Original investigation

Sex Differences in Subjective and Behavioral Responses to Stressful and Smoking Cues Presented in the Natural Environment of Smokers

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Abstract

Introduction: Some evidence suggests that female smokers may show more context-dependent smoking and that males may show more stereotyped smoking (regardless of stress or cue exposure). The goal of this study was to characterize sex differences in response to stressful and smoking cues ecologically presented in daily life and variability in day-to-day smoking behavior.

Methods: Adult smokers ($N = 177$) provided ratings of mood and cigarette craving before and after stress and smoking cues were presented four times daily for 14 days via a mobile device. Linear mixed models tested whether (1) female smokers exhibited greater reactivity to stressful cues than male smokers; (2) pre-cue negative affect increased reactivity to smoking cues more in female smokers than male smokers; (3) across both sexes, greater reactivity to stressful and smoking cues correlated with greater quantity of smoking within a day; and (4) female smokers exhibited greater variability in cigarettes per day (CPD) relative to males.

Results: Relative to male smokers, female smokers reported greater negative affect, stress, and craving in response to stressful cues, but not smoking cues, after accounting for time since last cigarette and pre-cue responding. No sex differences in CPD or variability in CPD were detected. Days with higher subjective reactivity to cues were not associated with increased smoking, in either males or females.

Conclusions: Sex differences were observed in response to stress but not smoking cues in the natural environment of regular cigarette smokers. Further research is necessary to evaluate whether

stress reactivity in female smokers is associated with reduced latency to smoke following stress exposure in daily life.

Implications: This study provides naturalistic evidence that female smokers may not be more reactive to smoking cues than males, but experience heightened stress and craving following stress exposure. There was no evidence to support the hypothesis that amount smoked per day varied more for females, relative to males, as a result of more context-driven smoking for females.

Introduction

Despite an overall decline in cigarette smoking, approximately 15% of adults in the United States continue to smoke daily or almost daily.¹ Males smoke at higher rates than females.¹ However, this gap is narrowing and smoking rates among males have declined more rapidly.¹ Female smokers have greater difficulty achieving and maintaining smoking abstinence.²⁻⁴ This suggests that different processes may sustain smoking for males and females, and that unique treatments may be required to address sex-specific processes.

Some evidence suggests that smoking among females is more context dependent than driven by nicotine's pharmacological properties,⁵ suggesting that females may be more likely to smoke in particular contexts, such as when exposed to stressful situations or smoking cues. Reduction of negative affect (eg, anger, fear, sadness), stress, and other aversive states is a commonly reported reason for using substances,^{6,7} but it may be a more salient motivator for females⁸ (except see Allen et al.⁹). Females are more susceptible to withdrawal-related increases in negative affect and experience greater tension relief when smoking a cigarette following abstinence or withdrawal.¹⁰⁻¹² Sex differences in cessation outcomes may be driven by heightened stress reactivity and stress-related smoking among females.¹³⁻¹⁵

In laboratory studies, female smokers report greater stress and craving following exposure to stressful cues.^{13,14} In addition, females are quicker to smoke a cigarette following a subtle, negative mood induction.¹⁶ Sex differences in response to smoking cues (eg, image of a person holding a cigarette) have been more mixed.¹⁷⁻²⁰ Thus, laboratory cue reactivity research supports the notion that female smoking may be largely influenced by negative affect and stress, but not smoking cues. However, it is possible that heightened negative affect or stress among females increases the salience of smoking-related cues,^{7,21} prompting smoking to relieve negative affect. Most cue reactivity research is conducted in a laboratory setting under controlled circumstances. These methods, although tightly controlled, may not easily translate to exposure to cues under real-life conditions. One study examined the association between exposure to everyday cues (eg, being with someone who is smoking, negative affect) using ecological momentary assessment (EMA)²² and found negligible sex differences,²³ with the exception of males being more likely to smoke in response to the presence of other smokers. Consistent with other EMA studies examining mood and smoking,²⁴⁻²⁶ this study did not find that females were more likely than males to smoke in response to negative affect.²³ In fact, some EMA studies show that, compared to females' smoking, males' smoking is more strongly associated with negative affect.^{24,26}

Controlled laboratory and EMA studies have thus produced conflicting results. A potential explanation for this discrepancy is that females are more stress reactive than males when stress exposure, recent abstinence, and environmental context are standardized across the sexes in the laboratory. However, in real-world settings, females and males may be differentially exposed to contexts that prevent

or facilitate stress and cue reactivity. For example, given females' increased susceptibility to withdrawal-related negative affect,^{10,12} they may be more likely to smoke to preemptively avoid "predictable" negative affect, making it difficult to observe an association between negative affect and smoking in daily life.⁷ EMA studies are naturalistic and do not systematically expose smokers to relevant cues, so they offer qualified insight into the relationship between ambient mood and reactivity to stressful and smoking cues. The literature is lacking in studies that experimentally manipulate type and timing of cue exposure in ecological settings (ie, the real-world) and evaluate sex-specific response to these cues.

This study design merges standardized administration of stressful and smoking cue exposure (consistent with laboratory-based studies) with a repeated sampling schedule in naturalistic settings (consistent with EMA). Such methods, known as Cue Reactivity Ecological Momentary Assessment (CREMA),^{15,27,28} typically present stress-related and smoking cues via a mobile device multiple times per day for extended periods. Because these cues are unpredictable in timing and content, smokers cannot smoke in anticipation. Using CREMA in an interim subsample of participants from the current dataset, we have previously shown that female smokers reported greater stress, negative affect, and craving in response to stressful cues than male smokers, but these sex differences were not evident in response to smoking cues.¹⁵ It remains unclear whether these associations would hold after accounting for ambient mood, craving, and recent smoking. We now expand upon that study by accounting for effects of pre-cue affective and craving states and recent smoking in a larger sample of male and female adult smokers. Inclusion of the methodological control is important, given that reactions to cues may be dependent on factors irrespective of the cue (eg, withdrawal, craving, and baseline levels of negative affect or stress).

We also expand upon this prior publication¹⁵ by examining sex differences in smoking behavior in participants' natural environments. Prior research suggests that male smokers endorse more "continuity" in their smoking than female smokers, suggesting that smoking may occur on regular intervals regardless of environmental cues⁸ (cf Ferguson et al.²³). Given that female smokers may show more stress-specific patterns in smoking than male smokers, female smokers may exhibit greater variability across days in number of cigarettes smoked (ie, cigarettes per day [CPD]). Finally, to better understand how increased stress and/or smoking cue reactivity might affect smoking behavior, we examined whether days with increased cue reactivity (ie, higher craving in response to cues) were associated with an increase in the number of reported cigarettes smoked on that same day.

In sum, we hypothesized that (1) females would report greater stress, negative affect, and craving following the presentation of a stressful cue (consistent with Wray et al.¹⁵) after accounting for pre-cue affective and craving states; (2) females (to a greater extent than males) would show increased reactivity to smoking cues when pre-cue stress was elevated; (3) both males and females would report an

increased number of cigarettes on days that they were more reactive to stressful or smoking cues; and (4) females would show greater variability in number of cigarettes smoked per day.

Method

The current procedures were part of a larger parent study examining sex and hormone influences on cue reactivity. Procedures were approved by the local institutional review board prior to study onset. Eligible participants attended an in-person laboratory visit at which they completed baseline questionnaires and received instructions from a research assistant on how to use the CREMA app.²⁹ Participants were provided with a loaner iPhone with the CREMA app installed or downloaded it on their own device. They carried the iPhone for 14 days and completed CREMA sessions four times per day. CREMA procedures for this study have been described in previous publications.^{15,30} The 2-week monitoring period was followed by an in-person laboratory visit on day 15, when participants returned study equipment and completed additional questionnaires.

Participants

Non-treatment-seeking smokers ($N = 178$) aged 18–45 years were recruited from the community. Applicants were eligible if they provided a carbon monoxide sample ≥ 5 parts per million (ppm) and reported smoking at least five CPD on average in the 6 months prior to screening. Applicants were excluded for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* substance dependence (other than nicotine or caffeine dependence), use of nicotine products other than cigarettes (eg, chewing tobacco, e-cigarettes), unstable medical conditions as assessed by a medical clinician, unstable psychiatric disorders as assessed via the Mini-International Neuropsychiatric Interview,³¹ and (if female) use of hormonal birth control or hormone replacement medication, irregular menstrual cycles, or if pregnant or breastfeeding. Females could begin the study at any phase of their menstrual cycle.

Procedures and Measures

Retrospective Smoking Measures

CPD was assessed via the timeline follow-back³² for the 30 days leading up to the 2-week monitoring period. Timeline follow-back data were also collected at the final visit (day 15) to cover all days in the study. Nicotine dependence was assessed via the Fagerström Test for Nicotine Dependence (FTND).³³

Cue Reactivity Ecological Momentary Assessment

Stress-related, smoking, or neutral images were presented in each CREMA session, four times per day (randomly administered during four consecutive 3-hour blocks based on the participants' preferred schedule).^{15,27,28} Stress-related images were drawn from the International Affective Picture System.³⁴ Smoking and neutral images were obtained from prior cue-reactivity studies^{27,28} as described previously.^{15,30} Each CREMA session included the presentation of two cues (two trials) that were randomly assigned (eight total cues presented on a study day) and no cues were repeated over the course of the study. Cue types on any given day included three stress images, three smoking images, and two neutral images. The ordering of cue presentation was random on each day and any combination of cue types could be presented. Each CREMA session involved a baseline (pre-cue) assessment of negative affect (ie, sad, worried, angry,

frustrated each on a 5-point Likert scale), craving (4-item Craving Questionnaire³⁵), and time since last cigarette (in minutes). Then, the first cue (trial 1) was shown for 10 seconds and craving and mood were reassessed. Finally, a second cue (trial 2) was shown for 10 seconds and craving and mood were again reassessed. After each cue, participants were asked to confirm that they were able to see the cue. Participants were asked to refrain from smoking during CREMA sessions. The maximum possible number of sessions per person was 56 (4 sessions per day for 14 days) for a total of 112 possible cue trials (42 stress, 42 smoking, and 28 neutral). In addition to CREMA sessions, participants completed a daily morning report that included number of cigarettes smoked in the past 24 hours.

Data Analytic Procedure

Study data were automatically uploaded from mobile devices to the REDCap (Research Electronic Data Capture) platform.³⁶ To examine whether sex was associated with outcomes (ie, post-cue stress, post-cue negative affect, post-cue craving, CPD; Hypotheses 1–3), we conducted linear mixed effects models (LMMs). We used a Gaussian distribution because residual diagnostics indicated the assumptions of normality and homoscedasticity were satisfactory. LMMs were chosen as they are robust to unequal intervals between observations, missing data (when missing at random), and varying numbers of observations across participants.³⁷ Therefore, missing data were not imputed. To accommodate the nested structure of the design, a multilevel approach was used through appropriately specifying random effects in the model. As recommended by Snijders and Bosker,³⁸ nonsignificant interactions ($p < .05$) were dropped from the model. Residual maximum likelihood³⁹ was used for variance estimation.

For Hypotheses 1 and 2, cue-level (level 1) predictors included order of cue administration (first vs. second cue) and cue type (ie, stressful = 1 vs. neutral = 0); session-level (level 2) predictors included baseline stress, negative affect, and/or craving (centered on the individual's mean baseline ratings so that a positive value represents a greater than average within-person response), and time since last cigarette in minutes; a day (level 3) variable was included in the model as a covariate. Lastly, person-level (level 4) variables included sex and the person's average pre-cue negative affect, stress, or craving (depending on the model) centered on the average pre-cue ratings for all smokers, with positive values representing an average response greater than most smokers in the sample. To account for the nesting and within-subject variability, a random intercept was specified in the model at the session and day levels. At the person level, a random intercept and random slopes for pre-cue affective and craving states were modeled and unspecified covariance structure was used. Theoretically relevant random slopes were added to the models one at a time and chi-square tests using deviance were performed. If significant, the random slope was retained. Relevant interactions were examined in all models.

For models predicting change in CPD (Hypothesis 3), a two-level LMM was used. Level 1 represented daily variables (average minutes since last cigarette prior to each cue; average pre- and post-cue affect, and craving centered around a person's mean response across all time points) and level 2 represented person-level variables (average CPD, sex). Random slopes for daily affective and craving states were included. The dependent variable was number of cigarettes smoked that day centered on average CPD for that individual such that a positive value meant more cigarettes were smoked on a given day than was typical for that individual.

Within-person variability in CPD was measured via the coefficient of variation (within-person standard deviation of cigarettes across days divided by the within-person mean) consistent with a method used by Hughes et al.⁴⁰ For this analysis, those without variability in CPD ($n = 11$) were assigned a coefficient of variation of zero. A t -test was used to test the difference between male and female average coefficient of variation (Hypothesis 4).

Significance of LMM fixed effects and t -tests was evaluated at a conservative p value ($<.01$). All statistical analysis was performed using SAS, version 9.4.⁴¹

Results

Participants, CREMA Compliance, and Quality Checks

Of 15 218 completed CREMA trials (of a possible 19 936), participants ($N = 178$) reported that they were unable to see 205 (1.4%) of the administered cues due to technical issues with the app or mobile device. Sessions with unseen cues were removed from analysis, resulting in a final sample of 15 013 trials (5631 smoking, 5647 stressful, and 3735 neutral) and a final analytic sample size of 177 participants (115 females, 62 males), as one participant did not see any cues. Demographic information for the sample is shown in Table 1. Age, ethnicity, marital status, education, employment status, income, average CPD, and FTND scores did not significantly differ by sex (all $ps >.05$). Male smokers were slightly more racially diverse than female smokers ($X^2 = 9.82, p = .04$).

As shown in Table 2, compliance with morning reports was 78.1% ($SD = 24.3$). On average, individuals completed 76.7% ($SD = 22.1$) of administered CREMA sessions and completion rate did not significantly differ by sex. For morning reports, 20.2% of missed sessions were monotone missing (due to discontinuation of the protocol at some point prior to the end of the 2-week period; $n = 14$). For CREMA sessions, 18.7% of missed sessions were monotone missing. All other missed morning reports or sessions were missed intermittently. All participants were retained for analysis, regardless of compliance rate. When including compliance with CREMA sessions as a covariate, results remain the same for all four-level models. Data were discarded and considered missing for one participant who did not understand how to respond to the cues during the first week of participation. However, corrective feedback was provided and this individual's second week of sessions were retained. Average pre- and post-cue stress, negative affect, and craving ratings (not model adjusted) are also shown in Table 2.

Cigarette Use

Participants reported smoking an average of 13.7 CPD ($SD = 6.7$) via morning reports, as shown in Table 2. Participants reported that their last cigarette was smoked 50.7 minutes ($SD = 99.8$) before each CREMA session, on average, and the time since last cigarette did not significantly differ by sex. The average within-person standard deviation for CPD was 3.7.

Table 1. Baseline Demographic Information

	Total sample ($N = 177$)	Females ($n = 115$)	Males ($n = 62$)
Age			
M	30.4 ($SD = 7.3$)	30.8 ($SD = 7.2$)	29.7 ($SD = 7.5$)
Race (%) [*]			
White/Caucasian	54.8	61.7	41.9
Black/African American	39.5	34.8	48.4
Biracial	4.5	2.6	8.1
Other	1.2	0.9	1.6
Ethnicity (%)			
Hispanic or Latino	3.4	4.3	1.6
Not Hispanic or Latino	96.6	95.7	98.4
Marital status (%)			
Single, divorced, separated, widowed	85.9	83.5	90.3
Married	14.1	16.5	9.7
Highest level of education (%)			
No high school diploma or GED	15.3	14.8	16.1
High school diploma or GED	29.4	27.0	33.9
Vocational school graduate	1.1	0.9	1.6
Some college	32.8	33.0	32.3
Associate's degree or equivalent	8.5	10.4	4.8
Bachelor's degree or equivalent	10.2	11.3	8.1
Graduate or professional degree	2.8	2.6	3.2
Employment/income			
Currently unemployed (%)	32.8	29.6	38.7
Income less than \$25 001 (%) ^a	61.1	60.4	62.3
Cigarette use (prior to study enrollment)			
Average cigarettes/day (30-d TLFB)	15.3 ($SD = 7.1$)	15.3 ($SD = 7.0$)	15.1 ($SD = 7.3$)
Nicotine dependence (FTND)	4.7 ($SD = 2.0$)	4.7 ($SD = 2.0$)	4.8 ($SD = 2.1$)

GED= General Education Development, FTND = Fagerström Test for Nicotine Dependence, TLFB = timeline follow-back

^aIncome data not available for 2 participants.

^{*}Race significantly differed by sex at $p < .05$.

Table 2. Descriptive Cue Reactivity Ecological Momentary Assessment (CREMA) and Morning Report Data

	Total sample (N = 177)	Females (n = 115)	Males (n = 62)
Compliance with CREMA sessions	76.7% (SD = 22.1)	74.8% (SD = 23.2)	80.2% (SD = 19.7)
Compliance with morning reports	78.1% (SD = 24.3)	76.6% (SD = 26.0)	81.0% (SD = 20.8)
Average CPD (morning report)	13.70 (SD = 6.67)	13.46 (SD = 6.47)	14.14 (SD = 7.05)
Average coefficient of variation for CPD	0.30 (SD = 0.21)	0.29 (SD = 0.22)	0.30 (SD = 0.19)
Pre-cue assessments			
Average pre-cue stress	1.69 (SD = 1.07)	1.73 (SD = 1.07)	1.63 (SD = 1.08)
Average pre-cue NA	1.42 (SD = 0.73)	1.43 (SD = 0.73)	1.39 (SD = 0.73)
Average pre-cue craving	2.32 (SD = 1.31)	2.32 (SD = 1.33)	2.32 (SD = 1.27)
Stress cue			
Average poststress cue stress	2.03 (SD = 1.22)	2.14 (SD = 1.26)	1.84 (SD = 1.14)
Average poststress cue NA	1.98 (SD = 1.03)	2.07 (SD = 1.06)	1.83 (SD = 0.96)
Average poststress cue craving	1.85 (SD = 1.15)	1.91 (SD = 1.18)	1.74 (SD = 1.09)
Smoking cue			
Average postsnoking cue stress	1.55 (SD = 0.97)	1.57 (SD = 0.96)	1.51 (SD = 0.97)
Average postsnoking cue NA	1.36 (SD = 0.69)	1.36 (SD = 0.67)	1.35 (SD = 0.71)
Average postsnoking cue craving	2.57 (SD = 1.36)	2.55 (SD = 1.37)	2.60 (SD = 1.33)
Neutral cue			
Average postneutral cue stress	1.38 (SD = 0.87)	1.40 (SD = 0.88)	1.36 (SD = 0.87)
Average postneutral cue NA	1.26 (SD = 0.63)	1.26 (SD = 0.63)	1.26 (SD = 0.63)
Average postneutral cue craving	1.77 (SD = 1.09)	1.79 (SD = 1.10)	1.74 (SD = 1.06)

CPD = cigarettes per day, NA = negative affect (average rating of sad, worried, angry, frustrated); compliance did not significantly differ by sex (all p s > .05).

Hypothesis 1: Females Endorse Greater Subjective Stress Cue Reactivity (ie, Negative Affect, Stress, and Craving)

Model-based mean estimates of poststressful cue stress, negative affect, and craving are shown in Figure 1A. Significant Sex $\times$ Cue Type interactions were detected such that females (relative to males) endorsed greater stress [$b = 0.27$, SE = 0.04, $p < .01$, $M_{\text{female}} = 2.12$, 95% confidence interval (CI) = 2.04% to 2.19%, $M_{\text{male}} = 1.89$, 95% CI = 1.79% to 2.00%], negative affect ($b = 0.24$, SE = 0.03, $p < .01$, $M_{\text{female}} = 2.06$, 95% CI = 1.99% to 2.13%, $M_{\text{male}} = 1.86$, 95% CI = 1.76% to 1.95%), and craving ($b = 0.10$, SE = 0.03, $p < .01$, $M_{\text{female}} = 1.92$, 95% CI = 1.83% to 2.00%, $M_{\text{male}} = 1.74$, 95% CI = 1.63% to 1.84%) following the administration of stressful cues (relative to neutral cues). Results of the final model with craving as the outcome are shown in Table 3. Additional post hoc analysis suggested that reactivity to stressful cues administered second (trial 2) differed depending on which cue type was administered first (trial 1). In particular, when preceded by a smoking cue, stress and negative affect responses were attenuated relative to stressful + stressful cue combinations (both p s < .01) and showed a trend for attenuation relative to neutral + stressful cue combinations ($p = .08$ for stress, $p = .06$ for negative affect).

Hypothesis 2: Females Endorse Greater Smoking Cue-Reactivity When Baseline Negative Affect Is Elevated

Presmoking cue negative affect was significantly predictive of post-smoking cue craving ($b = 0.10$, SE = 0.02, $p < .01$); however, this effect did not differ by sex. The three-way interaction between cue type, sex, and pre-cue negative affect, as well as the two-way interactions between (1) sex and pre-cue negative affect and (2) cue type and pre-cue negative affect were all nonsignificant and thus not retained in the final model, shown in Table 4. Though there was some evidence for differential effects across Cue Type $\times$ Sex

Figure 1. Model-adjusted subjective responses to stressful and smoking cues by sex. Bars denote significant difference between post-cue model-based means ($p < .01$). Error bar represents 1 SE above and below the mean.

Table 3. Craving Reports Following Stressful Cue (Relative to Neutral Cues)

	<i>b</i>	SE	<i>p</i>
Fixed effects			
Intercept	1.75	0.06	<.001
Sex (reference = males)	0.08	0.06	.204
Stressful trial (reference = neutral trials)	0.02	0.03	.346
Sex × Stressful Trial	0.10	0.03	<.001
Time-varying covariates			
Time since smoked (Min)	<0.01	<0.01	.278
Cue order (reference = second cue)	−0.04	0.01	.003
Pre-cue negative affect ^a	0.10	0.02	<.001
Pre-cue craving ^a	0.35	0.02	<.001
Person-level covariates			
Average pre-cue craving ^b	0.59	0.03	<.001

Beta estimates are unstandardized. Day is included as a covariate, but not shown in table, as there were no significant day effects.

^aCentered based on individual's average pre-cue negative affect/craving.

^bCentered based on all smoker's average pre-cue craving.

Table 4. Craving Reports Following Smoking Cue (Relative to Neutral Cues)

	<i>b</i>	SE	<i>p</i>
Fixed effects			
Intercept	1.71	0.11	<.001
Sex (reference = males)	0.04	0.13	.753
Smoking trial (reference = neutral trials)	0.84	0.03	<.001
Sex × smoking trial	−0.06	0.03	.082
Time-varying covariates			
Time since smoked (min)	<0.01	<0.01	.008
Cue order (reference = second cue)	−0.02	0.02	.189
Pre-cue negative affect ^a	0.10	0.02	<.001
Pre-cue craving ^a	0.48	0.02	<.001
Person-level covariates			
Average pre-cue craving ^b	0.63	0.13	<.001

Beta estimates are unstandardized. Day is included as a covariate, but not shown in table; however, day 1 was a significant predictor of elevated post-cue craving (with day 14 as the reference group). No other days differed from day 14 at $p < .01$. All two- and three-way interactions between pre-cue negative affect, smoking trial, and sex that are not shown were not significant ($p > .10$).

^aCentered based on individual's average pre-cue negative affect/craving.

^bCentered based on all smoker's average pre-cue craving.

interaction ($b = -0.06$, $SE = 0.03$, $p = .08$), difference tests between model-based least squares means suggested that this was not driven by sex differences in postsmoking cue-induced craving ($d = -0.02$, $SE = 0.13$, $p = .89$, $M_{\text{female}} = 2.56$, 95% CI = 2.42% to 2.71%, $M_{\text{male}} = 2.58$, 95% CI = 2.38% to 2.78%). Model-based mean estimates of postsmoking cue stress, negative affect, and craving are shown in Figure 1B. Males and females did not differ in postsmoking cue stress ($M_{\text{female}} = 1.54$, 95% CI = 1.49% to 1.59%, $M_{\text{male}} = 1.54$, 95% CI = 1.47% to 1.61%) or negative affect ($M_{\text{female}} = 1.35$, 95% CI = 1.31% to 1.38%, $M_{\text{male}} = 1.36$, 95% CI = 1.32% to 1.41%) ratings. Reactivity to smoking cues administered second (trial 2) did not differ depending on the cue type administered first (trial 1).

Hypothesis 3: Days Characterized by Greater Cue Reactivity Are Associated With Increased CPD (Regardless of Sex)

There were no main effects of daily average post-cue stress, negative affect, or interactive effects between post-cue variables and sex, on

number of cigarettes smoked (all $ps > .10$). This was true across cue types (ie, stressful and smoking cues). There was also no main effect of daily average postsmoking cue craving or interactive effects with sex on number of cigarettes smoked (all $ps > .10$). As there was not an effect of average post-cue responses on CPD, we examined average pre-cue stress, negative affect, and craving as separate predictors of CPD (alone and interaction with sex) and these did not predict CPD (all $ps > .10$).

Hypothesis 4: Females Evince Greater Within-Person Variability in CPD

The average coefficient of variation in the sample was 0.30 ($SD = 0.21$, median = 0.25). The average coefficient of variation in CPD did not significantly differ between female ($M = 0.29$) and male smokers ($M = 0.30$, $t = -.31$, $df = 175$, $p = .75$).

Discussion

Consistent with prior analyses that did not control for baseline affect and craving,¹⁵ our models that now take into account pre-cue affective and craving states suggested that female smokers were more likely than male smokers to endorse stress, negative affect, and craving following exposure to stressful cues. This is consistent with an emerging body of laboratory-based cue-reactivity research^{13,14} and supports the premise that females may be more susceptible to stress-related maintenance of smoking and/or relapse.

Male and female smokers did not differ in their subjective responses to smoking cues. Though previous literature in this area has been mixed,^{17–20} the present study is consistent with evidence suggesting that sex differences in smoking cue reactivity are negligible. Contrary to our hypothesis, we did not observe a significant effect of pre-cue negative affect on reactivity to smoking cues, for either males or females. Though pre-cue negative affect was highly predictive of post-cue negative affect and craving, regardless of sex, pre-cue negative affect was not significantly associated with craving reactivity following exposure to smoking cues. This is interesting because it suggests that females, though more stress reactive, may not be at increased risk for reactivity to smoking cues when experiencing stress or negative affect. We examined within-person-centered pre-cue negative affect, which means that heightened negative affect represents negative affect that is higher than the individual's average level. This also adjusts for reporting differences across individuals. The lack of an interaction between pre-cue negative affect and smoking cue exposure was surprising given that prior work has suggested that drug cue reactivity is enhanced when preceded by negative affect and/or stress²¹ and that negative affect increases attentional bias toward drug cues.⁷ Perhaps higher than typical levels of negative affect lead to increased craving regardless of smoking cue exposure, making it difficult to detect an additional increase in craving. This may be the case if females have particularly strong conditioned associations between negative affect and smoking.

Prior work has suggested that sex differences may be most pronounced when comparing males to females in a particular phase of the menstrual cycle.^{42,43} The present study included females in both the follicular and luteal phases, and it is interesting to note that sex differences in stress reactivity were still detected. However, future research should take into account circulating hormone levels, as these may influence responses to cues for both sexes.

Our results suggest that days in which smokers report greater stress and/or smoking cue reactivity (regardless of sex) are not associated with an increased number of CPD. There are a number of potential explanations for this null finding. First, cues may not

have been sufficiently salient and/or personalized to affect smoking behavior. Second, exposure to cues may have expedited smokers' time to next cigarette even if not increasing their overall cigarette count for the day. Precise timing of smoking following cue exposure was not available in this study. Third, exposure to daily smoking cues and/or stressors may be so ubiquitous among smokers that CPD do not vary on the daily level. Fourth, CPD was assessed the next day via morning report. Because the smokers were relatively consistent in their number of cigarettes smoked, errors in retrospection may have resulted in slight but meaningful reporting errors. Finally, it is possible that relatively transient cue-reactive negative affect, stress, or craving does not result in real-world smoking among established daily smokers. This is consistent with prior research²⁷ that suggested exposure to smoking cues did not expedite smoking relative to exposure to neutral cues. Perhaps an independent risk factor, impaired executive functioning or self-control, must also be present for smokers to act on resulting urges to smoke. Appetitive craving in response to drug-related cues (incentive salience), appetitive craving in response to stress (negative reinforcement), and impaired executive control may be separate, but overlapping, risk factors for substance use behavior.⁴⁴

Also inconsistent with our hypothesis, variability in CPD did not differ by sex. Two recent studies examined variability in CPD, and neither found a main effect of sex on variability in CPD.^{40,45} This may be inconsistent with the proposition that female smoking is under greater stimulus control⁵ and that male smoking shows greater continuity.⁸ However, as noted earlier, there are limitations in the use of variability in CPD as an indicator of one's propensity for cue and/or stress-reactive smoking. The lack of a sex difference in CPD variability does not rule out the possibility of a differential proximal cue effect (ie, latency to next cigarette), which should be assessed in a future study with real-time smoking data.

To the best of our knowledge, this is the first CREMA study to examine the effect of subjective reactivity to stressful cues on actual smoking behavior, within an ecologically valid context. Future CREMA studies should collect event-level cigarette data (ie, cigarettes reported in real time as they are smoked) to (1) determine whether exposure to cues expedites smoking (particularly stressful cues, as this has not been previously examined in naturalistic settings), (2) minimize errors in recall of cigarettes smoked over the course of 24 hours, and (3) determine the direct effect of cue exposure, on smoking behavior, irrespective of subjective response to cues. Future research would also benefit from using personally relevant cues, to rule out the possibility that the stressful cues are simply more effective stressors for females, whereas alternative stressors may have been more effective for males.

In sum, relative to male smokers, female smokers reported greater subjective response (ie, stress, negative affect, craving) to stressful cues presented in the natural environment via a mobile device, but not greater subjective response to smoking cues, even when baseline negative affect was elevated. When examining cigarettes smoked, no sex differences emerged. Male and female smokers reported a similar number of CPD and did not differ in day-to-day variability in cigarettes smoked. Neither sex showed a clear link between cue reactivity and smoking; however, more research examining smoking behavior proximal to cue exposure²⁷ is necessary. Taken together, these results suggest that, on average, female smokers have heightened subjective stress reactivity that may predispose them to negative smoking-related outcomes. Treatment options for female smokers

may be more effective if they address negative affect regulation or target neurobiological pathways that influence stress response.

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Declaration of Interests

CLM declares ownership of intellectual property related to the CREMA mobile application. KMG has provided consultation to Pfizer, Inc. RLT, MES, NLB, EAM, MJC, ViRR, BWH, JMW, KTE, and STT declare that they have no conflict of interest.

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