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Review
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Review

Differences in Magnitude of Cue Reactivity Across Durations of Smoking History: A Meta-analysis

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Abstract

Background: Cue-elicited craving may vary due to duration of smoking history, increasing as more years of smoking strengthen associations between nicotine intake and cues. However, research on this relationship is virtually absent. This project assessed the relationship between cue reactivity and years of smoking.

Methods: Data from 53 studies (68 effect sizes) were analyzed. Eligible studies were those measuring self-reported craving following cue exposure in nontreatment seeking smokers and reporting mean years smoking. Preliminary subgroup analyses identified methodological factors influencing cue-reactivity effect sizes; primary meta-regression analysis assessed differences across years smoking; exploratory analyses assessed potential for ceiling effects.

Results: Effect sizes varied due to abstinence requirement and cue presentation modality, but not dependence severity. Unexpectedly, meta-regression analysis revealed a decline in effect sizes across years smoking. Exploratory analyses suggested declines may have been due to a ceiling effect in craving measurement for those with longer smoking histories—more experienced smokers reported higher levels of craving at baseline or following neutral cue exposure, but all reported similar levels of craving after smoking cue exposure.

Conclusions: Methodological factors and duration of smoking history influenced measurement of cue reactivity. Highlighted were important relationships between years smoking and magnitude of cue reactivity, depending on use of baseline or neutral cue comparisons. Further research is needed to assess differences in cue reactivity due to duration of smoking history using participant-level data, directly testing for ceiling effects. In addition, cue-reactivity studies are needed across young adults to assess onset of associations between nicotine intake and cues.

Implications: This meta-analysis project contributes to the cue-reactivity literature by reporting on the previously ignored relationship between duration of smoking history and magnitude of cue-elicited craving. Results suggest that declines in cue-reactivity effect sizes across years of smoking may have been due to study-level methodological factors, but not due to differences in sample-level dependence severity. Cue-reactivity effect sizes were stable across years of smoking in studies using a neutral cue comparison but declined sharply in studies when baseline assessment (typically coupled with an abstinence requirement) was used.

Introduction

For decades, researchers have known that drug craving can be triggered by environmental stimuli frequently paired with drug intake, or "cues," in those with drug use histories.[1] This effect, known as cue reactivity, has been demonstrated across a variety of drugs[2] and is supported by a large body of research in which participants are systematically exposed to actual or representations of cues (eg, lighter, ashtray, lit cigarette) then report their craving.[2,3] The clinical utility of cue-reactivity research in smokers lies in its relationship to indices of nicotine dependence, such as its potential to predict subsequent smoking behavior.[4,5] Ecological research has found that many lapses and relapses during a quit attempt follow exposure to cues in the real world,[6,7] suggesting that cue-elicited craving experienced in vivo may precipitate failed cessation attempts. Yet, cue-elicited craving assessed in lab settings is not affected by proven pharmacotherapies for smoking cessation,[8,9] and does not consistently correlate with measures of dependence severity.[10,11] Cue reactivity has been found to be predictive of more immediate smoking behavior; greater cue-elicited craving (relative to baseline assessment or exposure to neutral control cues) has been associated with shorter latency and greater amount of immediate subsequent smoking.[12–15] Taken together, support for the clinical utility of cue reactivity is mixed—its predictive ability has been reliably demonstrated for immediate smoking behavior but not yet for more temporally distal outcomes (ie, relapse during a quit attempt[4,5]). Elucidating factors affecting cue reactivity in smokers may lead to a better understanding of cue reactivity's clinical utility.

The magnitude of cue-reactivity craving response may vary due to an index of smoking persistence, duration of smoking history. A framework for this potential relationship comes from two learning-based theories. According to classical conditioning theory, repeated association of cues with nicotine intake would strengthen conditioned responses to those cues.[16,17] The incentive-sensitization theory[18–20] adds a psychobiological basis—repeated drug use progressively sensitizes the primary reward center in the brain, rendering this system hyperreactive to drug-associated stimuli, resulting in intense feelings of craving or wanting for drug when presented with such stimuli.[18–20] Both theories predict that the magnitude of cue reactivity will increase with repeated pairings of nicotine and drug-associated stimuli, eventually reaching an asymptote.[16–20] However, it is unclear how quickly cue reactivity develops and whether it reaches an asymptotic phase once established. If the magnitude of cue-elicited craving response varies due to duration of smoking history, the clinical utility of cue-reactivity research (ie, reliable prediction of lapse and relapse risk due to environmental factors) may vary due to an individual's smoking history.

Despite many studies of cue reactivity in smokers, the potential relationship between cue-elicited craving and duration of smoking history has been largely ignored. One study—possibly the only—which did report on the relationship between cue reactivity and years of smoking in abstinent tobacco smokers found a small, but still statistically significant, inverse relationship between years of smoking and change in craving from pre- to post-cue exposure.[21] In other words, after being asked to light (but not smoke) a cigarette, those with more years of smoking reported less of an increase in craving than those with fewer years of smoking. However, this effect may have been due to a ceiling effect in craving measurement. The authors reported a significant positive relationship between pre-cue craving levels and years of smoking and no relationship between post-cue craving and years of smoking. Thus, when compared to less experienced smokers, more experienced smokers reported significantly higher levels of craving before cue exposure but similar craving levels after exposure to the cue, resulting in diminished increases due to exposure to the smoking cue per se.

In light of the lack of research in this area, the current article used meta-analytical techniques to integrate data from cue-reactivity studies which reported sample mean years of smoking. The primary aim of this project was to assess the relationship between craving response to smoking cues (relative to neutral cues and/or baseline assessment) and years of smoking in the extant cue-reactivity literature. Other aims included: identifying methodological (eg, abstinence requirement, mode of cue presentation) and theoretical variables (eg, age, cigarettes per day [CPD], level of dependence) which modulate the magnitude of cue reactivity; and exploring the potential for ceiling effects in craving measurement in cue-reactivity research.

Methods

Search Procedures and Selection Criteria

Three electronic databases (PsycINFO, PubMed, and Google Scholar) were searched in January 2018 to identify relevant full-text articles. Searches used the following combination of keywords: cue-reactivity AND (self-reported craving OR urge) AND (smok* OR cigarette). The wildcard asterisk (*) was used to allow for alternate forms of the respective keyword (eg, smoker, smokers, smoking). In addition, reference lists of relevant or related review and meta-analysis papers were also examined to identify additional studies for inclusion.

Studies were eligible if they: (1) included only nontreatment seeking smokers (cue reactivity has been shown to be blunted in treatment seeking smokers[22,23]); (2) recruited either adolescent smokers or adult smokers (with outcomes reported separately for each group if both groups were recruited in the same study); (3) measured self-reported craving; (4) reported mean years of smoking for the sample (if mean years smoking not reported, mean age and mean age started smoking were reported); (5) exposed smokers to both smoking-related cues and a control procedure of neutral cues (or, if neutral cues were not used, a baseline assessment of craving); (6) no administration or use of another drug, medication, or nicotine replacement therapy that may have influenced cue-elicited craving; (7) presented original data published in a peer-reviewed journal; and (9) were written in English.

Data Extraction

All data were entered into a database using Comprehensive Meta-Analysis 3.0 software. Data extracted from each study included sample size, age, percent male, hours abstinent, cue presentation mode, use of neutral cue or baseline assessment, order of cue presentation, years of smoking, age started smoking, craving measure used, and craving response (ie, the dependent measure).

Data Synthesis and Analysis Plan

Comprehensive Meta-Analysis software computed Hedges' *g*, a standardized within-subjects measure of effect size, calculated as the difference in craving response between smoking and neutral cues (or baseline assessment) for each study. In the sections later, "cue reactivity" will refer to the difference between smoking and neutral cues/baseline assessment; craving values obtained at a specific timepoint (eg, baseline assessment only, post smoking cue exposure only) will be referred to as "absolute craving." When available, means and standard deviations were used to calculate the effect size

for each study. Otherwise, *t* scores or one-way *F* values (converted to *t*; $t = \sqrt{F}$) were used to estimate the effect size. All meta-analyses used random-effects models.[24,25]

Heterogeneity in effect sizes was assessed using Cochran's *Q* and I^2 statistics. When significant, Cochran's *Q* test indicates that differences exist between studies and further testing to identify factors contributing to heterogeneity is warranted.[24,26] The I^2 statistic quantifies the amount of heterogeneity between studies, with values of 0%, less than 30%, and greater than 50% indicating no, moderate, and high levels of heterogeneity, respectively.[26]

Preliminary Analyses

Preliminary omnibus meta-analysis was performed using effect sizes from all studies to determine whether cue reactivity (ie, difference in craving measured after smoking cue exposure vs. baseline assessment/neutral cue exposure) was different from zero. Publication bias was then assessed across all studies using Kendall's tau,[27] Duval and Tweedie's trim and fill method,[28,29] and funnel plots. Subsequent preliminary subgroup meta-analyses examined the influence of methodologically relevant variables: use of baseline versus neutral cue comparisons, craving measure, abstinence requirement (any abstinence vs. no abstinence), cue presentation mode (in vivo, images, scripted imagery, video, or virtual reality), and order of cue presentation (fixed order vs. other). Variables found to significantly influence cue-reactivity effect sizes were included as covariates in the primary analyses.

Primary and Secondary Analyses

The primary analyses used random effects meta-regression to assess whether mean years of smoking (entered as a continuous covariate) was related to cue-reactivity effect sizes, controlling for variables identified in the preliminary subgroup analyses. Secondary analyses examined the effect of theoretically relevant variables: age, CPD, and level of dependence (Fagerström Test for Nicotine Dependence [FTND] scores).

Exploratory Analyses

In their review on craving measurement, Sayette et al.[30] identified methodological factors which may facilitate ceiling effects for self-reported craving in cue-reactivity studies. According to the authors, use of baseline assessment only (ie, not including neutral control cues) and requiring abstinence prior to cue exposure procedures may lead to ceiling effects. A series of exploratory analyses examined whether these methodological variables contributed to ceiling effects in the current sample of studies. First, two separate meta-regression models were run; the first model tested use of study abstinence requirement and the second model examined use of baseline versus neutral cue comparison. Both models included cue presentation mode, years of smoking, and the interaction of years of smoking and abstinence (model 1) or use of baseline assessment or neutral cue exposure (model 2). Simple slopes analysis was used to follow up significant interaction effects.

Additional exploratory regression analyses were conducted in SPSS 25.0. These analyses examined the relationship between absolute craving scores (expressed as percent of scale max to standardize scores across different measures[23]) and years of smoking, controlling for abstinence requirement, use of baseline or neutral cue comparison, and the interaction between mean years smoking and use of baseline/neutral cue. Following Donny et al.,[21] separate regression models were used to test effects on absolute craving assessed at baseline or following neutral cue exposure, absolute craving following smoking cue exposure, and change in absolute craving from baseline or neutral cue to smoking cue.

Results

Characteristics of Included Studies

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[31] A total of 807 articles were identified using the procedures described earlier. After removing 105 duplicates, titles and abstracts of the remaining 702 articles were screened and an additional 535 were excluded due to lack of relevance to the topic of interest. Of the 167 remaining full-text articles reviewed for eligibility, 53 studies were included in the analysis.[12,14,15,32–81]

Sample-Level Characteristics

All study characteristics are presented in Supplementary Table 1. Of the 53 studies included in the analyses, seven presented data from the same participants under differing conditions (eg, abstinent and nonabstinent, standardized and personalized cues, in vivo and imaginal cues) and eight presented data from separate samples (ie, pilot study and main study, heavy smokers and lighter smokers, abstinent and nonabstinent groups), for a total of 68 sets of data ($k = 68$). The following sample characteristics do not repeatedly count participants measured more than once ($k = 60$, unless otherwise noted). Sample sizes ranged from 8 to 225 (combined $n = 3372$), with a mean (SD) sample size of 56.2 (47.75). The mean sample age ranged from 16.2 to 55 years (grand mean 31.11 [8.63] years). Overall, samples tended to have slightly more males (mean 52.06% [17.58] male). Mean (SD) smoking characteristics across samples were 18.42 (5.46) CPD, smoking for 14.10 (7.95) years, and FTND score of 4.93 (1.26) ($k = 35$).

Study Methodologies

Across all studies ($k = 68$), 28 did not require abstinence before cue exposure procedures. Abstinence requirements in the other 40 studies included durations of 0.5–5 hours ($k = 14$), 6–12 hours ($k = 23$) and more than 12 hours ($k = 3$). Most studies included a neutral cue condition ($k = 55$), whereas a few others only reported baseline craving before exposure to smoking cues ($k = 13$). Most studies ($k = 51$) reported whether the cues were presented in a fixed or other order (ie, randomized or counterbalanced). Of those reporting, fewer studies presented cues in a fixed order ($k = 14$) than other cue presentations ($k = 37$). Craving was measured using the Shiffman–Jarvik Craving Scale[82] ($k = 2$; separate samples in the same study), the Cigarette Craving Questionnaire[83] ($k = 7$), a single item ($k = 24$), Factor 1 of the Questionnaire on Smoking Urges[84] ($k = 1$), Questionnaire on Smoking Urges-10[85] ($k = 23$), or the Questionnaire on Smoking Urges-4[86] ($k = 11$). Cue modes included photographic images ($k = 24$), handling or seeing smoking paraphernalia (ie, in vivo; $k = 26$), scripted imagery ($k = 13$), virtual reality ($k = 3$), and video ($k = 2$).

Preliminary Analyses

Omnibus Effect Size

Overall, participants reported significantly more craving following exposure to smoking cues versus baseline or neutral cues, Hedge's $g = 0.77$, 95% CI = 0.65 to 0.89, $Z = 12.96$, $p < .001$. There was high

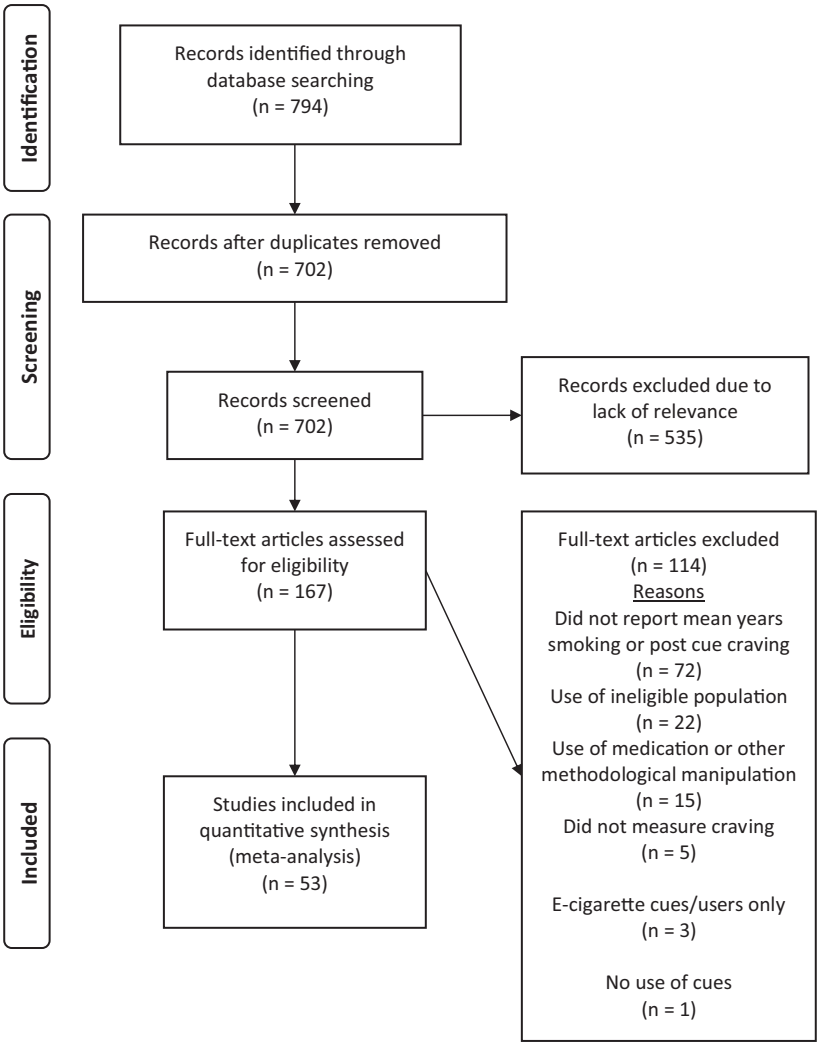

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

heterogeneity of effect sizes, $Q(67) = 667.35$, $p < .001$ with between-study variance, τ^2, estimated at 0.20. Thus, the true effect size most likely varied from study to study and the observed variance was not due to sampling error. Almost all observed variance ($I^2 = 90.0\%$) reflected differences in study effects.

Publication Bias

Kendall's tau was marginally significant, $\tau = 0.15$, $Z\tau = 1.82$, $p = .07$, indicating potential publication bias. To explore this further, Duval and Tweedie's trim and fill method was used to estimate the impact of potential publication bias, resulting in an adjusted Hedge's $g = 0.47$, 95% CI = 0.34 to 0.60). This adjusted omnibus effect size retained statistical significance (ie, 95% CI does not overlap with 0), despite the reduction in magnitude. A funnel plot illustrating possible publication bias is presented in Supplementary Figure 1.

Subgroup Analyses

Results of the subgroup analyses organized by methodologically relevant variables are displayed in Supplementary Table 2. There was low heterogeneity among (i.e., similar) effect sizes between studies across most variables, including cue presentation order (fixed vs. other) and craving measure used. However, effect sizes varied due to abstinence requirement, $Q(1) = 5.29$, $p = .02$, and cue presentation mode, $Q(4) = 15.25$, $p = .004$. As shown in Supplementary Table 2, studies requiring any abstinence prior to cue exposure had lower effect sizes than those without an abstinence requirement. For cue presentation mode, each cue modality resulted in significantly greater reactivity following smoking cue presentation versus neutral control cue/baseline, except for video. After excluding studies that used video cue presentation, there was still significant heterogeneity due to cue mode, $Q(3) = 10.31$, $p = .02$. Both the abstinence requirement (any vs. none) and cue presentation mode variables were included as covariates in subsequent analyses.

Primary Meta-regression Analysis

Results of the meta-regression analysis are presented in Table 1. An omnibus test of the model indicated it as a whole was related to effect size, $Q(6) = 25.01$, $p = .0003$. There was a high level of between-study variance in effect sizes observed in the model, $I^2 = 86.2\%$, $p < .0001$. Unexpectedly, mean years of smoking had a significant negative linear relationship with cue-reactivity effect size, $\beta = -0.01$, $p = .04$. As shown in Figure 2A, the magnitude of cue-reactivity

Table 1. Meta-regression Results

				95% CI	
	Q	β	SE	LL	UL
Overall model	25.01***				
Intercept		0.98***	0.15	0.69	1.27
Mean years smoking					
Linear effect		−0.01*	0.007	−0.0268	−0.0005
Cue mode	16.34**				
Images		0.27*	0.13	0.02	0.52
Scripted imagery		0.44**	0.15	0.15	0.73
Video		−0.54†	0.31	−1.14	0.07
Virtual reality		0.16	0.27	−0.37	0.69
In vivo (reference)					
Abstinence requirement					
None		0.21†	0.11	−0.01	0.43
Any (reference)					

CI = confidence interval; LL = lower limit; *Q* = Cochran's *Q*; SE = standard error; UL = upper limit.
†$p < .10$, *$p < .05$, **$p < .01$, ***$p < .001$.

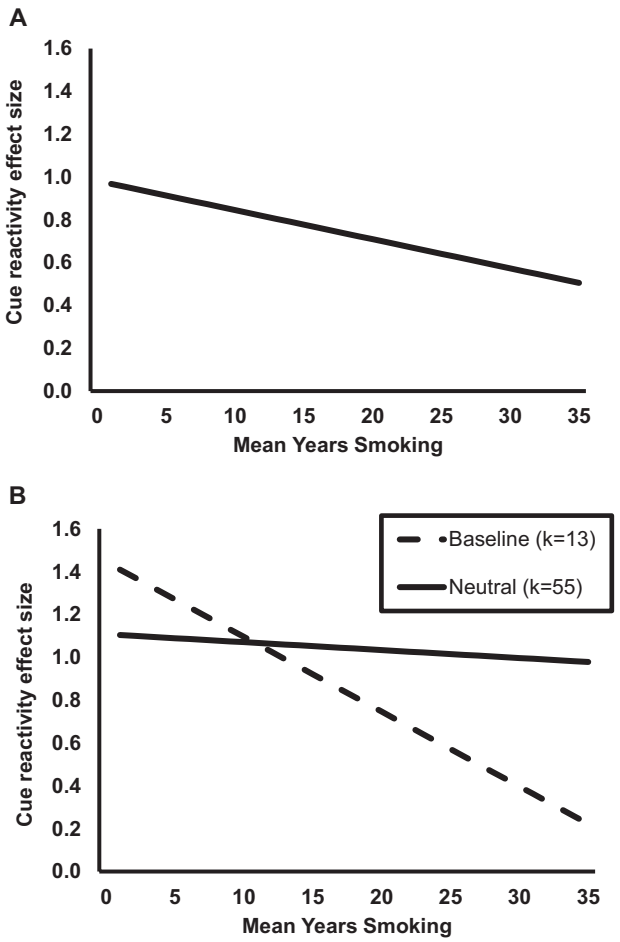

Figure 2. (**A**) Plot of the significant linear relationship between cue-elicited craving effect size and mean years smoking, estimated using meta-regression analysis controlling for effect of cue presentation mode and abstinence requirement. (**B**) Plot of simple slopes for cue-reactivity effect size and mean years smoking, comparing between studies using a baseline comparison (dashed line) versus studies using a neutral cue comparison condition (solid line).

effect sizes declined 0.01 units for each one-year increase in mean years of smoking.

Secondary Analyses

Separate meta-regression analyses tested whether CPD ($k = 68$), age ($k = 67$), and FTND ($k = 40$) were related to effect size heterogeneity, controlling for cue mode and abstinence requirement. None of these theoretically relevant variables had significant influence on effect size heterogeneity: CPD β = 0.01, 95% CI = −0.01 to 0.04, $p = .24$; age β = −0.01, 95% CI = −0.021 to 0.004, $p = .18$; FTND β = −0.07, 95% CI =−0.20 to 0.07, $p = .33$.

Exploratory Analyses

Exploratory Meta-regressions

Results of the exploratory meta-regression analyses are displayed in Table 2. The first model examined the relationship between years of smoking and use of an abstinence requirement (controlling for cue presentation mode), with specific interest in the interaction between these variables. The interaction between years smoking and abstinent requirement was not significant, β = −0.02, 95% CI = −0.04 to 0.01, $p = .17$.

The second exploratory model focused on the interaction between years of smoking and use of baseline versus neutral cue comparison, which was significant, β = 0.032, 95% CI = 0.003 to 0.062, $p = .03$. Simple slopes follow-ups are displayed in Figure 2B. In studies using a baseline comparison ($k = 13$), there was a significant negative relationship between years of smoking and cue-reactivity effect sizes, β = −0.03, 95% CI =−0.06 to −0.01, $p = .01$. Looking at studies using a neutral cue comparison ($k = 55$), the relationship between years of smoking and cue-reactivity effect sizes was not significant, β = −0.004, 95% CI = −0.021 to 0.013, $p = .67$. In sum, cue-reactivity effect sizes were consistent over years of smoking in studies using a neutral cue comparison and declined over years of smoking in studies using baseline assessment.

Exploratory Regression Analyses of Absolute Craving Scores

The final set of exploratory analyses examined the relationship between mean years of smoking and absolute craving ratings obtained at two timepoints: baseline/neutral cue exposure and smoking cue

Table 2. Exploratory Meta-regression Results

				95% CI	
	Q	*β*	SE	LL	UL
Exploratory model 1	27.32***				
Intercept		1.07***	0.18	0.70	1.44
Cue mode	17.61**				
In vivo		−0.29*	0.13	−0.54	−0.04
Scripted imagery		0.14	0.16	−0.17	0.46
Video		−0.88**	0.31	−1.49	−0.26
Virtual reality		−0.09	0.27	−0.63	0.44
Images (reference)					
Mean years smoking					
Linear effect		−0.003	0.010	−0.023	0.017
Abstinence requirement					
Abstinent		0.05	0.22	−0.38	0.48
Not abstinent (reference)					
Years smoking × abstinence		−0.02	0.01	−0.04	0.01
Exploratory model 2	29.26***				
Intercept		1.07***	0.18	0.73	1.42
Cue mode	14.37**				
In vivo		−0.25†	0.13	−0.50	0.01
Scripted imagery		0.17	0.16	−0.15	0.49
Video		−0.79*	0.32	−1.41	−0.17
Virtual reality		−0.14	0.28	−0.69	0.41
Images (reference)					
Mean years smoking					
Linear effect		−0.04**	0.01	−0.06	−0.01
Abstinence requirement					
Abstinent		−0.28*	0.12	−0.51	−0.04
Not abstinent (reference)					
Baseline/neutral comparison					
Baseline		0.47†	0.27	−0.07	1.01
Neutral (reference)					
Years Smoking × Baseline/neutral		0.03*	0.015	0.003	0.062

CI = confidence interval; LL = lower limit; *Q* = Cochran's *Q*; SE= standard error; UL = upper limit.
†p <.10, *p < .05, **p < .01, ***p < .001.

exposure. Abstinence requirement, use of baseline/neutral cue comparison, and the interaction between use of baseline/neutral cue and years of smoking were also entered into the regression model. Only studies which reported absolute mean craving at these timepoints were included in this series of exploratory analyses (k = 51). To standardize craving scores across the various measures used, mean craving ratings were converted into percent of scale maximum value.[22]

Somewhat consistent with Donny et al.,[21] there was a marginal positive relationship between years of smoking and baseline/neutral cue craving ratings, B = 0.69, 95% CI = −0.09 to 1.46, p = .08, no relationship between mean years of smoking and smoking cue craving, B = −0.04, 95% CI = −0.76 to 0.68, p = .92, and a significant negative relationship between years of smoking and change in craving from baseline/neutral cue to smoking cue, B = −0.72, 95% CI = −1.39 to −0.05, p = .04. In other words, more experienced smokers reported marginally higher craving at baseline or following neutral cue exposure compared to less experienced smokers, and all smokers (regardless of amount of smoking history) had similar craving ratings following smoking cue exposure.

Discussion

It is well established that smoking-associated stimuli can elicit drug craving in those with smoking histories.[1–3] Less well known is whether the magnitude of cue-elicited craving varies due to amount of smoking history. Both classical conditioning and Incentive-Sensitization theories support a hypothesized increase in cue-elicited craving as years of smoking accumulate, eventually reaching an asymptote.[16–20] As noted, this specific relationship has been ignored by the large body of cue-reactivity research in smokers. The current project aimed to address this gap in the literature using meta-analytical procedures.

An omnibus meta-analysis indicated that smokers had moderate to large increases in self-reported craving following exposure to smoking cues, relative to neutral cue exposure or baseline assessment. Subgroup and secondary meta-analyses indicated that cue-reactivity effect sizes were consistent within most methodologically and theoretically relevant variables, although they did vary between cue presentation modes and abstinence requirements. Among the various cue presentation modes, scripted imagery was found to elicit the largest magnitude of cue reactivity, followed by pictorial images, virtual reality, in vivo, and video. Further, studies requiring any abstinence prior to cue exposure procedures had a lower magnitude of cue reactivity than studies not requiring abstinence.

Contrary to expectations, meta-regression analyses revealed a significant negative linear relationship between cue-elicited craving effect sizes and mean years of smoking. One possible explanation—supported by a series of exploratory analyses—is that the observed

declines in cue reactivity over years of smoking were due to a ceiling effect for more experienced smokers.

The relationship between mean years of smoking and cue reactivity varied between studies depending on whether they used a baseline or neutral cue comparison. As shown in Figure 2B, cue-reactivity effect sizes declined sharply across years of smoking in studies using baseline craving measurement (k = 13) but remained steady in those using neutral cue exposure (k = 55). This suggests that use of baseline measurement in cue-reactivity research may be less stable across durations of smoking histories compared to use of a neutral cue comparison.

Consistent with the current findings, an earlier study reported declines in cue reactivity across durations of smoking histories.[21] Although not addressed by the authors, examination of the reported relationship between years of smoking and absolute craving scores separately by timepoint (ie, baseline and post-cue exposure) supports a hypothesized ceiling effect. The researchers reported a significant positive relationship between years of smoking and pre-cue craving, but no relationship between years of smoking and post-cue rating. In other words, more experienced smokers rated their baseline craving significantly higher than less experienced smokers, but all smokers rated their post-cue craving similarly. When cue reactivity responses were calculated as the change in craving from baseline to post-cue exposure, more experienced smokers appeared to have a smaller magnitude response to smoking cues than less experienced smokers. This effect appears to have been due to higher craving at baseline for the more experienced smokers—leaving less room toward the top of the scale for subsequent increases due to smoking cue exposure leading to an artificial decline in cue reactivity over years of smoking when the difference between timepoints was computed. A similar pattern was observed in exploratory analyses among a subset of studies (51 of 68) in the current project. Absolute craving scores obtained at baseline/following neutral cue exposure had a marginally positive relationship with years of smoking, but no relationship was found between absolute craving following smoking cue exposure and years of smoking. This pattern suggests that ceiling effects likely contributed to declines in cue reactivity across years of smoking. However, without participant-level data this cannot be directly determined. It is possible that using aggregated, sample-level data may have reduced the ability to detect differences in cue reactivity across varying durations of smoking histories.

The lack of relationship between absolute craving elicited by smoking cues and years of smoking may have been due smokers developing an asymptotic craving response, as predicted by classical conditioning and Incentive-Sensitization theories.[16–20] Cue-reactivity effect sizes were already robust at the lowest end of years smoking for studies included in the project, suggesting that associations between nicotine intake and environmental cues were firmly established within 2 years of smoking. Although the timeline of when these associations were formed is unclear, the observed consistency in craving response following exposure to smoking cues across smokers—regardless of how long they have been smoking—suggests that cue-elicited craving reached asymptote within this time as well.

Implications

The findings of the current meta-analysis can inform design of future cue-reactivity studies. The results suggest a possible ceiling effect may have reduced the magnitude of cue reactivity in more experienced smokers and for all smokers in studies requiring abstinence before cue exposure procedures. Owing to the possible risk of ceiling effects, abstinence may raise the pre-cue level of craving so high that the magnitude of craving due to cue reactivity per se cannot be fully evaluated. Somewhat relevant to this is peak provoked Craving, which focuses on extreme craving states triggered by the combination of abstinence and smoking cues to model real-world antecedents to lapse and relapse.[87] Thus, including an abstinence requirement—which itself clearly raises craving in the absence of any control cue exposure—may increase the risk of a ceiling effect. Further, baseline craving may not be adequate when used as the only point of comparison. Studies may need to use a neutral cue condition to compare against smoking cues to better control for the effects of time per se while also isolating reactions to cues specific to smoking per se. In the current study, 10 of the 13 studies using a baseline comparison also had an abstinence requirement, limiting evaluation of the magnitude of cue reactivity.

The magnitude of cue reactivity was found to be stable across years of smoking when using a neutral cue for comparison. These findings add to the cue-reactivity literature to show that this phenomenon is relatively consistent across the duration of smoking histories contained in the studies assessed here and are important for researchers to take into consideration when designing and reporting future cue-reactivity studies.

Limitations and Future Directions

Limitations of the current study need to be taken into consideration when interpreting the results. The search terms used to identify relevant studies may have been too narrow, potentially excluding studies that would have otherwise qualified for inclusion. Reference sections from related review studies were also examined to identify studies absent from the literature search, but there is a potential that not all possible studies were included in the present analysis. Also, there was no formal method used to assess the quality of each study included in the analysis. Analyses suggested a potential for publication bias, but after adjusting the omnibus effect size for publication bias, the resulting overall effect size was still statistically significant. Thus, although the potential for publication bias was not trivial, the omnibus results were still valid.[88]

Participant characteristics included as covariates in the analyses (eg, mean years of smoking, mean age) were aggregates of sample means. As noted earlier, use of this study-level data rather than participant-level data may have led to ecological bias (ie, discrepancies between associations made using aggregate-level vs. individual-level data[89]). Without participant-level data, the extent of ecological bias cannot be determined.[89,90]

Another limitation was that studies included in the meta-analysis were mostly those on smokers with extensive smoking histories—there were a limited number of studies with smokers at the earlier spectrum of years of smoking. Of the 60 studies, 12 had samples with less than 6 mean years of smoking, with only two studies coming close to initial smoking at approximately 2 mean years of smoking. There is a lack of cue-reactivity research in early smokers—possibly due to the ethical issues that arise when studying youth substance use.[91]

Despite the limitations, results of the current meta-analysis updated our knowledge of methodological factors affecting the measurement of cue reactivity, highlighting important relationships between years of smoking and magnitude of cue reactivity, depending on use of baseline or neutral cue comparisons and abstinence requirements. Additional research is needed to replicate and extend these findings and fill gaps in the literature. The

current results suggest a ceiling effect, but this was not able to be directly tested without participant-level data. Additional research directly testing for a ceiling effect in cue-reactivity research is needed to confirm the implications from the current meta-analysis. One such study could measure cue reactivity in a large sample of smokers with heterogenous durations of smoking histories, to directly assess how cue reactivity varies due to years of smoking. As also noted earlier, there is a lack of cue-reactivity research using early or adolescent smokers. This is a glaring hole in the literature that needs to be addressed with additional studies to more fully understand how cues come to promote smoking persistence in earlier smokers.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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