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## Addictive Behaviors



## Exposure to smoking cues: Cardiovascular and autonomic effects

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## ARTICLE INFO

## Keywords:

Smoking  
Cue  
Craving  
Blood pressure  
Autonomic control

## ABSTRACT

Laboratory exposures to smoking cues have been shown to reliably induce self-reported cigarette cravings among smokers, a model of environmentally triggered urges to smoke that can contribute to poorer cessation success. Several studies have also demonstrated that cue exposures give rise to changes in heart rate and blood pressure. Few studies, however, have investigated possible cue effects on heart rate and blood pressure variability (HRV and BPV). Particularly intriguing in this regard are cardiac oscillations in the low (i.e., 0.04–0.15 Hz), and high (i.e., 0.15–0.50 Hz) frequency range, which are thought to reflect components of autonomic control and response to environmental challenges. A closer examination of cardiovascular reactivity may thus help characterize the autonomic response to smoking cue exposure. To that end, an experimental study was conducted in which nicotine dependent daily smokers ( $n = 98$ ) were exposed to guided imagery of neutral and smoking situations, while continuous, noninvasive, beat-to-beat cardiovascular data were collected. Consistent with previous research, the findings revealed significant increases in both systolic and diastolic blood pressure during smoking imagery, relative to neutral imagery. In addition, power spectral density analyses of heart rate and blood pressure variability revealed elevated HRV and BPV in both the low- and high-frequency ranges during the smoking imagery. The results suggest the presence of an autonomic component to smoking cue reactivity, and also raise the possibility of long-term negative cardiac consequences for smokers who ubiquitously encounter cues in their daily environments.

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## 1. Introduction

Despite significant advances in tobacco control, cigarette smoking remains a frustratingly resilient public health concern, with cessation efforts unsuccessful for large numbers of smokers (American Cancer Society, 2009). Consideration of evidence from clinical and laboratory studies points to the importance of classically conditioned reactivity to environmental smoking cues as an antecedent to smoking cessation failure (Ferguson & Shiffman, 2008). Waters et al. (2004) found that laboratory exposure to smoking cues induced significant self-reported cigarette cravings, and the magnitude of these cravings were predictive of cessation success among smokers attempting to quit using nicotine replacement therapy. Although some investigators (e.g., Perkins, 2009) have questioned the strength of the existing data in support of cue-reactivity as a predictor of smoking cessation, others (Shiffman, 2009; Tiffany & Wray, 2009) maintain that cue-reactivity may play a central role in understanding cessation. Consistent with this possibility, analog studies in animals have found that rats exposed

to classically conditioned nicotine cues exhibit increases in nicotine-seeking behavior (LeSage, Burroughs, Dufek, Keyler, & Pentel, 2004; Liu et al., 2006).

While numerous human studies have examined self-reported cigarette craving responses to smoking cue exposures (Carter & Tiffany, 1999), far less is known about autonomic responses to such cues. It has long been recognized that smoking cues can elicit physiological responses, as well as the more widely studied increases in self-reported cigarette craving (Abrams, Monti, Carey, Pinto, & Jacobus, 1988). Changes in blood pressure and heart rate during smoking cue exposures have been most commonly investigated. Most studies (Tong, Bovbjerg, & Erblich, 2007; Rickard-Figueroa & Zeichner, 1985; Taylor & Katomeri, 2006), but not all (Miranda, Rohsenow, Monti, Tidey, & Ray, 2008), have found increases in blood pressure during laboratory exposure to smoking cues. Suggesting the generalizability of this response, increases in blood pressure have also been observed with alcohol cues (Jansma, Breteler, Schippers, de Jong, & Van Der Staak, 2000) and food cues (Nederkoorn, Smulders, & Jansen, 2000). The results are more mixed when considering heart rate responses to smoking cues. In early studies for example, Abrams et al. (1988) found increases in heart rate during smoking cue exposures, whereas Niaura, Abrams, Demuth, Pinto, and Monti (1989) found decreases in heart rate. A series of studies by Tiffany and colleagues (Drobes & Tiffany, 1997; Cepeda-Benito & Tiffany, 1996; Tiffany &

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Drobes, 1990) consistently found increases in heart rate during smoking cue exposures, while four studies from other investigators found no change in heart rate associated with smoking cue exposures (Tong et al., 2007; Taylor & Katomeri, 2006; Miranda et al., 2008; Tidey, Rohsenow, Kaplan, & Swift, 2005).

Substantially less attention has been paid to possible effects of smoking cue-exposures on cardiovascular dynamics, in particular, blood pressure variability (BPV) and heart rate variability (HRV), which is increasingly recognized to provide a noninvasive means of exploring sympathetic and parasympathetic autonomic responses (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). Despite increasing appreciation of the relationships between subtle changes in autonomic control mechanisms and emotional regulation (Appelhans & Luecken, 2006; Sloan, Shapiro, Bagiella, Myers, & Gorman, 1999; Pagani et al., 1996; Malliani, Pagani, & Lombardi, 1994; Pomeranz et al., 1985), measures of HRV and BPV have been included in remarkably few studies of cue-exposure. Rajan, Murthy, Ramakrishnan, Gangadhar, and Janakiramaiah (1998) found that although exposure to alcohol cues did not affect HR, it did induce increases in both time- and frequency-domain measures of HRV in alcoholic participants. In particular, they found the standard deviation of the inter-beat intervals, as well as low frequency spectral power (<0.15 Hz) were heightened during exposure to alcohol cues. In another study of inpatient alcoholics, Jansma et al. (2000) found that alcohol cue exposures elicited significant decreases in HR, increases in BP, and increases in (0.07–0.14 Hz). Other studies have found similar results when examining effects of alcohol and food-cue exposures on HRV (Nederkoorn et al., 2000; Ingjaldsson, Thayer, & Laberg, 2003; Mun, von Eye, Bates, & Vaschillo, 2008). To our knowledge, the effects of smoking cue-exposures on BPV have not previously been investigated. The objective of the current study was therefore to investigate the possibility that exposure to smoking cues would result in changes not only in widely studied measures of heart rate and blood pressure, but also in both time- and frequency-domain measures of HRV and BPV.

## 2. Methods and materials

### 2.1. Participants

Ninety-eight non-treatment seeking nicotine-dependent adults were recruited in response to ads requesting smokers for a research study. Participants were included if they smoked on average a minimum of 10 cigarettes per day for at least 5 years and were at least 18 years old. Participants with histories of hospitalization or treatment for major mental illness (e.g., schizophrenia) were excluded to avoid ethical concerns about exposing potentially vulnerable subjects to stress. To reduce the likelihood of cravings induced by polysubstance use (Erblich, Montgomery, & Bovbjerg, 2009), participants reporting illicit substance abuse/alcohol dependence were also excluded. Other exclusions included pregnancy and current cardiovascular disease. The sample consisted of participants from a larger data set (Erblich & Bovbjerg, 2004), for whom cardiovascular data were available.

### 2.2. Procedures

When participants arrived at the study site, their eligibility was re-confirmed, and they provided written consent, in accordance with the guidelines of the Institutional Review Board at the Mount Sinai School of Medicine. All participants then smoked one cigarette prior to initiating study procedures (about 30 min prior to the cue exposures) to standardize deprivation levels and to reduce the likelihood of ceiling effects in craving. They then completed the study questionnaires. Following the questionnaires, they were connected to an Ohmeda Finapres 2300 noninvasive blood pressure monitor using an inflatable cuff placed on the middle finger of their non-dominant hand. In addition, they were connected to a Tektronix ECG monitor

with 2 Ag/AgCl electrodes placed in the right and left subclavicular regions, lateral to the sternum. Data from the blood pressure and ECG monitors were recorded at 500 Hz and digitized using a National Instruments analog-to-digital converter and sent automatically to a dedicated desktop computer for storage and analysis. After being connected to the apparatus, participants were exposed to a practice imagery script, which described a trip to the grocery store, to familiarize them with the task. They then sat quietly for a 10-minute rest period to establish a stable cardiovascular state. Following the rest period, participants were exposed to two script-guided imaginal scenes<sup>1</sup>: 1) a neutral scene, describing changing a light bulb, and 2) a smoking scene, describing lighting up after a meal. For each scene, participants were read a 60-second vignette by the experimenter, and were then given 30 s of silence to continue to imagine the scene, “drawing on their own experiences.” These scripts have been employed in previous research both in our lab (Erblich, Lerman, Self, Diaz, & Bovbjerg, 2005; Erblich & Bovbjerg, 2004) and others' (Maude-Griffin & Tiffany, 1996). The craving assessments were administered immediately before and immediately after each of the two imaginal exposures. Cardiovascular assessments were taken in real-time during each of the two exposures. To reduce concerns of carryover craving as recently reported (Sayette, Griffin, & Sayers, 2010), the smoking and neutral imagery exposure were not counterbalanced; the smoking script was always administered second. To further control for possible carryover, the exposures were separated by a 3-minute rest period, during which time participants viewed an aquatic nature video found in previous research to bring cardiovascular indices back to pre-stimulus levels (Piferi, Kline, Younger, & Lawler, 2000). After the study procedures, participants were thanked for their participation, were paid a \$50 honorarium for their time, and were provided with referrals for smoking cessation programs in the area, if desired.

### 2.3. Measures

#### 2.3.1. Background variables

This questionnaire included basic demographic information, including age, gender, race/ethnicity, income, and education levels. In addition, smoking variables, including the number of cigarettes per day, number of years having smoked, and previous cessation attempts, were assessed. Finally, participants completed the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), a brief, validated measure assessing the strength of nicotine dependence.

#### 2.3.2. Craving

A 5-item questionnaire was used to assess craving on a 0–100 scale. Consistent with recommendations in the literature (e.g., Kozlowski & Wilkinson, 1987), items with several different descriptors were used (e.g., craving, urge, want, desire). This approach, employed by our lab and others (Erblich et al., 2005; Erblich & Bovbjerg, 2004; Hutchison, Niaura, & Swift, 1999) represents an improvement over traditional single-item assessments, and is sufficiently brief to allow for rapid assessments under experimental conditions. The instrument demonstrated excellent internal consistency, surpassing 0.90 for each administration in the study. The instrument was administered before and after each of the two experimental cues (neutral, smoking).

#### 2.3.3. Imagery vividness

A 4-item face-valid questionnaire was used to assess the vividness with which participants imagined the neutral and smoking scenes. The items were: “How vivid and clear did your images seem to you?”

<sup>1</sup> We would like to thank Dr. Stephen Tiffany of the University at Buffalo, SUNY, who provided the neutral and smoking scripts.

“How real did your images seem to you?” “How much did you feel bodily sensations during the imagery?” and “How much were you able to stay focused on the imagery?” Participants responded to these items on a 0–25 scale anchored by “not at all” and “very much.” The questionnaire was administered following each of the imaginal exposures. Internal consistency was high for both administrations of the instrument ( $\alpha = 0.85$  following neutral imagery and 0.93 following the smoking imagery), and has been used in previous studies (Erblich et al., 2005; Erblich & Bovbjerg, 2004).

#### 2.4. Data analysis

Cardiovascular data were cleaned and analyzed as described elsewhere (Sloan et al., 1997). Briefly, HR and BP traces were scanned for outliers (e.g., ectopic beats, movement artifacts) using cardiovascular analysis software. When necessary, beats were interpolated using the data from the immediately preceding and following intervals. Fewer than 1% of the beats required interpolation. Mean HR, SBP and DBP were calculated for the two 90-second epochs of interest (neutral imagery, smoking imagery). In addition, following the approach of Sloan et al. (1999), measures of HRV were calculated, including the standard deviation of the R–R intervals from the ECG trace (a time-domain measure), and power spectral density (beats/min<sup>2</sup>/Hz) in the low (0.04–0.15 Hz) and high (0.15–0.50 Hz) frequency ranges. Similar calculations were made for systolic and diastolic BPV (mm Hg<sup>2</sup>/Hz). All HRV and BPV indices were log-transformed prior to analyses. Repeated measures ANOVAs were then performed for each outcome of interest, controlling for covariates when necessary (see Results section). A stepwise modified Bonferroni correction (Rom, 1990) was employed to control for Type I error associated with multiple testing.

### 3. Results

#### 3.1. Background variables

The mean age of the sample was 39.2 ( $\pm 10.2$ ) years, and 54% ( $n = 53$ ) were female. Forty-nine percent ( $n = 48$ ) of the participants reported being African-American, 33% ( $n = 32$ ) reported being Hispanic, 13% ( $n = 13$ ) reported being Caucasian, and the remaining participants reported other backgrounds. Half of the sample ( $n = 49$ ) reported household incomes of less than \$20,000 per annum, and 47% ( $n = 46$ ) reported having at least a high school diploma. Participants reported having smoked a mean ( $\pm$ SD) of 21.5 ( $\pm 11.7$ ) cigarettes per day for an average of 20.4 ( $\pm 10.8$ ) years. They also reported having made a mean of 2.7 ( $\pm 2.8$ ) attempts to quit smoking at some point in their past, and had a mean FTND score of 6.2 ( $\pm 2.2$ ).

Preliminary analyses of the effects of demographic and smoking-related variables (including imagery vividness) were conducted to identify potential covariates. To err on the side of inclusion, any variable that was predictive of outcomes at an uncorrected  $p < 0.05$  level was included as a covariate. The results revealed that race/ethnicity, but no other covariate, was significantly related to diastolic blood pressure. In particular, Caucasian participants had significantly lower DBP than minority participants ( $62.8 \pm 2.1$  vs.  $70.3 \pm 1.2$ ):  $t(96) = 2.35$ ;  $p = 0.018$ . Race/ethnicity was therefore added as a covariate to the analyses of DBP.

#### 3.2. Self-reported craving

To test for possible effects of time elapsed between the two exposures, preliminary analyses were conducted comparing pre-neutral imagery craving levels ( $52.5 \pm 3.6$ ) to pre-smoking imagery craving levels ( $55.1 \pm 4.1$ ). A paired  $t$ -test did not support any change in the trend of craving levels across time;  $t(96) = 0.79$ ;  $p = 0.43$ , suggesting that there was no carry over effect. An Imagery (Neutral vs.

Smoking)  $\times$  Condition (Pre-imagery vs. Post-imagery)  $2 \times 2$  repeated-measures ANOVA was then conducted to evaluate the effects of exposure to smoking imagery on cigarette craving. There was a highly Significant imagery  $\times$  Condition interaction  $F(1, 96) = 69.8$ ,  $p = 0.0009$ , with significant increases in craving in response to the smoking imagery, but not the neutral imagery, which actually induced a decrease in craving (see Fig. 1).

#### 3.3. Heart rate

One-way repeated measures (Neutral vs. Smoking) ANOVAs were performed for each of the cardiovascular indices (to allow for the inclusion of covariates [i.e., race/ethnicity in the DBP analyses]). Consistent with previous studies, there was a marginally lower (see Table 1) mean HR during the smoking imagery, relative to the neutral imagery;  $F(1, 97) = 8.3$ ,  $p = 0.043$ . This effect however, was not significant after correcting for Type I error. As indicated above, to assess heart rate variability, both time-domain and frequency-domain measures were employed. The time-domain measure calculated here was the log-transformed standard deviation of the R–R intervals during each of the imaginal exposures. Findings indicated that participants' time-domain heart rate variability was marginally greater during the smoking imagery than the neutral imagery;  $F(1, 97) = 9.1$ ,  $p = 0.03$ ; not significant after Type I error correction. Finally, the frequency-domain index of HRV calculated here was the log-transformed power spectral density (PSD) of R–R interval variability (beats/min<sup>2</sup>/Hz) in the low (0.04–0.15 Hz) and high (0.15–0.50) frequency ranges. Findings indicated that both low- and high-frequency PSD was significantly higher during smoking imagery than during neutral imagery;  $F(1, 97) = 18.6$ ,  $p = 0.0009$  and  $F(1, 97) = 10.8$ ,  $p = 0.0014$ , respectively.

#### 3.4. Blood pressure

As with HR, repeated measures (Neutral, Smoking) ANOVAs were performed to assess effects of exposure to smoking imagery on systolic (SBP) and diastolic (DBP) blood pressure parameters. As described above, the analyses of DBP included race/ethnicity as a covariate. We found (see Table 2) that both SBP and DBP were higher during smoking imagery than during neutral imagery:  $F(1, 97) = 24.5$ ,  $p = 0.0009$ , and DBP,  $F(1, 96) = 19.9$ ,  $p = 0.0009$ . As with HR, we calculated both time- and frequency-domain indices of BPV for both systolic and diastolic blood pressure. As above, the time-domain measure of BPV was the log-transformed standard deviation of beat-to-beat changes in BP during each of the imagery exposures. Unlike our findings with respect to time-domain HRV, differences between smoking and neutral imagery in time-domain BPV did not reach statistical significance for either SBP;  $F(1, 97) = 2.5$ ,  $p = 0.68$ , or DBP;  $F(1, 96) = 6.2$ ,  $p = 0.13$ . When examining the frequency-domain

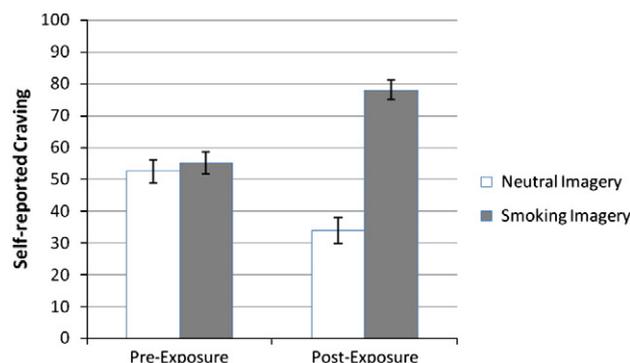


Fig. 1. Self-reported craving (0–100) before and after exposure to neutral and smoking imagery (Significant imagery  $\times$  Time interaction;  $p < 0.0009$ ).

**Table 1**  
Mean ( $\pm$  standard error) heart rate parameters during neutral and smoking imagery.

	Neutral imagery	Smoking imagery	F-value	p-value
Heart rate <sup>a</sup>	73.9 ( $\pm$ 0.9)	73.0 ( $\pm$ 0.9)	8.3	0.043*
Time-domain HRV <sup>b</sup>	3.69 ( $\pm$ 0.07)	3.83 ( $\pm$ 0.07)	9.1	0.03*
Frequency-domain LF HRV <sup>c</sup>	5.27 ( $\pm$ 0.18)	5.95 ( $\pm$ 0.16)	18.6	<b>0.0009</b>
Frequency-domain HF HRV <sup>d</sup>	5.80 ( $\pm$ 0.17)	6.13 ( $\pm$ 0.17)	10.8	<b>0.0014</b>

Values in bold represent statistical significance after correcting for Type I error.

\* Not significant at the 0.05 level after correcting for Type I error.

<sup>a</sup> Beats/minute.

<sup>b</sup> log standard deviation of R–R intervals.

<sup>c</sup> log PSD (beats/min<sup>2</sup>/Hz) in 0.04–0.15 Hz (LF) range.

<sup>d</sup> log PSD (beats/min<sup>2</sup>/Hz) in 0.15–0.50 Hz (HF) range.

indices of BPV (low- and high-frequency PSD), however, we did observe significant differences for both SBP;  $F(1, 97) = 12.6$ ,  $p < 0.005$  (low frequency),  $F(1, 97) = 23.9$ ,  $p < 0.0001$  (high-frequency), and DBP;  $F(1, 96) = 20.0$ ,  $p = 0.0009$  (low frequency),  $F(1, 97) = 7.0$ ,  $p = 0.0095$  (high-frequency).

### 3.5. Correlation between self-reported cravings and cardiovascular indices

In addition to the primary analyses, we examined the relationships between self-reported cigarette cravings and each of the cardiovascular indices. Pearson partial correlation-coefficients were calculated between self-reported craving and each cardiovascular index during smoking imagery, controlling for craving and the cardiovascular index during neutral imagery. Findings revealed no significant correlations between craving and any of the cardiovascular indices ( $r$ s ranged from  $-0.03$  to  $0.13$ ; all  $p$ s  $> 0.15$ ).

## 4. Discussion

The objective of this study was to examine the effect of exposure to imaginal smoking cues on self-reported cigarette craving and cardiovascular indices. Consistent with the study hypotheses, we found that smoking imagery induced increases in frequency-domain measures of both heart rate and blood pressure variability. There were no significant effects, however, of smoking imagery on time-domain indices of cardiovascular variability. Cardiovascular measures were not found to be related to self-reported cravings. The lack of significant correlations between self-reported craving and cardiovascular indices raises the possibility that the two effects may be independently

**Table 2**  
Mean ( $\pm$  standard error) blood pressure parameters during neutral and smoking imagery.

	Neutral imagery	Smoking imagery	F-value	p-value
Systolic blood pressure				
SBP <sup>a</sup>	116.7 ( $\pm$ 1.9)	124.9 ( $\pm$ 2.2)	24.5	<b>0.0009</b>
Time-domain BPV <sup>b</sup>	1.56 ( $\pm$ 0.05)	1.64 ( $\pm$ 0.04)	2.5	0.68
Frequency-domain LF BPV <sup>c</sup>	1.13 ( $\pm$ 0.13)	1.63 ( $\pm$ 0.11)	12.6	<b>0.005</b>
Frequency-domain HF BPV <sup>d</sup>	$-0.87$ ( $\pm$ 0.11)	$-0.36$ ( $\pm$ 0.10)	23.9	<b>0.0001</b>
Diastolic blood pressure				
DBP <sup>a</sup>	66.8 ( $\pm$ 1.2)	71.9 ( $\pm$ 1.2)	19.9	<b>0.0009</b>
Time-domain BPV <sup>b</sup>	0.97 ( $\pm$ 0.05)	1.10 ( $\pm$ 0.04)	6.2	0.13
Frequency-domain LF BPV <sup>c</sup>	0.12 ( $\pm$ 0.13)	0.75 ( $\pm$ 0.11)	20.0	<b>0.0009</b>
Frequency-domain HF BPV <sup>d</sup>	0.84 ( $\pm$ 0.08)	1.06 ( $\pm$ 0.09)	7.0	<b>0.0095</b>

<sup>a</sup> mm Hg.

<sup>b</sup> log standard deviation of beat-to-beat BP.

<sup>c</sup> log PSD (mm Hg<sup>2</sup>/Hz) in 0.04–0.15 Hz (LF) range.

<sup>d</sup> log PSD (mm Hg<sup>2</sup>/Hz) in 0.15–0.50 Hz (HF) range.

important in understanding cue-reactivity and its potential association with smoking cessation failure.

These results are generally in concert with previous work in the cue-reactivity literature. Cue reactivity studies have generally found robust increases in self-reported craving, and consistent, but smaller differences in blood pressure as a function of exposure to smoking cues (Carter & Tiffany, 1999). In terms of self-reported craving, our results are consistent with other labs (e.g., Conklin & Tiffany, 2001), in which smoking cues elicited increases in craving, whereas neutral cues elicited decreases, possibly due to momentary distraction from smoking urges. Our relatively robust SBP and DBP effects (8.2 and 5.1 mm Hg increases in SBP and DBP, respectively) may be due in part to our more sensitive measurement of BP, which involved beat-to-beat assessments throughout each of the cue-exposures. Alternatively, it is possible that imaginal exposures provide a more engrossing and contextually rich experience (Tiffany, 1990), yielding greater effects than are typically reported in studies of in vivo cue exposures. Our finding of marginally reduced HR during smoking imagery is consistent with some (e.g., Niaura et al., 1989), but not all (e.g., Drobes & Tiffany, 1997) previous work in this area, and adds to a conflicted literature on the effects of cue-exposures on HR.

To our knowledge, this is the first study to examine the effects of exposure to smoking cues on HRV and BPV, although similar studies of responses to alcohol cues have obtained analogous results (e.g., Jansma et al., 2000; Rajan et al., 1998). The changes in heart rate and blood pressure variability we observed in response to smoking imagery raises the intriguing possibility that exposure to smoking stimuli has an aversive or stressful component. Indeed, frequency-domain HRV and BPV are thought to reflect homeostatic responses to environmental challenges by the autonomic nervous system (Appel, Berger, Saul, Smith, & Cohen, 1989; Malliani et al., 1994; McEnery et al., 2008); perturbations due to smoking cue exposures may thus reflect autonomic regulation of the aversiveness associated with coping with the induced cravings.

Considered in conjunction with the increased cravings for a cigarette, the cardiovascular effects observed in the present study suggest both an appetitive motivational component and a stress component to the cue reactivity phenomenon (Sayette et al., 2003). It is tempting to speculate that cue-exposure-based smoking cessation interventions geared purely toward extinction may have had limited success (Drummond, 2000) in part because such treatment modalities do not adequately address the aversive/stressful nature of exposure to smoking cues in the context of a quit attempt. Future research should consider assessing self-reported stress levels following cue exposures.

Another possible implication of the autonomic cardiovascular effects of cue-exposure is the potential for negative health effects that are associated with increased BPV. Although there is little information about negative effects associated with elevated HRV, some have suggested that the shearing forces within blood vessels associated with increased BPV may contribute to the development of thromboses, occlusion of the coronary artery, and other manifestations of cardiovascular disease (Sloan et al., 1999; Fuster, Badimon, Badimon, & Chesebro, 1992b; Fuster, Badimon, Badimon, & Chesebro, 1992a; Lee, Grodzinsky, Frank, Kamm, & Schoen, 1991). The current findings of increased BPV during exposure to smoking imagery may thus raise the intriguing possibility that smokers, who ubiquitously encounter smoking cues in their environments, may be at elevated risk for cardiovascular disease, not only because of their actual smoking behavior, but also because of what may prove to be chronic elevations in BPV associated with real-world cue-exposures. If this speculation were to be supported in future studies with ambulatory monitoring, it could be argued that elevated cue-reactivity may be important not only as a predictor of smoking cessation failure, but also as a risk factor for cardiovascular disease.

The current study has limitations. First, the study recruited smokers and assessed them at a single time-point in a controlled laboratory

setting. Although internal validity may have been high, it is possible that reactivity would be different in real-world naturalistic circumstances. In addition, the study did not counterbalance the neutral and smoking exposures. We, therefore, cannot formally rule out the possibility that effects were due simply to passage of time. This possibility is unlikely, however, because during the 3-minute inter-stimulus interval, participants viewed a nature video that has been shown empirically to return cardiovascular indices back to a resting state (Piferi et al., 2000). In light of the data demonstrating a high risk of carryover effects for self-reported cigarette cravings when administering smoking cues before neutral cues (Hutchison et al., 1999; Heishman, Saha, & Singleton, 2004), it would have been difficult to interpret craving results had we counterbalanced the exposures.

Future research in this area might include a prospective component to permit assessment of smoking- (and perhaps cardiovascular health) related outcomes. Finally, naturalistic assessments of cardiovascular variables, including ambulatory monitoring during daily life, would help elucidate the applicability of the current findings to real-world cues in smokers' natural environments.

#### Role of Funding Sources

Funding for this study was provided by NIH Grants #K22CA124800, #R21CA118703, and #UL1RR029887. NIH had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

#### Contributors

Drs. Erblisch and Bovbjerg designed the study and wrote the protocol. Dr. Sloan consulted on cardiovascular assessment issues in the study. All authors contributed to and have approved the final manuscript.

#### Conflict of Interest

All authors declare that they have no conflicts of interest.

#### Acknowledgment

This project was supported by the research grants #K22CA124800, #R21CA118703, and #UL1RR029887, from the National Institutes of Health.

#### References

- Abrams, D. B., Monti, P. M., Carey, K. B., Pinto, R. P., & Jacobus, S. I. (1988). Reactivity to smoking cues and relapse: Two studies of discriminant validity. *Behaviour Research and Therapy*, 26, 225–233.
- Acharya, U. R., Joseph, K. P., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: A review. *Medical & Biological Engineering & Computing*, 44, 1031–1051.
- American Cancer Society (2009). *Cancer facts and figures 2009*. Atlanta: American Cancer Society.
- Appel, M. L., Berger, R. D., Saul, J. P., Smith, J. M., & Cohen, R. J. (1989). Beat to beat variability in cardiovascular variables: Noise or music? *Journal of the American College of Cardiology*, 14, 1139–1148.
- Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of General Psychology*, 10, 229–240.
- Carter, B. L., & Tiffany, S. T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction*, 94, 327–340.
- Cepeda-Benito, A., & Tiffany, S. T. (1996). The use of a dual-task procedure for the assessment of cognitive effort associated with cigarette craving. *Psychopharmacology (Berl)*, 127, 155–163.
- Conklin, C. A., & Tiffany, S. T. (2001). The impact of imagining personalized versus standardized urge scenarios on cigarette craving and autonomic reactivity. *Experimental and Clinical Psychopharmacology*, 9, 399–408.
- Drobes, D. J., & Tiffany, S. T. (1997). Induction of smoking urge through imaginal and in vivo procedures: Physiological and self-report manifestations. *Journal of Abnormal Psychology*, 106, 15–25.
- Drummond, D. C. (2000). What does cue-reactivity have to offer clinical research? *Addiction*, 95(Suppl 2), S129–S144.
- Erblich, J., & Bovbjerg, D. H. (2004). In vivo versus imaginal smoking cue exposures: Is seeing believing? *Experimental and Clinical Psychopharmacology*, 12, 208–215.
- Erblich, J., Lerman, C., Self, D. W., Diaz, G. A., & Bovbjerg, D. H. (2005). Effects of dopamine D2 receptor (DRD2) and transporter (SLC6A3) polymorphisms on smoking cue-induced cigarette craving among African-American smokers. *Molecular Psychiatry*, 10, 407–414.
- Erblich, J., Montgomery, G. H., & Bovbjerg, D. H. (2009). Script-guided imagery of social drinking induces both alcohol and cigarette craving in a sample of nicotine-dependent smokers. *Addictive Behaviors*, 34, 164–170.
- Ferguson, S. G., & Shiffman, S. (2008). The relevance and treatment of cue-induced cravings in tobacco dependence. *Journal of Substance Abuse Treatment*, 36, 235–243.
- Fuster, V., Badimon, L., Badimon, J. J., & Chesebro, J. H. (1992a). The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *The New England Journal of Medicine*, 326, 242–250.
- Fuster, V., Badimon, L., Badimon, J. J., & Chesebro, J. H. (1992b). The pathogenesis of coronary artery disease and the acute coronary syndromes (2). *The New England Journal of Medicine*, 326, 310–318.
- Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction*, 86, 1119–1127.
- Heishman, S. J., Saha, S., & Singleton, E. G. (2004). Imagery-induced tobacco craving: Duration and lack of assessment reactivity bias. *Psychology of Addictive Behaviors*, 18, 284–288.
- Hutchison, K. E., Niaura, R., & Swift, R. (1999). Smoking cues decrease prepulse inhibition of the startle response and increase subjective craving in humans. *Experimental and Clinical Psychopharmacology*, 7, 250–256.
- Ingjaldsson, J. T., Thayer, J. F., & Laberg, J. C. (2003). Craving for alcohol and pre-attentive processing of alcohol stimuli. *International Journal of Psychophysiology*, 49, 29–39.
- Jansma, A., Bretelet, M. H., Schippers, G. M., de Jong, C. A., & Van Der Staak, C. F. (2000). No effect of negative mood on the alcohol cue reactivity of in-patient alcoholics. *Addictive Behaviors*, 25, 619–624.
- Kozlowski, L. T., & Wilkinson, D. A. (1987). Use and misuse of the concept of craving by alcohol, tobacco, and drug researchers. *British Journal of Addiction*, 82, 31–45.
- Lee, R. T., Grodzinsky, A. J., Frank, E. H., Kamm, R. D., & Schoen, F. J. (1991). Structure-dependent dynamic mechanical behavior of fibrous caps from human atherosclerotic plaques. *Circulation*, 83, 1764–1770.
- LeSage, M. G., Burroughs, D., Dufek, M., Keyler, D. E., & Pentel, P. R. (2004). Reinstatement of nicotine self-administration in rats by presentation of nicotine-paired stimuli, but not nicotine priming. *Pharmacology, Biochemistry and Behavior*, 79, 507–513.
- Liu, X., Caggiula, A. R., Yee, S. K., Nobuta, H., Poland, R. E., & Pechnick, R. N. (2006). Reinstatement of nicotine-seeking behavior by drug-associated stimuli after extinction in rats. *Psychopharmacology (Berl)*, 184, 417–425.
- Malliani, A., Pagani, M., & Lombardi, F. (1994). Physiology and clinical implications of variability of cardiovascular parameters with focus on heart rate and blood pressure. *The American Journal of Cardiology*, 73, 3C–9C.
- Maude-Griffin, P., & Tiffany, S. T. (1996). Production of smoking urges through imagery: The impact of affect and smoking abstinence. *Experimental and Clinical Psychopharmacology*, 4, 198–208.
- McEniery, C. M., Yasmin, McDonnell, B., Munnery, M., Wallace, S. M., Rowe, C. V., et al. (2008). Central pressure: Variability and impact of cardiovascular risk factors: The Anglo-Cardiff Collaborative Trial II. *Hypertension*, 51, 1476–1482.
- Miranda, R., Jr., Rohsenow, D. J., Monti, P. M., Tidey, J., & Ray, L. (2008). Effects of repeated days of smoking cue exposure on urge to smoke and physiological reactivity. *Addictive Behaviors*, 33, 347–353.
- Mun, E. Y., von Eye, A., Bates, M. E., & Vaschillo, E. G. (2008). Finding groups using model-based cluster analysis: Heterogeneous emotional self-regulatory processes and heavy alcohol use risk. *Developmental Psychology*, 44, 481–495.
- Nederkoorn, C., Smulders, F. T., & Jansen, A. (2000). Cephalic phase responses, craving and food intake in normal subjects. *Appetite*, 35, 45–55.
- Niaura, R., Abrams, D., Demuth, B., Pinto, R., & Monti, P. (1989). Responses to smoking-related stimuli and early relapse to smoking. *Addictive Behaviors*, 14, 419–428.
- Pagani, M., Lucini, D., Rimoldi, O., Furlan, R., Piazza, S., Porta, A., et al. (1996). Low and high frequency components of blood pressure variability. *Annals of the New York Academy of Sciences*, 783, 10–23.
- Perkins, K. A. (2009). Does smoking cue-induced craving tell us anything important about nicotine dependence? *Addiction*, 104, 1610–1616.
- Piferi, R. L., Kline, K. A., Younger, J., & Lawler, K. A. (2000). An alternative approach for achieving cardiovascular baseline: Viewing an aquatic video. *International Journal of Psychophysiology*, 37, 207–217.
- Pomeranz, B., Macaulay, R. J., Caudill, M. A., Kutz, I., Adam, D., Gordon, D., et al. (1985). Assessment of autonomic function in humans by heart rate spectral analysis. *The American Journal of Physiology*, 248, H151–H153.
- Rajan, I., Murthy, P. J., Ramakrishnan, A. G., Gangadhar, B. N., & Janakiramaiah, N. (1998). Heart rate variability as an index of cue reactivity in alcoholics. *Biological Psychiatry*, 43, 544–546.
- Rickard-Figueroa, K., & Zeichner, A. (1985). Assessment of smoking urge and its concomitants under an environmental smoking cue manipulation. *Addictive Behaviors*, 10, 249–256.
- Rom, D. (1990). A sequentially rejective test procedure based on a modified Bonferroni inequality. *Biometrika*, 77, 663–665.
- Sayette, M. A., Griffin, K. M., & Sayers, W. M. (2010). Counterbalancing in smoking cue research: A critical analysis. *Nicotine & Tobacco Research*, 12, 1068–1079.
- Sayette, M. A., Wertz, J. M., Martin, C. S., Cohn, J. F., Perrott, M. A., & Hobel, J. (2003). Effects of smoking opportunity on cue-elicited urge: A facial coding analysis. *Experimental and Clinical Psychopharmacology*, 11, 218–227.
- Shiffman, S. (2009). Responses to smoking cues are relevant to smoking and relapse. *Addiction*, 104, 1617–1618.
- Sloan, R. P., Demeersman, R. E., Shapiro, P. A., Bagiella, E., Chernikova, D., Kuhl, J. P., et al. (1997). Blood pressure variability responses to tilt are buffered by cardiac autonomic control. *The American Journal of Physiology*, 273, H1427–H1431.
- Sloan, R. P., Shapiro, P. A., Bagiella, E., Myers, M. M., & Gorman, J. M. (1999). Cardiac autonomic control buffers blood pressure variability responses to challenge: A psychophysiological model of coronary artery disease. *Psychosomatic Medicine*, 61, 58–68.
- Taylor, A., & Katomeri, M. (2006). Effects of a brisk walk on blood pressure responses to the Stroop, a speech task and a smoking cue among temporarily abstinent smokers. *Psychopharmacology (Berl)*, 184, 247–253.

- Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., & Swift, R. M. (2005). Subjective and physiological responses to smoking cues in smokers with schizophrenia. *Nicotine & Tobacco Research*, 7, 421–429.
- Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior — Role of automatic and nonautomatic processes. *Psychological Review*, 97, 147–168.
- Tiffany, S. T., & Drobes, D. J. (1990). Imagery and smoking urges: The manipulation of affective content. *Addictive Behaviors*, 15, 531–539.
- Tiffany, S. T., & Wray, J. (2009). The continuing conundrum of craving. *Addiction*, 104, 1618–1619.
- Tong, C., Bovbjerg, D. H., & Erblich, J. (2007). Smoking-related videos for use in cue-induced craving paradigms. *Addictive Behaviors*, 32, 3034–3044.
- Waters, A. J., Shiffman, S., Sayette, M. A., Paty, J. A., Gwaltney, C. J., & Balabanis, M. H. (2004). Cue-provoked craving and nicotine replacement therapy in smoking cessation. *Journal of Consulting and Clinical Psychology*, 72, 1136–1143.