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Experimental model of smoking re-exposure: effects on relapse

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Abstract. This study used a short-term laboratory model of smoking cessation and relapse to prospectively examine the effects of programmed self-administered smoking re-exposure during early abstinence. Sixty-seven subjects who had quit smoking for 3 days were randomly assigned either to smoke five cigarettes in their natural environment or to remain abstinent during the exposure period. The main hypothesis, that relapse to regular smoking would be quicker and more prevalent in exposed subjects, was supported. All exposed subjects had relapsed by 2 days post-exposure while 16% of unexposed subjects remained continuously abstinent throughout the 8 day study. This behavioral effect was seen in spite of acute decreases in reported desire to smoke and increases in guilt measured just after exposure. The study supports a role for stimulus re-exposure effects in the relapse process and suggests that additional research on experimental re-exposure is warranted.

Key words: Cigarette smoking – Abstinence – Relapse – Drug stimulus exposure

Relapse to smoking is the most likely outcome of a given quit attempt. Studies designed to understand the factors affecting relapse have focused on the various behavioral, emotional and cognitive circumstances surrounding relapse. These studies have identified several factors which are associated with the return to smoking including smoking cues, negative affect/stress, alcohol and food consumption, and withdrawal symptoms (Shiffman et al. 1985; Shiffman 1986; O'Connell and Martin 1987; Baer and Lichtenstein 1988; West et al. 1989; Brandon et al. 1990). Generally, smoking relapse has been attributed to a complex interaction of interoceptive and environmental stimulus cues.

Regardless of the circumstances surrounding the relapse, recent research has shown that about 85–90% of ex-smokers who ever experience a smoking lapse eventually return to regular smoking (Marlatt et al. 1988; Brandon et al. 1990). In their recent study, Brandon et al. (1990) examined latency to lapse and found that the initial lapse episode was followed by a second cigarette within 24 h for 47% of the cases while the latency to resumption of regular smoking followed an irregular pattern. The average time between the first lapse cigarette and subsequent relapse to regular smoking was 41 days (standard deviation = 56 days) suggesting that relapse following the first lapse, while imminent, may not always be immediate and, in fact, is quite variable.

Historically, studies examining the process of relapse have not developed models for understanding the importance or significance of the initial lapse episode in which recently abstinent smokers are re-exposed to tobacco smoke. However, there is precedent for using controlled re-exposure in abstinent subjects as a relapse prevention technique (Brandon et al. 1987; Hill 1988). Because of the near certainty with which lapse becomes relapse, models for understanding the initial re-exposure to cigarette smoking may prove helpful in further understanding the mechanisms of relapse and in devising better relapse prevention techniques for cigarette smokers.

While there is little available data in humans concerning the effects of systematic drug re-exposure on relapse, this question has been addressed more thoroughly using animal models. For example, de Wit and Stewart (1981) trained rats with a reinforcement procedure to respond for intravenous cocaine. After the drug-seeking behavior was established, extinction conditions were initiated so that cocaine was no longer available, and responding eventually ceased. Noncontingent cocaine injections were then given and responding resumed even though extinction conditions remained in effect. This result suggests that brief exposure to drug stimuli can reinstate drug-seeking behaviors. This reinstatement effect following re-exposure to an addictive substance seems to generalize to a wide variety of drugs including amphetamine (Gerber and Stretch 1975; Davis and Smith

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1976) and heroin (de Wit and Stewart 1983) in animal experiments.

Bickel and Kelly (1988) review the reinstatement phenomenon in human experiments of addiction. Their review highlights the importance of stimulus control in precipitating the resumption of drug use for a variety of drugs and settings. In one experiment, Bigelow, Griffiths and Liebson (1977) demonstrated the reinstatement phenomenon with alcoholics living on a research ward. They showed that a single response-independent dose of alcohol produced reliable increases in ethanol self-administration under conditions where baseline self-administration was suppressed. Perhaps recognizing the implicit dangers of re-exposure to drug stimuli, programs such as AA or NA emphasize the importance of continuous total abstinence.

The present study extends observations concerning the role of stimulus exposure in human smokers. The purpose of the present study was to determine whether an experimentally-induced lapse during early abstinence would influence the probability or time course of subsequent relapse. Using a short-term laboratory model of smoking cessation and relapse, this study prospectively assigned recently abstinent subjects to either a smoking exposure or non-exposure condition. The main hypothesis was that relapse to regular smoking would be quicker and more prevalent in subjects exposed to the experimental smoking lapse compared to non-exposed subjects. Effects of smoking re-exposure on subjective withdrawal symptoms were also examined.

Materials and methods

Subjects

Study participants were volunteer adults recruited from the community and hospital staff via advertisements for a brief out-patient research study that involved smoking cessation. Potential subjects were excluded if they reported any chronic or debilitating disease, current drug or alcohol addiction, pregnancy, or use of any psychotropic medications. Eligible subjects reported smoking for at least 3 years and had an expired air carbon monoxide level of at least 20 ppm at the screening interview.

The group of 67 subjects who completed the study was drawn from a recruitment sample of 130 volunteers. Of this original sample, 37 dropped out after the initial interview, 18 were dropped prospectively because of an inability to quit smoking or detected relapse to smoking, and 8 completed the study but were dropped from the analyses retrospectively due to incomplete data sets or detection of outlying cotinine values (> 50 ng/ml) in saliva samples collected immediately prior to the randomization. In t-test comparisons, baseline demographic and smoking characteristics of the drop outs ($n = 63$) showed no significant differences from those of subjects who completed the study ($n = 67$). For example, percent of white (Caucasian) subjects was 49% and 58% in dropouts and completers, respectively (nonwhite subjects were primarily Black), while the percentage who claimed to be using the study to quit smoking was 75% and 79% in these two groups. Mean baseline CO values were 26.9 and 28.2 ppm in drop outs and completers, respectively. Mean baseline cigarettes per day were 29.1 and 26.8 and mean Fagerstrom scale scores were 7.7 and 7.2 in the two groups.

Procedures

Screening visit. Study intake information was obtained during an initial phone screening and a subsequent clinic screening visit. At the screening visit, subjects were informed that this was a research project and not a treatment program for smoking cessation but that if they wanted to quit smoking the project would provide brief behavioral counseling. The study protocol was discussed and eligibility criteria were assessed. At the screening interview, subjects completed a consent form which explained that the experimental procedure involved a 50% chance of having to smoke cigarettes following 3 days of abstinence. At this interview, subjects reported on a variety of demographic and smoking history variables, and completed the Fagerstrom Tolerance questionnaire (Fagerstrom 1978).

Abstinence baseline. In order to participate in the randomized portion of the study, subjects were required to remain continuously abstinent for 3 consecutive days from Monday morning through Thursday morning as verified by CO ≤ 8 ppm measured at six study contacts Monday afternoon through Thursday morning. During this phase, subjects reported to the laboratory twice daily: in the morning between 7:30–10:30 A.M. and in the afternoon between 3:30–6:30 P.M. At these and subsequent lab visits, subjects were provided with coaching and suggestions for behavioral (e.g., exercise) and cognitive (e.g., distraction) changes to help them achieve and maintain abstinence. Subjects who failed to comply with abstinence during this phase of the study were dropped from the study and not included in data analyses.

Exposure phase. Those participants who successfully maintained abstinence from Monday morning through Thursday morning (day 4 A.M.) were given their randomization assignment to one of two stimulus exposure conditions on Thursday morning after the CO check and data collection. In the *Exposed* condition participants were required to smoke five cigarettes in their natural environment between the day 4 A.M., and day 4 midday (11:30 A.M. $-$ 2:30 P.M.) clinic visit. In the *Unexposed* control condition participants were required to remain abstinent until the day 4 midday clinic visit. While subjects in the Exposed condition were not under observation when they smoked the five prescribed cigarettes, several physiological and subjective report measures to validate exposure were used (see below). Two subjects in the exposed condition did not comply with the instructions to smoke five cigarettes; one smoked none while another subject smoked two cigarettes. One subject in the Unexposed condition reported smoking a single cigarette. These subjects were included in the data analysis following an intent-to-treat model.

Post-exposure phase. One hour following completion of the day 4 midday session, participants were free to return to smoking without risking loss of payment or premature termination from the study. During this phase, subjects made five laboratory visits: one late afternoon on day 4 (day 4 P.M.), two on Friday (day 5 A.M. and P.M.) and two on Monday (day 8 A.M. and P.M.). Subjects completed smoking self-report questionnaires at home on days 4 through 7 (bedtime). Subjects were paid $95 for successful completion of the abstinence baseline and attendance at all the required sessions.

Measures

Physiological. To assess CO exposure and to verify smoking abstinence, alveolar carbon monoxide level was measured at each study contact using a MiniCo Model 1000 from a breath sample obtained following 15 s of breath holding. Saliva samples were taken for cotinine analysis at the baseline screening session, prior to random assignment on day 4 A.M., and at the last study contact on day 8 P.M. The latter was used to further validate self-reported smoking status at the study's end. Cotinine analysis was conducted at an indepen-

dent laboratory (LABSTAT, Inc., Toronto, Canada) using gas chromatography. Heart rate was obtained manually at the wrist for a 15 s interval at the baseline screening session, prior to random assignment on day 4 A.M., and after the experimental intervention at day 4 midday. Decreases in heart rate provided additional concurrent validation of abstinence (West and Schneider 1988).

Subjective report – continuous. Smoking and tobacco withdrawal measures were assessed at each study contact from day 1 through day 8. Subjects reported the number of cigarettes smoked since the last visit with even a single puff counted as one cigarette. Withdrawal was measured with a 12-item tobacco withdrawal scale. Listed were signs and symptoms of tobacco withdrawal as defined by DSM–III including craving, irritability, anxiety, anger, difficulty concentrating, restlessness, and hunger (Hughes and Hatsukami 1986; APA 1987). Also listed was urge to smoke, impatience, drowsiness, depression, and guilt. Items were individually rated on a scale from zero (none) to ten (severe).

Subjective report – post-exposure phase. At the day 4 midday clinic visit, subjects rated eight items associated with smoking re-exposure: nausea, clammy skin, dizziness, light headed, burning throat, tingling sensations, heart racing, and anxiousness. Ratings were on a ten point scale with zero indicating none, and ten indicating severe. This measure was designed as a validity check for the Exposed condition and as a measure of the subjective effects of re-exposure. At the day 4 A.M. and midday visit, subjects also rated their confidence that they would be a non-smoker on the last day of study (1 = not confident; 10 = extremely confident) and how long they felt they would be able to maintain abstinence following the day 4 midday session (< 1 day, 1–30 days, and more than 30 days).

Relapse definition. Indicators of relapse were measured at each assessment point. At the first post-exposure measurement point (day 4 P.M.), subjects who had smoked in the morning as part of the protocol were considered to have relapsed only if their CO reading was higher than it had been at midday. Thereafter, relapse was evaluated by measuring the latency to any of the following three criteria: 1) first reported puff from a cigarette, 2) first elevated CO (>8 ppm), or 3) a saliva cotinine value greater than 14 ng/ml.

Data analyses

Between group comparisons of descriptive smoking information, and behavioral and physiological effects of smoking re-exposure were analyzed with *t*-tests. ANCOVA was used to assess the acute effects of smoking re-exposure on withdrawal scores using day 4 A.M. withdrawal scores as covariates. A survival analysis using the Lee-Desu statistic was used to quantify the time course of relapse to smoking.

Results

Screening assessment

Table 1 shows demographic, smoking history and baseline physiological assessments obtained at the screening interview for the final eligible sample of 67 individuals. There were no significant group differences on any of the baseline measures.

Abstinence baseline

Table 1 also shows the mean values for CO, total withdrawal scores, and heart rate for the two groups at day 4 A.M., the assessment point immediately prior to the smoking intervention. Using *t*-tests, there were no significant differences on CO, cotinine, or HR measures. A separate *t*-test comparison for each of the withdrawal scale items at this time point showed that group means for impatience and restlessness were higher in the Exposed group (2.8 and 2.8, respectively) compared to the Unexposed group (1.1 and 1.4; $P<0.02$ and $P<0.04$, respectively). However, the total withdrawal score did not differ significantly between the groups (28.9 versus 21.8).

Table 1. Baseline subject measures and day 4 A.M. smoking measures

	Exposed group ($n=30$)		Unexposed group ($n=37$)	
Demographics				
Gender (% female)	47		54	
Race (% white)	47		68	
Education (% high school or more)	87		92	
Age (M, SD)	36.6	(8.8)	37.5	(9.3)
*Smoking history**				
Previous quit attempts	1.8	(2.3)	2.4	(2.4)
Number of years smoking	13.1	(8.8)	15.9	(11.7)
Cigarettes per day	26.5	(8.2)	27.0	(10.4)
Using study to quit (% yes)	86.7		73.0	
Fagerstrom Scale	7.4	(2.1)	7.1	(1.8)
*Baseline physiological measures**				
Carbon monoxide (ppm)	26.7	(9.7)	29.5	(9.9)
Cotinine (ng/ml)	183.2	(128)	198.8	(117)
Heart rate (bpm)	77.2	(12.3)	77.7	(10.6)
*Day 4 A.M. smoking measures**				
Carbon monoxide (ppm)	4.0	(1.4)	4.1	(1.7)
Cotinine (ng/ml)	17.1	(15.4)	11.8	(11.9)
Total withdrawal score	28.9	(23.2)	21.8	(20.1)
Heart rate (bpm)	72.7	(12.3)	72.5	(10.1)

* Mean (standard deviation)

Intervention validation analyses

The mean length of time taken to smoke the five cigarettes assigned in the Exposed condition was 3.8 h (range: 2.5–5.5 h). Similarly, for the Unexposed group, the mean length of time between the day 4 A.M. and day 4 midday sessions was 3.5 h (range: 1.8–5.5 h). Four measures obtained at the day 4 midday contact were used to validate compliance with the assignment to either smoke or remain abstinent: 1) number of cigarettes smoked, 2) expired breath carbon monoxide level, 3) heart rate, and 4) total and item scores on a smoking exposure symptom questionnaire. Subjects in the Exposed group smoked an average of 4.73 (SD = 1.05) cigarettes while those in the Unexposed group smoked zero (SD = 0.2). Consistent with this self-report, the mean carbon monoxide level for the Exposed group (18.3, SD = 6.6) at the day 4 midday visit was significantly higher than that obtained for the Unexposed group (4.0,

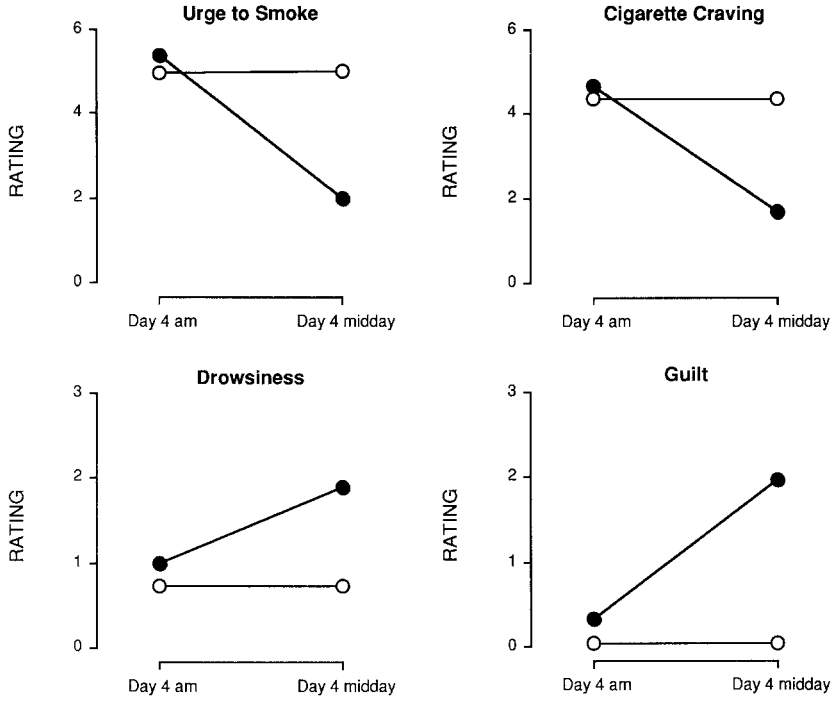

Fig. 1. Total withdrawal symptoms reported before (day 4 A.M.) and immediately after (day 4 midday) the experimental intervention. The four items shown were drawn from a 12-item scale and were the only items with significant Group main effects ($P<0.05$). Items were rated on a scale of 0 (none) to 10 (severe). (—●—) Exposed ($n=30$); (—○—) unexposed ($n=37$)

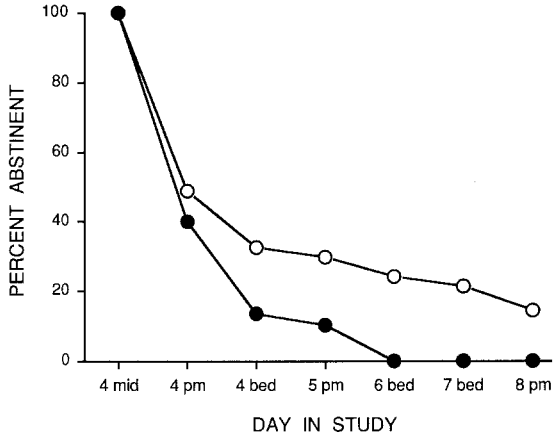

Fig. 2. Abstinence survival curve for 30 Exposed (—●—) and 37 Unexposed (—○—) subjects for the 5 day post-intervention period. For day 4 midday, day 4 P.M., day 5 P.M. and day 8 P.M. abstinence was verified by CO < 8 ppm

SD = 1.2; $P<0.0001$). Similarly, the Exposed group had a higher mean heart rate of 80.9 (SD = 14.5) post-intervention compared to 72.2 (SD = 11.0) in the Unexposed group ($P<0.007$). The mean exposure symptom total score was significantly higher for the Exposed group (18.6, SD = 15.0) post-intervention than for the Unexposed group (7.0, SD = 6.1; $P<0.0001$). Seven of the eight individual items from the smoking exposure symptom questionnaire showed statistically significant ($P<0.05$) group differences: nausea, clammy skin, dizziness, light-headed, burning throat, tingling sensation and heart racing. Only the mean score for the item "anxious" did not differ across the two groups. Thus, even though subjects in the exposed condition were not observed while smoking, results from the four validation measures offer strong support for compliance with the smoking assignment.

Post-intervention effects

Subjective effects. To compare the withdrawal effects between groups, an analysis of covariance was performed on the day 4 midday tobacco withdrawal questionnaire items using the respective day 4 A.M. withdrawal items used as covariates. There were significant group main effects for urge ($P<0.0001$), craving ($P<0.0001$), drowsiness ($P<0.01$), and guilt ($P<0.0001$). Figure 1 illustrates the smoke exposure effects on these four items. Urge to smoke and craving decreased substantially following the intervention in the Exposed condition. Subjects in the Exposed group also reported more drowsiness and increased guilt after smoking. Overall, the groups did not differ on the confidence to remain abstinent measures as a function of the intervention; both groups remained moderately confident that they would maintain abstinence throughout the study. Following the intervention, one-third of the subjects in each condition predicted that they would remain abstinent for more than 1 month.

Behavioral effects. Following the day 4 midday visit, subjects could return to smoking at will without violating the protocol. However, all subjects were encouraged to remain abstinent and offered behavioral suggestions to promote abstinence. Figure 2 shows the abstinence survival curves for the two groups. Starting with 100% abstinence directly following the day 4 midday intervention, the greatest drop in abstinence occurred by the day 4 P.M. assessment point for both groups which was approximately 3–5 h after the smoking exposure. By this

point over half of all subjects in both groups had relapsed. By day 5 A.M. (data same as shown for day 5 P.M.), 10% of the subjects in the Exposed group compared to 29.7% in the Unexposed group were abstinent. A z-test for comparison between two proportions (Bruning and Kintz 1977); was significant ($z = 1.97$, $P < 0.05$). All subjects in the Exposed group had relapsed by day 6 bedtime while six subjects in the Unexposed group, or 16%, remained continuously abstinent until the last study contact (day 8 P.M.). While statistical analysis of the survival function indicated no significant differences between the groups (Lee-Desu Statistic = 1.94, $P = 0.16$), a z-test comparing the percentage of continuously abstinent subjects by day 8 (0% versus 16%) was significant ($z = 2.31$, $P < 0.05$).

Discussion

This study used an experimental model of short-term smoking cessation, a prospective random assignment design, and objective intervention validation to examine the impact of self-administered smoking re-exposure on subjective reports and subsequent return to smoking in recently abstinent smokers. The study hypothesis was that exposed subjects would relapse faster than unexposed subjects and this hypothesis was supported. Relapse was rapid for both groups following the intervention but a 20% difference in the abstinence rate was noted between the groups by the end of the experimental intervention day (day 4 bedtime). By the second post-intervention day, all subjects in the exposed group had relapsed. In contrast, a small number of subjects in the unexposed group (16%) remained continuously abstinent throughout the 8 day experimental protocol as verified by biological abstinence criteria. Thus the study supports a role for stimulus re-exposure effects as a potential determinant of smoking relapse.

Results are also consistent with reports from animal studies that have investigated the effects of drug stimulus re-exposure. In these studies, a history of self-administering cocaine (de Wit and Stewart 1981) or heroin (de Wit and Stewart 1983) was established in animals and the drug-seeking response was then extinguished by substituting saline in the delivery pump. When the animals were then passively exposed to the drug they had been self-administering, they began responding again on the lever associated with drug deliveries. These observations suggested that exposure to the drug stimuli could precipitate a return to drug use. In the present study, some exposed subjects returned immediately to smoking after experimental re-exposure, but there was a delay before experimental subjects had relapsed to a greater extent than controls. This temporal pattern of effects is most likely due to the high dose (five cigarettes) employed in the human exposure protocol, and is consistent with animal studies in which latency to resume responding for drug was increased at higher exposure doses (de Wit and Stewart 1981, 1983).

Results are not consistent with the reports by Brandon and co-workers (Brandon et al. 1987) and Hill (1988). Both previous studies employed programmed smoking exposure in newly abstinent subjects as a maintenance treatment intervention. At follow-up, relapse was less prevalent among re-exposed subjects than among the comparison groups. A major procedural difference that could account for the discrepancy in results was that both of these clinical treatment studies used aversive rapid smoking as the intervention rather than self-administered exposure to smoking in a familiar environment as in the present study. Not only might the physiological effects of rapid versus normal smoking be different, but subject expectancies about the effects of re-exposure would have differed as well since rapid smoking was presented as a relapse prevention strategy in the previous studies.

Self-administered experimental tobacco re-exposure in the present study produced some robust subjective effects. Most notably, subjects re-exposed to smoking during abstinence reported large decreases in desire to smoke immediately after the exposure period (urge and craving measures). The magnitude and direction of this effect on reported cravings and urges may be due in part to the high dose of tobacco re-exposure employed in this study (five cigarettes), which was chosen to maximize impact on the behavioral relapse measure that was the study's central focus. However, it is possible that magnitude and direction of subjective effects on cravings and urges, as well as behavioral effects on relapse, would be related to re-exposure dose. It would be interesting to explore in future studies the effects of lower doses of tobacco re-exposure (e.g., a single puff, a single cigarette) since clinical reports of symptoms in low level smokers (e.g., Shiffman and Jarvik 1976) suggest that increases rather than decreases in craving and desire to smoke might be observed. Drowsiness, the other symptom elevated in the exposed group, is most likely a physiological effect of reduced tolerance to tobacco smoking. It is interesting to note that smoking re-exposure did not reduce subjects' self-reports of common withdrawal symptoms such as irritability, impatience, anger, hunger or restlessness. This may have been due to generally low scores observed on these items in both groups prior to the experimental manipulation. Nevertheless, since the effects of re-exposure on withdrawal symptoms may be related to the current level of withdrawal the smokers are experiencing, future studies may want to investigate the effects of re-exposure at different post-cessation time points both when withdrawal sympomts of varyng intensity are expected and after withdrawal symptoms have dissipated.

In addition to stimulus re-exposure, at least two alternate explanations of the results should be considered. The first is abstinence violation. We observed a significant elevation in endorsement of a guilt item among exposed subjects, and this occurred in spite of the fact that the subjects could have attributed their smoking resumption entirely to the experimental procedures in which they were participating. A guilt-induced return to smoking following a lapse is consistent with the abstinence violation effect described by Marlatt and Gordon (1985). A second explanation to be considered is that the instructions given to exposed subjects at the intervention

included implicit permission to return to smoking after the re-exposure without any risk of violating the study protocol. This explanation seems unlikely, however, as both groups were given identical instructions regarding smoking at the day 4 midday session.

The generality of these findings is limited to smokers who were paid for temporary abstinence and then given the choice to relapse or remain non-smokers. Under these conditions, a very rapid relapse curve was generated, with 50% of all subjects relapsed within a few hours of the choice point. It should be noted that the relapse function generated under this short-term model of abstinence and relapse is qualitatively similar to that seen in clinical smoking cessation populations, with the modal pattern being rapid early relapse (e.g. Brandon et al. 1990). Nevertheless, it will be important to replicate findings of the present study with smokers more highly motivated for cessation and under conditions of prolonged abstinence in order to examine exposure effects on more clinically relevant relapse curves.

In summary, this study has shown that recently abstinent subjects who received self-administered experimental re-exposure to tobacco smoking were more likely than unexposed subjects to relapse by the end of a short-term (5 day) protocol. This behavioral effect was seen in spite of acute decreases in reported desire to smoke and was accompanied by increases in guilt measured just after exposure. The study supports a role for stimulus re-exposure effects in the relapse process and suggests that additional research on experimental re-exposure is warranted.

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