Introduction

Smoking is the leading cause of preventable disease and death in the United States, with 88%–95% of quitters relapsing in the year following a quit attempt. One mechanism by which relapse may occur is through cue-reactivity whereby a specific stimulus (S) leads to a drug-seeking response (R) to attain a drug outcome (O). This stimulus–response–outcome relationship (S–R–O) is probed in the

Original investigation

Pavlovian-to-Instrumental Transfer of Nicotine and Food Cues in Deprived Cigarette Smokers

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Abstract

Introduction: Smoking-related cues can promote drug-seeking behavior and curtail attempts to quit. One way to understand the potential impact of such cues is to compare cue-elicited behaviors for smoking and other reinforcers (eg, food) using the Pavlovian-to-instrumental transfer paradigm, which measures how much control cues can exert over reward-seeking responses.

Methods: We tested the influence of appetitive cues on smokers’ behavior following 12 hours of abstinence from smoking and eating. First, we equated the value of cigarette and food by assessing a Willingness-to-Pay measure for each reinforcer. Second, we evaluated behavioral differences between cues with Pavlovian-to-instrumental transfer. In two phases, participants learned (1) the association between distinct stimuli and cigarette or food outcomes and, (2) specific instrumental responses that yielded such outcomes. Motivated behavior was probed under extinction in a subsequent transfer test assessing instrumental responding in the presence of the cues.

Results: Participants showed an increase in specific responding (eg, instrumental response associated with cigarette) when faced with the corresponding appetitive cue (eg, stimulus associated with cigarette) despite absence of outcome. Notably, they made more cigarette-seeking than food-seeking instrumental responses, suggesting that cues representative of cigarette outcomes exert stronger influences on behavior than non-drug (food) cues. Using a measure of subjective preference, we also observed that greater preference for cigarette—compared to food—cues correlated with increased cigarette-seeking behavior in the test phase.

Conclusion: Taken together, these results highlight how drug and non-drug cues differentially influence reward-seeking behaviors during deprivation, which has implications for smoking cessation treatment and relapse.

Implications: This study examines the motivational influence of both drug and non-drug cues within a single sample of cigarette smokers. Our results demonstrate that the motivational properties of smoking cues differ from cues relating to other types of reward, such as food. This research informs smoking cessation programs to target the salience of nicotine cues and the maladaptive drug-seeking behaviors prompted by them.
Pavlovian-to-instrumental transfer (PIT) paradigm, which measures the control exerted by a particular cue over instrumental responses expected to yield an outcome.2–4 The PIT paradigm has been widely used in animals5 and humans6,7–9 for a variety of reinforcers including cocaine,10 nicotine,11–13 food,14–16 and money.17,18

The use of PIT with nicotine-related cues has yielded several key observations. First, presentation of a smoking cue promotes increased reward-seeking behavior—an effect that does not differ from other appetitive reinforcers such as chocolate.19–21,22,23 Secondly, consistent with observations in craving paradigms,21 this nicotine PIT effect is not related to dependence level.13 Third, cue-reactivity is unaffected by nicotine deprivation and satiety as measured by craving,22,23 and PIT,11,12 suggesting reward-seeking behaviors are not updated by the current incentive value of the outcome.

As existing research involves preselected nicotine and chocolate rewards, and behavior for drug and food is compared across differing levels of satiety (when either cigarette or chocolate is devalued), a natural extension is to measure reward-seeking behavior when the drug and food outcomes are equated and when smokers are under equal deprivation from nicotine and food. Thus, in the current study, we used PIT to assess the effects of drug-related (nicotine) cues and non-drug-related (food) cues on reward-seeking behaviors by equating the subjective value of nicotine and food reinforcers, and requiring deprivation of both rewards.

To equate the reinforcers, we used a willingness-to-pay (WTP) scale, in which the value of an item was calculated by the amount of resources the individual was willing to give up for that item.24 This measure has been used in several studies with food,25,26 and with demand and delayed reward discounting tasks in smokers.27 In the present study, we first adapted the WTP measure to compare values of the different smoking and food rewards, and then used the equated amounts of cigarette and food reinforcers as the outcomes in the PIT paradigm. Specifically, we measured differences in cigarette and food-seeking responses to nicotine and food-related conditioned stimuli (CS) under acute deprivation of nicotine and food. The 12 hours of overnight abstinence from both smoking and eating was required to foster a natural craving state and allow behavioral comparisons for the two primary reinforcers without confounds of last consumption. Based on existing research demonstrating (1) an increase in drug-seeking for tobacco rewards in extinction,13 (2) theories that drug taking is mediated by a general hyposensitivity to natural rewards,28 and (3) evidence of enhanced neural responses to smoking cues relative to food cues29 we hypothesized that in a state of deprivation, and absence of reinforcement, smokers would respond in the presence of both cigarette and food cues, but that cigarette-seeking behavior would exceed food-seeking behavior.

Materials and Methods

Participants

Thirty-four participants were recruited via flyers posted on the Rutgers campus and advertisements on Craigslist. Participants were deemed eligible if they smoked 6 or more cigarettes per day consistently for the past year, and if they were not taking active measures to quit smoking at the time of the study. Out of 34 individuals initially recruited, five were excluded from participation prior to completing the experiment (exclusion based on the SCOFF questionnaire,20 n = 3; inability to abstain, n = 2), and six were excluded from analyses (failure to demonstrate learning during Pavlovian phase, n = 6). The remaining 23 participants (11 male, Mage = 23.52 years, SDage = 3.89), smoked between 6 and 20 cigarettes per day (mean = 11.30, SD = 4.73), and ranged from very low to high dependency on the Fagerstrom Test for Nicotine Dependence (very low = 11, low = 7, moderate = 4, high = 1; mean = 2.74; SD = 1.86). All participants provided informed consent as approved by the Rutgers University Institutional Review Board and were monetarily compensated upon completion of the study.

Procedure

The study was conducted over 2 days on a computer in a private office with no windows. Both sessions were conducted between the hours of 9 AM and 1 PM, and the 2 sessions occurred within a 48-hour window.

Session 1

Participants arrived for the first session after smoking and eating as usual. They completed a screening form assessing smoking habits, medical and psychiatric history, and drug use. Participants also rated their current cravings for cigarettes and food under normal consumption on a scale from 0 (not at all) to 100 (extremely). Computer-administered Likert scales measured how much participants liked a cigarette puff and different foods. Specifically, participants were asked “how much do you like this food?” for each food item (goldfish, chip, cookie, pretzel, M&M, and animal cracker) and “how much do you like a cigarette puff?” Participants rated each item on a scale from 1 to 7 and the food item that was rated equal or closest to a cigarette puff was used for the duration of the experiment. At the end of Session 1, participants smoked one cigarette outside of the laboratory and immediately provided a baseline expired-air carbon monoxide (CO) measurement in parts per million (ppm) using a Vitalograph CO monitor. Due to the use of food cues in the task we used the SCOFF questionnaire to detect potential existence of an eating disorder, and excluded individuals according to the questionnaire guidelines.

Session 2

Participants were required to abstain from smoking and eating for 12 hours overnight prior to the second session. Participants were also instructed not to consume alcohol or other drugs during this abstinence period; however, water and coffee or tea (if typically consumed) were permitted. Upon arrival to the laboratory, participants rated their cigarette and food cravings as in session 1 and provided an expired-air CO sample. Consistent with other studies, abstinence was verified via either a CO level of < 10 ppm,31,32 or a 40% reduction from the baseline reading.33

WTP Scale

A WTP procedure was then used to equate the reinforcers by assessing how much participants would be willing to pay for varying quantities of cigarette puffs and the chosen food item (1, 2, 3, 5, 8, and 10 puffs/food items). Importantly, the quantity of the food item used in the PIT task was subjectively equal to the value of one cigarette puff. For instance, if a participant was willing to pay 50 cents for one cigarette puff and 10 cents for a cracker, instead of mathematically equating the cigarette puff with five crackers as the food outcome which would assume that each subsequent cracker was of equal worth, the participant’s WTP for 2, 5, 8, and 10 crackers was used to find the amount that was equal to 50 cents in value. In the event that there was no perfect match, the next highest value and number of food items was used. This process of equating the reinforcers was novel
and necessary to ensure that any behavioral difference observed to the cigarette and food cues in the PIT task was not due to the inherent value of the cigarette and food reinforcers, but rather to differences in cue-reactivity and the result of the S–R–O process. The procedure for each session is outlined in Figure 1.

**Pavlovian-to-Instrumental Task**

Before beginning the PIT task, participants were informed that any cigarette puffs or food earned in the task would be given to them for consumption following the experiment. Based on their performance, they could earn a break immediately following the task during which they would be permitted to consume their (own) cigarette and (provided) food earnings before filling out post-experimental questionnaires. Participants were told that if their performance did not meet the standard for a break, they would have to fill out several questionnaires prior to consuming their earned foods and cigarette puffs. Participants proceeded to perform three phases of the PIT task: (1) Pavlovian phase, (2) instrumental phase, and (3) transfer test phase, as shown in Figure 2.

**Pavlovian (S–O).** In the first phase of the task, participants were asked to learn four stimulus–outcome (S–O) contingencies. On each trial, one of four S–O pairings was presented. The four stimuli consisted of colored squares presented visually on the computer screen. The four possible outcomes included images of a cigarette puff, the previously equated food, a paperclip (neutral outcome) and a pound sign (representing no outcome). Each stimulus was paired with a specific outcome. On a given trial, the stimulus appeared on the screen for 4 seconds. Outcomes were subsequently presented at stimulus offset for 1 second, and a jittered ITI with a duration of 6, 8 or 10 seconds separated each trial. Each of the four S–O pairs was presented 9 times for a total of 36 trials. The stimuli and outcomes were presented in random order and S–O contingencies were counter-balanced across subjects. Participants were told to refrain from making instrumental responses during this phase. As done in other studies with appetitive cues post-phase, we used ratings to assess whether S–O contingencies had been learned and whether the CS had garnered affective properties. While explicit ratings test contingency knowledge, our use of implicit affective ratings measured both awareness of S–O contingencies and preference for the different stimuli. For each of the colored cues, we asked participants “how do you feel about the [BLUE] square?” using a Likert scale ranging from 1 (strongly dislike) to 5 (strongly like). We expected to see higher affective ratings for the rewarding cigarette and food-paired cues relative to the non-rewarding neutral and no outcome-paired cues. Participants were excluded from further analyses if the average rating of the non-rewarding cues when subtracted from the average rating of the rewarding cues resulted in a value less than 0. This suggested that the participant did not learn the S–O contingencies and would have no motivation to make instrumental responses in the presence of either of the rewarding cues in upcoming phases of the task.

**Instrumental (R–O).** The instrumental phase was modeled after appetitive learning tasks used extensively to study positive reinforcement learning. In the instrumental phase, participants learned three distinct response–outcome (R–O) contingencies. Specifically, participants were instructed to use the three available key presses (R1–R3,
the 1, 2, and 3 buttons on the keyboard) to earn three rewarding outcomes (O1–O3, cigarette puff, food, paperclip). This phase was divided into three mini blocks lasting 180 seconds each. Participants were not informed in the beginning of the phase that the opportunity to earn the different rewards was divided into three mini sessions—this was learned on their own. In each mini block only one R–O contingency was in effect (e.g., R1–O1). On every trial, a target symbol appeared for 1 second, alternating with a 1 second fixation point unless the participant pressed the correct key. If the correct response was made, then the corresponding outcome (e.g., a cigarette puff) would appear for 1 second in place of the fixation point. To discourage participants from randomly responding at all times, any button presses that occurred while the outcome was on the screen were without any consequences. At the end of each mini block, the screen read, “Next session starting...” to indicate the beginning of a new mini block. At the end of the entire instrumental phase, participants were asked to rate on a scale of 1 (not at all) to 10 (extremely effective) how effective each key (R1, R2, and R3) was at obtaining the different outcomes (cigarette or O1, food or O2, and paperclip or O3).

Transfer (S–R). During the transfer phase, participants viewed the stimuli from the Pavlovian phase (S1–S3) and were told that they were free to use the available button presses (R1–R3) as they saw fit. Outcomes were not presented in the transfer phase; that is, the phase was performed under extinction conditions. Each trial began with a jittered 4–12 second fixation period. One of the Pavlovian stimuli (S1–S3) was then presented for 4 seconds, followed by a jittered 2–10 second screen that read, “Recalibrating” during which participants were instructed to refrain from pressing any keys. Participants were free to make instrumental responses as they saw fit during either the pre-CS fixation period or during CS presentation. Each of the three stimuli was presented 20 times for a total of 60 trials. Due to the long duration of the test phase, the no outcome CS was removed and responses to the neutral CS were used for baseline comparison with responses to the cigarette and food stimuli.

Post-PIT
After completing the PIT task, participants were asked whether they would prefer to smoke or consume their food first. They were then given the opportunity for a break during which they were able to go outside with the experimenter and have five cigarette puffs (of their own cigarette), and consume the equivalent number of provided foods (5 times the quantity of the food used in a single trial). Following this break, participants filled out several questionnaires. These included the BIS/BAS, assessing behavioral inhibition and activation,24 the Fagerstrom Test for Nicotine Dependence,25 measuring tobacco dependence based on smoking frequency, the Alcohol and Drug Use Questionnaire,26 detecting symptoms of alcohol and drug addiction, and the Beck Depression Inventory,27 assessing mood and depressive symptoms. The experimenter then debriefed the participant and answered any questions related to the study.

Results

Abstinence Verification
All included participants had a second session CO reading (mean = 6.39; SD = 5.00; range = 1–24) of either <10 ppm or a 40% reduction from day 1 (mean = 15.83; SD = 11.41; range = 4–57) confirming smoking abstinence. Further, we conducted paired-samples t tests to verify that self-reported time when the last food item and cigarette were consumed (p = .112) and craving for food (mean = 73.04), and cigarette (mean = 78.26; p = .363) did not differ.

Willingness-to-Pay
There was a significant difference between the participants’ WTP for the one cigarette puff (mean = 16.48; SD = 18.75) and one food item (mean = 6.48; SD = 9.332) in the second session (p = .004). Thus for each participant, the quantity of the food outcome in the PIT task was customized such that the chosen quantity of food was rated as equal in value to one cigarette puff.

Pavlovian Conditioning
Analyses were performed using SPSS 23.0 (IBM, Armonk, NY). After the Pavlovian learning phase participants completed implicit affective ratings,14,15 which gauged liking of the various CS without explicitly asking participants to recall the S–O pairings. A one-way ANOVA revealed a main effect of CS (F19, 45.186; p < .001), suggesting there was some difference in participants’ liking of the different stimuli. As expected, post hoc paired samples t tests revealed greater liking of the cigarette and food than neutral and no outcome CS (all p’s < .001). Note that ratings are for 22 participants due to script malfunctioning for one participant.
Instrumental Conditioning

To verify learning of the response–outcome contingencies, participants were asked to rate the efficacy of each available instrumental response (R1–R3) for earning each outcome (O1–O3) on a scale from 1 to 10. A two-way ANOVA examining the factors of response and outcome revealed a response by outcome interaction ($F_{2,11} = 156.193; p < .001$). Post hoc $t$ tests comparing each correct response (eg, R1) to each incorrect response (eg, R2 and R3) for each outcome (eg, O1) indicated that participants correctly paired each outcome with a specific instrumental response (eg, R1–O1; all $p's < .001$). Instrumental learning was also assessed by the number of times participants made the correct response (eg, R1 to obtain O1) in each mini block of this phase. Each 180 second block was divided into 30 second bins to evaluate learning over time. Collapsed across all blocks, we observed a significant increase in the number of times participants made the correct response (eg, R1) across the transfer phase. Similar to post-Pavlovian conditioning, there was no difference in mean responses for each of the outcomes (cigarette: 10.13, food: 11.78, neutral: 10.26) in the last 30 seconds of the respective block, indicating that participants learned correct R–O pairings (Figure 3).

Transfer

To determine whether stimuli sustained their affective value even in the absence of reinforcement (ie, under extinction conditions), participants were again administered implicit affective ratings at the end of the transfer phase. Similar to post-Pavlovian conditioning, there was a main effect of CS ($F_{2,20} = 17.721; p < .001$), with post hoc tests revealing greater liking for the cigarette and food CS than the neutral CS (both $p's < .001$).

In this phase, behavioral responses to each CS previously paired with the cigarette, food, or paperclip outcome were also assessed. A two-way repeated-measures ANOVA comparing instrumental responses across all three CS revealed a significant CS by response interaction ($F_{2,15} = 5.149; p = .006$). Participants made specific responses to each CS, whereby when a stimulus and response were both associated with the same outcome, in the presence of that CS the response was elicited. An expected response will herein be used to denote a specific response (ie, cigarette-seeking) to a CS (ie, cigarette-paired cue) wherein both the response and the CS share an association with the same outcome (cigarette). A paired samples $t$ test assessed whether there were differences in expected responses to the two rewarding CS, cigarette and food. Interestingly, participants made greater expected cigarette than expected food responses to the respective cues, ($t_{12} = 2.346; p = .028$; Figure 4a). Further, a correlation between correct responses to the cigarette CS (mean = 98.12) and correct responses to the food CS (mean = 82.53) was also significant ($R = 0.926; p < .001$), suggesting a paired effect whereby those individuals who responded more for the cigarette also responded more for the food (Figure 4b).

Individual Differences

Other variables may potentially explain the difference in responses to the cigarette and food cues. To examine whether the motivation to smoke was a driving factor in the number of expected responses that were made to the rewarding CS, a three-way repeated measures ANOVA assessing the effects of CS (cigarette and food), expected response (cigarette-seeking and food-seeking), and end desire (to smoke or to eat) was conducted. Indeed, those individuals ($n = 11$) who at the end of the task reported the desire to either smoke only $t$ test. The graph shows the amount of instrumental responses (R1-cigarette, R2-food, R3-neutral) made per minute in the presence of each individual CS (S1-cigarette, S2-food, S3-neutral). Participants made correct instrumental responses to each CS indicating specific transfer. The difference in correct responses to the cigarette and food CS suggests greater reward-seeking behavior to the drug relative to the food CS. Error bars represent standard error of the mean (SEM). (b) A correlation between expected cigarette and food responses to the respective stimuli suggests an interdependence of transfer responses.
or smoke prior to eating, made more expected than unexpected responses to the cigarette CS (mean = 133.50 vs. 7.43) and food CS (mean = 114.95 vs. 7.09), than those individuals (n = 12) who reported the desire to either eat only or eat prior to smoking (expected vs. unexpected responses to cigarette CS, mean = 65.69 vs. 19.38; to food CS, mean = 52.81 vs. 21.75) in the transfer phase (F_{1,11} = 7.186; p = .014).

We also examined whether preference for a CS after Pavlovian conditioning correlated with expected responses to that preferred CS during the subsequent transfer phase, as other studies support this relationship.\textsuperscript{39–42} A bivariate Pearson correlation was used to test whether the liking difference between the cigarette and food CS post-conditioning was associated with the response difference to the cigarette and food CS in the test phase. This correlation revealed that the higher the liking-difference between the cigarette and food-paired CS, the greater the response-difference to those CS in the test phase (R = 0.471, p = .027). In other words, the more a smoker likes a cigarette cue as compared to a food cue, the greater the difference in his or her drug-seeking relative to food-seeking behavior. However, because several participants reported no difference in liking between the rewarding and non-rewarding CS post-Pavlovian conditioning, this result should be interpreted with caution.

Two final analyses were conducted with gender and smoking level. Specifically, two separate one-way ANOVAs examining total responses made during the test phase by (1) gender and by (2) total number of cigarettes smoked revealed that overall more responses were made by males compared to females (F_{1,21} = 6.341; p = .02), and heavier smokers compared to light smokers (consuming ≤ 10 cigarettes/day; F_{1,21} = 6.299; p = .02). These results suggest that both gender and smoking level may play a role in cue-reactivity, although given that the sample size of males (N = 11) and heavy smokers (N = 14) is low, this result is exploratory and noted for future investigations. No significant differences were found in instrumental responses for the cigarette and food outcomes by gender or smoking level (all p’s > .05).

Discussion

The aim of the current study was to evaluate how stimuli representative of both drug and non-drug rewards influence reward-seeking behaviors in cigarette smokers. Specifically, we measured reactivity to both cigarette and food cues associated with equally valued rewards in smokers under deprivation from both smoking and eating. We observed a specific transfer effect for CS (ie, cigarette and food), such that presentation of each Pavlovian cue prompted a specific instrumental response based on the shared expectancy with a particular reward. Notably, cigarette-seeking responses to the cigarette cue surpassed food-seeking responses to the food cue. This finding highlights how under deprivation, and when reinforcers are equally valued, cigarette cues may have a stronger effect in eliciting reward-seeking behaviors than alternative non-drug food cues. The greater reactivity to drug cues suggests that smokers may experience difficulty inhibiting their drug-seeking behaviors and maintaining abstinence from nicotine.

One explanation of the transfer effect with drug cues is that these cues elicit feelings of expectancy,\textsuperscript{39–42} which in turn results in greater craving and appetitive drug-seeking behavior. For instance, when a previous smoker who feels no urge to smoke encounters a nicotine cue, she/he may automatically experience an expectancy of the high and in turn seek out the drug. As greater neural reactivity to smoking cues has been shown to predict decreased success at smoking cessation,\textsuperscript{36–42} albeit with some mixed evidence with craving and treatment outcome,\textsuperscript{21,43} it may be necessary for those individuals who show a greater transfer effect to receive more personalized cessation treatments. Further, our data suggest that the difference in liking between drug and non-drug cues is associated with the magnitude of appetitive behaviors made in the presence of those cues. The increased salience of drug cues provides an explanation for why cigarette stimuli may motivate appetitive responses to a greater extent relative to food stimuli.

There are some limitations that should be considered in future research. For example, the small sample size and limited variability in smoking level and nicotine dependence prevent broad generalizations to the diverse cigarette smoking population. While the current study finds that participants who reported a greater desire to smoke than eat at the end of the transfer phase made more instrumental responses overall during this phase, several other studies have shown greater cue reactivity is not associated with dependence,\textsuperscript{11,12,44,45} and as such this finding should be interpreted with caution. It is also possible that the differential behavior observed in the current study was driven by the absence of some objective measures. For example, the lack of an objective verification of eating abstinence may have detracted from the importance of the food outcome and thus created demand characteristics. Despite the use of the WTP measure, perhaps the reinforcers were not completely matched, thus leading to differential responding for the outcomes. Further, two outlier CO measurements suggest there may have been some error in initial subjective reports of nicotine use. However, removing these outliers from the sample does not affect the results.

An important aspect of the study was the use of a willingness-to-pay measure to equate the cigarette and food rewards paired with the stimuli. Using equated amounts of smoking and food rewards in the PIT paradigm, we had more confidence that any differences observed in drug-seeking and food-seeking to the respective cues was not due to variance in the value of the associated rewards. Our results show cigarette smokers made a greater number of reward-seeking behaviors in the presence of drug cues as compared to non-drug cues, even when smoking and food reinforcers were equally valued and the cues were presented under extinction conditions. Further, a greater difference in liking between the drug and food CS post-conditioning was associated with greater drug-seeking relative to food-seeking behavior in extinction. In this way, drug-seeking behaviors exhibited in the PIT paradigm may characterize the affective and motivational properties of reward cues, and provide a tool for assessing maladaptive reward-seeking important for cessation programs.

Funding

This research was supported by funding from the National Institute on Drug Abuse to MRD (R01DA027764).

Declaration of Interests

None declared.

References


