AN EXAMINATION OF THE ROLES OF NICOTINE AND NON-NICOTINE SENSORY STIMULI IN ATTENTIONAL BIAS AND THE SUBJECTIVE EFFECTS OF SMOKING

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ABSTRACT

Smoking nicotine (NIC) or denicotinized (DN) cigarettes reduces craving and withdrawal in smokers (Donny et al., 2006; Gross et al., 1997; Butchsky et al., 1995). Both the sensory aspects (e.g. taste, smell, feel) of cigarettes and nicotine exposure affect smokers. An attentional bias to smoking-related stimuli exists among smokers (Zack et al., 2001; Johnsen et al., 1997; Gross, Jarvik, & Rosenblatt, 1993), particularly after abstinence (Zack et al., 2001; Gross et al., 1993). Paying greater attention to smoking-related cues than neutral cues could promote smoking and impede cessation (Niaura et al., 1988). The current study examined attentional bias and subjective behaviors in 63 daily smokers assigned to smoke a NIC, DN, or no cigarette after 12 hours of abstinence. NIC and DN smokers reduced urge to smoke, mood disturbance, and withdrawal more than controls, but did not differ from each other. Contrary to predictions, the three conditions did not show differences in attentional bias to smoking-related stimuli.

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TABLE OF CONTENTS

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LIST OF TABLES

Table

LIST OF ILLUSTRATIONS

Figure

CHAPTER 1

INTRODUCTION

It has been established that nicotine is the active pharmacological ingredient in cigarette smoke responsible for its reinforcing and rewarding effects (Jaffe, 1979). However, a growing body of research also demonstrates that non-nicotine aspects of smoking including sensory stimuli (e.g., feel of smoke in the back of the throat and lungs) play an important role in the rewarding and reinforcing effects of cigarette smoking in regular smokers. It has been posited that the act of smoking and sensations derived from smoking become conditioned stimuli as a result of their associations with nicotine. These conditioned stimuli then become highly valued and rewarding aspects of the smoking experience that contribute to the maintenance of cigarette smoking and difficulty quitting (Rose et al., 2010). For example, pepper spray, which stimulates the throat much like cigarettes, has been shown to reduce cigarette craving and withdrawal in smokers (Rose & Behm, 1994; Rose, Behm, & Levin, 1993). A recent carefully controlled research study showed that smokers preferred smoking denicotinized (DN) cigarettes to nicotine that was delivered in naturalistic doses in the absence of the sensory aspects of smoking (Rose et al., 2010). Such findings highlight the very important role of conditioned sensory cues in smoking and have been used to explain why nicotine replacement products such as the patch have low effectiveness rates (Rose, 2006; Fagerström et al., 1993). A better understanding of both the conditioned and pharmacological aspects of

smoking is necessary to inform the development of more effective strategies to decrease smoking.

Denicotinized (DN) cigarettes are a helpful tool used to investigate the sensorimotor aspects of smoking because they provide the sensory and motor experiences of smoking in the absence of the direct pharmacological effects of nicotine. It has been recently suggested that DN cigarettes may even facilitate smoking cessation attempts (Rose, 2010; Becker, Hatsukami & Zeller, 2009; Rose & Albino, 2008). For example, it has been theorized that repeated use of DN cigarettes may extinguish associations between smoking-related conditioned stimuli (e.g., respiratory tract and olfactory sensations) and nicotine, thereby decreasing the extent to which conditioned stimuli can subsequently motivate smoking behavior.

A number of studies have compared smokers' immediate reactions to nicotine and DN cigarettes. Such double-blind studies have shown that DN cigarettes are capable of alleviating cravings and withdrawal among smokers (Rezaishiraz et al., 2007; Donny, Houtsmuller, & Stitzer, 2006; Buchhalter et al., 2005; Dallery et al., 2003; Gross, Lee, & Stitzer, 1997; Butschky et al., 1995) as well as poor mood (Juliano, Fucito, & Harrell, 2011). DN cigarettes delay the self-administration of subsequent cigarettes and are rated as satisfying by smokers (Barrett, 2010). In addition, double-blind studies have shown that smokers will work to obtain DN cigarettes, but will work harder for nicotine cigarettes when they are concurrently available (Shahan et al., 1999). It is important to note that studies that have manipulated smokers' expectations about the type of cigarette smoked have also revealed that reactions to nicotine and DN cigarettes depend in part on

what type of cigarette the smoker thinks he is smoking (e.g., Juliano & Brandon, 2002; Perkins et al., 2004). As a whole, research suggests that DN cigarettes produce rewarding and reinforcing effects and are preferred over receiving nicotine in the absence of smoking. The rewarding effects of DN cigarettes, although sometimes less than nicotine cigarettes, are generally not significantly different from nicotine cigarettes. However, most studies that have been conducted to date simply compare reactions to nicotine and DN cigarettes without a non-smoking control condition. These studies do not control for the passage of time and cannot shed light on the rewarding effects of DN cigarettes relative to not smoking at all, such as may be the case if someone were smoking only DN cigarettes as a means to quit. Thus, one of the aims of the present study was to evaluate subjective reactions to nicotine and DN cigarettes relative to a no smoking control group.

The vast majority of research studying DN cigarettes has evaluated subjective and behavioral smoking outcomes. Another important area of inquiry pertains to cognitive aspects of drug taking, which are theorized to play a central role in drug taking motivation (Waters & Sayette, 2006). One cognitive factor that is believed to play an important role in drug taking motivation is attentional bias. Smokers are distracted by emotionally salient stimuli in their environments, particularly by smoking-related stimuli (MacLeod & MacDonald, 2000). This biased distraction, known as attentional bias, draws smokers' attention specifically toward smoking-related stimuli, helping sustain the desire to smoke (Williams, 1996).

A number of theories support the idea that attentional bias plays a role in drug taking motivation. Robinson and Berridge's Incentive Salience theory (1993) claims that drug-related stimuli are associated with the pleasure of drug using, and therefore become motivationally salient to drug users. According to this theory, drug-related stimuli grab the attention of drug users, motivating them to continue using. On the other hand, Tiffany (1990) has proposed the model that automatic and non-automatic cognitive processes control continued drug use. He argues that drug taking behavior occurs quickly and automatically in users. But, if drug taking behavior is halted, non-automatic processes take over, redirecting cognitive resources to seek out drugs. These non-automatic processes allow drug users to direct their attention to stimuli that promote drug use. Both models concur that drug-related stimuli hold special value to drug users, and therefore receive more attention from users than non drug-related stimuli. Serving as cues, drug-related stimuli can often motivate continued drug use in users.

The smoking emotional Stroop task is a common measure of attentional bias in smokers. It has been used in a number of studies to show that smokers pay greater attention to smoking-related stimuli than to neutral stimuli. The task requires participants to identify the color of a smoking-related or non-smoking related word as quickly as possible while ignoring the meaning of the word. This test of cognitive interference has revealed that smokers take longer to identify the color of smoking-related words than neutral words, compared to non-smokers (Domier et al., 2007; Munafo et al., 2003; Ehrman et al., 2002).

Attentional bias to smoking-related cues in the environment can impede smoking cessation attempts by directing smokers' attention toward smoking-related stimuli while forcing them to ignore other stimuli, thereby increasing the likelihood that they will pursue smoking behavior (see Niaura et al., 1989). This smoking Stroop effect has been shown to be particularly robust in smokers who have abstained from nicotine and who are experiencing symptoms of withdrawal (Field, Mogg, & Bradley, 2004; Waters and Feyeraband, 2000; Gross, Jarvik, & Rosenblatt, 1993).

A significant body of research has used the smoking emotional Stroop task to compare how quickly active smokers respond to smoking-related stimuli during periods of satiation compared to periods of nicotine abstinence. While these studies vary in their methodology, most have successfully produced a smoking emotional Stroop effect in smokers by administering the computerized smoking emotional Stroop task (Munafo et al., 2003; Mogg & Bradley, 2002; Zack et al., 2001; Waters & Feyeraband, 2000; Johnsen et al., 1997), which presents neutral and smoking-related words, one at a time, on a computer screen. Among these studies, one consistent finding is that smokers show a significantly greater attentional bias (longer reaction times) to smoking-related words compared to neutral words after twelve or more hours of nicotine abstinence (Munafo et al., 2003; Mogg & Bradley, 2002; Waters & Feyeraband, 2000; Johnsen et al., 1997) compared to shorter periods of abstinence (Zack et al., 2001) or no abstinence. While this computerized task requests participants to respond to stimuli as quickly as possible either verbally (Munafo et al., 2003; Mogg & Bradley, 2002; Wertz & Sayette, 2001; Zack et al., 2001; Waters & Feyeraband, 2000; Johnsen, et al., 1997), or manually using a

keyboard (Waters et al., 2003b; Johnsen et al., 1997), the manual response allows for easier and more accurate recording of response times to stimuli.

In addition to modifying the length of smokers' abstinence and method of stimulus response, researchers have administered variations of the computerized smoking emotional Stroop task by presenting smoking-related words and neutral words in either a blocked (Munafo et al., 2003; Mogg & Bradley, 2002; Waters & Feyeraband, 2000; Johnsen et al., 1997) or mixed (Waters & Feyeraband, 2000) format. The mixed format presents a randomized combination of smoking-related and neutral words consecutively on the computer screen, one at a time, for participants to respond to. The blocked format presents a block of only smoking-related words on the computer screen, one at a time, preceded by or followed by a block of only neutral words on the computer screen one at a time. In a noteworthy 2005 article, however, Waters and colleagues provide evidence that carry-over effects reduce the validity of the mixed format of the smoking emotional Stroop task. Carry-over effects describe the phenomenon that occurs when a participant responds to one stimulus while still under the influence of a previous stimulus. The mixed format of the smoking emotional Stroop task often presents a smoking-related stimulus right before a neutral stimulus, providing the opportunity for participants to continue thinking about the previous smoking-related word when responding to the new neutral word. Carry-over effects can similarly occur when a block of smoking-related words are presented before a block of neutral words.

Additional findings in the smoking emotional Stroop literature have identified strong positive correlations between attentional bias and cigarette craving (Zack et al.,

2001), urge to smoke (Mogg & Bradley, 2002), and number of cigarettes smoked per day (Mogg & Bradley, 2002; Zack et al., 2001), as well as positive correlations with time to first cigarette (Waters & Feyeraband, 2000), time to first smoking lapse (Waters et al., 2003b), and smoking reward (Munafo et al., 2003).

While studies investigating attentional bias in smokers have manipulated length of nicotine abstinence, order of stimulus presentation, and method of stimulus response, no study to date has used nicotine and denicotinized cigarettes to investigate the roles that nicotine and non-nicotine sensory stimuli play in influencing attentional bias in smokers. The current study was designed to improve upon previous investigations by looking at how the nicotine and non-nicotine aspects of smoking affect attentional bias and subjective measures in smokers, and by comparing smokers who smoke a nicotine or denicotinized cigarette with a control group of smokers in continued abstinence. Based on findings from previous studies, it was expected that self-reported urge, mood disturbance, and symptoms of withdrawal would decrease more for participants who smoke nicotine and DN cigarettes than for participants in the control group, and that amount of change on these measures would not be significantly different between the two smoking groups (Donny et al., 2006; Gross et al., 1997; Butschky et al., 1995). It was also hypothesized that participants in the continued abstinence control group would show greater attentional bias to smoking-related stimuli after the manipulation than participants who smoked either nicotine or DN cigarettes (Waters et al., 2003b).

CHAPTER 2

METHOD

Participants

Sixty-three cigarette smokers (38 male) who were recruited from the campus of American University and the local Washington D.C. area completed this experiment. Prior to participation, participants were screened for eligibility by phone. Eligible respondents reported being at least 18 years old (*M* age = 25.25 yrs, *SD* = 12.00, range = 18-60 yrs), and smoking at least 1 nicotine cigarette per day (cpd), every day, for the last year (*M* cpd = 10.40, *SD* = 5.78, range = 2 to 25 cpd, *Mode* = 10 cpd; *M* years smoked = 7.06, *SD* = 10.88). The racial breakdown of participants is as follows: 55.5% White, 19% Black/African American, 16% Other, 8% Asian, and 1.5% American Indian/Alaskan Native. Individuals who were colorblind or reported having chronic smoking-related health problems were excluded. After completing two experimental sessions, participants (81% students) were compensated with either $25.00 (50/63 participants) or extra credit points (13/63 participants) that could be applied to undergraduate psychology courses.

Procedure

Participants attended two experimental sessions scheduled an average of 2 days apart (*Range* = 1 to 12 days, *Mode* = 1 day). A double-blind between-subjects design was used. At the time of informed consent, participants were told that they would be randomized into one of three conditions, two of which involved smoking a cigarette after

12 hours of abstinence, and one that did not involve smoking a cigarette after abstinence.

Figure 1 outlines the design of this experiment.

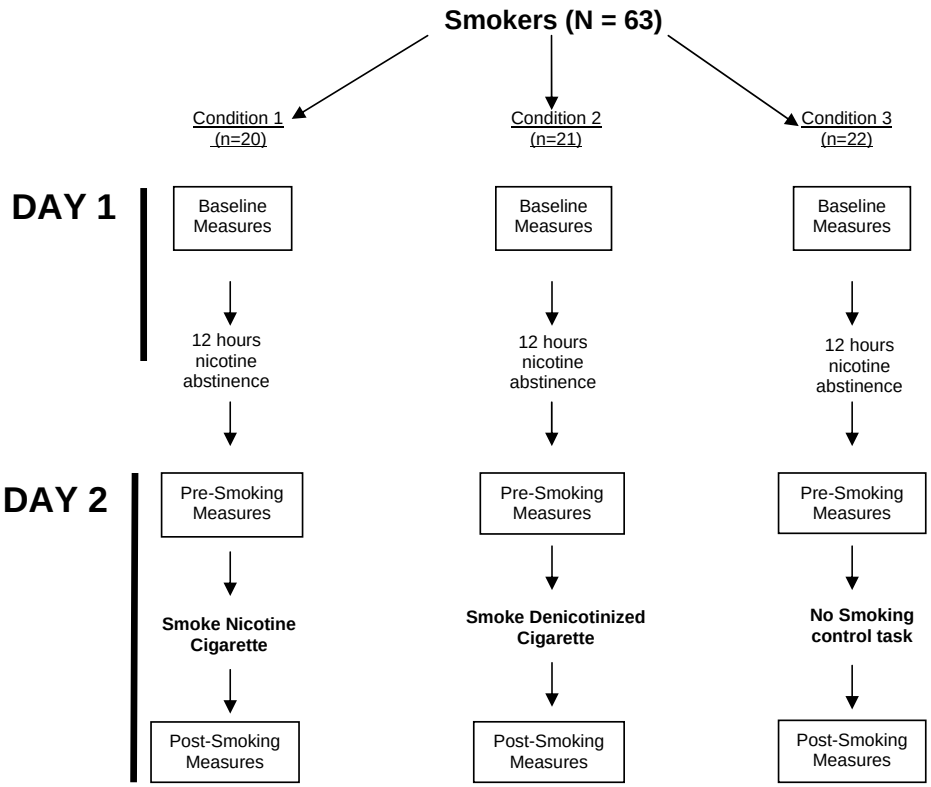

Figure 1. Study Flowchart

During the first study session (Day 1), participants completed informed consent and baseline measures including demographic information, the Fagerström Test for Nicotine Dependence (FTND), the Urge Rating Scale, the Shiffman-Jarvik Withdrawal Scale, and a 30-item version of the Profile of Mood States (POMS-Brief). In addition, participants completed a baseline trial of the smoking emotional Stroop task. A baseline breath sample was also obtained to measure carbon monoxide level, an indicator of smoking. Participants were asked not to smoke for one hour prior to their first appointment to control for recent cigarette exposure. All questionnaires and the computerized smoking emotional Stroop task were administered on a computer using Media Lab and Direct RT software (Empirisoft, New York, NY). Upon completion of Day 1, participants were instructed to abstain from nicotine products for 12 hours prior to their second appointment (*Mean* = 12.82), which was usually scheduled for the next day.

Upon arriving for Day 2, participants provided a second breath sample to measure their Carbon Monoxide level. Participants then completed pre-smoking measures of urge (Urge Rating Scale), withdrawal (Shiffman-Jarvik), and mood (POMS-Brief), and completed the smoking emotional Stroop task. At this point, based on prior randomization, participants experienced one of three conditions. For participants in Condition 1 (NIC), a nicotine cigarette (.6 mg nicotine, 10 mg tar) had been set out ahead of time to smoke. For participants in Condition 2 (DN), a denicotinized cigarette (.05 mg nicotine, 10 mg tar) had been set out ahead of time to smoke. Both the experimenter and participants were blind to the nicotine content of the cigarette. Immediately after

completing the pre-smoking measures, the following instructions appeared on the computer screen to participants in Conditions 1 and 2:

> You are now ready for the next task. Please open the wooden box on the right hand side of the desk. Inside you will see 1.) a plastic bag containing a cigarette, 2.) an ashtray, and 3.) a lighter. Please remove the plastic bag from the box, open the bag, and take out the cigarette. When you are ready, you may light the cigarette and begin to smoke. The lighter and ashtray are available for your use. Please stay in this room while you smoke. When you are finished, please press the buzzer, and the researcher will come to you with further instructions.

Participants in Condition 3 engaged in a control task that did not involve any smoking cues. It was designed to require approximately the same amount of time and activity as the smoking conditions. For participants in Condition 3, a pen and several blank sheets of white paper were set out ahead of time for them to use, and the following instructions appeared on the screen:

> You are now ready for the next task. Please open the wooden box on the right hand side of the desk. Inside you will see 1.) a plastic bag containing a pen and 2.) several blank sheets of paper. Please remove the plastic bag from the box, open the bag, and take out the pen. Your task is to draw whatever you wish on the paper provided for the next 8 minutes. When you are ready, you may begin to draw. Please stay in this room while you complete this task. When you are finished, please press the buzzer, and the researcher will come to you with further instructions.

During the smoking conditions (1 and 2), the experimenter observed the participant smoking via a one way mirrored window and recorded the number of puffs and amount of time spent smoking or drawing. After the participant completed smoking, each cigarette butt was collected and weighed to measure how much of the cigarette had been smoked. The researcher also recorded the amount of time it took for participants in

Condition 3 to complete the drawing task. Condition 1 participants spent an average of 3.63 minutes smoking nicotine cigarettes, Condition 2 participants spent an average of 3.70 minutes smoking denicotinized cigarettes, and Condition 3 participants spent an average of 5.98 minutes on the drawing task. Upon completion of the smoking or no smoking tasks, participants in all three conditions provided a final CO reading, and completed the urge, withdrawal, and mood measures and the smoking emotional Stroop task. Participants in Conditions 1 and 2 then completed the Cigarette Evaluation Scale (CES).

Materials/Measures

Cigarettes (Conditions 1 & 2). All cigarettes smoked in this experiment were smoked under double-blind conditions. Participants in Condition 1 smoked a *Quest 1* brand "low nicotine" cigarette (.6 mg nicotine, 10 mg tar). Participants in Condition 2 smoked a *Quest 3* brand "nicotine free" cigarette (.05 mg. nicotine, 10 mg tar). Participants in conditions 1 and 2 who reported smoking menthol cigarettes during their phone screen prior to participation were given menthol cigarettes to smoke during the study (24%), and participants who reported smoking non-menthol cigarettes were given non-menthol cigarettes during the experiment (76%).

CO Testing. Breath samples provided by participants were analyzed for volume of carbon monoxide using a portable Smokerlyzer (Bedfont Scientific Ltd., Medford, NJ).

Smoking History. Smoking behavior and history was assessed using a 21-item measure, including 6 items from the *Fagerström Test for Nicotine Dependence (FTND)* (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), a widely used measure of nicotine dependence, and questions about participant demographics.

Urge Rating Scale. Respondents rated three items (1. *I have a desire for a cigarette right now.*, 2. *I do want to smoke now.*, and 3. *I crave a cigarette right now.*) on a seven point scale ranging from *strongly disagree* (1) to *strongly agree* (7). This scale has demonstrated adequate reliability and validity in assessing urge to smoke (Kozlowski, Pillitteri, Sweeney, Whitfield & Graham, 1996). In this study, the mean Cronbach's alpha for urge items across three time points was 0.94, indicating that the three items were internally consistent in measuring urge to smoke.

Profile of Mood States Questionnaire (POMS Brief) (McNair, Lorr, & Droppleman, 1971). This 30-item questionnaire is used to measure fluctuation in mood state. Respondents were asked to rate each item in terms of how they were feeling at that time using a scale that ranged from 0=*not at all*, to 4=*extremely*. The six subscales of this measure are Tension/Anxiety, Depression/Dejection, Anger/Hostility, Vigor/Activity, Fatigue/Inertia, and Confusion/Bewilderment. The POMS-Brief has good psychometric properties and is highly correlated with the full 65-item scale (Curran, Andrykowski, & Studts, 1995). In this study, the mean Cronbach's alphas for each of the six factors across all three data collection points were .830, .813, .852, .909, .912, and .583. Due to low alpha values for the Confusion/Bewilderment factor at all three data collection time

points, ratings from items in the Confusion/Bewilderment factor are not considered reliable. Total Mood Disturbance was calculated by summing the scores of the Tension/Anxiety, Depression/Dejection, Anger/Hostility, Fatigue/Inertia, and Confusion/Bewilderment factors (negative mood items), then subtracting the Vigor/Activity (positive mood items) score.

Shiffman-Jarvik Withdrawal Scale (Shiffman & Jarvik, 1976). This measure asks participants to rate how they are feeling right now for each of 25 items using a scale ranging from 1=*very definitely not* to 7=*very definitely*. Items are clustered into five subscales: Craving (6 items), Psychological Discomfort (3 items), Physical Symptoms (3 items), Stimulation/Sedation (3 items), and Appetite (2 items). A total score and five factor scores were calculated for withdrawal data at each of the three time points. Reliability and validity on this measure have been established (Patten & Martin, 1996; Shiffman, West, & Gilbert, 2004). In this study, Cronbach's alphas were calculated for each of the five factors. Alpha values across all three time points for the respective factors were .788, .493 (b .035, pre .692, post .752), .729, .724, and .327. The Appetite scale and the Psychological Discomfort baseline scores were not used in the final analyses of data in this study due to low internal consistency.

Smoking Stroop task (Gross et al., 1993; Waters & Feyeraband, 2000; Waters et al., 2003b). The computerized smoking emotional Stroop task (Williams, Mathews, & MacLeod 1996) is designed to assess smokers' attentional bias to, and cognitive interference from, smoking related words. In this study, participants were

instructed to identify the color of a word on a computer screen as quickly as possible using the four arrow keys on the keyboard, each labeled with one of four color choices (red, blue, yellow, green), while ignoring the meaning of the word as best as they could. They were presented with one word at a time flashing on the computer screen; each word was categorized as either a smoking-related or a neutral word. Performance was measured by reaction time (in milliseconds) and number of errors in identifying the color of each word. This task was administered in a blocked format such that all of the neutral words were presented in one set first (11 words, one after another), followed by a set of 11 smoking-related words for all participants. This was done to prevent carry-over effects where participants continue to think about the previously shown smoking-related words while reacting to the color of neutral words (Waters et al., 2005; Waters, Sayette, & Wertz, 2003c). At all data collection time points, participants were first administered a practice Stroop session where they were asked to identify the color of ninety-six strings of letters such as “PPPP” and “XX” (24 randomized strings each appearing once in one of four colors) before identifying the colors of eleven neutral words in a block, and then eleven smoking-related words in a block. The smoking-related stimulus words used in this experiment were ASHTRAY, CIGARETTE, CRAVING, DRAG, INHALATION, NICOTINE, PACK, PUFF, SMOKE, TOBACCO, and URGE. The neutral stimulus words used were ARRIVAL, CLOCK, FOLD, GLYCERIN, LOCKER, METAL, NETTLE, PAUSE, SHIVER, TABLESPOON, and TROPHY (Waters et al., 2003b). Strings and words appeared in the center of the computer screen in bold, capital letters, approximately 6 millimeters high. Each string or word appeared on the screen until the

participant pressed the correct color key, after which the next stimulus would appear. If a participant pressed an incorrect key, an orange "X" would appear on the screen alerting the participant to try again. The next stimulus word would not appear on the screen until the participant had correctly responded to the previous word.

Using an online randomizer program, the order of all practice, neutral, and smoking-related word sets were randomized such that each word or string appeared once in each of the four colors (red, blue, yellow, green) during each set. As a result, each participant identified the colors of 96 strings, 44 neutral words, and 44 smoking-related words at each of the three data collection points. All participants responded to the same sets of strings, neutral words, and smoking-related words during baseline data collection, the same sets of each word type during pre-smoking data collection, and the same sets during post-smoking data collection. However, the randomized sets of words at baseline, pre-smoking, and post-smoking were independent of each other.

Reaction time and number of errors were recorded for each participant's performance on the smoking emotional Stroop task at all three data collection points using Direct RT software (Empirisoft, New York, New York). Based on reaction time ranges deemed acceptable in the smoking Stroop literature (Waters et al., 2003b, Wertz and Sayette, 2001), two sets of smoking Stroop reaction time and error data were analyzed; one set of data retained participants' reaction times and corresponding errors to smoking-related or neutral words between 100 to 3000 milliseconds, while the second set of data retained reaction times and errors between 100 and 1500 milliseconds. Mean

reaction time and mean numbers of errors were calculated for both ranges of data. No differences were found between the two sets of data in reaction time and number of errors. Therefore, our results are reported based on the wider range of reaction time data from 100 to 3000 milliseconds.

Cigarette Evaluation Scale (Rose, Behm & Westman, 2001; Westman, Levin, & Rose, 1992). This 14-item questionnaire (Rose, Behm, & Westman, 2001) assessed participants' immediate reactions to the experimental cigarettes using a 7-point scale ranging from *not at all* (1) to *extremely* (7). In reference to the cigarette that participants had just smoked, they were asked questions such as: Was it satisfying?, Did it taste good?, Did you enjoy the sensations of smoke in your throat and chest? In addition to the 10 original items described by Rose et al. (2001), the following four items were also included: (a) Did it immediately reduce your cravings for cigarettes?, (b) Did it taste different than your usual brand?, (c) Did it make you feel more alert? and (d) Did it make you feel less anxious? This questionnaire was administered to participants in the two smoking conditions after they smoked to assess immediate reactions to the experimental cigarettes.

CHAPTER 3

RESULTS

Outlier Analysis

Box plots and Stem and Leaf plots were created to identify outlying Stroop reaction times. Five participants were identified as providing outlying reaction time data. Analysis of Variance was conducted to compare mean reaction time between each condition at each data collection time point, both with and without these outlying data. Eliminating outlying data did not change the results. Therefore, outliers were retained in the final analysis.

Baseline Data

Smoking Emotional Stroop. A 3 x 2 mixed factorial analysis was conducted to determine if there were baseline differences across groups on smoking emotional Stroop performance with Condition (NIC vs. DN vs. no smoking) as a between-subjects factor and Word Type (smoking vs. neutral) as a within-subjects factor. As expected, there was an effect of Word Type with participants taking significantly longer to respond to smoking words (M = 807.90, SE = 19.30) than neutral words (M = 750.33, SE = 17.30), $F(1, 60) = 54.59$, $p < .0001$. There was no difference in reaction time across the three conditions, $F(2, 60) = .12$, $p = .884$, and no Word Type by smoking Condition interaction, $F(2, 60) = 1.34$, $p = .270$. There were also no differences when the individual cell means were compared. This later analysis was conducted even in the absence of a significant interaction as later analyses involved planned comparisons of the cell means.

There were also no baseline differences in reaction time between conditions when the two smoking conditions were combined and compared to the no smoking condition, $F(1, 60) = .037$, $p = .848$.

Carbon Monoxide. One-way ANOVAs showed no significant differences in mean Carbon Monoxide level across the three conditions at Baseline, $F(2,60) = .614$, $p = .55$, or at the Pre-Smoking time point $F(2,60) = .549$, p = .58.

Self-Report Measures. A series of analyses of variance (ANOVAs) were conducted to rule out baseline differences across the conditions on self-report measures. As shown in Table 1, there were no baseline differences across conditions on any of the self-report dependent measures or other relevant baseline variables (e.g. smoking history, age).

Table 1

Baseline Measures across Conditions

	Nicotine (n=20)	DN (n=21)	No Smoking Control (n=22)		
Measure	*M(SD)*	*M(SD)*	*M(SD)*	*Statistic*	*p*
Age (years)	22.65(8.84)	27.05(13.73)	25.91(12.84)	$F(2,60)=0.73$	.485
Sex	13 Male	13 Male	12 Male	$\chi^2(2, N=63) =0.51$	.774
Race	65% White	45% White	59% White	$\chi^2(8, N=63) =9.41$	.309
Cigarettes per day	9.95(6.13)	10.00(4.98)	11.18(6.33)	$F(2,60)=0.31$	.738
Years smoked daily	5.58(9.24)	8.31(13.48)	7.20(9.76)	$F(2,60)=0.32$	.728

# Quit attempts	2.55(1.99)	3.43(6.49)	6.50(21.00)	$F(2,60)=0.54$	.585
Total FTND (maximum 10)	2.35(2.13)	2.57(1.89)	2.73(2.19)	$F(2,60)=0.17$	.840
Total Urge (maximum 21)	10.95(3.38)	10.71(4.86)	13.32(5.92)	$F(2,60)=1.88$	.162
Total Mood Disturbance (maximum 120)	23.20(14.53)	27.29(10.33)	25.36(14.50)	$F(2,60)=0.49$	.617
Total Withdrawal (maximum 175)	97.80(13.36)	98.95(10.74)	102.68(16.08)	$F(2,60)=0.75$	.478
CO level (ppm)	16.90(15.62)	14.90(13.46)	12.05(13.81)	$F(2,60)=0.61$	.545
Stroop reaction time NEUTRAL words (ms)	736.64(108.54)	750.90(146.60)	763.44(150.47)	$F(2,60)=0.20$	.819
Stroop reaction time SMOKING words (ms)	796.26(126.35)	822.77(180.35)	804.69(146.65)	$F(2,60)=0.16$	.851

FTND = Fagerstrom Test for Nicotine Dependence
M=mean
SD=standard deviation

Main Outcomes

Smoking Stroop Performance. A series of 3 x 2 x 2 mixed factorial ANOVAs were conducted to evaluate the effects of the experimental manipulation on Smoking Emotional Stroop performance with Condition (Nicotine vs. DN vs. no smoking) as a between-subjects factor, Word Type (smoking vs. neutral) as one repeated measures factor, and Time (pre vs. post-manipulation) as a second repeated measures factor. The

main outcome of interest would be indicated by a significant interaction between Condition and Word Type, which would suggest that the experimental manipulation had an effect on smokers' attentional bias for smoking-related words relative to neutral words.

As expected (see Figures 2, 3, and 4), a main effect of Word Type was found with all participants responding more quickly to neutral words (M = 736.17, SE = 20.96) than smoking-related words (M = 773.33, SE = 21.45), revealing an overall smoking Stroop effect, $F(1,59) = 28.82$, $p < .0001$. A main effect of Time was also found, $F(2,59) = 14.51$, $p < .0001$, with all participants responding more quickly to word stimuli post-manipulation (M = 709. 57, SD = 20.17) than pre-manipulation (M = 776.25, SD = 28.06), revealing a likely practice effect. A significant interaction was also found between Time and Word Type, $F(2,59) = 10.56$, $p < .0001$, such that the smoking Stroop effect (longer reaction times to smoking vs. neutral words) was more pronounced pre-manipulation than post-manipulation. Contrary to predictions, a mixed factorial ANOVA, with Condition as the between-subjects factor, revealed no effect of smoking condition on reaction time (see Table 2). There were also no interactions involving condition.

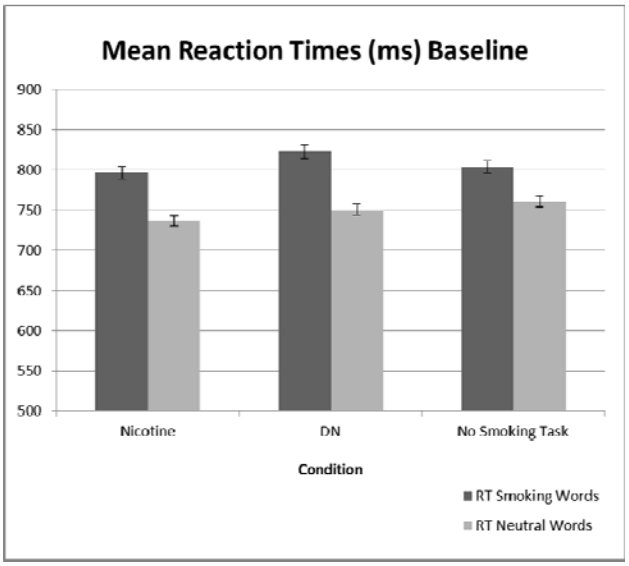

Figure 2. Stroop Reaction Times Baseline

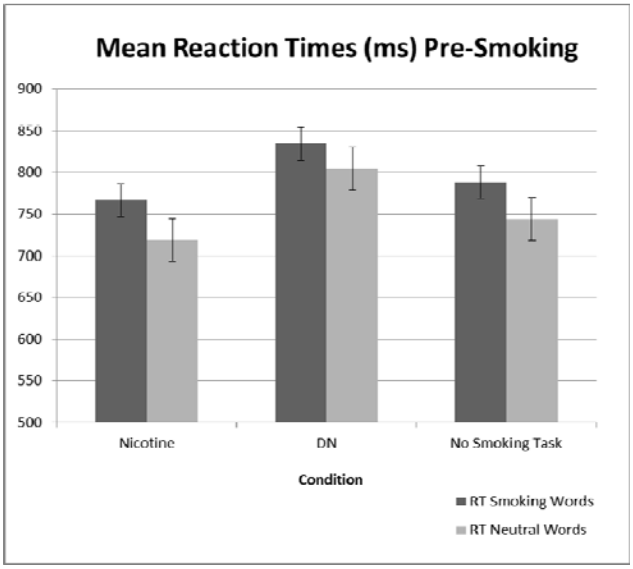

Figure 3. Stroop Reaction Times Pre-Smoking

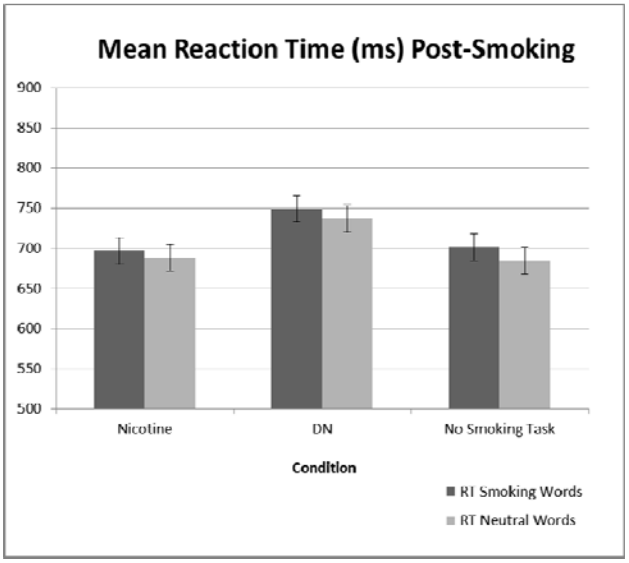

Figure 4. Stroop Reaction Times Post-Smoking

Table 2

Stroop Reaction Times across Conditions

		Nicotine (n=20)	DN (n=21)	No Smoking Control (n=22)		
Time Point	Measure	*M(SD)*	*M(SD)*	*M(SD)*	*F(df)*	*p*
PRE-Manipulation	Stroop reaction time NEUTRAL words (ms)	719.19(99.50)	804.57(320.26)	745.58(204.88)	*F(2,60)*=0.76	.473
PRE-Manipulation	Stroop reaction time SMOKING words (ms)	766.87(108.30)	834.64(300.54)	792.84(196.78)	*F(2,60)*=0.51	.604

POST-Manipulation	Stroop reaction time NEUTRAL words (ms)	687.98(88.64)	736.97(205.63)	684.79(162.72)	*F(2,59)*=0.69	.505
POST-Manipulation	Stroop reaction time SMOKING words (ms)	696.81(99.85)	749.06(225.71)	701.83(138.00)	*F(2,59)*=0.64	.530

ms=milliseconds
M=mean
SD=standard deviation

Urge. A between-subjects ANOVA was conducted to evaluate the change in mean urge ratings from pre-manipulation to post-manipulation across conditions using difference scores (post urge score minus pre urge score). There was a significant overall effect of condition, $F(2,60) = 10.59$, $p < .001$, on self-reported change in urge. Comparison of individual cell means revealed that compared to participants who did not smoke, there was a greater decrease in urge after smoking nicotine cigarettes ($p < .001$) and after smoking DN cigarettes ($p < .001$). The two smoking conditions did not differ from one another ($p = .786$) (see Table 3 and Figure 5).

Mood. A between-subjects ANOVA was conducted to evaluate change in mean rating of total mood disturbance (POMS-Brief) from pre-manipulation to post-manipulation across conditions using difference scores. There was a significant overall effect of condition on reported change in mood, $F(2,60) = 6.08$, $p = .004$. Compared to participants who did not smoke, total mood disturbance decreased more after smoking nicotine cigarettes ($p = .012$) or smoking DN cigarettes ($p = .002$). Like urge, the two smoking conditions did not differ from one another in change in total mood disturbance ($p = .503$; see Table 3 and Figure 6). There were, however, significant effects of the

experimental manipulation on five of the six POMS-Brief mood factors (see Table 3 and Figure 6). Compared to those who did not smoke, individuals who smoked a DN cigarette had greater decreases in *Tension-Anxiety* ($p = .014$), *Depression-Dejection* ($p = .010$), *Anger-Hostility* ($p = .001$), and *Fatigue-Inertia* ($p = .003$), and greater increases in *Vigor-Activity* ($p = .01$). There was only one significant difference between participants who did not smoke and those who smoked nicotine cigarettes, with those smoking nicotine cigarettes reporting greater decreases in *Anger-Hostility*, $p = .003$. Differences in mood change between participants who smoked nicotine cigarettes and participants who did not smoke approached significance with items related to *Tension-Anxiety* ($p = .056$), *Vigor-Activity* ($p = .074$), and *Fatigue-Inertia* ($p = .051$). Differences between participants who smoked DN cigarettes and participants who did not smoke appeared to approach significance on items related to *Confusion-Bewilderment* ($p = .085$), but again, *Confusion-Bewilderment* items had low internal consistency. There were no differences between the two smoking conditions on any of the mood variables.

Withdrawal. A between-subjects ANOVA was conducted to evaluate the change in mean withdrawal ratings from pre-manipulation to post-manipulation across conditions using difference scores. There was a significant overall effect of condition on reported change in total withdrawal, $F(2,60) = 10.33$, $p < .001$. Compared to the no smoking condition, total withdrawal decreased to a greater extent after smoking nicotine cigarettes ($p < .002$), or DN cigarettes ($p < .001$), but the two smoking conditions did not differ from one another ($p < 1.001$). (see Table 3 and Figure 7). Condition was found to significantly affect change in *Craving*, $F(2,60) = 12.26$, $p < .0001$, but not in

Psychological Discomfort, *Physical Symptoms*, *Stimulation/Sedation*, or *Appetite*. As with total withdrawal, change in *Craving* decreased more after smoking nicotine cigarettes ($p < .0001$) or DN cigarettes ($p < .002$) than after continued abstinence, but the two smoking conditions did not differ from each other ($p < 1.001$).

Table 3

Change in Self-Reported Urge, Mood Disturbance, and Withdrawal across Conditions: (Post minus Pre)

	Nicotine (n=20)	DN (n=21)	No Smoking Control (n=22)			
Measure	*M(SD)*	*M(SD)*	*M(SD)*	*F(2,60)*	*p*	*Planned Comparisons*
Change in Total Urge	-6.00(3.74)	-5.57(6.52)	+0.32(4.35)	10.59*	<.0001	NIC>No Smoke, DN>No Smoke
Change in POMS Total Mood Disturbance	-4.15(7.34)	-5.71(8.27)	+1.77(6.65)	6.08*	.004	NIC>No Smoke, DN>No Smoke
POMS *Tension-Anxiety*	-1.25(2.84)	-1.71(2.99)	+0.36(2.17)	3.57*	.034	NIC>No Smoke, DN>No Smoke
POMS *Depression-Dejection*	-0.45(1.15)	-1.14(2.90)	+0.50(1.60)	3.56*	.035	DN>No Smoke
POMS *Anger-Hostility*	-1.20(1.74)	-1.43(3.64)	+1.23(1.84)	7.09*	.002	NIC<No Smoke, DN>No Smoke
POMS *Vigor-Activity*	+0.60(3.59)	+1.43(3.76)	-1.23(2.25)	3.77*	.029	DN>No Smoke
POMS *Fatigue-Inertia*	-1.30(2.96)	-2.24(3.45)	+0.55(2.54)	4.81*	.012	DN>No Smoke
POMS	-0.55(1.90)	-0.62(2.01)	+0.36(1.59)	1.91	.157	

Confusion-Bewilderment						
Change in Total Withdrawal	-10.10(13.42)	-11.24(13.61)	+4.32(10.40)	10.33*	<.0001	NIC>NoSmoke, DN>No Smoke

M=mean
SD=standard deviation
N=Nicotine cigarettes, DN=Denicotinized cigarettes, NS=No Smoking
*p<.05

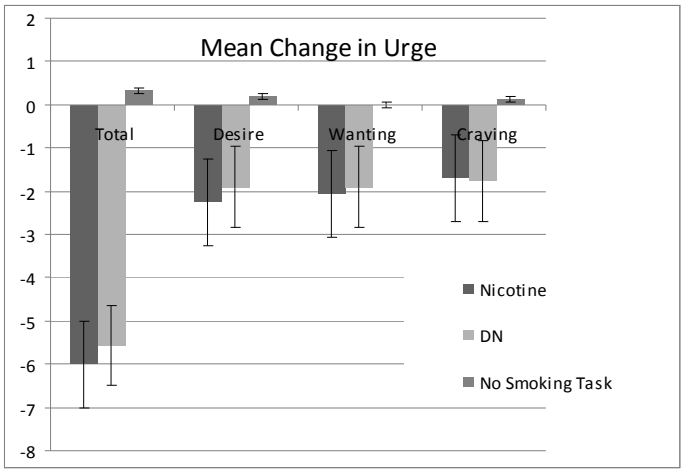

Figure 5. Change in Urge, Pre-Smoking to Post Smoking

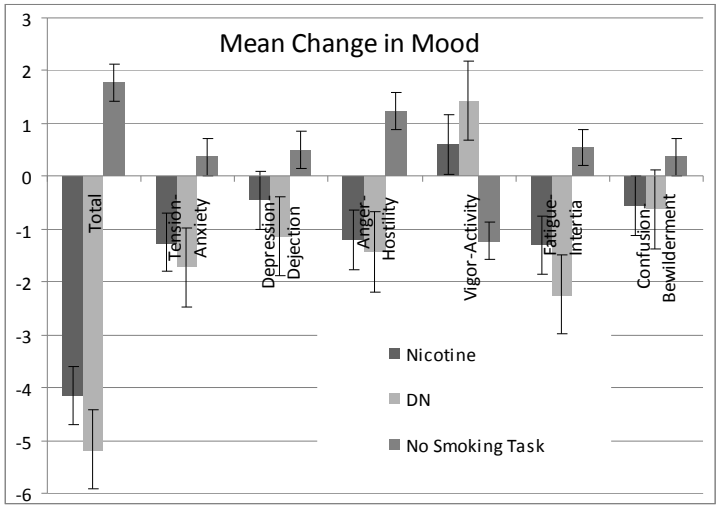

Figure 6. Change in Mood Disturbance, Pre-Smoking to Post-Smoking

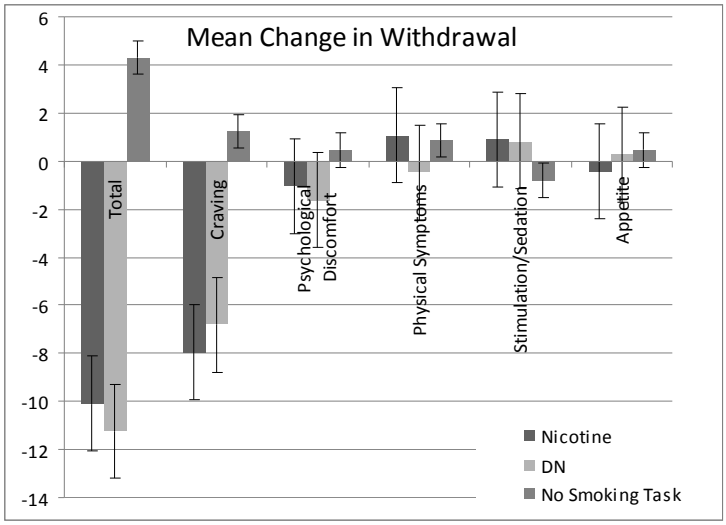

Figure 7. Change in Withdrawal, Pre-Smoking to Post-Smoking

Subjective Ratings of Cigarettes. A series of one-way ANOVAs were conducted on the post-smoking subjective ratings of cigarettes from the Cigarette Evaluation Scale to evaluate any self-reported differences in smoking experience between participants in nicotine and DN conditions. Results revealed a significant difference between the Nicotine (M = 4.15, SD = 1.90) and DN (M = 1.57, SD = .68) groups in response to "Did it make you dizzy?", $F(1,39) = 34.19$, $p <. 001$; participants who smoked nicotine cigarettes reported more dizziness than participants who smoked DN cigarettes (see Table 4).

A one-way ANOVA revealed a main effect for the amount of time spent smoking or completing the no smoking task at the Post-Smoking time point across conditions ($F(2, 60) = 11.68$, $p <. 00$); participants in the Nicotine (M = 3.63 minutes, SD = 0.74) and DN conditions (M = 3.70 minutes, SD = 1.29) spent significantly less time smoking than participants in the No Smoking conditions (M = 5.98 minutes, SD = 2.71) spent drawing.

Table 4

Cigarette Ratings across Conditions

	Nicotine (n=20)	DN (n=21)		
CES Item	*M(SD)*	*M(SD)*	*F(1,39)*	*p*
Satisfying	4.20(1.54)	3.48(1.81)	1.90	.176
Tastes Good	3.35(1.50)	3.00(1.73)	0.48	.494
Dizzy	4.15(1.90)	1.57(0.68)	34.19*	<.00001
Calm	3.75(1.97)	3.05(1.47)	1.69	.201
Concentrate	3.55(1.67)	3.10(1.73)	0.73	.397

More Awake	3.55(2.09)	3.24(2.02)	0.24	.630
Reduce Hunger	2.95(1.64)	3.00(2.00)	0.01	.931
Nauseous	2.25(1.71)	1.62(1.16)	1.92	.173
Less Irritable	2.60(1.43)	2.67(1.49)	0.02	.885
Throat and Chest	3.30(1.69)	3.33(1.98)	0.003	.954
Reduce Craving	4.55(2.06)	3.76(1.79)	1.71	.198
Less Anxious	3.45(1.85)	3.24(1.64)	0.15	.700
Taste Different	5.60(1.39)	6.33(1.11)	3.50	.069
More Alert	3.75(1.77)	3.38(1.72)	0.46	.502

M=mean
SD=standard deviation
*p<.05

Smoking Exposure. As expected, change in CO levels from pre-smoking to post-smoking, $F(2,60) = 15.31$, $p < .001$, confirmed a significant increase in CO levels for participants who smoked Nicotine ($p < .0001$) and DN cigarettes ($p < .0001$) relative to those who did not smoke (see Table 5). There was no difference in CO increase between the two smoking conditions. There were no differences in the amount of time spent smoking the nicotine and DN cigarettes, $F(2,60) = 11.68$, $p = .902$, the number of puffs, $F(1,39) = 1.90$, $p = .176$, or the weight of the cigarette remains after smoking, $F(1,39) = .643$, $p = .428$. (see Table 5).

Table 5

Smoking Behaviors by Condition

	Nicotine (n=20)	DN (n=21)	No Smoking Control (n=22)		
Measure	*M(SD)*	*M(SD)*	*M(SD)*	*F(2,60)*	*p*
Time spent smoking (minutes)	3.63(0.74)	3.70(1.29)	5.98(2.71)	11.68*	<.0001
Number of puffs	10.30(3.53)	8.95(2.69)	N/A	1.90	.176
Cigarette butt weight (grams)	0.45(0.07)	0.44(0.06)	N/A	0.64	.428
Change in CO level (ppm)	+7.95(6.14)	+8.48(7.61)	-0.14(2.05)	15.31*	<.00001

M=mean
SD=standard deviation
*$p<.05$

CHAPTER 4

DISCUSSION

This study was designed to investigate the effects of smoking cigarettes with or without nicotine on subjective outcomes and attentional bias in daily smokers. Participants were randomly assigned to smoke a nicotine cigarette (Condition 1), a DN cigarette (Condition 2), or no cigarette (Condition 3) after twelve hours of nicotine abstinence. Main outcome measures included self-reported urge to smoke, smoking withdrawal symptoms, total mood disturbance, and attentional bias as measured by smoking Stroop performance. It was hypothesized that smoking urge, nicotine withdrawal, and mood disturbance would decrease to a greater extent among those who smoked either nicotine or DN cigarettes than among those who did not smoke. Based on prior research, we did not expect differences between the two smoking conditions. It was hypothesized that participants who smoked either nicotine or DN cigarettes would show less attentional bias to smoking-related stimuli than those who continued to abstain.

Contrary to predictions, the experimental manipulation had no effect on attentional bias to smoking-related stimuli as measured by the smoking Stroop task. Not surprisingly, there was a main effect of word type such that participants responded more slowly to smoking-related words than neutral words, confirming a smoking emotional Stroop effect. Consistent with findings from previous studies which compared smokers in abstinence with satiated smokers (Munafo et al., 2003; Mogg & Bradley, 2002; Waters & Feyeraband, 2000; Johnsen et al., 1997), this effect was more pronounced prior to the experimental manipulation after participants experienced twelve hours of smoking

abstinence. Participants in all three conditions also responded more quickly to Stroop stimuli after the experimental manipulation, suggesting strong practice effects. However, no differences were found between the three conditions in Stroop reaction times, refuting the prediction that smoking a nicotine or DN cigarette would reduce attentional bias in smokers to a greater extent than continued abstinence. These results add a new perspective to the current literature which had not investigated the effects of smoking nicotine and DN cigarettes on attentional bias in smokers, and had not compared those effects with a group of smokers in continued abstinence. Further investigation is necessary to explore why attentional bias to smoking-related stimuli in smokers after twelve hours of abstinence is not significantly different from attentional bias after smoking nicotine or DN cigarettes.

As predicted, the experimental manipulation influenced reports of smoking urge. Participants who smoked either nicotine or DN cigarettes reported a greater reduction in urge to smoke than participants who had no cigarette exposure. As expected, reports of urge reduction did not differ between participants who smoked nicotine versus DN cigarettes, showing similar results to that of previous studies that explored nicotine dose and cigarette craving (Donny et al., 2006; Dallery et al., 2003, Gross et al., 1997). However, these previous studies did not compare their nicotine and DN cigarette groups with a control group of smokers in continued abstinence. The presence of a non-smoking control group of smokers in this study enlightens us to the fact that smoking a DN cigarette reduced urge in smokers after twelve hours of abstinence almost as much as a nicotine cigarette, while urge persisted in the control group of smokers.

A main effect of condition on total mood disturbance was also found. Participants who smoked either NIC or DN cigarettes reported a greater reduction in total mood disturbance than participants who did not smoke. As predicted, reports of reduction in mood disturbance did not differ between participants who smoked nicotine versus DN cigarettes. Participants who smoked nicotine cigarettes reported a greater decrease in the Anger-Hostility factor on the POMS than participants who did not smoke. Participants who smoked DN cigarettes reported a greater reduction in Tension-Anxiety, Depression-Dejection, Anger-Hostility, and Fatigue-Inertia, but a greater increase in Vigor-Activity than participants who did not smoke. Participants in the two smoking conditions did not differ from each other in producing change in mood disturbance. These results suggest that DN cigarettes alleviate negative mood as much as nicotine cigarettes do. It also suggests that DN cigarettes may improve positive mood better than continued abstinence would; a conclusion that could only be made in this study because of the presence of a control group of smokers in continued abstinence.

A main effect of smoking condition on withdrawal was found as well. Participants who smoked nicotine and DN cigarettes reported a greater reduction in total withdrawal than participants who did not smoke. As anticipated, participants in the two smoking conditions did not differ in how much their withdrawal symptoms reduced. Participants who smoked nicotine and DN cigarettes also reported a greater decrease in the Craving factor of withdrawal than participants who did not smoke. Participants in the two smoking conditions did not differ from each other in reduction of Craving. Like with mood, these results imply that DN cigarettes reduce symptoms of withdrawal, especially

craving, as well as nicotine cigarettes do. The presence of a control group of smokers in continued withdrawal also allows us to confirm that the non-nicotine sensory stimuli of cigarettes are sufficient enough to reduce nicotine withdrawal in smokers to a significantly greater extent than twelve hours of continued abstinence.

During the administration of this study, a number of limitations existed which may have affected the overall outcomes. While the age of participants in this study ranged from eighteen to sixty years, mean age was only twenty-five years, and mean number of years smoked was only seven. In addition, eighty-one percent of participants were college students. These factors are not representative of the larger, more general population of smokers. Evaluation of a larger population with a greater range in age would provide a more accurate portrayal of how nicotine and the behavioral aspects of cigarettes affect attentional bias in smokers who have used cigarettes for a greater range of time.

In the interest of exposing all participants in this study to the same environment, smokers' self-reported urge, mood, and withdrawal after smoking were evaluated in an artificial context. The experimental environment was no doubt different from where each participant typically smokes, leading to questions of the ecological validity of the observed and reported data collected during this study. Since participants did not smoke their own cigarettes during the experiment, smoking satisfaction was an important and necessary measure in this study, revealing only higher reports in dizziness in NIC smokers compared to DN smokers. However, while participants in the smoking conditions were asked to complete the Cigarette Evaluation Scale after smoking, they

were not asked which type of cigarette they believed they had smoked. As a result, any drug or response expectancies that participants may have had about the cigarette during the smoking experience remain unknown, and may have affected the outcomes (Juliano et al., 2011).

While the measures used in this study have been validated with acceptable alpha values, a few characteristics of these tests may have affected the results. For example, the modified Stroop task administered in this study provided a practice set of stimuli for participants to respond to before responding to the actual test blocks of stimuli. The practice set was administered separately to prevent data collected during the learning curve portion of the task from skewing the larger data set. Nevertheless, participants responded to both the practice set and the actual Stroop task three times during the course of the study, potentially leading to either an effect of time or practice effects. Additionally, the actual cognitive mechanisms involved in producing and reducing attentional bias in smokers remain unknown, which is why several different measures of attentional bias exist, including the smoking emotional Stroop task, and the dot-probe task (Munafo et al., 2003). This lack of knowledge complicates any interpretation of how and why no significant differences were found between participants who smoked nicotine cigarettes, DN cigarettes, or no cigarettes in their attentional bias to smoking-related stimuli post-smoking.

This study did improve upon previous research investigating the effects of nicotine and denicotinized cigarettes on subjective measures and attentional bias in smokers by introducing a comparison control group of smokers in continued abstinence.

However, such a design could have also benefited from 1.) a group of smokers who were administered nicotine without a cigarette (i.e. transdermal patch) to evaluate attentional bias and subjective measures in a drug only group (no behavioral smoking cues), 2.) a comparison group of former smokers, and 3.) a comparison group of nonsmokers. While the idea of comparing the effects of smoking nicotine or DN cigarettes in former smokers vs. current smokers, or with former smokers in continued abstinence piques interest, notable ethical constraints do exist.

Future studies should address how a nicotine-only condition that does not provide any smoking cues (i.e. nicotine patch) might compare to the other three conditions in this study, in reducing urge, withdrawal, and mood disturbance, and attentional bias. Further investigation into how smokers show attentional bias to different kinds of smoking cues, such as smoking-related words (smoking emotional Stroop task) vs. smoking related pictures (dot-probe task) vs. smoking paraphernalia (visual cues of actual ashtrays, cigarettes, or lighters) should also be addressed. Finally, based on our lack of significant findings between groups in post-manipulation attentional bias, a similar study could compare attentional bias in smokers who have smoked nicotine cigarettes or DN cigarettes with a group of smokers in continued abstinence, where the length of abstinence is manipulated to determine if a period other than twelve hours might change the post-manipulation difference in attentional bias between the control group of smokers and the other two smoking groups.

Overall, this study failed to provide evidence that smoking either nicotine or DN cigarettes after a period of twelve hours of nicotine withdrawal reduces attentional bias to

smoking-related stimuli in daily smokers as compared to smokers in continued withdrawal. This experiment does, however, confirm that smoking DN cigarettes after a twelve hour period of nicotine abstinence reduces urge to smoke, symptoms of withdrawal, and mood disturbance, as well as smoking nicotine cigarettes does, and better than continued abstinence after twelve hours.

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