However, other work has shown that sensorimotor replacement of smoking on its own ameliorates abstinence-induced withdrawal in adult smokers with and without psychiatric illness (Donny et al. 2007; Higgins et al. 2017; Rose 2006; Tidey et al. 2013). For example, acute “denicotinized” cigarette use with or without concurrent nicotine replacement reduces abstinence-induced withdrawal and craving in adult smokers with and without schizophrenia (Tidey et al. 2013). A crucial step in understanding smoking processes in those with ADHD is to elucidate the impact of smoking and nicotine restatement after a controlled-period of abstinence on ameliorating these subjective withdrawal states. It is important to examine the independent contributions of reinstatement of smoking behavior as well as those of nicotine replacement in order to dissect the impact of the pharmacological effects of nicotine vs. the effects of smoking sensorimotor replacement on withdrawal states in adolescent smokers with ADHD, thereby guide treatment efforts in targeting these particular components of smoking (Donny et al. 2015). For example, if nicotine replacement and sensorimotor replacement are equally effective at reducing withdrawal symptoms in smokers with ADHD, these smokers could be provided with very low nicotine content cigarettes for a 1 to 2-month period prior to quitting, as use of these cigarettes has been found to reduce cigarette dependence, cigarette craving, and to increase quit attempts in adults not trying to quit smoking (Donny et al., 2015).

The present study looked at withdrawal severity in adolescents with and without ADHD after an acute period of smoking abstinence and after smoking reinstatement. We examined the separate and combined effects of nicotine vs. smoking reinstatement by manipulating both cigarette nicotine content and patch nicotine content. After overnight abstinence, withdrawal symptom and affect measures were administered before and after: 1) smoking one nicotine (nicotine-containing) cigarette while wearing a placebo nicotine patch (CIG + PLA), 2) smoking one nicotine-free cigarette while wearing a placebo nicotine patch (NF CIG + PLA), and 3) one nicotine-free cigarette while wearing a nicotine-replacement patch (NF CIG + NRT). We hypothesized that: (1) adolescents with ADHD would report greater subjective withdrawal after overnight abstinence than those without ADHD; (2) sensorimotor smoking replacement, with or without nicotine replacement, would reverse abstinence effects in adolescent smokers with and without ADHD; (3) sensorimotor smoking replacement with nicotine replacement would more effectively reduce withdrawal than sensorimotor smoking replacement without nicotine replacement in those with and without ADHD; and (4) the effects of nicotine replacement would be stronger in smokers with ADHD than in smokers without ADHD.

Method

Participants

Participants between the ages of 14 and 19 who reported smoking an average of at least 30 cigarettes per month were recruited by advertisements placed online, in local buses, and posted in the Providence, Rhode Island community. Participants were excluded if they reported daily alcohol, marijuana, or other drug use, were pregnant or nursing, intending to become pregnant, reported current suicidal ideation or had a Wechsler Abbreviated Scale of Intelligence – II (WASI-II) score of less than 80.

Procedures

Baseline session—Those who called the study phone line were provided with a description of the study and were asked several questions to assess initial eligibility. Those who appeared eligible asked to come in for a baseline lab session to confirm their eligibility and provide informed assent/consent. Those who were under the age of 18 were accompanied by a parent/guardian to the baseline session to obtain parental consent. After eligibility was confirmed, participants completed the questionnaires described below.

Smoking sessions—Each participant completed each of the following three smoking conditions, with condition order counter-balanced across participants: nicotine cigarette with placebo patch (CIG + PLA), nicotine-free cigarette with placebo patch (NF CIG + PLA), and nicotine-free cigarette with nicotine patch (NF CIG + NRT). The cigarettes used in the nicotine cigarette (CIG) condition were Basic Brand cigarettes (which contain 1.1% nicotine) manufactured by Phillip Morris. The NF cigarettes used were Bravo® non-nicotine cigarettes. Masking tape was applied to each cigarette to cover the brand name/symbol. A standard nicotine-containing cigarette was used in this study, rather than the participants' usual brands, to ensure that cigarette novelty was consistent across smoking conditions, and thus, avoid confounding novelty of cigarette with the nicotine content manipulation. The

NRT patch was either a 7 mg or 14 mg Nicoderm CQ patch (Alza Pharmaceuticals, Vacaville, CA), depending on the individual's baseline smoking level (7 mg if baseline smoking rate was < 2 cigarettes per day), and the PLA patch (Rejuvenation Labs, Salt Lake City, UT) was visually identical to the NRT patch but contained no nicotine.

Participants were asked to refrain from smoking after midnight the night prior to their lab sessions as has been done previously in adolescent smoking laboratory studies (Bidwell et al. 2012; Colby et al. 2009). Consistent with these prior studies, sessions were typically held in the afternoon after school, limiting the variability in abstinence. To confirm smoking abstinence, CO levels (Bedfont Instruments) were measured at the beginning of each smoking session, with CO < 8 ppm considered abstinent. Notably, robust abstinence effects have been observed using this CO criterion in prior studies of adolescent smokers (Bidwell et al. 2013; Colby et al. 2010). Next, participants completed subjective measures of withdrawal severity, including self-report of withdrawal symptoms and measures of positive and negative affect, described below. Then, the research assistant applied the placebo or nicotine patch to the participant's upper arm, under double-blind conditions, and participants rested in the laboratory for 45 min prior to smoking the nicotine or NF cigarette. This patch duration was based on previous studies that found significant effects of transdermal nicotine on cognition after 45 min patch use (time lapse modeled after Potter and Newhouse 2004; 2008). At each session, participants smoked one cigarette ad libitum under double-blind conditions while being observed through a one-way mirror. Immediately after the participant finished the cigarette, breath CO levels were re-measured and the participant repeated the subjective withdrawal and affect measures. Sessions were scheduled three to seven days apart. 27 smokers with ADHD and 19 without ADHD were enrolled and all participants completed all sessions.

Measures

Baseline Session—*Demographic variables* included age, gender, race/ethnicity, and years of education. A *tobacco use history questionnaire* was used to collect age of tobacco use milestones and history of abstinence and quit attempts.

Nicotine dependence: The modified Fagerström Tolerance Questionnaire (mFTQ; Prokhorov et al. 2000), a 7-item assessment that has been validated with adolescents, was used to measure nicotine dependence.

Timeline Followback (Lewis-Esquerre et al. 2005), a calendar-assisted interview validated for assessing adolescent cigarette smoking behavior, was used to assess past 30 day smoking quantity and frequency.

Diagnostic Interview for Children and Adolescents-IV (DICA-IV; Reich et al. 1997), a structured diagnostic interview, was given via computer to assess DSM-IV diagnoses, including the presence of ADHD and common comorbidities. For minors, both parents and adolescents completed the DICA simultaneously and separately. Participants age 18 and older (76% of the ADHD group; 86% of the control group) completed the DICA themselves. While under-reporting of ADHD symptoms in young adults has been reported (Sibley et al. 2012), self-report of symptoms in this age range is considered valid and has been used in

several prior studies (Kollins et al., 2005; Zucker et al., 2002). In order to be included in the ADHD group an individual had to meet DSM criteria for ADHD for at least one of the subtypes via the DICA, including impairment in multiple functional domains and symptom present prior to age 12.

ADHD Self-Report Scale (ASRS; Kessler et al. 2005), a self-report scale, was used to provide an additional assessment of ADHD symptom dimensions in adolescent participants. This measure consists of 18 items that correspond to the DSM-IV ADHD symptoms and are rated over the past six months on a 1 (never) to 5 (very often) scales. ASRS ratings are summed into two subscales: inattentive (IN) symptoms and hyperactivity/impulsivity (HI) symptoms.

Measures taken across experimental smoking conditions

Subjective Withdrawal Severity: Both of the below subjective measures have been validated for measuring withdrawal in adolescent smokers following overnight abstinence (e.g. Bidwell et al. 2013; Colby et al. 2010).

Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami 1986), a widely-used measure of nicotine withdrawal symptoms, includes seven symptoms that participants are asked to rate on scales from 0 (not present) to 4 (severe). The symptoms include feeling angry or irritable, feeling anxious or nervous, having difficulty concentrating, feeling impatient or restless, being hungrier than usual, feeling depressed, and having a desire to smoke. Reliability for this measure was high ($\alpha = .87$). Both a sum score including ratings across all seven items as well as individual item ratings were examined in the current study.

The Positive/Negative Affect Scale (PANAS; Watson et al. 1988), a widely used 20-item measure with reliable subscales, was used to measure positive (PANAS-PA; $\alpha = .96$) and negative (PANAS-NA; $\alpha = .93$) affect. Participants rated adjectives describing their affect “right now” from 1 (very slightly or not at all) to 5 (extremely).

The Cigarette Evaluation Scale (CES; Westman et al. 1992), was used to assess the participant’s experience with smoking the study cigarette after each laboratory session. This measure was added after recruitment had been initiated, and was therefore collected in a subsample of participants ($n=26$; 15 ADHD and 11 control). After smoking each cigarette, participants were asked to think about their experience while smoking the study cigarette and respond to 12 items including “was smoking satisfying” and “did the cigarette taste good”. Participants responded to each item on a 7-point scale, ranging from 1 (not at all) to 7 (extremely). The CES produces three primary subscales which were examined in our analysis: Satisfaction, Psychological Reward, and Aversion.

Data Analysis Plan

The ADHD and non-ADHD groups were compared on baseline variables using Pearson’s Chi-Square tests for discrete variables and t-tests for continuous variables. We also calculated correlations among ADHD IN symptoms, ADHD HI symptoms, and baseline smoking characteristics. In order to examine whether there were differences in participant’s subjective evaluation of the nicotine and NF cigarettes, the between-subject effects of Group

(ADHD vs non-ADHD) and within-subject effect of Condition (CIG + PLA, NF CIG + PLA, NF CIG + NRT) on the three CES subscale scores were tested using mixed factorial 2×3 ANOVA.

In our primary analyses, we examined the effects of smoking condition on abstinence-induced withdrawal symptoms and mood in the ADHD and non-ADHD groups, the between-subject effects of Group (ADHD vs non-ADHD), and within-subject effects of Time (pre- vs post-smoking) and Condition (CIG + PLA, NF CIG + PLA, NF CIG + NRT) on withdrawal severity (MNWS sum score and individual items) and mood (PANAS positive and negative subscales) were tested using mixed factorial $2 \times 3 \times 2$ ANCOVAs. All models controlled for baseline average number of cigarettes per day, which differed between groups. All possible two-way and three-way interactions were tested. Where significant omnibus main effects or interactions were present, follow-up pairwise t-tests were used to determine the nature of the effects. Because of the within-subject design, sphericity was evaluated using Mauchly's *W* and, where violated, a Greenhouse-Geisser correction was implemented and adjusted degrees of freedom are provided.

Results

Demographic, ADHD, and smoking variables—Age, gender, ethnic identity, psychiatric comorbidities, and smoking characteristics for the ADHD ($n=27$) and non-ADHD ($n=19$) groups are reported in Table 1. The non-ADHD group had slightly higher number of cigarettes smoked per day ($p = .01$), but did not differ from the ADHD group any other aforementioned variables. Two individuals in the ADHD group reported current use of Adderall (by prescription) and, consistent with prior studies in ADHD smokers, were asked to discontinue medication for 24 hours prior to all study sessions.

IN and HI symptom scores were moderately correlated ($r = .46, p < .001$), which is consistent with prior studies and indicates that the two indexes assess related, but separable constructs (Willcutt et al. 2012). IN symptoms were negatively correlated with average daily cigarette use ($r = -.35, p = .02$), but were not correlated with mFTQ score or age of smoking initiation. Similarly, HI was negatively correlated with average daily cigarette use ($r = -.40, p = .01$), but not with mFTQ score or age of smoking initiation. Negative correlations among cigarettes per day and ADHD symptom dimensions were unexpected.

Cigarette Evaluation Scale—Among the sub-sample of participants who completed the CES, ratings across the smoking sessions indicate that participants across both groups rated the nicotine cigarettes higher than the nicotine-free cigarettes on Satisfaction ($F(1,24) = 28.1, p < .0001$) and Psychological Reward ($F(1,24) = 8.42, p = .008$). CES ratings indicated that the ADHD smokers rated both kinds of cigarettes significantly higher on Psychological Reward ($F(1,24) = 8.79, p < .007$) than the non-ADHD smokers across condition. There were no effects of Condition or Group on the Aversion subscale. The Group by Condition interaction was not significant across any of the subscales.

Primary analyses

Effects of Group, Time, and Experimental Condition on Subjective Withdrawal States—Pre- and post- smoking means and standard deviations for the ADHD and non-ADHD groups in the three smoking conditions are presented in Table 2. There were no significant 3-way interactions between condition, time, and group on any measure, nor were there any significant 2-way interactions.

Main Effects of Group on Pre- and Post-smoking ratings: The ADHD group scored higher scores than the non-ADHD group on several withdrawal measures after overnight abstinence. There was a significant main effect of Group on MNWS summary score ($F(1,40) = 6.68, p = .01$), difficulty concentrating ($F(1,40) = 14.57, p < .001$) and impatience/restlessness ($F(1,40) = 8.45, p = .01$). Follow-up comparisons of group differences at each session and time point found that the ADHD group reported higher MNWS summary scores than the non-ADHD group across all sessions, prior to smoking (p 's $< .05$). However, after smoking, the groups only differed on MNWS summary score in the NF CIG + NRT condition ($p < .05$), with scores remaining higher in the ADHD group. Likewise, those in the ADHD group reported greater difficulty concentrating than those in the non-ADHD group prior to smoking across all conditions (p 's $< .02$). After smoking, those in the ADHD group still reported greater difficulty concentrating than the non-ADHD group in the CIG + PLA and NF CIG + NRT conditions (p 's $< .01$). The ADHD group had higher scores on impatience/restlessness than the non-ADHD group in the CIG + PLA and the NF CIG + NRT conditions prior to smoking (p 's $< .01$) and did not differ post-smoking in any condition. See Figure 1 for pre- and post-smoking scores across group and condition for the MNWS summary score and the individual difficulty concentrating and impatience/restlessness items. There were no significant main effects of Group on the anger/irritability, anxiety/nervousness, hunger, feeling depressed, or desire to smoke MNWS items nor on positive mood or negative mood from the PANAS.

Main Effects of Time: Changes from Pre- to Post-smoking: Most of the withdrawal item scores as well as scores on both PANAS subscales decreased pre- to post smoking, across both groups and all three experimental conditions. There were significant main effects of Time on MNWS summary scores ($F(1,40) = 15.91, p < .001$) and on the scores for the MNWS items anger/irritability/frustration ($F(1,40) = 5.48, p = .02$), anxiety/nervousness ($F(1,40) = 4.76, p = .04$), difficulty concentrating, ($F(1,40) = 4.17, p = .047$), impatience/restlessness ($F(1,40) = 11.32, p = .002$), and desire to smoke ($F(1,40) = 18.72, p < .001$). In addition, there were significant effects of time on the PANAS positive mood and negative affect scale scores ($F(1,40) = 15.15, p < .001$; $F(1,40) = 5.52, p = .03$, respectively). There were no significant effects of Time on hunger or depression scores.

Main Effects of Condition: There were no significant main effects of cigarette/nicotine condition.

Discussion

This study is the first laboratory-based study of effects of abstinence and smoking reinstatement on withdrawal severity in adolescent smokers with and without ADHD. The inclusion of varied experimental conditions allowed us to test the impact of smoking behavioral replacement with and without nicotine delivery on withdrawal symptoms. Findings suggest important mechanisms underlying smoking maintenance in ADHD smokers specifically as well as factors important for maintaining smoking in adolescents more broadly. First, the main effects of Group on difficulty concentrating and impatience/restlessness indicate that smokers with ADHD had elevations in these withdrawal symptoms after abstinence. This was true even though participants with ADHD smoked fewer cigarettes per day than controls. Second, across both groups of smokers, the act of smoking relieved subjective withdrawal states regardless of the presence or absence of nicotine, as indicated by main effects of Time on withdrawal items. This was true despite participants evaluating the nicotine-free cigarettes as less satisfying and less rewarding. Thus, negative reinforcement of withdrawal relief by smoking in adolescents may not be dependent on the drug itself - nicotine - but on the behavior of smoking, which has been paired as a conditioned reinforcer with nicotine delivery over time. Similar effects have long been noted in adults (e.g., Rose et al., 2003), and we now extend them by showing that sensorimotor cues associated with smoking may be a particularly salient mechanism for smoking maintenance, even in these lighter adolescent smokers.

More specifically, our findings examining withdrawal symptoms after overnight abstinence suggest that adolescent smokers with ADHD experience higher levels of difficulty concentrating and impatience/restlessness and that the act of smoking (including in the absence of nicotine) provides relief from those elevated symptoms. It is not clear from our study whether these pre-smoking symptom elevations are due to 1) exacerbations during periods of abstinence, 2) chronic elevations in ADHD smokers (i.e., due to overlap between withdrawal symptoms and ADHD symptoms), or 3) both. If the first interpretation is true, then smoking in adolescents with ADHD may be even more strongly negatively reinforced, as compared to those without ADHD, due its role in relieving more severe withdrawal symptoms than those experienced by other smokers. This interpretation is consistent with several studies in the adult literature that have reported that smokers with ADHD report greater withdrawal severity, impulsivity, and disrupted cognition following abstinence (McClernon et al. 2008; McClernon et al. 2011) and support theories suggesting that withdrawal severity is a primary driver of smoking maintenance and relapse in this clinical group (McClernon and Kollins 2008).

However, if the second interpretation is true, this suggests another mechanism for maintaining smoking in ADHD outside of withdrawal relief. If these particular ADHD-associated withdrawal symptoms (difficulty concentrating and impatience/restlessness) are chronically elevated in adolescent smokers with ADHD due to overlap with ADHD symptomatology (regardless of whether they are in withdrawal or not), smoking may be maintained in this group via providing relief from these chronically impairing symptom states. Regardless of the interpretation, or whether both of these processes are at play, these findings highlight important factors that may be maintaining smoking in this group. In

addition, ADHD smokers rated both kinds of cigarettes (nicotine and nicotine-free cigarettes) as more psychologically rewarding regardless of nicotine content, suggesting that reward processes connected with smoking behavior may interact with withdrawal relief in maintaining smoking in adolescent smokers with ADHD symptomatology. Here, we provide novel data that smoking is even further reinforced in these young ADHD smokers via its ability to provide relief from uncomfortable and potentially functionally impairing withdrawal and/or symptom states. Additional work dissecting the impact of abstinence and smoking reinstatement on ADHD symptom and withdrawal relief and reward processes is likely to shed further light on the high rates of smoking in this group.

Findings also contribute to the understanding of sensorimotor effects on adolescent withdrawal relief and smoking reinforcement. Our study suggested that sensorimotor replacement, with and without nicotine replacement, provided withdrawal relief across each of the subjective withdrawal and mood measures, with the exception of feeling depressed and hunger. Notably, our study included young smokers who smoke relatively infrequently and are theoretically at an earlier stage of dependence. Although a larger study may be able to better differentiate among the experimental smoking conditions, these findings are broadly consistent with prior laboratory work that suggests that even relatively light adolescent smokers report a change in withdrawal symptoms during abstinence and that these withdrawal states can be ameliorated with smoking reinstatement (Bidwell et al. 2013; Colby et al. 2010). Given that the severity of subjective abstinence-induced withdrawal experiences and their amelioration after smoking reinstatement strongly predicts smoking progression and relapse (Shiffman et al. 2006), these findings directly contribute to the theory of smoking uptake, dependence, and treatment in individuals with ADHD and adolescent smokers more broadly. Findings provide a data driven framework for developing smoking treatment approaches for smokers with ADHD that encourage non-smoking alternative strategies to target and improve these particular withdrawal or symptom states both before and during abstinence. Our results also highlight an important role for the sensorimotor aspects of smoking in withdrawal relief and smoking maintenance across smokers broadly, suggesting that treatments that alter the conditioned responses related to pairing the reinforcing effects of nicotine with smoking behavior may be effective in smokers with and without ADHD.

Methodological considerations

Although our laboratory manipulations and within-subjects design improved power, our findings on the effects of smoking reinstatement across experimental conditions should be considered preliminary. Larger studies should be conducted in order to draw stronger conclusions regarding the impact of nicotine replacement over and above sensorimotor smoking replacement. A related limitation is that the study did not include conditions in which participants received nicotine or placebo replacement without sensorimotor replacement. Inclusion of these conditions could have strengthened this study by demonstrating the relative efficacy of providing only nicotine replacement, only sensorimotor replacement, and the combination of nicotine and sensorimotor replacement (e.g., Rose et al. 2003; Tidey et al. 2013).

In another limitation, participant's ADHD status was determined by parental and self-report of symptoms (Kollins et al., 2005; Zucker et al., 2002) and not a clinical interview. Further, data from some studies report that the withdrawal and ADHD symptom constructs are significantly correlated (Berlin et al. 2012). As stated above, we are not able to discern whether observed differences in self-reported withdrawal symptoms following acute smoking abstinence in ADHD vs. non-ADHD smokers may be better explained by either elevation in or abstinence-induced changes in ADHD symptoms in the ADHD smokers. 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), suggesting our findings may not be fully explained by ADHD symptom exacerbations. Regardless, this distinction between withdrawal and symptom states in ADHD smokers remains a challenging issue for studies in this area. Future work should assess changes in both withdrawal and ADHD symptoms under these experimentally manipulated abstinence and smoking conditions. In addition, although this study was not powered to address it, ADHD symptom dimension and subtype are important potential moderators of reported effects that should be addressed in future work. Finally, negative correlations with baseline daily cigarettes and ADHD symptom dimensions were unexpected and need to be replicated given data in adult smokers suggesting a linear relationship among both ADHD symptom dimensions and cigarettes per day (Kollins et al. 2005).

Summary

Our study is among the first to examine withdrawal and smoking reinstatement processes in adolescent smokers with and without ADHD in a laboratory environment. We found that adolescent ADHD smokers experienced significant disruptions in restlessness and concentration that may be relieved by smoking reinstatement with or without nicotine administration, demonstrating alterations in smoking abstinence and negative reinforcement processes in these young ADHD smokers. We also highlight a role for sensorimotor replacement in relieving many subjective withdrawal states across both ADHD and non-ADHD smokers, highlighting the need for additional laboratory and clinical research into this conditioned reinforcer.

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Figure 1.

Self-reported withdrawal symptoms from pre-smoking to post-smoking in the ADHD and non ADHD smoking groups.

Note: The graphs above represent the differences in self-reported withdrawal symptoms from pre-smoking to post-smoking. Those lines denoted with circles represent those in the non-ADHD group, while those denoted with a diamond represent those in the ADHD group. The three colors correspond with the three laboratory conditions: red for CIG + PLA (nicotine cigarette + placebo patch), blue for NF CIG + PLA (nicotine free cigarette + placebo patch), and green for NF CIG + NRT (nicotine free cigarette + nicotine patch).

Table 1

Participant Characteristics

	Control <i>n</i> = 19		ADHD <i>n</i> = 27		<i>t</i> or χ^2	<i>p</i>
	<i>M</i> or <i>N</i>	<i>SD</i> or %	<i>M</i> or <i>N</i>	<i>SD</i> or %		
Age	18.16	0.69	17.81	1.04	1.26	.22
Male	12	44%	15	56%	0.27	.61
Average daily cigarettes	8.69	6.51	4.43	3.78	2.80	.01
Baseline CO	8.79	7.07	7.37	7.60	0.64	.52
mFTQ ¹	3.67	1.78	3.22	1.58	0.88	.38
14mg Patch (vs 7mg)	16	44%	20	56%	2.23	.14
HI symptoms	1.47	1.61	3.89	2.33	-3.91	<.001
IN symptoms	1.58	1.39	5.44	2.22	-6.70	<.001
Pre-smoking CO level ²	5.92	6.84	3.54	2.84	6.77	.10

Notes.

¹ Modified Fagerstrom Score

² Average across three conditions

Means and Standard Deviations in ADHD and Non-ADHD Smokers for Subjective Measures of Withdrawal and Mood across Smoking Conditions: Pre-smoking, post-smoking, and change scores.

Table 2

	Non-ADHD Smokers (<i>n</i> = 19)						Smokers with ADHD (<i>n</i> = 27)					
	CIG + PLA			NF CIG + PLA			CIG + PLA			NF CIG + PLA		
	<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>	
<u>MNWS Sum score</u> ^{<i>a, b</i>}												
Pre-smoking	7.76 [*]	5.72		7.41 ^{**}	4.47		11.85 [*]	6.66		12.93 ^{**}	7.25	
Post-smoking	6.18	5.82		6.76	5.08		9.63	7.07		10.62	7.60	
Change score	-1.16	3.18		-0.65	1.37		-2.22	2.83		-2.50	3.73	
<u>Anger, irritability, frustration</u> ^{<i>b</i>}												
Pre-smoking	0.76	1.03		0.88	1.05		1.41	1.22		1.41	1.39	
Post-smoking	0.53	0.94		0.82	1.13		1.07	1.27		1.07	1.30	
Change score	-0.24	0.56		-0.06	0.56		-0.33	0.73		-0.33	0.96	
<u>Anxiety/nervousness</u> ^{<i>b</i>}												
Pre-smoking	1.12	1.11		1.06	1.09		1.33	1.18		1.52	1.31	
Post-smoking	0.82	1.19		0.82	1.07		1.11	1.31		1.22	1.22	
Change score	-0.29	0.85		-0.24	0.66		-0.22	1.01		-0.30	0.87	
<u>Difficulty concentrating</u> ^{<i>a, b</i>}												
Pre-smoking	0.59 [*]	0.80		0.71 ^{***}	0.77		1.52 [*]	1.37		1.96 ^{***}	1.26	
Post-smoking	0.47 ^{**}	0.80		0.76	0.90		1.30 ^{**}	1.17		1.41	1.39	
Change score	-0.12	0.60		0.06	0.43		-0.22	0.75		-0.56	0.89	
<u>Impatience or restlessness</u> ^{<i>a, b</i>}												
Pre-smoking	0.94 ^{*a}	1.03		1.06	1.25		2.00 ^{*a}	1.21		1.78	1.25	
Post-smoking	0.65	1.00		1.06	1.09		1.26	1.13		1.37	1.31	
Change score	-0.29	1.05		0.00	0.35		-0.74	0.98		-0.41	1.08	
<u>Hunger</u>												
Pre-smoking	1.00	1.41		0.71	0.99		1.07	1.07		1.00	1.21	
Post-smoking	0.82	1.24		0.88	0.99		0.89	1.05		0.93	1.21	

	Non-ADHD Smokers (<i>n</i> = 19)						Smokers with ADHD (<i>n</i> = 27)					
	CIG + PLA			NF CIG + PLA			CIG + PLA			NF CIG + PLA		
	<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>	
Change score	-0.18	0.53		0.18	0.53		-0.19	0.48		-0.07	0.47	
Depressed												
Pre-smoking	0.41	0.80		0.29	0.47		0.96	1.29		1.04	1.34	
Post-smoking	0.41	0.87	0.18*	0.39	0.65	0.86	1.00	1.24	1.00*	1.30	0.85	
Change score	0.00	0.35	-0.12	0.33	-0.18	0.39	0.04	0.34	-0.04	0.44	-0.11	
Desire to smoke ^b												
Pre-smoking	2.35	1.22		2.35	0.91	2.53	2.59	1.05		2.89	1.05	
Post-smoking	2.00	1.41		1.88	1.32	2.06	2.22	1.19		2.38	1.36	
Change score	-0.35	0.79	-0.47	0.87	-0.47	0.72	-0.37	0.84	-0.46	0.99	-0.19	
PANAS positive subscale ^b												
Pre-smoking	34.13	10.32		33.25	13.79	34.29	37.44	12.11		34.81	13.09	
Post-smoking	31.47	12.62		30.41	13.51	29.76	33.59	12.29		31.56	12.76	
Change score	-3.75	9.08	-3.38	7.06	-4.53	5.26	-3.85	8.67	-3.26	6.35	-1.44	
PANAS negative subscale ^b												
Pre-smoking	18.47	5.58		17.19	3.02	19.00	20.85	8.60		20.12	7.08	
Post-smoking	16.29	2.17		16.94	2.02	17.65	20.56	7.95		18.58	5.88	
Change score	-2.18	4.03	-0.47	2.17	-1.35	4.89	-0.40	4.08	-1.60	2.74	-0.76	

Note.

^a indicates there was a main effect of group for ADHD vs. non-ADHD smokers for that measure;

^b indicates a main effect of time for pre- vs post-smoking ratings for that measure.

* indicates significance level in post-hoc comparisons of group differences at each time point and condition,

* p<.05;

** p<.01;

*** p<.001.