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Prolonged Duration of Craving, Mood, and Autonomic Responses Elicited by Cues and Imagery in Smokers: Effects of Tobacco Deprivation and Sex

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Abstract

Increases in self-reported craving and changes in autonomic functioning are reliably elicited when smokers are exposed to tobacco-related stimuli compared with neutral stimuli. However, few studies have reported the time course of cue-elicited craving or have directly compared the effectiveness of smoking cues versus imagery to evoke a craving response. In addition to these two issues, we investigated the influence of tobacco deprivation and sex on craving, mood, and autonomic responses. Sixty cigarette smokers (30 men, 30 women) were tested in two counterbalanced sessions, one after overnight tobacco deprivation and one during ad libitum smoking. At each session, participants were exposed to four randomized experimental trials: smoking imagery, neutral imagery, smoking cues, and neutral cues. Tobacco craving and mood were assessed repeatedly and physiological measures were recorded continuously for 30 min after imagery or cue exposure. Compared with neutral trials, smoking cues and smoking imagery reliably increased tobacco craving, negative mood, heart rate, and blood pressure and decreased positive mood ratings. Changes were observed immediately after cue and imagery presentation and remained unchanged for 30 min. Responding was greater in the nondeprived condition, and cues elicited more robust responding than imagery for most measures. Women responded more robustly to smoking cues only in the nondeprived condition, whereas imagery evoked greater responses in men during both conditions. These findings provide new data on the time course, magnitude, and tobacco deprivation effects on elicited craving. Sex differences were dependent on stimulus type and deprivation condition.

Keywords

tobacco craving; cue-reactivity; in vivo cues; imagery; time course; sex differences

Drug craving is a nearly universal response to the absence of drug in dependent individuals (O'Brien, 2005; Singleton & Heishman, 2004). Smokers who try to quit experience craving for cigarettes (Hughes & Hatsukami, 1986), and craving intensity predicts relapse to smoking (Killen et al., 2006; Shiffman et al., 1997). Intense tobacco craving also occurs during continued smoking (Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996), and smokers not attempting to quit

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report multiple craving episodes each day (Heishman, Singleton, & Moolchan, 2003). A critical environmental source of tobacco craving is unconditioned and conditioned smoking-related stimuli. Over the past 20 years, investigators have studied craving and mood alterations resulting from the presentation of drug-related stimuli in the laboratory (Ferguson & Shiffman, 2009). In their meta-analysis, Carter and Tiffany (1999) found that increases in self-reported craving and changes in autonomic functioning are reliably evoked when smokers are exposed to tobacco-related stimuli compared with neutral stimuli.

Most laboratory studies have focused on the magnitude of cue-elicited responding and have not reported the time course of subjective and physiological responses. The few studies examining the duration of cue-evoked tobacco craving have used different designs, yielding, not surprisingly, inconsistent findings. Two studies investigated the effects of nicotine gum on cue-elicited responses during a 35-min laboratory session. Shiffman et al. (2003) exposed smokers to smoking cues (holding a lit cigarette) after participants had been tobacco deprived and had used either nicotine or placebo gum for 2 days. After cue exposure, participants chewed their respective gum for 30 min. Shiffman et al. observed an increase in self-reported craving immediately after the cue in both groups, which declined to baseline 5 min later. Craving ratings continued to decline below baseline in the nicotine gum group, but responses of the placebo gum group remained at baseline levels until the end of the session. Niaura et al. (2005) tested two formulations of nicotine gum in overnight-deprived smokers using the same cue-exposure paradigm. Self-reported cigarette craving declined over the 30-min gum administration. In contrast, using an imagery script containing smoking-urge content, Heishman, Saha, and Singleton (2004) found that self-reported craving was increased immediately after the imagery script in nondeprived smokers and remained elevated during the 15-min session. Thus, when treated with placebo gum or when not disturbed, cue-elicited craving can last at least 15 min.

In vivo cues and imagery reliably evoke tobacco craving in the laboratory. Lighting and holding a cigarette (without smoking) or watching a confederate smoke increase craving and alter autonomic responses (Niaura et al., 1998; Sayette & Hufford, 1994). Imagery scripts describing smoking urges also reliably increase self-reported craving and heart rate compared with scripts containing no smoking-urge content (Drobes & Tiffany, 1997; Singleton, Anderson, & Heishman, 2003). The use of in vivo cues offers replicability and ecological validity, whereas with imagery, affective content can be manipulated (Maude-Griffin & Tiffany, 1996) or script content can be personalized to smokers' experiences (Conklin & Tiffany, 2001). Few studies, however, have directly compared the magnitude of craving and autonomic reactivity elicited by in vivo cues versus imagery. Drobes and Tiffany (1997) exposed smokers to imagery scripts and watching a confederate smoke a cigarette. Both manipulations produced comparable increases in self-reported craving; however, heart rate was increased only by imagery, whereas skin conductance was increased only by cues. Using a similar design, Burton and Tiffany (1997) found that imagery and a cigarette-smoking confederate produced equivalent changes in craving and mood; skin conductance was increased only by in vivo cues. Similarly, Erblich and Bovbjerg (2004) found no difference in craving response between imagery scripts and holding an unlit cigarette. In contrast, Niaura et al. (1998) reported that exposure to a confederate smoking elicited greater increases in self-reported craving and mean arterial pressure than imagery scripts.

Perkins and colleagues (Perkins, 1996; Perkins et al., 2001, 2006; Perkins, Jacobs, Sanders, & Caggiula, 2002) have shown that women, compared with men, are more sensitive to nonpharmacological factors associated with smoking and nicotine reinforcement and less sensitive to pharmacological factors, such as nicotine dose. Thus, women should report greater tobacco craving or exhibit increased autonomic reactivity compared with men following presentation of smoking-related cues or imagery, which has been documented (Field & Duka, 2004; Knott et al., 2008; Niaura et al., 1998; Tong, Bovbjerg, & Erblich, 2007; Waters et al.,

2004). A similar sex difference has been reported in studies investigating craving and autonomic reactivity to heroin-related (Yu et al., 2007) and cocaine-related cues (Robbins, Ehrman, Childress, & O'Brien, 1999). Other studies, however, have not found sex differences in response to smoking-related stimuli (Erblich & Bovbjerg, 2004; Niaura et al., 2005; Shadel et al., 1998; Shiffman et al., 2003). Given the nearly equal number of studies on both sides of the issue, the question of sex differences warrants further investigation.

In this study, we attempted to resolve some of the inconsistencies in the literature with respect to smoking cue reactivity. First, we investigated whether the magnitude and time course of craving and autonomic responses differed between in vivo cues and imagery. Based on the majority of previous studies, we hypothesized that cues and imagery would elicit comparable reactivity and that craving responses would decline during the 30 min following cue and imagery presentation. Second, we examined the effect of tobacco deprivation because some studies showed that cue-elicited responses were enhanced following deprivation (McDonough & Warren, 2001; Sayette et al., 2001; Sayette & Hufford, 1994), whereas others reported that deprivation either nonspecifically increased reactivity to neutral and smoking stimuli (Drobes & Tiffany, 1997; Maude-Griffin & Tiffany, 1996) or had no effect on cue reactivity (Geier, Mucha, & Pauli, 2000). Third, we examined sex differences by recruiting an equal number of men and women, hypothesizing that women would respond more strongly than men to in vivo cues and imagery.

Method

Participants

Sixty cigarette smokers (30 men, 30 women) participated in the study. Inclusionary criteria were 18–45 years old, smoking a minimum of 15 cigarettes daily for the past 2 years, not currently interested in quitting or reducing smoking, and no history of drug dependence, excluding tobacco. Participants were healthy as determined by medical and psychological screening before the study. The NIDA Institutional Review Board approved the study. Participants provided written informed consent according to the guidelines for the protection of research volunteers of the U.S. Department of Health and Human Services and were paid for their time.

Design and Procedure

General procedure—The study was conducted at the NIDA Intramural Research Program. We used a within-subjects design, consisting of an initial adaptation session and two experimental sessions separated by at least 48 hr. At the adaptation session, participants were familiarized with the study equipment and procedures. Participants smoked ad libitum before one experimental session and were tobacco deprived for 12 hr before the other session. Bell, Taylor, Singleton, Henningfield, and Heishman (1999) reported that mean breath carbon monoxide (CO) level was 11.1 and 6.7 parts per million (ppm) after 8 and 16 hr of enforced tobacco deprivation, respectively. Thus, we chose a breath CO cutoff of ≤ 12 ppm to verify abstinence. Order of the two conditions was counterbalanced across participants.

Before the start of the nondeprived session, participants smoked one of their preferred-brand cigarettes to standardize time since last tobacco exposure (Henningfield & Griffiths, 1981). Sessions began with participants completing a series of self-report questionnaires (see below) and providing CO and breathalyzer samples. Participants were seated in a comfortable chair and connected to physiological recording devices. They were then exposed to four randomized experimental trials lasting 30 min each: smoking imagery, neutral imagery, smoking cues, and neutral cues. Participants completed craving and mood questions at 0, 5, 10, 20, and 30 min after imagery or cue exposure. There was a 10-min break between trials. In the nondeprived

session, participants smoked one preferred-brand cigarette during the break between the second and third trial to avoid the confound of tobacco withdrawal.

Imagery trials—Imagery scripts recorded on compact disc were presented to participants via stereo speakers. They either consisted of scenes that described a person experiencing a strong desire to smoke cigarettes (smoking imagery) or had no mention of smoking (neutral imagery). For each participant, smoking imagery and neutral imagery scripts were chosen randomly from a pool of scripts that elicited equivalent ratings of craving (Lee, Myers, Taylor, Moolchan, & Heishman, 2007). Participants closed their eyes and actively imagined themselves in the scene while listening to the script and continued imagining until they heard a tone. Each imagery exposure consisted of 60 s of script presentation and 30 s of silent continued imagery.

Cue Trials—Trials began with the experimenter placing a tray containing an opaque cover on a table in front of the participant. In the smoking cue trial, a pack of their preferred brand of cigarettes, a lighter, and an ashtray were under the cover (Sayette & Hufford, 1994). In the neutral cue trial, a pack of unsharpened pencils and a pencil sharpener were under the cover (Shadel, Niaura, & Abrams, 2001). When instructed, participants removed the cover from the tray. In the smoking cue trial, they took one cigarette from the pack, lit it without puffing, and held it while looking at it. At the end of the exposure period, they extinguished the cigarette and replaced the cover on the tray. Participants then closed their eyes and thought about the cue. In the neutral cue trial, participants took one pencil out of the pack, sharpened it, and held it while looking at it. Consistent with imagery trials, cue exposure entailed 60 s of cue presentation and 30 s of continued thinking about the cue.

Measures

Tobacco Craving Questionnaire-Short Form (TCQ-SF)—The 12-item TCQ-SF assesses craving in four dimensions: (a) *emotionality* (Factor 1, smoking in anticipation of relief from withdrawal or negative mood); (b) *expectancy* (Factor 2, anticipation of positive outcomes from smoking); (c) *compulsivity* (Factor 3, inability to control tobacco use); and (d) *purposefulness* (Factor 4, intention and planning to smoke for positive outcomes). The TCQ-SF was developed from the 47-item TCQ (Heishman et al., 2003) and is as valid and reliable as the TCQ (Heishman, Singleton, & Pickworth, 2008). Factor scale scores for each participant were obtained by summing the items in each of the factors.

Visual analog scale (VAS)—Five VAS items were used to assess mood and craving: (a) vividness of mental image of the scene (imagery trials), (b) crave a cigarette, (c) urge for a cigarette, (d) positive mood, and (e) negative mood. Participants responded to each item by placing a vertical mark along a 100-mm line anchored by *not at all* on the left and *extremely* on the right. We have found that these VAS items correlate with the factor scales of the TCQ (Heishman et al., 2003; Singleton et al., 2003) and TCQ-SF (Heishman et al., 2008).

Minnesota Nicotine Withdrawal Scale (MNWS)—Comprising seven DSM-IV symptoms of nicotine withdrawal, excluding decreased heart rate (Hughes & Hatsukami, 1998), the MNWS was administered at the start of each session to assess the effects of tobacco deprivation. Each symptom was rated on a 4-point ordinal scale (none, mild, moderate, severe), and a total score was obtained by averaging the items. The MNWS has high reliability and good construct validity (Hughes & Hatsukami, 1986; West, Ussher, Evans, & Rashid, 2006).

Autonomic measures—Heart rate, blood pressure, skin temperature, and skin conductance were measured for 5 min before each trial (baseline), during the imagery or cue exposure, and continuously for 30 min after exposure using a physiological monitoring system (Coulbourn

Instruments, Lehigh Valley, PA). Breath CO was measured using a hand-held breath monitor (Vitalograph, Lenexa, KS) at the start of each session.

Data Analysis

To examine effects of overnight tobacco deprivation, baseline breath CO and MNWS scores from each session were compared using within-group *t* tests. For the primary analysis, data from the TCQ-SF and VAS items were expressed as change scores using baseline data from each session. Physiological data were averaged for the 5-min baseline, the duration of imagery or cue exposure, and in 5-min intervals over the 30-min trial; data were expressed as change from the 5-min baseline recorded immediately before each imagery or cue exposure.

We were interested in answering the following questions: (a) Did the magnitude and time course of responses differ between smoking imagery and neutral imagery?, (b) Did the magnitude and time course of responses differ between smoking cues and neutral cues?, and (c) Did the magnitude of responses differ between smoking imagery and smoking cues? For each question, we also asked whether responses differed as a function of tobacco deprivation and sex. Data were analyzed for the first two questions using a four-way analysis of variance (ANOVA) with stimulus intensity (smoking and neutral), condition (tobacco deprived and nondeprived), time (30-min trial), and sex as factors. Data for the third question were analyzed using a four-way ANOVA with stimulus type (smoking imagery and smoking cue), condition, time, and sex as factors. ANOVAs were conducted using the mixed models procedure in SPSS (SPSS, Inc., Chicago, IL). Because ANOVAs were based on all available observations, rather than casewise deletion of subjects, we report Satterthwaite's (1946) approximation for the denominator degrees of freedom for the approximate *t* statistic comparing unequal subsample means. Post hoc comparisons between means were conducted using Fisher's least significant difference test. All statistical tests were two-tailed, and results were considered significant at $p < .05$.

Results

Participant Characteristics

Demographic and smoking history variables are shown in Table 1. The sample comprised a nearly equal proportion of Blacks and Whites. There was no difference between men and women in age or on any smoking history variable.

Deprivation Effects

Breath CO was significantly lower after 12 hr of tobacco deprivation than during ad libitum smoking, $t(58) = 12.53$, $p < .001$. Mean baseline CO level was 27.3 ppm ($SD = 11.9$) in the nondeprived condition and 8.5 ppm ($SD = 2.0$) after deprivation, confirming compliance with the overnight smoking restriction (cf., Bell et al., 1999). Scores on the MNWS were significantly higher after tobacco deprivation ($M = 1.0$, $SD = 0.6$) compared with the nondeprived condition ($M = 0.4$, $SD = 0.5$), $t(57) = 6.71$, $p < .001$.

As expected, there were significant baseline differences between the deprived and nondeprived conditions on all measures of tobacco craving ($ps < .001$); however, scores in the deprived condition were not at ceiling. The maximum score on each factor of the TCQ-SF is 21. Mean (SD) baseline scores for Factors 1–4, respectively, in the deprived condition were 14.8 (5.4), 18.7 (4.5), 13.1 (5.9), and 15.8 (4.5) and in the nondeprived condition were 9.9 (4.9), 14.1 (5.0), 8.8 (5.1), and 11.8 (4.5). The number of participants who scored at maximum on Factors 1–4, respectively, in the deprived condition were 9, 36, 10, and 11 and in the nondeprived condition were 0, 8, 0, and 2. Mean (SD) baseline scores on the VAS item (0–100) crave a cigarette were 82.4 (20.1) and 41.3 (26.9) in the deprived and nondeprived conditions,

respectively. Mean (*SD*) baseline scores on the VAS item urge for a cigarette were 81.8 (20.3) and 42.7 (27.1) in the deprived and nondeprived conditions, respectively. The number of participants who scored at maximum on the VAS items crave and urge, respectively, in the deprived condition were 7 and 5; no one scored at maximum in the nondeprived condition.

Smoking Imagery Versus Neutral Imagery

Craving and mood measures—Smoking imagery increased self-reported craving and negative mood compared with neutral imagery, as evidenced by a stimulus intensity main effect for TCQ-SF Factor 1, $F(1, 1074) = 7.40, p < .01$; Factor 2, $F(1, 973) = 6.52, p < .05$; Factor 3, $F(1, 1031) = 11.57, p < .01$; Factor 4, $F(1, 1101) = 8.46, p < .01$; crave a cigarette, $F(1, 878) = 8.58, p < .01$; urge for a cigarette, $F(1, 841) = 7.96, p < .01$; and negative mood, $F(1, 1088) = 6.71, p < .05$. Smoking imagery decreased positive mood, $F(1, 1085) = 13.56, p < .001$. Figure 1 shows the time course of these effects for selected measures. Most responses were affected immediately after imagery presentation and remained relatively stable over the 30-min trial, indicated by the lack of any time main effects or interactions.

Figure 1 also shows that smoking imagery had a more robust effect on responses in the nondeprived condition compared with tobacco deprivation, indicated by a condition main effect for TCQ-SF Factor 3, $F(1, 1031) = 13.51, p < .001$; crave, $F(1, 878) = 132.12, p < .001$; urge, $F(1, 841) = 94.21, p < .001$; positive mood, $F(1, 1085) = 12.68, p < .001$; and negative mood, $F(1, 1088) = 11.70, p < .01$. There was an Intensity $\times$ Condition interaction for TCQ-SF Factor 2, such that responses were increased after smoking imagery only during the nondeprived condition, $F(1, 973) = 4.57, p < .05$.

Ratings of imagery vividness did not differ between smoking imagery and neutral imagery trials ($p = .15$). However, vividness ratings in the nondeprived condition were greater than in the deprived condition, $F(1, 1073) = 19.26, p < .001$, and ratings for both imagery scripts and conditions declined gradually over the 30-min trial, $F(4, 441) = 6.33, p < .001$.

Autonomic measures—Compared with neutral imagery, smoking imagery increased autonomic activity, as shown by an intensity main effect for systolic blood pressure, $F(1, 1520) = 4.33, p < .05$, and skin conductance, $F(1, 1154) = 11.14, p < .01$. There was also an intensity main effect, $F(1, 1081) = 14.92, p < .001$, and a condition main effect, $F(1, 1081) = 4.63, p < .05$, for skin temperature, such that smoking imagery increased and tobacco deprivation decreased temperature. Cardiovascular measures tended toward baseline by the end of the 30-min trial, whereas skin conductance and skin temperature remained elevated. No other autonomic measures were significantly affected by imagery intensity or condition.

Smoking Cues Versus Neutral Cues

Craving and mood measures—An Intensity $\times$ Condition interaction was observed for TCQ-SF Factor 1, $F(1, 1084) = 4.03, p < .05$; Factor 2, $F(1, 1034) = 9.02, p < .01$; Factor 3, $F(1, 1024) = 7.36, p < .01$; Factor 4, $F(1, 1037) = 5.27, p < .05$; crave, $F(1, 942) = 11.14, p < .01$; urge, $F(1, 937) = 10.94, p < .01$; negative mood, $F(1, 1073) = 4.95, p < .05$; and positive mood, $F(1, 1073) = 8.24, p < .01$. Figure 2 shows the time course of these effects for selected measures. Post hoc comparisons indicated that smoking cues elicited a more robust response than neutral cues only in the nondeprived condition for all measures ($ps < .01$). Post hoc tests also revealed that all responses were significantly ($ps < .05$) changed immediately following cue presentation and remained stable over the 30-min trial.

Autonomic measures—Smoking cues increased physiological responses in deprived and nondeprived conditions, shown by an intensity main effect for heart rate, $F(1, 1411) = 29.80, p < .001$; systolic pressure, $F(1, 1450) = 30.52, p < .001$; and diastolic pressure, $F(1, 1450) =$

42.58, $p < .001$. Post hoc tests showed that heart rate and blood pressure were significantly ($p < .05$) increased during cue presentation and remained stable for the duration of the trial. Skin conductance showed a condition main effect, $F(1, 1186) = 8.10$, $p < .01$, such that tobacco deprivation increased reactivity, and a trend ($p = .08$) for smoking cues to increase conductance. Skin temperature revealed an intensity main effect, $F(1, 716) = 4.33$, $p < .05$, and a condition main effect, $F(1, 716) = 27.58$, $p < .001$. Post hoc tests indicated the increase in skin temperature after smoking cues occurred only in the nondeprived condition ($p < .05$), gradually increasing over the first 15 min and then remaining unchanged during the last 15 min of the trial.

Smoking Cues Versus Smoking Imagery

Craving and mood measures—Smoking cues typically elicited greater responses than smoking imagery, as shown for selected measures in Figure 3. This pattern was supported by a stimulus type main effect for crave, $F(1, 938) = 7.31$, $p < .01$, and a Type $\times$ Condition interaction for urge, $F(1, 912) = 4.47$, $p < .05$ (Figure 3A); negative mood, $F(1, 1073) = 5.02$, $p < .05$ (Figure 3C); and positive mood, $F(1, 1065) = 8.98$, $p < .01$. Post hoc analysis of the significant interactions indicated that the greater response to smoking cues was observed in the nondeprived condition ($ps < .05$). A Type $\times$ Condition interaction was also observed for TCQ-SF Factor 3, $F(1, 1024) = 5.59$, $p < .05$ (Figure 3B), and Factor 4, $F(1, 1075) = 4.17$, $p < .05$, such that cues produced greater responses than imagery in the nondeprived condition. Responses on TCQ-SF Factors 1 and 2 were greater in the nondeprived than deprived condition ($ps < .001$), but there was no significant difference between imagery and cues.

Autonomic measures—For all measures, smoking cues increased responses over smoking imagery, as shown by a stimulus type main effect for heart rate, $F(1, 1314) = 46.60$, $p < .001$ (Figure 3D); systolic pressure, $F(1, 57) = 33.51$, $p < .001$; diastolic pressure, $F(1, 1421) = 42.37$, $p < .001$; and a trend ($p = .09$) for skin conductance. There was a Type $\times$ Condition interaction for skin temperature, $F(1, 541) = 12.94$, $p < .001$, such that the cue-induced increase was observed only in the nondeprived condition ($p < .01$).

Sex Differences

The analyses of the first two questions found, in general, that men responded more robustly to smoking imagery, whereas women were more sensitive to smoking cues. Because there were no Sex $\times$ Time interactions and because of the close similarity in sex differences between those analyses and analysis of the third question (smoking cue versus smoking imagery), we present sex difference data from the third analysis. Figure 3 shows selected measures.

Craving and mood measures—There was a Sex $\times$ Condition $\times$ Stimulus Type interaction for crave, $F(1, 938) = 12.44$, $p < .001$, and urge, $F(1, 912) = 10.86$, $p < .01$ (Figure 3A). Post hoc tests for both measures indicated that smoking imagery elicited greater responses in men during both conditions compared to women ($p < .01$). In contrast, women responded more robustly to the smoking cue only in the nondeprived condition ($p < .01$). A Sex $\times$ Condition interaction was observed for TCQ-SF Factor 1, $F(1, 1055) = 61.17$, $p < .001$, and Factor 3, $F(1, 1024) = 18.96$, $p < .001$ (Figure 3B), such that women scored higher than men in the nondeprived condition on both factors, whereas men scored higher in the deprived condition on Factor 1. Men scored higher than women on Factor 2, as indicated by a sex main effect, $F(1, 1032) = 15.28$, $p < .001$. There was a Sex $\times$ Condition interaction for ratings of negative mood, $F(1, 1073) = 6.62$, $p < .01$ (Figure 3C), and positive mood, $F(1, 1066) = 4.52$, $p < .05$. Post hoc tests indicated that men scored higher than women on negative mood in the deprived condition ($p < .01$). For positive mood, the difference between scores in the deprived and nondeprived condition was greater for women than for men ($p < .001$).

Autonomic measures—There was a Sex $\times$ Condition $\times$ Stimulus Type interaction for heart rate, $F(1, 1314) = 7.48, p < .01$ (Figure 3D); systolic pressure, $F(1, 1413) = 4.96, p < .05$; and diastolic pressure, $F(1, 1422) = 7.40, p < .01$. Post hoc tests on all measures indicated that women were more responsive than men to the smoking cue in the nondeprived condition ($p < .001$). In contrast, men exhibited an increase in systolic and diastolic pressure compared with women following smoking imagery in the nondeprived condition ($p < .05$). There was a Sex $\times$ Condition interaction for skin conductance, $F(1, 1252) = 11.64, p < .01$. Post hoc tests revealed that women exhibited greater conductance in the deprived condition ($p < .05$), whereas men showed greater conductance in the nondeprived condition ($p < .01$). Women showed a trend ($p < .07$) toward increased skin temperature in response to the smoking cue in the nondeprived condition.

Discussion

To our knowledge, this is the first cue-reactivity study to demonstrate that increases in self-reported tobacco craving and autonomic measures were sustained for 30 min following exposure to imagery and in vivo cues. Although both smoking imagery and smoking cues increased responding over neutral imagery and cue conditions, smoking cues elicited a greater magnitude in craving, mood, and autonomic reactivity compared with smoking imagery.

The prolonged duration of an evoked craving state in the laboratory replicates and extends our previous work (Heishman et al., 2004), but contrasts with studies characterizing naturalistic tobacco craving as episodic (Shiffman et al., 1996, 1997) and with retrospective reports that craving episodes last on average 6–10 min (Heishman et al., 2003). One possible explanation for this discrepancy is that smoking-related stimuli alone or combined with the demand characteristics of a laboratory setting evoke a more intense, prolonged craving response than cues in the real world. A more likely explanation is that in our laboratory studies, participants were undisturbed during the period following the imagery or cue manipulation, whereas in the real world, a variety of distractions or even smoking a cigarette may interrupt or lessen the intensity of a craving episode. For example, Shadel, Niaura, Goldstein, and Abrams (2001) found that smokers instructed to “focus on something else” during presentation of smoking cues reported attending less to the smoking cues than smokers not given the cognitive avoidance manipulation.

There are two obvious reasons for needing to know the duration of a cue-elicited state in the laboratory (cf., Heishman et al., 2004). First, knowing the time course of an elicited craving episode is critical for the design of studies investigating the influence of craving on various dependent measures, such as brain activation (Franklin et al., 2007; Hester & Garavan, 2009) and cognition (Heishman et al., 2006; Madden & Zmann, 2001) and of psychopharmacological studies evaluating medications to reduce craving (Niaura et al., 2005; Reid & Thakkar, 2009; Shiffman et al., 2003). Second, presentation order of neutral and smoking cues ideally should be counterbalanced. Carter and Tiffany (1999) reported that 69% of studies in their meta-analysis did not control for order effects. Because of potential carry-over effects, researchers typically present the neutral cue before the craving cue, which confounds cue with time in the study. Based on the prolonged duration of effects observed in this study, we recommend that neutral and smoking cues be presented on separate days. Alternatively, if both cue conditions are presented within a single session, a lengthy interval should intervene or relaxation techniques could be used to reduce craving to baseline levels after cue exposure (Ehrman et al., 1998; Singleton et al., 2003). Whether presented within or across sessions, the order of cue conditions could then be counterbalanced with minimal concern for carry-over effects.

Smoking cues and smoking imagery significantly increased craving, mood, and autonomic responses compared with neutral stimuli. Contrary to our hypothesis, smoking cues elicited

greater responses than smoking imagery for most craving and mood measures and for all autonomic measures. This result is not consistent with studies reporting comparable effects between in vivo cues and imagery (Burton & Tiffany, 1997; Drobles & Tiffany, 1997; Erbllich & Bovbjerg, 2004) or between imagery and visual cues (Warthen & Tiffany, 2009). Other studies, however, reported that in vivo cues evoked more robust responding than imagery or other smoking-related stimuli (Niaura et al., 1998; Shadel, Niaura, & Abrams, 2001). Differences in the nature and presentation of stimuli within and across studies obviously account for some of these inconsistencies. We used cue and imagery manipulations that have reliably elicited craving and autonomic responses (Lee et al., 2007; Sayette & Hufford, 1994), matched their exposure time, and presented them randomly to control for order and carryover effects. The in vivo cue of having participants light and hold one of their preferred-brand cigarettes is a robust method to elicit craving, mood, and autonomic responding.

We found that smoking imagery and smoking cues elicited greater craving and mood responses when participants had been smoking ad libitum than when they were tobacco deprived for 12 hr. As expected, our participants reported increased tobacco craving and withdrawal symptoms at baseline after overnight deprivation, but ratings were not at ceiling, which might have explained a blunted subjective response. According to incentive motivational theories of addiction (Robinson & Berridge, 1993, 2001; Stewart, de Wit, & Eikelboom, 1984), deprivation-induced increases in drug craving (wanting) accompany the attribution of salience to drug-related stimuli. Several studies reported that cue-elicited responses were enhanced following tobacco deprivation (McDonough & Warren, 2001; Sayette et al., 2001; Sayette & Hufford, 1994); however, our finding of less robust subjective responding to smoking cues and imagery after deprivation compared with nondeprivation does not support the incentive model in this regard. Our data are consistent with several other studies. Geier et al. (2000) reported no influence of tobacco deprivation (12 hr) on cue-elicited ratings of desire to smoke. Cooney, Cooney, Pilkey, Kranzler, and Oncken (2003) found that 34 hr of tobacco deprivation produced a nonspecific increase in smoking urge after alcohol and water cues. Similarly, Tiffany and colleagues (Drobles & Tiffany, 1997; Maude-Griffin & Tiffany, 1996) reported that 6 to 24 hr of tobacco deprivation, compared with nondeprivation, produced a general increase in imagery-elicited craving and mood, which was not specific to smoking-related stimuli. Maude-Griffin and Tiffany (1996) postulated that the insensitivity of responses to deprivation was due to their use of imagery-based stimuli and that in vivo cues would produce results consistent with incentive theories. Our results with imagery and in vivo cues clearly indicate that this is not the case. Further research is required to resolve the effect of tobacco deprivation as a modifier of cue-elicited responding.

We hypothesized that women would exhibit greater stimulus reactivity compared with men, as previously shown (Field & Duka, 2004; Knott et al., 2008; Niaura et al., 1998; Tong et al., 2007; Waters et al., 2004). We found qualified support for this hypothesis; sex differences varied depending on measure, tobacco deprivation, and stimulus type (cue and imagery). On measures of self-reported craving, women were more sensitive to in vivo cues in the nondeprived condition, whereas men showed increased craving responses to imagery after tobacco deprivation. Similarly, women showed increased heart rate and blood pressure to cues on the nondeprived condition, and men exhibited an increase in blood pressure in response to imagery in the deprived condition. Niaura et al. (1998) reported that men showed increased mean arterial pressure to in vivo cues, whereas women were more responsive to imagery scripts, the opposite of our findings. The only other study comparing in vivo cues and imagery found no sex difference in craving response (Erbllich & Bovbjerg, 2004). Waters et al. (2004) suggested that sex differences are observed only with a weak stimulus cue (e.g., an unlit cigarette), but not with a stronger cue (e.g., a lit cigarette). However, one study using an unlit cigarette cue found no sex differences (Erbllich & Bovbjerg, 2004), and studies, including the present, using a lit cigarette have reported sex differences (Knott et al., 2008; Niaura et al.,

1998). Clearly, more research is required to reach a consensus on how men and women respond to smoking-related cues and imagery.

Several limitations and caveats of this research should be noted. The in vivo cues and imagery scripts used in this study and the measurement of craving using the TCQ-SF and VAS items were validated in smokers who were not attempting to reduce or quit smoking (Heishman et al., 2004, 2008; Sayette & Hufford, 1994; Singleton et al., 2003). Although some studies have reported cue-elicited craving in smokers motivated to quit (Shiffman et al., 2003; Waters et al., 2004), Shadel et al. (1998) reported that imagery scripts did not elicit tobacco-craving responses in smokers seeking treatment for tobacco dependence. Thus, the present results may not extend to smokers trying to quit, former smokers, and smokers who are not tobacco dependent. Another limitation was that we did not control for menstrual cycle phase of women. During the luteal phase of the menstrual cycle, women experience more intense tobacco withdrawal and craving (Allen, Allen, & Pomerleau, 2009; Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006). Thus, the sex differences observed in elicited craving and mood in this study may have been influenced by premenstrual symptoms. Finally, some investigators (Donny, Griffin, Shiffman, & Sayette, 2008; Perkins, 2009) have noted the lack of relation between cue-elicited craving and clinically important aspects of tobacco dependence, such as relapse risk or dependence severity, whereas others have reported such predictive relationships (Carpenter et al., 2009; Shadel et al., 1998; Waters et al., 2004). We should always strive to make our laboratory models relevant to the clinical situation; however, the cue-reactivity paradigm remains a useful model with which to investigate phasic evoked craving states, which smokers experience on a daily basis (Epstein, Marrone, Heishman, Schmittner, & Preston, 2009; Ferguson & Shiffman, 2009).

In summary, in vivo smoking cues and imagery scripts describing smoking urge reliably increased tobacco craving, negative mood, heart rate, and blood pressure and decreased positive mood compared with neutral stimuli. These changes lasted for 30 min. Magnitude of responding was greater in the nondeprived condition, and cues elicited more robust responding than imagery for most measures. Women responded more strongly to smoking cues only in the nondeprived condition, whereas imagery evoked greater responses in men during both conditions. Laboratory studies of cue reactivity provide a model in which the effects of novel behavioral and pharmacological interventions on conditioned smoking cues can be tested.

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Figure 1.

Effect of imagery scripts (smoking and neutral) on selected craving, mood, and physiological measures as a function of time after imagery exposure. Graphs on left show data after 12 hr of tobacco deprivation, and graphs on right show data during ad libitum smoking. Each symbol represents the mean of 60 tobacco-dependent smokers; error bars show the standard error of the mean.

Figure 2.

Effect of cues (smoking and neutral) on selected craving, mood, and physiological measures as a function of time after cue exposure. Graphs on left show data after 12 hr of tobacco deprivation, and graphs on right show data during ad libitum smoking. Each symbol represents the mean of 60 tobacco-dependent smokers; error bars show the standard error of the mean.

Figure 3.

Effect of smoking cues and smoking imagery by sex on selected craving, mood, and physiological measures. Graphs on left show data after 12 hr of tobacco deprivation, and graphs on right show data during ad libitum smoking. Each column represents the mean of 30 male or 30 female tobacco-dependent smokers; error bars show the standard error of the mean. Post hoc comparisons: * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 1

Demographics and Smoking Characteristics of Sample and by Sex

Variable	Sample (n = 60)	Women (n = 30)	Men (n = 30)
Black, percent	48.3	43.3	53.3
White, percent	51.7	56.7	46.7
Mean age (<i>SD</i>)	34.1 (7.6)	33.2 (7.8)	35.0 (7.3)
Mean years smoking (<i>SD</i>)	12.4 (7.7)	13.3 (8.4)	11.1 (6.9)
Mean cigarettes per day (<i>SD</i>)	21.9 (7.8)	20.9 (7.9)	22.9 (7.6)
Mean breath CO (<i>SD</i>)	26.0 (10.7)	25.2 (11.1)	26.8 (10.4)
Mean FTND score (<i>SD</i>)	5.7 (1.9)	5.5 (1.6)	5.9 (2.2)

Note. Breath CO = breath carbon monoxide in parts per million, measured at adaptation session during ad libitum smoking. FTND = Fagerström Test for Nicotine Dependence, a valid and reliable measure of nicotine dependence with scores ranging from 0 to 10 (Heatherton, Kozlowski, Frecker, & Fagerström, 1991).