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Peak Provoked Craving: An Alternative to Smoking Cue-Reactivity

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Abstract

Smoking cue-exposure research has provided a powerful tool for examining cravings in the laboratory. A key attraction of this method is that tightly controlled experimental procedures can model craving experiences that are presumed to relate to addiction. Despite its appeal, key assumptions underlying the clinical relevance of smoking cue reactivity studies recently have been questioned. For both conceptual and methodological reasons it may be quite difficult to tease apart cue-based and abstinence-based cravings. Moreover, conventional cue-reactivity procedures typically generate levels of craving with only minimal clinical relevance. We argue here that sometimes it is unfeasible—and in some instances conceptually misguided—to disentangle abstinence-based and cued components of cigarette cravings. In light of the challenges associated with cue reactivity research, we offer an alternative approach to smoking cue exposure experimental research focusing on peak provoked craving (PPC) states. The PPC approach uses nicotine-deprived smokers and focuses on urges during smoking cue exposure without subtracting out urge ratings during control cue or baseline assessments. This design relies on two factors found in many cue exposure studies—nicotine deprivation and exposure to explicit smoking cues–which, when combined, can create powerful craving states. The PPC approach retains key aspects of the cue exposure method and in many circumstances may be a viable design for studies examining robust laboratory-induced cravings.

A common approach to studying craving is to expose individuals to cues associated with their addicted substance under controlled laboratory conditions and observe their reactions. Cue-reactivity research uses this cue exposure manipulation to focus on the difference between urges found during smoking cue exposure and those during an abstinence-based "baseline" or control cue exposure. Presumably this difference in urge reflects cue-elicited or cue-specific craving. Despite demand for established laboratory-based procedures to elicit cravings, important concerns related to smoking cue-reactivity have moved to the fore. Perkins[1] recently questioned the clinical relevance of self-reported craving in response to smoking cues, cautioning that investigators still must "justify why studies of cue-induced craving contribute to our understanding of dependence." (p.1610). His review indicates that, despite its promise, there is little evidence that cue-elicited cigarette craving predicts smoking relapse [see also 2].

Others have defended the potential clinical relevance of cue-elicited craving. Its inconsistent association to relapse may be due to poor psychometric properties of craving instruments[3],

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poor representativeness of cues[1,3], small sample sizes[4], or recruitment of smokers not currently interested in quitting[4,5]. Some suggest that expanding the set of craving-related measures beyond self-report may help support the validity of cue-reactivity[1,3,5–7].

Cue-reactivity

Although these explanations have merit, there remain fundamental questions about smoking cue-elicited craving research that suggest that in many instances the smoking cue-reactivity paradigm may not achieve what it is designed to do. A primary issue is the degree to which cue-specific cravings can be disentangled from abstinence-based cravings. When smokers, who sometimes are nicotine-deprived, enter a laboratory rich with smoking cues, completing a "baseline" urge questionnaire likely cues their cravings, making it difficult to obtain uncued ratings. While there is scant evidence that abstinence enhances cue-specific craving[8], self-reported cravings may be poorly equipped to detect such differences. Studies using response time probes[9], eye-tracking[10], and smoking Stroop tasks[11] suggest it may not take a strong smoking cue during withdrawal to provoke cravings. At least among abstinent dependent smokers, cue-elicited urge indexed as the difference between the cued and "uncued" condition likely underestimates the effect of smoking cue-exposure on urges[6].

Overall, cue-specific craving effects can be strong[12]. It is important to distinguish, however, between a substantial cue-specific craving effect and a robust level of craving. Although a study may yield significant cue-specific craving, the absolute level of craving generated in a cue-reactivity study (or absolute difference between the neutral- and drug-cue conditions) may be clinically unremarkable. Indeed, this is common when participants smoke just before the study. In many of the studies cited by Perkins[1] that failed to show links between cue-elicited craving and relapse, smokers were non-deprived beforehand and reported fairly mild urge levels during cue exposure.

Conversely, a study may generate a relatively weak cue-specific craving effect while the overall level of craving observed in the research was strong. For instance, a smoker could rate a 90 (on a 100-point scale) during the control condition and 100 during a smoking cue-condition. The cue-specific craving produced may appear to be weak (+10), yet the overall high level of craving in the drug-cue condition may be informative. Many studies relying on dependent nicotine-deprived smokers may capture some cued craving during baseline craving assessments, and when deprived and nondeprived groups differ during this initial assessment, it may be difficult to show additional craving enhancement once the explicitly manipulated smoking cue is presented. Even without ceiling effects, high pre-cue urge scores can limit sensitivity to detect further increases related to smoking cue-reactivity[13].

Peak-Provoked Cravings

Given these concerns with traditional smoking cue reactivity studies, we offer an alternative approach to cue exposure, "peak provoked craving" (PPC), which may prove useful for understanding smoking etiology. [We use the term "cue exposure" to denote an experimental manipulation used in both cue-reactivity and PPC studies, and are not referring to a clinical intervention.] PPC is not meant to replace cue reactivity but can be seen as a complementary approach. The PPC approach uses nicotine-deprived smokers and focuses on urges during smoking cue exposure without subtracting out urge ratings during control cue or baseline assessments. PPC relies on two factors found in many cue exposure studies-nicotine deprivation and exposure to explicit smoking cues-which, when combined, can create powerful craving states[14–16]. Traditional cue-reactivity studies attempt to isolate cue-specific sources of craving. In contrast, the goal of PPC is to examine *strong* craving irrespective of its source. PPC does not aim to disentangle different components that

contribute to relapse, but attempts to provide a more ecologically valid and clinically potent methodology by focusing on the impact of the synergistic effects of abstinence and cue-induced cravings.

The PPC approach assumes that sometimes it is unfeasible-and in some instances conceptually misguided-to disentangle abstinence-based and cued components of cigarette cravings. As opposed to milder craving states produced with just nicotine deprivation or just a smoking cue, the assumption motivating use of PPC is that we can obtain valuable data about addiction by examining a smoker in a peak craving state. Consistent with this "critical mass" perspective are findings from both laboratory[14, 16] and field studies. For instance, following a quit attempt, pre-lapse urges were uncorrelated with abstinence self-efficacy judgments except during peak urges when confidence in remaining abstinent plummeted, suggesting that extremely high urges may be "a categorically different experience for the smoker than urge at any other level"[17, p. 659; see also 18]. Moreover, the potentially discontinuous nature of craving when mapped onto a sudden discontinuous relapse process suggests that the relationship between craving and relapse may be captured inadequately by simple linear modeling[19]. Analogous to this PPC approach is classic research examining diabetes heritability. Twin studies originally revealed surprisingly modest concordance rates for the disease. When exposed to an extreme infusion of glucose (glucose tolerance test), however, concordance rates rose dramatically[20, p. 256], suggesting that extreme conditions were necessary to observe vulnerability.

Moreover, PPC recreates what is likely a very common relapse situation. Many relapse episodes occur when smokers are in the early phases of abstinence and are confronted with cues that remind them of smoking. In this real-world amalgam of risk, the particular sources of craving may be less relevant than the combined effects of the manipulations on cognitions, emotions, and behaviors associated with cigarette craving. To investigate reactions to those scenarios, we need to study it under controlled conditions where we replicate the full complement of factors that may drive lapses. The rationale for use of PPC to investigate both individual differences and mean state-level effects of craving manipulations are next addressed.

Individual differences

In contrast to many of the cue-reactivity findings noted by Perkins[1], PPC is consistently related to clinical outcomes. Only one relapse study reviewed by Perkins included both smoking abstinence and cue-exposure. Peak urge ratings predicted first-week lapsing and time to first lapse[21]. Moreover, though not addressed by Perkins, peak cravings were correlated with nicotine dependence[22]. Similarly, there was a link between PPCs and smoking rate, but no such relation for cue-specific craving[23].

Three studies reviewed by Perkins[1] evaluating transdermal nicotine also provide general support for PPC. Tiffany et al.[24] found an effect of nicotine patch on peak-level cravings during cue exposure, with abstinent smokers on placebo patch reporting stronger urges than abstinent smokers on nicotine patch. Elsewhere, nicotine patch did not reduce cravings during cue exposure, though this study used a brief (4-hr) abstinence period[25]. In the third study, the patch again reduced urges during peak craving[21]. Finally, in two nicotine gum studies noted by Perkins, gum chewing post-cue exposure led to a faster and more extensive drop in urge ratings than chewing placebo gum[26], and chewing a rapid release nicotine gum led to a faster drop than a standard nicotine gum[27]. Together, the same cue exposure studies suggesting that smoking cue-reactivity are not linked to clinically meaningful outcomes[28] support the clinical relevance of PPCs. Urges rated during peak cravings-irrespective of their source-were lower for the medicated than for placebo participants.

State-level craving effects

In addition to relating individual differences in peak cravings to clinical outcomes, PPC studies can provide valuable information about craving states and related experiences. To address these aims, low- and high-craving conditions are contrasted. This section addresses several studies from the Sayette laboratory that illustrate the variety of "craving state" questions amenable to the PPC design. Whether construed as examining correlates or effects of craving, these studies suggest plausible explanations for why cravings may promote lapses[30]. Research using all four cue X abstinence conditions (abstinent + smoking cue, abstinent + control cue, nonabstinent + smoking cue, nonabstinent + control cue) indicates that abstinence + smoking cues typically produce the highest cravings, whereas nonabstinence + control cue produces the lowest cravings[9]. For instance, urge ratings during the abstinent + smoking cue condition averaged 71 (on a 0–100 scale), which was significantly greater than the 21 rating for the nonabstinent + control cue, and the 34 and 48 ratings for the two "intermediate" conditions[13]. Consequently, in the following studies, only these two "extreme" conditions were used. Although the studies we cite do not directly test the superiority of the PPC design, they do suggest that the PPC condition has significant associates not found with the low-urge comparison condition.

Sayette and Hufford[31] found that smokers asked to list pros and cons of smoking generated significantly more positive items about smoking during the high- than the low-urge assessment. No such pattern emerged for negative information. Elsewhere, high-crave smokers evaluated the probability of positive outcomes to be greater than did low-crave smokers[13,32]. Together, the generation and evaluation of smoking-related information from these PPC studies suggest that smoking becomes more attractive while craving[30,33]. Although one might include these measures in a cue-reactivity design, it would be hard to assess smoking-related information for deprived smokers in the control cue condition without cuing smoking.

The PPC design examined the impact of craving on temporal cognition[32]. High-craving participants reported time passed more slowly than did low-craving smokers while waiting for the chance to smoke a cigarette[32; see also 34]. Time appears to slow during moments requiring self-regulation, which may reduce capacity for self-control[35]. Because the opportunity to smoke was a central component of the delay period (i.e., time before one can smoke) a deprived + neutral cue condition would have been difficult to execute, as the known opportunity to smoke following the delay would have become a smoking cue.

Using PPC, smokers in a low craving state, but not those in a high-craving state, under-predicted the value of smoking during a subsequent high craving session[36]. Clinically, this study suggests that smoking evaluations completed in a clinic in a neutral state may not resemble a smoker's attitudes about smoking during high-risk moments. Use of a deprived + neutral cue group as part of a traditional four-cell cue-reactivity design would have been impractical, as the task required assessing the value of smoking a cigarette, which necessarily would cue these subjects to smoking.

Finally, a PPC approach linked affect-related facial responses to smoking cues to clinically meaningful individual differences. During cue exposure, smokers simultaneously displaying both positive and negative affect-related expressions were more likely than those not showing this facial pattern to report ambivalence about quitting[37].

Peak Provoked Cravings vs. Abstinence-Based Cravings

As suggested by the studies reviewed above, PPCs may relate to nicotine dependence-related variables. Yet, in many studies, the pre-cue (putatively abstinence-based) craving

levels reveal similar associations to these outcome variables[22]. Admittedly, considerable variance linking PPCs to clinical outcomes is also captured in the "abstinence only" baseline assessment. At least when studying individual variation in cravings, it is important to justify the cue-exposure manipulation in addition to a smoking abstinence requirement.

Before offering a defense of PPC to evaluate individual differences, we consider why the relations between relapse and either PPC or abstinence-only cravings may be similar. Perkins[1] concluded that the addition of smoking cues may not offer clinically meaningful information over an abstinence-only condition. Alternatively, smoking cues may be important-at least under high-urge conditions-but the supposedly pre-cue or control-cue craving assessment already may include a cued component, and the additional cuing offered by the explicit cue manipulation does not add substantively to the prediction afforded by the implicitly cued abstinence condition. That is, smoking cues may matter, but the ability to demonstrate their predictive value often may be compromised.

The PPC focus on the cue exposure urge rating (rather than an abstinence-only rating) makes sense clinically. Consider the study by Tiffany et al.[24]. Patch use reduced urge ratings during neutral and control cues, but, "had no significant impact on craving generated by smoking-related cues." (p. 238). One might conclude that the patch had no effect on smoking cues-only on abstinence-related cravings. Accordingly, a smoker preparing to quit might assume that nicotine patch use will alleviate withdrawal-related cravings, but not episodic bursts of craving provoked by smoking cues. Yet during *in vivo* smoking cues, participants on the nicotine patch reported an urge of about 55 (on a 0–100 scale) while those on placebo patch reported levels at about a 65. If smokers worried about the overpowering cravings they might encounter while quitting, then arguably it is important to appreciate that urges experienced during cued high-risk moments are likely to be significantly reduced while using the patch. This point is emphasized in a PPC approach, but may be lost when research focuses solely on cue-reactivity effects: "However, smokers might be advised not to expect that craving triggered by smoking-related cues will be dampened by use of the patch"[24, p.238].

Because studies tend to control for "baseline" differences in urges, the smoking literature is replete with studies suggesting that one group is equally or less reactive to cues than another, when actual urge ratings during smoking cues for the two groups tell a different story. This point is important if, upon reaching a certain threshold, cravings trigger a smoking lapse. That is, if strong craving, irrespective of source, exceeds a threshold that generates lapse, then anything that reduces craving (e.g., nicotine patches) and brings it below the threshold for action will be clinically beneficial.

Limitations of PPC Research

Combining smoking cues with abstinence using a PPC approach precludes distinguishing between cued and abstinence-based cravings. This limitation must, however, be weighed against cue reactivity studies in which pre-cue or control cue assessments can themselves trigger cravings among participants who are in nicotine withdrawal. For drugs less prone than nicotine to short-term withdrawal, pre-cue or control cue assessments may be less likely to cue cravings. It remains critical, though, that sufficient craving be elicited during cue-exposure. For instance, alcohol cue-reactivity effects are substantially weaker than effects using other abused substances[12], and peak craving ratings for drugs other than tobacco often fall below the scale's midpoint[38].

Sometimes use of an explicit smoking cue may be unnecessary or impractical to implement. For instance, a measure may be time-consuming and require sustained attention[39]. Although such constraints could be addressed using certain smoking cues (e.g., cigarette

pack lying visible during the entire manipulation), smokers may habituate to such a cue. One then may wish to evaluate the impact of smoking withdrawal alone, without using smoking cues.

As with any cue exposure approach, the PPC design may need to address potential ceiling effects. Nevertheless, this concern may be less problematic for PPC than smoking cue-reactivity studies. A maximum urge score should reflect that a smoker is experiencing their highest possible craving. Yet sometimes nicotine-deprived heavy smokers report such scores before smoking cue-exposure. Consequently, ratings cannot increase, suggesting that smoking cues have no impact on urges, that peak craving is being under-reported, or that, in retrospect, the pre-smoking cue craving score was an overestimation. When 20% of smokers report maximal scores during cue exposure[22], ceiling effects cannot be ignored. At least when the PPC design is used, this potentially underreported maximum score during peak will not be further eroded by an inflated pre-cue score used to compute cue-reactivity. That is, such a smoker still is registering a maximum peak score, whereas that same person would have recorded a very small cue-reactivity effect due to the inflated pre-smoking cue score.

Future Directions

To avoid ceiling effects, studies might include approaches such as magnitude estimation[13] or questionnaires containing a wide range of craving levels represented across the items. Alternatively, research might benefit from computerized adaptive testing (CAT)[40] if ceiling or floor effects are an issue. CAT may be well-suited to deal with these issues and would force investigators to consider underlying parameters of craving responding. Unfortunately, these assessments are imperfect solutions: magnitude estimation is limited psychometrically, CAT is cumbersome to develop, and questionnaires with a wide range of items may become excessively long and reactive. Regardless, ceiling effects should be addressed-and at least evaluated-in any study. In addition to measurement issues, craving manipulations may need to generate stronger levels than is often created to study clinically meaningful levels of craving. The PPC approach is one attempt to do that.

The foregoing suggests that the response during peak craving is meaningful when predicting relapse particularly if the aim is to model potentially overwhelming real-world struggles derived from a combination of sources. Although intuitively appealing, this “critical mass” approach need not be true. A moderate craving state could prove most sensitive to relapse vulnerability. This possibility suggests conducting research testing which levels of craving are most clinically meaningful. By shifting away from the forced dichotomy of abstinence-based craving vs. cued cravings, research might instead develop manipulations that vary degree of craving intensity or complexity (e.g., altering degree of deprivation [41], strength of cues, or context of cue exposure).

Research is needed to test the extent to which PPC is more strongly associated with clinically relevant outcomes than either abstinence-induced or cue-induced craving alone. That is, what is the incremental clinical validity of combining cues and abstinence? We have described studies showing that variables that might be indirectly related to clinical outcomes (e.g., attractiveness of smoking) appear to be best predicted under PPC. Even a cursory review of the literature reveals the relationships between craving and relapse are mixed, but we believe that a clearer delineation of the conditions used to generate craving will reveal that the combination of cues and abstinence will yield the strongest predictive validity regarding treatment outcomes.

Summary and Conclusions

Smoking cue exposure research is a burgeoning research area, and the method has delivered valuable insights about drug-motivational processes[8]. Nevertheless, sometimes it may prove unproductive to try to disentangle nicotine deprivation and smoking cue reactivity. We advocate increased consideration of PPC designs to study the impact of smoking cues on abstinent smokers when disaggregating nicotine deprivation and smoking cue-reactivity is problematic. PPC may be the preferred approach for understanding smokers' reactions while craving when it is necessary to generate a craving level that has meaningful overlap with craving experienced during real-world high-risk situations (e.g., first days of a quit attempt).

The PPC approach may serve as a viable complementary design that, together with cue-reactivity research, can illuminate key aspects of cigarette craving. Despite some important concerns, we agree that cue-reactivity research should not be abandoned[4,42]. If executed properly, the payoff of distinguishing between abstinence-based and cued cravings is valuable. Continued interest in both approaches could elucidate clinically meaningful effects of craving (PPC), as well as somewhat subtler (and arguably more contrived) effects that may be of theoretical interest (cue-reactivity). Whether one is interested in PPC or cue-reactivity, there remains need to expand the battery of measures beyond self-report. Use of brain-imaging methods represents one current focus that may prove illuminating[43,44]. Broadening assessment to include measures of affect, cognition, and motivation may be useful[3,6]. Research also would benefit from inclusion of both distal and proximal smoking cues[45,46], and personalized cues[47,48]. As with PPC research, further development of virtual reality methods may be useful in this respect[49]. While promoting PPC research, we also aim to highlight the importance of smoking cue-reactivity research more generally. At issue is whether cued urge scores adjusted for baseline or neutral assessment levels are as critical as actual unadjusted urge scores during exposure to smoking cues for understanding addiction processes.

Elsewhere, Piasecki, Smith, and Baker[50] concluded: "Finally, our overwhelming feeling… is that we, like others in the field, have been very busy, but have not thought deeply enough about what we are doing.... However, if the aim of cue exposure research is to permit strong inference regarding stimulus control over drug motivational processes…it seems clear that our research strategies require scrutiny." (p. 343). This paper attempts to scrutinize various cue-exposure approaches. Nicotine-deprived smokers sometimes are at such elevated craving levels that they have insufficient room to increase their craving in response to smoking cues. On the other hand, nondeprived smokers may not experience a clinically meaningful level of craving. If we continue to conduct research in which baseline or control cue scores of deprived heavy smokers are presumed to be completely uncued, and when potential ceiling effects are brushed aside, then the impact of the cue-exposure method may be marginalized. The power of the cue-exposure paradigm is that it can elicit robust cravings that then can be studied in detail under controlled conditions. The PPC approach retains the strengths of cue-exposure research, recognizes the obstacles inherent in parsing abstinence from cues, and offers avenues for advancing knowledge regarding smoking. Thus, we believe that cue-exposure studies remain an important approach to improve understanding of addiction etiology, but that raw peak craving scores obtained during smoking cue exposure investigations should become an increased focus of study.

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