

Effects of Transdermal Nicotine Patches on Abstinence-Induced and Cue-Elicited Craving in Cigarette Smokers

Stephen T. Tiffany

Department of Psychological Sciences Purdue University

Lisa Sanderson Cox

Department of Psychological Sciences Purdue University

Celeste A. Elash

Department of Psychological Sciences Purdue University

ABSTRACT

The impact of a transdermal nicotine patch on smokers' craving for cigarettes and reactivity to smoking cues was investigated. Sixty-one smokers were assessed during 2 sessions separated by 6 hr. Cue reactivity to imaginal and in vivo smoking and nonsmoking stimuli was evaluated during both sessions. During the interval between sessions, participants were abstinent from cigarettes and wore either a nicotine transdermal (21 mg) or placebo patch. In both sessions, exposure to in vivo and imaginal smoking stimuli elicited cue-specific increases in craving, negative affect, vividness, heart rate, and skin conductance. The nicotine patch attenuated craving and other effects induced by abstinence from cigarettes but had no selective impact on craving or any other reaction elicited by smoking cues. These results are discussed in terms of models of craving and clinical implications of transdermal nicotine for craving reduction.

Lisa Sanderson Cox is now at the Nicotine Research Center, Mayo Clinic, Mayo Foundation, Rochester, Minnesota. Celeste A. Elash is now at the Smoking Research Group, University of Pittsburgh. This research was supported by Research Grant PBR-44 from the American Cancer Society and by Research Grant RO1 DA10264 from the National Institute on Drug Abuse.

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Correspondence may be addressed to Stephen T. Tiffany, Department of Psychological Sciences, Purdue University, Psychological Sciences Building, West Lafayette, Indiana, 47907.

Electronic mail may be sent to tiffany@psych.purdue.edu

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For many cigarette smokers, craving is the most prominent symptom of their addiction to nicotine. Regular smokers typically report fairly high levels of cigarette craving (Hughes, Higgins, & Hatsukami, 1990 ; Shiffman et al., 1997), and concerns about craving may discourage smokers from even attempting to quit smoking (Orleans, Rimer, Cristinzio, Keintz, & Fleisher, 1991). Smokers commonly describe their craving during quit attempts as the most salient, frequent, and disconcerting feature of cigarette abstinence (Center for Disease Control, 1994 ; Gritz, Carr, & Marcus, 1991 ; Shiffman & Jarvik, 1976 ; West, Hajek, & Belcher, 1989). Several studies have found that craving levels during the

early phases of quitting are moderately predictive of the probability of relapse (Baer & Lichtenstein, 1988 ; Brandon, Tiffany, & Baker, 1987 ; Doherty, Kinnunen, Militello, & Garvey, 1995 ; Killen & Fortmann, 1997 ; Shiffman et al., 1997 ; Swan, Ward, & Jack, 1996). For example, Killen and Fortmann (1997) presented the combined results of three studies in which smokers were asked to rate how upsetting craving had been over the first 24 to 48 hr of quitting smoking. Smokers who scored in the top quartile of this craving measure had a relapse rate over the next 12 months that was twice as high as those smokers in the lowest quartile.

Recent research from our laboratory has identified several conditions that can serve as potent triggers of craving in cigarette smokers. These include abstinence from smoking (Drobles & Tiffany, 1997 ; Maude-Griffin & Tiffany, 1996 ; Tiffany & Drobles, 1991), presentation of smoking-related scenarios and stimuli (e.g., Cepeda-Benito & Tiffany, 1996 ; Drobles & Tiffany, 1997 ; Elash, Tiffany, & Vrana, 1995 ; Maude-Griffin & Tiffany, 1996 ; Tiffany & Hakenewerth, 1991), induction of negative affect (Maude-Griffin & Tiffany, 1996 ; Tiffany & Drobles, 1990), and consumption of alcohol (Burton & Tiffany, 1997). Although there is substantial information about the conditions that can generate craving, considerably less is known about factors that might attenuate craving.

One of the most commonly used treatments for smoking, the transdermal nicotine patch, has been promoted in advertisements as effective for controlling craving to smoke, thus, ostensibly, enhancing the probability that smokers attempting to quit can maintain abstinence. Nicotine transdermal patches increase the success rates of smoking cessation treatments (Fiore, Smith, Jorenby, & Baker, 1994), and several clinical trials have shown that smokers wearing patches report lower levels of craving to smoke relative to participants in control conditions (e.g., Abelin, Buehler, Müller, Vesanen, & Imhof, 1989 ; Fagerström, Schneider, & Lunell, 1993 ; Jorenby et al., 1996 ; Tønnesen, Norregaard, Simonsen, & Sawe, 1991 ; Transdermal Nicotine Study Group, 1991). Of course, these treatment studies cannot reveal whether the nicotine patch directly decreases craving or whether lower craving levels are secondary to the higher rates of abstinence in smokers using the patch. This issue has been addressed in laboratory-based studies of nicotine patch effects with smokers not attempting to quit smoking. This research indicates that nicotine patches can reduce general levels of craving in participants abstinent for 90 min (Rose, Herskovic, Trilling, & Jarvik, 1985) or 24 hr (Leischow et al., 1997 ; cf. Pickworth, Fant, Butschky, & Henningfield, 1996).

Presumably, nicotine patches should be particularly effective in reducing the craving brought about by abstinence from cigarettes. Abstinent smokers report a generalized increase in craving that is detectable after 1 hr of abstinence (Tiffany & Drobles, 1991) and reaches fairly high levels within 3 to 6 hr of deprivation from cigarettes (Drobles & Tiffany, 1997 ; Maude-Griffin & Tiffany, 1996 ; Schuh & Stitzer, 1995 ; Tiffany & Drobles, 1991). A popular explanation for abstinence-induced craving is that it is caused, either directly or indirectly, by nicotine withdrawal (American Psychiatric Association, 1987 ; Shiffman & Jarvik, 1976 ; West & Schneider, 1987). To the extent that nicotine patches attenuate withdrawal by replacing the nicotine lost through cigarette deprivation, abstinent smokers using patches should experience a generalized decrease in craving.

Abstinence is only one of several possible sources of craving in smokers; laboratory studies have established that presentations of smoking-related cues to cigarette smokers can also have a substantial impact on craving. A recent meta-analysis of the cue-reactivity literature (Carter & Tiffany, 1999) found that effect sizes for cue-induced craving to smoke were, on average, extremely robust. These findings are consistent with anecdotal reports from smokers that their craving is readily activated by confrontations with situations and cues strongly associated with past episodes of smoking. Although smoking cues appear to play a major role in the generation of craving, there have been no investigations of the effect of transdermal nicotine on craving triggered by presentations of smoking-related stimuli.

The possibility that the nicotine patch might selectively dampen reactions generated when smoking-related cues are presented to abstinent smokers is consistent with positive-incentive models of drug craving (Baker, Morse, & Sherman, 1987 ; Stewart, deWit, & Eikelboom, 1984). These models propose that drug deprivation will increase the positive-incentive value of stimuli previously associated with smoking. That is, abstinent smokers should be particularly reactive to cues related to smoking. The nicotine patch, which replaces the nicotine lost through smoking deprivation, would be expected to block any hyperreactivity brought about by abstinence. Other data, however, suggest that the nicotine patch might not have any selective impact on cue-induced craving. Most importantly, there is no evidence that abstinence amplifies reactivity to smoking-related stimuli. For example, smokers abstinent for 6 or 24 hr (Drobos & Tiffany, 1997 ; Maude-Griffin & Tiffany, 1996) displayed a generalized elevation in craving to smoke but no selective increase in their craving, mood, or autonomic reactions to smoking-related scenarios. On the basis of these data, it might be expected that, in abstinent smokers, the nicotine patch would produce a generalized decrease in craving, but it would not selectively inhibit cue-elicited craving.

The present research examined the impact of a transdermal nicotine patch on cue-elicited craving in abstinent smokers. All of the smokers participated in two cue-reactivity sessions with a 6-hr intersession interval. During the interval between sessions, participants abstained from smoking and wore either a placebo or nicotine patch. The cue-reactivity procedure was designed to evaluate craving, mood, and autonomic responses to smoking-relevant and smoking-neutral cues. With this procedure, cues were manipulated through both imaginal and in vivo presentations of stimuli. Previous research from our laboratory has established that imagery of smoking-related narratives produces robust increases in craving levels and replicable changes in autonomic measures relative to imagery of smoking-neutral scenarios (Burton & Tiffany, 1997 ; Cepeda-Benito & Tiffany, 1996 ; Drobos & Tiffany, 1997 ; Elash et al., 1995 ; Maude-Griffin & Tiffany, 1996 ; Tiffany & Drobos, 1990 ; Tiffany & Hakenewerth, 1991). In the in vivo mode of cue presentation, smokers watched someone light and smoke a cigarette or pour and drink a glass of water. This procedure produces levels of self-report craving comparable with those generated by imagery (Burton & Tiffany, 1997 ; Drobos & Tiffany, 1997). The use of both imaginal and in vivo manipulations of smoking stimuli allowed for an examination of whether the nicotine patch might differentially affect reactivity to smoking cues as a function of presentation mode of those cues.

Method

Participants and Design

Participants were 61 (30 men, 31 women) cigarette smokers. Only individuals who were 21 years or older, who smoked at least a pack of cigarettes per day, who were not pregnant, who were not currently using any medication, and who were not attempting to quit smoking at the time of the study were invited to participate. Potential participants were examined by a physician at the Purdue University Health Center and screened for any conditions that would contraindicate the use of a nicotine transdermal patch. Those with expired-air carbon monoxide (CO) levels of less than 10 ppm at the screening session were excluded from participation in the study. The average participant was 31.5 years old, smoked 29 cigarettes/day, had been smoking that amount for 7.2 years, had made three previous attempts to quit smoking, had an expired-air CO concentration of 36.4 ppm at the beginning of the first cue-reactivity session, and scored 4.9 on the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

Each participant attended two laboratory sessions with a 6-hr interval between sessions. All the participants were instructed to remain abstinent between sessions. Participants were paid \$45 with an

additional \$15 bonus if they maintained complete abstinence over the interval between sessions. Twelve exposure trials were presented during each session. Within these trials, mode of stimulus presentation (imagery and in vivo) was completely crossed with cue content of the stimuli (cigarette vs. neutral). Each of the four resulting trial types (imagery—cigarette, imagery—neutral, in vivo—cigarette, and in vivo—neutral) were presented three times during each session. Trial orders were counterbalanced using a Latin square design to minimize order effects with different orders used for each session. At the end of the first session, participants were randomly assigned to wear either a nicotine patch ($n = 31$) or a placebo patch ($n = 30$) over the interval between sessions. There were no significant differences between patch conditions on any demographic or smoking history variables.

Measures and Apparatus Pretrial self-report measures.

Self-report measures collected at the beginning of Session 1 included the Questionnaire on Smoking Urges (QSU; Tiffany & Drobes, 1991), the Mood Form (Diener & Emmons, 1984), the Smoking History Form, the Reasons for Smoking Questionnaire (Ikard, Green, & Horn, 1969), and the Withdrawal Symptoms Checklist (WSC; Shiffman & Jarvik, 1976).

Posttrial ratings.

After each cue-reactivity trial, participants completed a rating form including an 11-item craving measure, the QSU—Brief, derived from the QSU. The QSU—Brief (Cox, Tiffany, & Christen, 1999) yields a general craving score with an excellent level of reliability ($\alpha = .97$). Participants were instructed to complete this questionnaire with regard to what they were experiencing when the scene was presented on the cue-exposure trial. Participants also rated scene vividness (imagery trials) or how carefully they thought about and observed the scene presentation (in vivo trials) and overall positive and negative affect during the trial. All of the ratings were made on 100-point scales. Participants were also asked to indicate the specific portion of the trial during which the strongest craving was experienced.

Physiological measures.

Heart rate and skin conductance were recorded during exposure trials with Coulbourn Instruments data acquisition modules and a Samsung S550 microcomputer using VPM software (Cook, Atkinson, & Lang, 1987). The procedures for collection, processing, and reduction of these measures were the same as those described by Drobes and Tiffany (1997).

The computer also controlled stimulus audiotapes and tones for the trials. White noise (60 dB) was played continuously throughout the trials to mask extraneous sounds.

Procedure Session 1.

Session 1 started between 8 a.m. and 12 p.m. and lasted approximately 90 min. At the beginning of the session, the participant supplied an expired-air sample for assessment of CO levels with an Ecolyzer CO Analyzer. The participant then smoked one cigarette and completed the pretrial questionnaire battery. After these questionnaires were completed, the participant sat in a recliner and physiological recording electrodes were attached. The participant was then given instructions and neutral practice trials for the imagery and in vivo cue exposures.

The procedures and imagery materials for cue-exposure trials were identical to those used by Drobes and Tiffany (1997). (Complete texts of the imagery scripts can be obtained from Stephen T. Tiffany on request.) On imagery trials, scripts were presented over headphones. The sequence of events for an

imagery trial was 30 s of baseline data collection, 50 s of script presentation, 30 s of active imagery terminated by the word *stop*, and a 30-s relaxation period. Participants had their eyes closed throughout the imagery procedure. The three cigarette imagery scripts contained explicit craving descriptors, and each included descriptions of watching people smoke to provide overlap with the primary stimulus content of the cigarette in vivo trials. The three neutral imagery scripts were devoid of any craving or smoking content. During the six in vivo trials, the participant opened his or her eyes when cued by a tone presented over the headphones. The participant then observed a same-gender experimenter, seated 10 ft (3 m) away, either lighting and smoking the participant's brand of cigarettes or pouring a glass of water and drinking from the glass. At the end of the cue-exposure period, the participant was signaled to close his or her eyes and think about what he or she had observed until hearing the word *stop*. The sequence of events for the in vivo trials paralleled the imagery trial sequence: 30 s of baseline, 50 s of cue exposure, 30 s of thinking about the cue presentation, and 30 s of relaxation.

After the exposure trials, the participant was assigned randomly to either the placebo or nicotine patch condition, with both the experimenter and the participant blind to the actual nicotine content of the patch. Participants applied the patch and wore it during the entire interval between sessions. The nicotine patch was a 21-mg Nicoderm transdermal system (Marion Merrell Dow, Kansas City, MO) that produces an average plasma nicotine concentration of approximately 17 ng/ml over a 24-hr period. The peak plasma effect achieved by the system, approximately 24 ng/ml, occurs within 4 hr of application and lasts approximately 4 hr (Marion Merrell Dow, 1991). Participants were instructed to remain abstinent from nicotine and alcohol over the interval between sessions. Participants were also told to engage in their usual daily activities during the 6-hr intersession interval.

Session 2.

On participants' return to the laboratory, abstinence status was determined by participant report and confirmed by CO analyses. Participants were required to show at least a 30% decline in CO levels across sessions as a criterion for abstinence. All the participants met this criterion. One participant in the placebo patch condition reported smoking one cigarette between sessions. As this individual had a marked decrease in CO levels across the two sessions, data from this participant were included in the subsequent analyses. The QSU—Brief, the WSC, and the Mood Form were readministered to all the participants. Participants were then given 12 exposure trials using procedures identical those used in Session 1. At the end of the session, the patch was removed and each participant was debriefed and paid.

Data Analyses

Our overall data-analytic strategy focused primarily on the impact of the nicotine patch on general levels of craving as well as on cue-specific reactions. The analyses used a 2 (patch condition) \times 2 (cue type) \times 2 (mode) \times 2 (session) mixed-design analysis of variance (ANOVA) for each of the posttrial ratings and physiological variables. Physiological measures were obtained by averaging responses from the 50-s stimulus presentation and 30-s active imagery or stimulus processing portion of each cue trial (80 s and expressing them as deviations from the last 25 s of the trial's baseline segment. Significant interactions were further evaluated with simple-effects tests and interaction contrasts (Keppel, 1991). The critical alpha level for these analyses was set at .05. We were particularly interested in evaluating interactions of cue type with session and/or patch condition to determine if (a) abstinence produced any evidence of augmented, cue-specific responding to cigarette stimuli and (b) the nicotine patch selectively attenuated responding to cigarette stimuli. Furthermore, in the presence of significant interactions between session and patch condition, we analyzed changes in responding across sessions for both nicotine and placebo conditions to evaluate whether the nicotine patch alleviated effects induced by abstinence. We conducted additional analyses on pretrial and baseline physiological measures with 2 (patch condition) \times 2 (session) ANOVAs to determine whether the nicotine patch had any generalized

impact on measures of craving, mood, withdrawal, or baseline physiological responding.

Results

Patch Condition: General Effects

Average CO and questionnaire measures taken at the beginning of Sessions 1 and 2 are shown in Table 1. CO levels dropped significantly from Session 1 to Session 2, $F(1, 59) = 89.18, p < .0001$, but there were no significant main or interactive effects of patch condition.

Participants' craving levels on the QSU and the Craving subscale of the WSC increased significantly from Session 1 to Session 2, $F(1, 59) = 48.58$ and 33.54 , respectively, $p < .0001$. In addition, there were significant Session \times Patch interactions on both craving measures, $F(1, 59) = 2.94$ and 5.50 , respectively, $p < .05$. Follow-up tests using interaction contrasts revealed that, on both measures, participants wearing the placebo patch had a significantly greater increase in craving across sessions than those wearing the nicotine patch. None of the other subscales of the WSC displayed significant effects. Although there were no significant effects in positive mood ratings from the Mood Form, negative mood ratings from this questionnaire showed a significant patch effect, $F(1, 59) = 4.46, p < .05$, and a significant Session \times Patch interaction, $F(1, 59) = 5.97, p < .05$. Participants in the placebo condition reported a significant increase in negative mood from Session 1 to Session 2, $F(1, 29) = 6.14, p < .05$, whereas participants in the nicotine patch condition displayed no significant change in negative mood across sessions.

[Table 1](#) also shows baseline heart rate and skin conductance levels for both sessions. Analyses of the heart rate data revealed a significant session effect, $F(1, 59) = 7.53, p < .01$, and a significant Session \times Patch interaction, $F(1, 59) = 14.28, p < .001$. There was no significant difference across sessions in baseline levels of heart rate for participants in the placebo condition; baseline heart rate was significantly higher from Session 1 to Session 2 for the smokers wearing the nicotine patch, $F(1, 30) = 24.38, p < .0001$. There were no significant effects in the baseline skin conductance data.

Cue-Reactivity Measures

Average posttrial ratings and autonomic responses for Session 1 and the two patch conditions of Session 2 are shown in Table 2.

Craving.

Across both sessions, participants reported significantly stronger craving on cigarette trials than neutral trials, $F(1, 59) = 123.41, p < .0001$. There was also a significant Cue \times Mode interaction, $F(1, 59) = 23.11, p < .0001$, with the cue-induced craving effect significantly more pronounced during in vivo than during imagery presentations of stimuli. In addition, there was a significant Session \times Cue interaction, $F(1, 59) = 11.93, p < .001$, with the cue-induced craving effects significantly stronger in Session 1 than in Session 2. Analyses also revealed significant effects of the patch manipulation with significant Patch \times Session, $F(1, 59) = 4.82, p < .05$, and Patch \times Session \times Mode interactions, $F(1, 59) = 5.22, p < .05$. Evaluation of these interactions indicated that the nicotine patch produced significantly lower levels of craving relative to the placebo patch across the stimulus trials of Session 2 (see Figure 1). This difference across patch conditions in Session 2 was significantly greater in the in vivo mode than in the imagery mode of cue presentation. A comparison of craving changes across the two sessions showed that smokers wearing the placebo patch had a significant increase in craving from Session 1 to Session 2, $F(1, 30) = 6.40, p < .05$, whereas those wearing nicotine patches displayed no significant change in

craving across the sessions ($F < 1.00$). There was no indication, however, that the nicotine patch selectively inhibited craving reactivity to the cigarette stimuli through either the imagery or in vivo mode, as none of the interaction terms involving Cue \times Patch were significant.

Vividness/observation.

Participants gave higher vividness/observation ratings on the cigarette trials than on the neutral trials, $F(1, 59) = 24.53, p < .0001$. In addition, these ratings were generally higher for in vivo trials than for imagery trials, $F(1, 59) = 6.78, p < .05$. There was also a significant Cue \times Mode interaction, $F(1, 59) = 12.59, p < .001$, with the cue-specific effects on vividness/observation ratings significantly more pronounced on the in vivo trials than the imagery trials. In addition, there were significant Patch \times Session, $F(1, 59) = 11.50, p < .01$, and Patch \times Session \times Cue interactions, $F(1, 59) = 5.03, p < .05$. Evaluation of these interactions showed that the nicotine patch produced significantly higher vividness/observation ratings than the placebo patch in Session 2. Tests of the three-way interaction indicated that the differences in these ratings across the two patch conditions were greater in the presence of neutral cues than cigarette cues. Analyses of changes across the two sessions revealed that participants in the placebo condition displayed a generalized decrease in vividness/observation ratings, $F(1, 29) = 7.77, p < .01$; this effect did not appear in the nicotine patch condition, $F(1, 30) = 4.11, p > .05$.

Affect.

Across both sessions, presentations of cigarette stimuli increased negative affect ratings relative to presentations of neutral stimuli, $F(1, 59) = 32.07, p < .0001$. There were no other significant effects in the analysis of these ratings. Positive affect ratings showed significant main effects for cue, $F(1, 59) = 15.62, p < .001$, and mode, $F(1, 59) = 34.71, p < .05$, as well as significant Cue \times Mode, $F(1, 59) = 22.64, p < .0001$, and Cue \times Mode \times Session interactions, $F(1, 59) = 7.43, p < .01$. Analyses of these interactions revealed that positive affect was significantly lower on imagery—cigarette trials than imagery—neutral trials, and this difference across mode of presentation was significantly more pronounced in Session 1 than in Session 2. In contrast, levels of positive affect did not differ significantly as a function of cue type or session on in vivo trials.

Heart rate.

Across both sessions and both modes of presentation, cigarette stimuli produced significantly higher levels of heart rate responses than presentations of neutral stimuli, $F(1, 59) = 10.64, p < .01$. There were no other significant effects in the analyses of these data.

Skin conductance.

Analyses of these data revealed significant effects for cue, $F(1, 59) = 58.43, p < .0001$, and mode, $F(1, 59) = 66.35, p < .0001$, and for Cue \times Mode, $F(1, 59) = 26.10, p < .0001$, and Cue \times Mode \times Session interactions, $F(1, 59) = 7.80, p < .01$. Follow-up tests of the interactions showed that, in Session 1, cigarette stimuli produced significantly higher skin conductance levels only during in vivo presentations. There was no significant effect for the cue manipulation during imagery trials. During Session 2, skin conductance levels were significantly higher on cigarette trials relative to neutral trials and significantly higher on in vivo trials relative to imagery trials. Unlike Session 1, there was no significant Cue \times Mode interaction for these effects. Finally, the patch manipulation had no significant impact on skin conductance responses.

Discussion

The results showed that the nicotine patch reduced craving to smoke in abstinent cigarette smokers. The impact of the nicotine patch was evident on craving levels assessed at the beginning of Session 2 as well as on craving ratings collected during the subsequent cue-reactivity trials. Overall, the nicotine patch appeared to attenuate the increase in craving triggered by deprivation from cigarettes. Craving levels rose from Session 1 to Session 2 for smokers wearing placebo patches. In contrast, for smokers wearing the nicotine patch, this increase across sessions was diminished on craving questionnaires given at the beginning of Session 2 and there was no increase across sessions on the craving ratings collected during the cue-reactivity trials. The effect of transdermal nicotine in this research parallels results from other laboratory investigations suggesting that nicotine patches attenuate craving arising from abstinence (Leischow et al., 1997 ; Rose et al., 1985).

Transdermal nicotine also appeared to influence other abstinence-induced effects. Relative to the placebo condition, smokers wearing the nicotine patch reported lower levels of negative mood at the beginning of Session 2 and reported higher levels of vividness/observation during the cue-reactivity procedure. Previous investigations from our laboratory have shown that the deprivation manipulation used in this research increases negative mood ratings (e.g., Drobles & Tiffany, 1997 ; Maude-Griffin & Tiffany, 1996). Negative affect is a prominent feature of the nicotine withdrawal syndrome (Hughes et al., 1990 ; Piasecki, Kenford, Smith, Fiore, & Baker, 1997), and the nicotine patch has been shown to reduce the dysphoria associated with abstinence from cigarettes (Leischow et al., 1997). In the present study, only smokers in the placebo condition reported increased negative mood across sessions; this effect was absent for smokers in the nicotine condition.

Smokers in the placebo, but not in the nicotine, condition also reported lower vividness/observation ratings in Session 2 as compared with Session 1. These ratings may have indexed, in part, the extent to which the participants were able to concentrate on and attend to the cue presentations. The pattern of results across the two patch conditions may reflect the common finding that abstinent smokers report difficulty concentrating (Hughes et al., 1990) and that this abstinence effect can be reversed by transdermal nicotine (e.g., Jorenby et al., 1996 ; Leischow et al., 1997).

Smoking cues presented during either session generated stronger craving to smoke, increases in negative affect, decreases in positive affect during imagery, increases in vividness/observation ratings, increases in heart rate, and increases in skin conductance levels relative to presentations of neutral stimuli. The general pattern and magnitude of these craving and physiological effects replicated previous findings from our laboratory and were consistent with data typically reported in the cue-reactivity literature (Carter & Tiffany, 1999).

The craving data showed that, as with our other studies using this paradigm (Burton & Tiffany, 1997 ; Drobles & Tiffany, 1997), these procedures elicited robust cue-specific craving to smoke. However, there was no indication that the nicotine patch attenuated any of the craving reactions or other responses generated by presentations of cigarette stimuli. In the case of craving report, cigarette cues increased craving and nicotine patches decreased craving, but there was no interaction between these two manipulations. Other variables also yielded both cue and patch effects, but there was no evidence from the self-report or physiological measures that transdermal nicotine blocked or reduced any cue-specific reactions.

The magnitude of cue-specific craving declined significantly from Session 1 to Session 2, and it is possible that a restricted craving effect in Session 2 might have reduced the chances of observing a differential impact of nicotine replacement on cue-induced craving. A consideration of the effect size for

cue-specific craving from Session 2 indicates that this craving effect, although smaller than in Session 1, was still substantial. The effect size (calculated as $d +$) of the difference between cigarette and neutral cues was 1.36 in Session 1 and 1.17 in Session 2. In both cases, these effect sizes greatly exceeded the convention used to describe a large effect size (0.80; Cohen, 1988). Moreover, these effects sizes were in line with the large craving effect sizes typically observed in cue-reactivity studies with cigarette smokers (Carter & Tiffany, 1999).

In this study, transdermal nicotine appeared to reduce craving induced by abstinence but had no significant impact on craving generated by smoking-related cues. This finding is not surprising given that there was no evidence that abstinence specifically enhanced reactivity to smoking cues. It is important to note that this research could not provide a direct test of the effects of abstinence on cue-specific reactivity. That is, there was no nonabstinent control condition for the Session 2 assessments. Nevertheless, the pattern of effects across sessions in this research is consistent with previous experiments from our laboratory that have included such control conditions. That research shows clearly that abstinence increases craving in smokers but does not sensitize them to cigarette-specific stimuli (Drobles & Tiffany, 1997 ; Maude-Griffin & Tiffany, 1996). Those results in combination with the present findings indicate that abstinence and cue presentations may make somewhat independent contributions to craving in cigarette smokers.

Other craving manipulations studied in our laboratory also appear to combine additively, rather than interactively, with cue presentations in the generation of craving. For example, Burton and Tiffany (1997) found that alcohol intoxication produced a generalized increase in craving levels in cigarette smokers but did not selectively enhance craving reactions to cigarette stimuli. Similarly, Maude-Griffin and Tiffany (1996) reported that induction of negative mood in cigarette smokers triggered craving but found no evidence that this manipulation sensitized either ongoing or abstinent smokers to imaginal presentations of smoking scenarios (see also Tiffany & Drobles, 1990). Taken together, these findings provide little support for the incentive-motivational prediction, represented in many models of craving (e.g., Baker et al., 1987 ; Robinson & Berridge, 1993 ; Stewart et al., 1984), that one class of craving triggers (e.g., abstinence or negative affect) should readily prime a nicotine-addicted individual's reactivity to other kinds of craving cues (e.g., cigarette stimuli).

The present results may offer some insight into the limits of any craving reduction smokers might anticipate when using transdermal nicotine to quit smoking. Nicotine replacement may reduce generalized craving associated with cigarette abstinence. However, smokers might be advised not to expect that craving triggered by smoking-related cues will be dampened by use of the patch. To the extent that cue-elicited craving is a major contributor to the overall magnitude of craving experienced by quitting smokers, craving levels could remain fairly high, even though abstinence-induced craving might be controlled adequately by nicotine replacement. This characterization of the effectiveness of the nicotine patch is consistent with clinical findings that the impact of nicotine replacement on craving tends to be relatively modest (e.g., Jorenby et al., 1996).

The potential clinical implications of the present research must be evaluated in light of the fact that the nicotine patch may not have achieved steady-state concentrations of plasma nicotine by Session 2, the abstinence interval was relatively brief, and the participants were not attempting to quit smoking. A consideration of the pharmacokinetics of the transdermal nicotine system used in this research suggests that there is no reason to believe that the participants were underdosed relative to abstinent smokers who might use the patch for more extended durations. This patch system produces peak plasma nicotine levels within 2 to 4 hr of application. Thus, nicotine from the patch, in combination with residual nicotine from cigarette smoking, likely produced levels of plasma nicotine at Session 2 that were higher than average levels that might be generated with more extended use of the patch. With regard to the adequacy of abstinence manipulation, abstinence-induced craving may reach near-maximal levels within

the deprivation duration used in this research (Maude-Griffin & Tiffany, 1996 ; Schuh & Stitzer, Also, longer periods of abstinence (i.e., 24 hr; Maude-Griffin & Tiffany, 1996) do not selectively amplify the craving reactivity of smokers not attempting to quit. Furthermore, there are no published studies examining whether patterns of cue reactivity are systematically influenced by the extent to which drug-addicted individuals are attempting to quit using drugs at the time of the cue-reactivity assessment. Nevertheless, evidence that nicotine patches can selectively dampen smokers' craving reactions to cigarette cues might emerge in quitting smokers who are abstinent for longer periods of time.

The cue reactions investigated in this research were limited to self-report and selected autonomic responses; there was no examination of the impact of smoking cues and transdermal nicotine on smoking behavior. Given the numerous examples of dissociations between craving report, autonomic reactions, and drug use behaviors (Kassel & Shiffman, 1992 ; Tiffany, 1990 ; Tiffany & Carter, 1998), the nicotine patch might have influences on cue-elicited smoking behavior that are not apparent with self-report craving or autonomic measures.

Beyond the theoretical and clinical implications of these findings, this experiment continues to provide strong support for the use of this cue-reactivity procedure to study craving. The research also demonstrates the general utility of this paradigm for investigations of pharmacological interventions to control craving. That is, this single paradigm allows for the generation of both abstinence- and cue-elicited craving and, further, permits the examination of cue-reactivity profiles across two different modes of stimulus presentation. Craving can arise from multiple sources, and as indicated by our research, these sources might contribute somewhat independently to the overall level of craving reported by the nicotine-addicted individual. Consequently, laboratory-based procedures for screening craving medications must be designed to evaluate a diversity of craving triggers. The cue-reactivity procedure used in this research offers an excellent vehicle for these investigations.

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Average Pretrial CO Levels, Pretrial Questionnaire Scores, and Baseline Physiological Measures for Session 1 and the Two Patch Conditions for Session 2

TABLE 2
Average Pretrial CO Levels, Pretrial Questionnaire Scores, and Baseline Physiological Measures for Session 1 and the Two Patch Conditions for Session 2

Measure	Session 1 (n = 101)		Patch (n = 51)		Control (n = 50)	
	M	SD	M	SD	M	SD
CO Level (ppm)	10.05	10.08	10.04	10.05	10.03	10.02
HR (b/min)	74.18	12.82	74.90	12.33	73.23	12.12
HRV (ms)	4.38	1.36	4.29	1.37	4.30	1.34
HRV (ln)	1.28	0.24	1.28	0.24	1.28	0.24
HRV (ln)	4.21	0.99	4.27	0.98	4.25	0.97
HRV (ln)	2.12	0.73	2.12	0.73	2.12	0.73
HRV (ln)	36.07	36.07	36.07	36.07	36.07	36.07

HRV = natural logarithm; HRV = Spectral Power in Smoking Cigarettes & Nicotine. HRV = HRV.

Posttrial Ratings and Physiological Responses From Sessions 1 and 2 for Each Trial Type and Patch Condition (Session 2)

Table 2
Physiological Ratings and Physiological Responses From Session 1 and 2 for Each
Leaf 7-leaf and Patch Condition (Session 2)

Session and condition	Session 1 (n = 31)		Session 2		P-value (n = 30)
	M	SE	M	SE	
Craving					
Imagery-cessant	55.46	22.58	55.14	24.05	48.35
Imagery-cessant	55.46	23.76	53.28	23.05	74.38
In-vivo-cessant	53.02	19.21	53.52	23.87	69.42
In-vivo-cessant	50.08	23.57	50.81	19.89	84.42
Imagery-cessant	57.30	23.71	56.82	22.85	72.11
Imagery-cessant	60.97	14.53	57.07	12.77	70.11
In-vivo-cessant	58.47	20.18	56.28	19.58	82.14
In-vivo-cessant	62.70	14.53	60.17	15.40	83.75
Heart rate (b/min)					
Imagery-cessant	72.07	13.20	71.08	22.87	74.87
Imagery-cessant	69.07	17.58	67.14	19.70	84.87
In-vivo-cessant	71.07	11.52	69.76	18.21	70.71
In-vivo-cessant	71.76	17.73	69.07	18.26	80.76
Respiration (l/min)					
Imagery-cessant	19.88	24.81	19.68	24.30	89.01
Imagery-cessant	19.70	11.28	17.71	14.88	57.80
In-vivo-cessant	19.70	22.48	17.68	19.71	85.17
In-vivo-cessant	17.27	13.48	17.13	14.07	74.10
HRV (ms)					
Imagery-cessant	61.57	14.61	61.47	14.01	83.87
Imagery-cessant	61.57	14.61	61.47	14.01	83.87
In-vivo-cessant	61.05	13.88	61.47	14.02	81.39
In-vivo-cessant	61.72	13.11	61.61	12.49	81.76
HRV (ms/beat)					
Imagery-cessant	-0.70	8.28	-0.56	10.27	-0.70
Imagery-cessant	-0.65	8.51	-0.52	10.26	-0.66
In-vivo-cessant	-0.87	8.28	-0.28	10.20	-0.48
In-vivo-cessant	-0.87	8.28	-0.28	10.20	-0.48

HRV = heart rate variability; SE = standard error. Physiological measures are average 6-minute mean. *P < .05; **P < .01; ***P < .001; ****P < .0001.

Mean (\pm SE) craving ratings from the cue-reactivity trials of Session 2 for the nicotine ($n = 31$) and placebo ($n = 30$) patch conditions. QSU = Questionnaire on Smoking Urges.

