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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

CRITICAL REVIEW

How laboratory studies of cigarette craving can inform the experimental alcohol craving literature

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Abstract

Interest in alcohol and other drug craving has flourished over the past two decades, and evidence has accumulated showing that craving can be meaningfully linked to both drug use and relapse. Considerable human experimental alcohol craving research since 2000 has focused on craving as a clinical phenomenon. Self-reported craving to drink typically has served as a catch-all for the craving construct in these studies, whereas few studies have considered craving as a process (or hypothetical construct) that interacts with other phenomena to affect use. In contrast to alcohol, we believe that recently there has been more mechanistic work targeting cigarette craving–related processes. Here, we briefly present a narrative review of studies of acute alcohol craving in humans that have been conducted during the past two decades. We then specify important ways in which alcohol and tobacco differ (e.g., the role of withdrawal), and we note the unique challenges in inducing robust alcohol craving states in the laboratory. Finally, we offer recommendations for how the alcohol field might advance its conceptual understanding of craving by adopting ideas and methods drawn from the smoking research literature. Specifically, we suggest that researchers extend their studies to not only examine the link between alcohol craving and relapse but also to focus on *why* and, in some instances, *how* alcohol cravings matter clinically, and the circumstances under which craving especially matters. We propose research to investigate the shifts in alcohol-related cognitive and affective processing that occur during alcohol craving states. Furthermore, we highlight the value of research examining the level of insight that individuals with varying levels of alcohol involvement possess about their own craving-related processing shifts. We believe that laboratory studies can provide rich opportunities to examine conceptual questions about alcohol craving that are central to addiction.

KEYWORDS
alcohol, cigarette, craving, cue-induced craving, experimental

INTRODUCTION

Researchers have long posited a relationship between craving and addiction (Lindesmith, 1938; Wikler, 1948; World Health Organization, 1955). Much of the seminal work on craving focused on individuals with alcohol dependence.[1] For instance, Jellinek (1960) proposed that craving underlies the loss of control at the heart of addictive behavior. Although interest in craving waned during the height of behaviorism (e.g., Mello, 1975), craving again became a focus of study once the cognitive revolution took hold in the addiction field (Sayette et al., 2000; Tiffany, 1990; Wilson, 1987). Studies began to focus on craving relief as a central component of interventions (e.g., Cooney et al., 1989). Craving remained a chief priority for alcohol research at the end of the past century. This clinical interest in craving peaked with a series of workshops and mini-conferences sponsored by both the U.S. *National Institute on Drug Abuse* and the *National Institute on Alcohol Abuse and Alcoholism* (NIAAA), which led to special issues in journals such as *Addiction* (Addiction, 2000) and *Alcohol Research and Health* (NIAAA, 1999). A clear message emanating from many of these articles and talks was that alcohol research would do well to examine theoretical issues germane to craving (e.g., Drummond, 2000; Niaura, 2000; Sayette et al., 2000; Tiffany & Conklin, 2000). In particular, there was a call to better understand craving mechanisms to develop more effective alcoholism treatments (Abrams, 2000; Drummond et al., 2000).

The purpose of the current narrative review is to address progress in alcohol craving research since this proliferation of work around the turn of the century. We focus on human experimental alcohol craving work, referred to hereafter simply as "craving") and first provide a brief summary of what we have learned over the past two decades. We argue that while much has been learned during this time, there has been relatively more mechanistic work published in the cigarette craving literature than the alcohol craving literature. After noting ways in which alcohol and tobacco differ, we offer suggestions for how the alcohol field might advance mechanistically by adopting ideas and methods from the smoking research literature. Specifically, we focus on studies that induced strong cigarette craving states so that important state-dependent cognitive and affective shifts could be captured as they unfolded. The goal of such studies is to provide a better understanding of what happens during strong craving states that make smoking especially likely. As applied to the alcohol field, these types of studies would extend beyond linking craving to relapse and instead would focus on *why* cravings matter and the mechanisms (the *how*) and circumstances under which craving especially matters.

HUMAN EXPERIMENTAL ALCOHOL CRAVING WORK OVER THE PAST TWO DECADES

Craving is commonly defined as a drug-acquisitive state motivating drug use (Sayette, 2016). Some researchers have distinguished between craving as a clinical phenomenon described by patients (typically using self-report rating scales) and craving as a process or construct that interacts with other phenomena to affect drug use. From the latter perspective, craving is typically acknowledged to be a hypothetical motivational construct that can be tested and measured using a variety of methods (Sayette, 2016). In other words, "craving is something patients experience and describe as a phenomenon of concern…It is also a process potentially interacting with a variety of other phenomena to maintain [drug use behavior]" Drummond et al., 2000, p. S248). Human experimental alcohol craving studies over the past two decades have tended to focus on craving as a clinical phenomenon, with self-reported craving often serving as a proxy for the craving construct (i.e., an urge rating was assumed to offer a fairly straightforward readout of the craving experience). This research approach has been productive and likely contributed to the elevation of craving as a criterion for the diagnosis of substance use disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association, 2013). Below, we first review the ways in which alcohol craving has been induced in laboratory settings and then we summarize the advances that have been made over the past two decades by conceptualizing craving as a clinical phenomenon, rather than a hypothetical construct.

Craving induction

There have been multiple approaches to elicit alcohol craving. The vast majority of laboratory studies have used alcohol cues to induce craving states (e.g., Jones et al., 2013; Kambouropoulos & Staiger, 2004), although some have used negative affect/stress exposure manipulations (e.g., Brady et al., 2006; Bresin et al., 2018; Mereish & Miranda, 2019), priming doses of alcohol (e.g., Christiansen et al., 2013; Courtney et al., 2015; Fernie et al., 2012; Schoenmakers et al., 2008), or placebo beverages (Leeman et al., 2009) to induce craving. When alcohol cues were used, most studies exposed participants to alcohol images or videos (e.g., Delonca et al., 2021; Field et al., 2005, 2011; Franken, 2002; Franken et al., 2003; Heinz et al., 2004; Hicks et al., 2015; Ingjaldsson et al., 2003; Van Dyke & Fillmore, 2015), or to in vivo alcohol cues with participants holding, sniffing, and/or tasting an alcoholic beverage (e.g., Filbey et al., 2008; Jones et al., 2013; Mackillop, 2006; Reid et al., 2006; Thomas et al., 2005). Other studies used imagery (e.g., Chaplin et al., 2008; Yarmush et al., 2016), virtual reality (Simon et al., 2020) or multiple cue types (e.g., imagery scripts combined with in vivo alcohol cues [Mackillop et al., 2007, 2010], alcohol images combined with in vivo alcohol cues [Field & Jones, 2017; Li et al., 2015], and negative affect induction combined with in vivo alcohol cues [Adams et al., 2019; Nesic & Duka, 2006]). Although the magnitude of these urge ratings is not always robust, these manipulations have generally reliably increased craving (see also Carter & Tiffany, 1999).

The methodological strengths of many of these studies using alcohol cue exposure paradigms are worth mentioning. First, many researchers used in vivo alcohol cues with participant preferred beverages serving as the cues (e.g., Manchery et al., 2017; Ramirez et al.,

2015a; Thomas et al., 2005; Van Den Wildenberg et al., 2007), which is thought to increase the likelihood of generating a strong craving level in the laboratory (Sayette & Tiffany, 2013).

We believe a second strength of many alcohol cue exposure studies is the use of single cue exposure manipulations rather than multiple trials of both alcohol and control cues. Our position is not universally held, however, and thus deserves elaboration. At issue are two key, yet potentially competing, research objectives: (a) to generate a robust and reliable alcohol cue "signal" by using multiple cue exposure trials and (b) to avoid generating carryover effects arising when some residual response to an alcohol cue presentation carries over into the experience of the subsequent (in some cases neutral) cue exposure trial. We refer the interested reader to a detailed analysis of this research quandary (Sayette et al., 2010). Here, we touch on some relevant conceptual and empirical points.

At first glance, the decision to counterbalance multiple alcohol and control trials seems obvious. Certainly, the inclusion of multiple trials of both drug and control cues adds to the reliability of the task relative to single-trial designs. Yet, such an approach is problematic if carryover effects interact with the different experimental treatments or orders of treatments. In a critical analysis of this issue, we have observed:

"Indeed, many prominent research methodologists have concluded that differential carryover effects across conditions preclude use of a counterbalanced design (e.g., Keppel, 1992). Winer (1971) warns of the harmful effects of counterbalancing in his classic research design text: "A strong word of warning is required in connection with order (or sequence) effects. If such effects exist, randomizing or counterbalancing does not remove them; rather such procedures completely entangle the latter [order effects] with treatment effects" (p. 517). This warning is reinforced by Campbell and Stanley (1963), who note that successful counterbalancing depends on the ability to rule out such interactions." (Sayette et al., 2010, p. 1069).

Unfortunately, the majority of studies using a multitrial approach fail to provide sufficient information to address possible carryover effects (Sayette et al., 2010). So how big of a deal is this concern? Betts et al. (2021) review studies that suggest that multitrial smoking cue studies are more effective in eliciting cued craving responses than their single-trial counterpart (suggesting the opposite of carryover effects). We are less confident of this conclusion for three reasons. First, as noted by Sayette et al. (2010), most studies that use a multitrial approach fail to provide the data necessary (main effects or interactions with order) to address the question of carryover properly. Second, studies that have provided relevant information suggest that it can be a concern (Field et al., 2009; Monti et al., 1987; Rohsenow & Niaura, 1999; Waters et al., 2005; Wilson et al., 2007. Third, some of the single-trial studies that provide relevant data supporting their effectiveness were not included in the Betts et al. (2021) review (see Sayette et al., 2021). These omitted studies reveal robust effects of smoking cues using single-trial designs. Further discussion of the Betts et al. (2021) meta-analysis extends beyond the scope of this article. We suspect the carryover issue will continue to be debated and hope that moving forward, investigators choosing to use a multitrial approach will provide the raw data (e.g., include order as a factor and offer adequate power to detect trial order interactions and not simply main effects) needed to sensitively evaluate possible carryover concerns (for additional consideration see Sayette et al., 2010).

Given these concerns about carryover effects, several alcohol cue exposure studies have used single in vivo cue exposure manipulations in either a between-subject design where participants were randomly assigned to either the alcohol or neutral cue (e.g., Adams et al., 2019; Field & Jones, 2017; Gauggel et al., 2010; Jones et al., 2013; Kreusch et al., 2017; Mackillop & Lisman, 2007; Mackillop et al., 2007) or a within-subject fixed order design in which neutral cues preceded alcohol cue (e.g., Ivory et al., 2014; Kambouropoulos & Staiger, 2004; Kambouropoulos et al., 2009; Li et al., 2015; Papachristou et al., 2012; Papachristou et al., 2013; Thomas & Deas, 2005; Van Den Wildenberg et al., 2007; Wildenberg et al., 2007). Researchers who counterbalanced the order of these single cue presentations often ran study sessions a week apart to minimize potential carryover effects (e.g., Baines et al., 2019). Taken as a whole, laboratory alcohol cue exposure manipulations over the past two decades have methodological strengths worth mentioning (i.e., using participant preferred beverages as in vivo alcohol cues and presenting alcohol and control cues in such a way as to avoid carryover effects). Importantly, these studies have advanced knowledge about craving as a clinical construct (see below).

Value of conceptualizing craving as a clinical construct

Laboratory studies that induced alcohol craving have revealed the clinical utility of craving. Perhaps most importantly, cue-elicited alcohol craving (as assessed *via* self-reported urge ratings) has predicted alcohol consumption in the lab (Baines et al., 2019; Bresin et al., 2018; Cahill et al., 2021; Field & Jones, 2017; Mackillop & Lisman, 2007) and outside the lab (Ramirez & Miranda, 2014), and has predicted increased operant responding to earn alcoholic drinks (Van Dyke & Fillmore, 2015). Studies have also shown that cue- and negative affect–elicited craving during alcohol dependence treatment predicts probability of a lapse (Papachristou et al., 2014), time to relapse (Brady et al., 2006; Cavicchioli et al., 2020; Sinha et al., 2011; though see Witteman et al., 2015), and alcohol consumption post treatment in a clinical trial (Miranda et al., 2020). These findings provide compelling evidence that craving is clinically meaningful.

Another focus of craving research has been to examine how people with varying experiences with alcohol differentially respond to alcohol cues (e.g., Field et al., 2011; Papachristou et al., 2012). For instance, individuals with alcohol dependence reported stronger craving in response to alcohol cues than did healthy controls (Reid et al., 2006; Strosche et al., 2021; Thomas et al., 2005) and social drinkers (Myrick et al., 2004), and individuals with alcohol dependence were less able than social drinkers to regulate their craving in response to cues (Naqvi et al., 2015). Similarly, individuals with

alcohol dependence reported higher craving in response to a priming dose of alcohol than heavy drinkers (Bujarski & Ray, 2014), and heavy drinkers reported stronger craving in response to alcohol cues than light drinkers (Blaine et al., 2019; Simon et al., 2020). These results illustrate that the strength of the cue-induced craving response increases as experience with alcohol increases, with heavy drinkers and those with alcohol dependence reporting stronger cue-elicited cravings than light drinkers.

Laboratory studies relying on craving ratings as a clinical outcome measure have also attempted to identify individual difference variables that predict the degree of cue-elicited craving. Numerous variables have been tested as moderators or predictors of craving, ranging from gender (Chaplin et al., 2008; Kaag et al., 2019; Nesic & Duka, 2006) to externalizing-related traits [e.g., impulsivity (Papachristou et al., 2012, 2012, 2013; Yarmush et al., 2016), response inhibition (Papachristou et al., 2013), distress tolerance (Lim et al., 2018), reward sensitivity (Kambouropoulos & Staiger, 2009), incentive salience sensitization (Cofresí et al., 2019), sensation seeking (Kambouropoulos & Staiger, 2004); behavioral activation (Franken, 2002)] to internalizing-related factors [e.g., stress/social anxiety (Adams et al., 2019; Snelleman et al., 2014), and thought suppression (Garland et al., 2012)]. Other researchers have investigated appetite-regulating hormones (e.g., Bach et al., 2019), particular genetic polymorphisms (e.g., Bach et al., 2015), and dopaminergic dysfunction in the striatum (Heinz et al., 2004). Taken together, these studies illustrate the many efforts underway to identify moderators of cue-induced craving. More research is required, however, to confirm the role of these individual difference variables in affecting cue-induced craving and the circumstances under which they matter (e.g., in continuing drinkers, following a quit attempt). In particular, models are needed to integrate these different factors to offer a more comprehensive and coherent analysis of which factors are most critical in moderating craving responding and why they do so (see Sher, 1991).

Finally, many laboratory studies using human participants over the past two decades have evaluated alcohol treatment approaches aimed at reducing self-reported cravings. For instance, a number of pharmacological approaches to reduce cue-elicited craving for alcohol have been investigated (e.g., Haass-Koffler et al., 2014; Ray et al., 2019), with promising results for naltrexone (Hendershot et al., 2017), oxytocin (Bach et al., 2019), prazosin (Fox et al., 2012; Milivojevic et al., 2020), memantine (Krupitsky et al., 2007), quetiapine (Ray et al., 2011), topiramate (Wetherill et al., 2021), and citalopram (Zorick et al., 2019). Furthermore, researchers have offered suggestions to improve cue exposure therapy for alcohol dependence (e.g., Buckfield et al., 2021; Conklin & Tiffany, 2002) after unsuccessful studies were noted to suffer from several methodological concerns (Mellentin et al., 2017).

As a whole, studies focusing on self-reported craving indicate that craving is a meaningful clinical construct. With some exceptions—such as studies of attentional bias and response inhibition (reviewed below), as well as those using electrophysiological (e.g., Herrmann et al., 2001; Martins et al., 2019; Petit et al., 2013) and brain imaging methods (see Schacht et al., 2013 and Zeng et al., 2021 for meta-analyses)—however, more work is needed to understand *why* craving is clinically significant. In other words, what happens when one is craving that may lead to alcohol use or relapse? To address this question, we suggest that alcohol craving research extends beyond viewing craving solely as a dependent variable that is assumed to provide a direct readout of one's craving state. Because self-report is subject to multiple influences, craving can also be viewed as a hypothetical construct to be assessed across a range of verbal and nonverbal measures, each with their own limitations: "By systematically manipulating craving levels, putative measures of craving can be evaluated. Such efforts are required in order to provide support for the construct validity of craving" (Sayette et al., 2000, p. S206). This type of research can identify mechanisms that promote drinking or at least make alcohol use especially likely during strong craving states. Such studies have appeared in the nicotine and tobacco literature where research has investigated underlying processes linking craving to smoking behavior. Below, we discuss ways in which tobacco and alcohol differ (e.g., role of withdrawal) and then we address how the alcohol field might advance mechanistically by adopting ideas and methods from the smoking research literature.

CIGARETTE CRAVING STUDIES

Differences between cigarette and alcohol craving studies

Alcohol and tobacco differ in many ways, including their neuropharmacological mechanisms (Benowitz, 2008; Tabakoff & Hoffman, 2013) and the topography of use (Veilleux & Skinner, 2015). There are also important differences between the samples and methods used to study cigarette versus alcohol craving, some of which may explain the relative lack of mechanistic alcohol craving studies. In many ways, smoking is an ideal domain to consider when studying craving (Sayette & Creswell, 2016). The relative ease and safety with which cigarette craving research can be conducted is notable. In contrast, clinical concerns surrounding alcohol withdrawal with severe alcohol dependence (e.g., seizures) may preclude cue reactivity investigations with some individuals in an abstinent state, but testing prior to withdrawal is often problematic as lingering effects of alcohol may act as a confounder.

Inducing intense (yet safe) craving states in the laboratory *via* deprivation manipulations in smokers who smoke throughout the day to maintain an even level of nicotine in the blood are also much easier than doing the same for heavy drinkers who often only drink sporadically (e.g., in the evenings or on the weekends when lab sessions are usually not held; Carter & Tiffany, 1999; Veilleux & Skinner, 2015). Indeed, daily, all-day alcohol use is typically only seen in the most extreme examples of AUD. As such, exposing a smoker to a smoking cue after smoking deprivation is not equivalent to exposing a heavy drinker to an alcohol cue after a similar deprivation period.

For instance, college age smokers exposed to smoking cues following a fairly short (≥6-h) abstinence period reported a strong cigarette craving in response to cues during a weekday laboratory study session (i.e., a mean urge rating of 83 on a 100-point scale; Sayette & Parrott, 1999), whereas it might not be possible to get a social drinker to crave an alcoholic beverage in the afternoon, even if one recruits heavy or hazardous drinkers. In fact, in a study comprising moderate social drinkers and binge drinkers (Blaine et al., 2019), average craving in response to an in vivo alcohol cue (i.e., glasses of chilled beer) only reached 3 on an 11-point scale for the binge drinkers (and reached two for the moderate social drinkers; see also Manchery et al., 2017; Ramirez et al., 2015; and Papachristou et al., 2012 for additional studies showing relatively weak absolute craving levels in response to alcohol cues). Responses this close to the zero (i.e., "not at all") scale anchor for desire to consume alcohol calls into question whether participants were actually craving at all. Indeed, a mild craving may be an oxymoron (Sayette, 2016; West & Brown, 2013), with leading addiction scientists instead applying the term *craving* to overwhelmingly intense desires (e.g., George & Koob, 2013; Volkow et al., 2010).[2] In contrast, exposing-deprived regular smokers to smoking cues elicits powerful cravings in laboratory studies, with craving levels approaching the maximum values on urge scales (Wertz & Sayette, 2001).

Although there are unique challenges for conducting alcohol cue exposure studies in individuals with alcohol dependence, there is precedence. For instance, some alcohol cue exposure studies have tested patients with alcohol dependence who were enrolled in treatment programs (Gauggel et al., 2010; Kreusch et al., 2017) or adolescents (Thomas et al., 2005) and adults (Reid et al., 2006) who met the criteria for alcohol dependence. Indeed, one group of researchers carried out an alcohol cue exposure study in an actual bar close to the inpatient clinic, and participants were exposed to real alcohol cues (Papachristou et al., 2013).

Perhaps, surprisingly, the abovementioned studies often failed to produce robust craving responses, with craving ratings that were either near the midpoint of the craving scale (Gauggel et al., 2010) or well below it (Kreusch et al., 2017; Papachristou et al., 2013; Reid et al., 2006). Such low craving ratings are likely explained by perceived drug use opportunity, which has been shown to influence the intensity of the craving experience. Specifically, individuals report higher craving when drug use is perceived to be available, and there is an intention to use the drug compared to when it is thought to be unavailable (Sayette, 2016; Veilleux & Skinner, 2015). A review of drug cue-exposure studies revealed that patients entering studies as part of drug treatment reported far less craving during cue exposure than continuing users (see Wertz & Sayette, 2001; Wilson et al., 2004). Thus, perceived drug use opportunity is a factor that appears to influence how well researchers can induce an alcohol craving state. For instance, one might assume that strong craving levels would be generated by exposing individuals who are currently engaging in inpatient alcohol treatment to real alcohol cues in an actual bar near the clinic (Papachristou et al., 2013). In fact, however, the average craving level reported only reached 15 on a 100-mm visual analog scale ranging from 0 ("not at all") to 100 ("very much") (see also Gauggel et al., 2010; Kreusch et al., 2017; Reid et al., 2006 for similar relatively low craving levels). Furthermore, one-quarter of the participants did not experience any increase in craving during alcohol cue exposure (see also Litt et al., 2000). Participants were engaged in treatment and were explicitly told that no alcohol consumption would be allowed during the cue exposure task, conditions that have been linked to significantly lower craving levels in response to smoking and alcohol cues (e.g., Carter & Tiffany, 2001; Wertz & Sayette, 2001). Indeed, studies that enroll patients with alcohol dependence who are in treatment often require complete detoxification prior to the cue exposure protocol (Franken et al., 2003; Gauggel et al., 2010; Kreusch et al., 2017), and thus it may be less surprising that craving levels are not particularly robust in these populations.

To permit investigation of changes in cognitive and affective processes that occur in strong alcohol craving states, it may be necessary to expand the methods used to conduct alcohol cue exposure studies. For select patients, one should not rule out implementing alcohol cue exposure protocols (using the participant preferred beverages) in hospital settings before the start of treatment and while they are still drinking alcohol. It is notable that many of the earliest alcohol administration studies, in which alcohol was consumed to points of intoxication, were conducted in this fashion (see Langenbucher & Nathan, 1990). Certainly, this approach will not work for participants who enter treatment in crisis. In addition, while legitimate ethical concerns have been raised, it is notable that NIAAA (2021) continues to express that with strong scientific justification and proper safeguards, alcohol exposure and alcohol cue exposure may be appropriate in individuals who are seeking or receiving abstinence-oriented treatment. We believe that it is under these conditions (i.e., when individuals with alcohol dependence are exposed to alcohol with the opportunity [or at least the belief] that subsequent alcohol consumption will take place) that strong craving states can be produced and conceptual questions about craving (insofar as craving is thought to reflect an intense desire to use [George & Koob, 2013; Volkow et al., 2010]) can be productively addressed (Sayette & Tiffany, 2013). Assuming it is possible to induce a strong alcohol craving state, we suggest below the types of studies that might be performed to inform mechanisms of alcohol craving, drawing on the cigarette craving literature.

Cigarette craving studies that may inform alcohol craving studies

Process research on cigarette craving has often been conducted by inducing craving levels in the laboratory (e.g., by exposing smokers to smoking cues). The peak-provoked craving (PPC) approach, which combines nicotine deprivation with in vivo smoking cue exposure, is particularly promising in this regard (Sayette & Tiffany, 2013). In contrast to traditional cue reactivity paradigms, the PPC design focuses on urges during smoking cue exposure without subtracting out urge ratings during control (neutral) cue or baseline assessments

(Creswell & Skrzynski, 2021; Sayette et al., 2021; Sayette & Tiffany, 2013). In this fashion, the PPC approach aims to generate robust craving states stemming from a combination of abstinence and environmental triggers, in contrast to milder craving states that are produced with nicotine deprivation or smoking cues alone. The idea behind the PPC approach is that researchers can obtain valuable information about addiction by testing a smoker in a peak craving state. A peak craving condition is compared to a low craving control condition, in which smokers smoke just before or at the beginning of the experiment and are exposed to a neutral cue. Below, we review studies using the PPC approach and other experimental manipulations (e.g., deprivation protocols alone) to provoke powerful laboratory craving states to better understand underlying drug motivational properties. In the first instance, both cigarette and alcohol literatures have progressed in parallel, while in the remaining areas, we propose that the studies conducted with smokers can be applied to alcohol craving research to offer insight into why alcohol cravings are clinically meaningful and how cravings may be related to self-regulation failures (see Table 1; Figure 1).

Craving and cognition

We review here shifts in three general cognitive processes that may offer insight into the power of cravings to affect self-regulation failure more generally, and more specifically, succumbing to an urge for a cigarette or an alcoholic beverage: attentional and monitoring/response inhibition processes, informational (reasoning) processes, and temporal cognition (for elaboration, see Sayette & Creswell, 2016).

While craving, attention becomes biased toward smoking and alcohol-related cues (Cahill et al., 2021; Field & Cox, 2008; Field et al., 2005, 2009; Manchery et al., 2017; Ramirez et al., 2015a, 2015b; Sayette & Hufford, 1994; Sayette et al., 1994; Schoenmakers et al., 2008; Waters & Sayette, 2006). More broadly, these findings fit with research indicating that craving draws upon limited capacity and nonautomatic cognitive processes (Tiffany, 1990). Indeed, smokers in a craving state show disruptions in cognitive control processes (e.g., task switching, conflict processing) that are not evident when they are in a non-craving state (Donohue et al., 2020). Similarly, exposure to alcohol-related cues produces transient impairments in inhibitory control (i.e., the ability to stop, change, or delay a response; Gauggel et al., 2010; Kreusch et al., 2017; Muraven & Shmueli, 2006 cf. Baines et al., 2019; Mainz et al., 2012; see Jones et al., 2018 for a meta-analysis) and poorer performance on decision making tasks (Waters & Green, 2003), providing support for the notion that craving can shift non-automatic cognitive processing resources toward drug-related cues (Sayette, 2016). Such shifts in attention with concomitant reductions in the ability to monitor these changes (Sayette et al., 2010; Zhao et al., 2020) or to engage in inhibitory control likely contribute to alcohol use (Field & Eastwood, 2005; Sayette & Creswell, 2016). Better understanding of how attentional biases mediate drinking behavior may help advance efforts to leverage attentional bias interventions to reduce alcohol consumption (cf. Jones & Field, 2021; Pennington et al., 2021).

TABLE 1 Examples of mechanisms linking craving to drug use

Craving and cognition
Enhanced attentional bias to drug cues
Reduction in the ability to monitor attentional biases to drug cues
Diminished response inhibition/disruptions in cognitive control processes
Altered information processing (e.g., enhanced positive outcome expectancies for drug use)
Reduction in the value of nondrug rewards
Altered time perception (i.e., time feels more extended than it actually is)
Craving and emotion
Enhanced positive affect in anticipation of drug use
Dampened stress reactivity in anticipation of drug use
Experience of ambivalence
Insight into cravings
Underestimation of the strength of future cravings (i.e., cold-to-hot empathy gap)

While several studies have shown that exposure to alcohol cues can grab attention and shift nonautomatic cognitive processing resources toward alcohol-related cues (reviewed above), alcohol craving studies generally have not focused on the content of these cognitions. In theory, were attention to refocus toward the unpleasant attributes of alcohol or cigarettes, then attentional shifts alone might not promote (and might even discourage) drinking or smoking. Smoking research using a PPC approach has examined the manner in which cigarette craving influences two cognitive processes that relate to how one makes judgements or decisions (see Kunda, 1990), namely, how one *generates* and *evaluates* smoking-related information (Sayette & Creswell, 2016). For instance, in a peak (vs. low) craving condition, smokers generated a list of smoking characteristics that were positively biased (Sayette & Hufford, 1997) and judged positive smoking consequences to be more probable, relative to negative ones (Sayette et al., 2001, 2005). Craving may bolster drug use outcome expectancies, such that positive outcomes appear more likely than negative ones (Marlatt, 1985). Furthermore, the value of non–drug-related stimuli (e.g., money) is diminished during craving (see Piper, 2015; Wilson et al., 2014). Collectively, these studies suggest that when smokers are craving, relative to when they are not craving, the way that they think about drug use changes in ways that increase the likelihood of use. Examining similar cognitive changes during peak alcohol craving states will likely be fruitful. Some research already has been conducted. For example, in heavy drinkers, MacKillop et al. (2010) found that exposure to alcohol (vs. neutral) cues significantly increased craving and multiple behavioral economic measures of the relative value of alcohol (cf. Mackillop et al., 2007). In addition, Grodin et al. (2018) found that willingness to experience aversive consequences to gain access to alcohol is increased in heavy drinkers when exposed to alcohol cues.

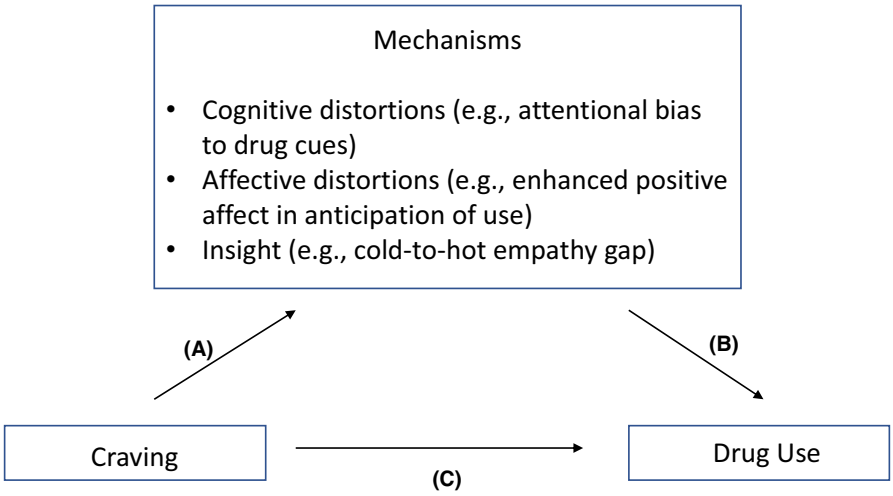

FIGURE 1 Heuristic figure illustrating the difference between treating craving as a clinical phenomenon (path c) versus as a process or hypothetical construct (paths ab)

Finally, a third cognitive domain that may be compromised during craving is time perception. Although we are unaware of any alcohol studies testing this idea,[3] when smokers are craving, time appears to pass more slowly than when they are not craving (Klein et al., 2003; Sayette, et al., 2005). Furthermore, when smokers are in a peak craving state, they tend to overestimate its intensity and duration, predicting that their already high craving will worsen over time (Sayette, et al., 2005). Presumably, if one thinks that resisting the temptation merely postpones the inevitable acquiescence, it is hard to sustain the effort (Baumeister et al., 1994). These findings are consistent with the idea that self-regulation efforts change the subjective experience of time, such that time feels more extended than it really is, which can lead to subsequent self-regulation failures (Vohs & Schmeichel, 2003).

In summary, these clinically relevant shifts in cognitive processing that occur during cigarette craving suggest just some mechanisms that may explain how craving can precipitate drug use. Parallel studies to understand cognitive changes beyond attentional bias and response inhibition that may occur during strong alcohol cravings are needed. There is reason to believe similar findings would emerge for alcohol as for cigarette craving. Nevertheless, potential differences in the time course, intensity, and individual differences (e.g., between daily and intermittent users), and situational contexts between alcohol and cigarette craving may lead to divergent findings, and future studies are warranted to determine just how pertinent these processing changes are in alcohol craving.

Craving and emotion

Research using experimental craving manipulations (e.g., the PPC approach) in smokers has also been helpful in clarifying the relationship between craving and emotion, which is complicated since craving itself is often thought to be fundamentally affective in nature (Baker et al., 1987; Franken, 2003; Naqvi et al., 2014; Panksepp, 2007; Sayette, 2016). Typically, the affect associated with craving is assumed to be negative (Tiffany, 1992; one is motivated to use the substance in order to attenuate the unpleasant craving). Consistent with this idea are studies showing associations between intolerance of abstinence and cigarette craving/withdrawal severity (Mathew et al., 2019; Mathew & Zhou, 2020; but see Germeroth et al., 2018) and laborator smoking behavior (Kahler et al., 2013). Cravings also occur in alternative contexts that merit scrutiny by investigators, though. For instance, when a smoker expects to satisfy an urge rather than resist it, they may actually experience positive effect (Sayette & Creswell, 2016). The moments just prior to use and even the beginning of consumption may be particularly positive, but it is often difficult to capture brief experiences of positive effect in the laboratory. Moment-to-moment fluctuations in effect over time are difficult to accurately be assessed using self-report measures as participants must aggregate their experiences over time. Moreover, affective experiences are thought to be inherently non-verbal in nature, and imposing language on such experiences may distort the affective experience itself (Creswell et al., 2018, 2019; Nisbett & Wilson, 1977).

Analysis of expressive behavior may compliment more traditional measures of effect. For instance, under particular circumstances, the Facial Action Coding System (FACS; Ekman & Friesen, 1978), which is the most established system for assessing facial expressions, can be used to probe emotion during craving states (e.g., Sayette et al., 2003). Two cigarette PPC studies using FACS indicated that smokers who anticipated smoking soon were more likely to show positive affect–related expressions than did those who were told that smoking was unavailable (Sayette & Hufford, 1995; Sayette et al., 2003). These findings indicate that under certain conditions, craving may be linked to positive affect (see also Carter & Tiffany, 2001), and suggest that some of the perceived reward generally associated with smoking may actually precede smoking a cigarette.

The studies reviewed above suggest that craving itself may be rewarding, particularly to individuals who anticipate using the drug very soon (Kavanagh et al., 2005). In fact, anticipation of smoking in craving smokers significantly dampened stress reactivity (i.e., startle response potentiation and self-reported anxiety) to shock cues, suggesting that craving is also negatively reinforcing (Bradford et al., 2015). Furthermore, craving smokers who were told that they could smoke soon preferred viewing smoking images (relative to alcohol images), more so than smokers who learned that they were not permitted to smoke, suggesting that smoking cues themselves may become more pleasant when smoking soon is anticipated (Sayette & Dimoff, 2016). This is consistent with what Loewenstein (1987) has described as savoring or the "positive utility derived from anticipation of future consumption" (p. 667). Taken together, this research suggests that in some instances, cigarette craving can be experienced as a positive emotional state. Clinically, these findings suggest that it may be beneficial to additionally address the loss of these positive emotional experiences during treatment. Quitting a drug means not only losing the rewarding aspects of consumption but also all the regularly occurring moments of pleasant anticipatory craving (e.g., the final hour of work for someone who usually drinks right after work). That is, although the person had been sober during this hour of work before quitting, clinically it may become a critical time to address from the perspective of the systematic loss of positively tinged cravings (Sayette & Dimoff, 2016).

Although alcohol craving studies have yet to investigate momentary emotional shifts using facial expressive data, there are some studies relying on self-reported affect that offer intriguing findings. For instance, when exposed to alcohol cues, social drinkers often respond with increases in craving and positive affect (Kambouropoulos & Staiger, 2004; Mackillop & Lisman, 2007; Van Den Wildenberg et al., 2007). Furthermore, one study found differential associations between craving and positive/negative affect after a priming dose of alcohol in heavy versus light drinkers (Kabbani et al., 2014). Future studies investigating the role of positive affect in alcohol craving are indicated.

Conceptualizing craving as an emotion also accommodates the possibility that craving can at times be experienced as affectively ambivalent. An ambivalence model of craving has been proposed in which both the desire to use (approach) the drug and the desire not to use (avoid) the drug is considered to fully understand craving (Breiner et al., 1999; Curtin et al., 2005; McEvoy et al., 2004; Smith-Hoerter et al., 2004; Stritzke et al., 2007; Wilson et al., 2013). Guided by this ambivalence model and using a PPC approach, research found that smokers who displayed ambivalent facial expressions (concurrent display of expressions related to both positive and negative affect) while holding a lit cigarette reported significantly higher scores on more traditional real-world measures associated with ambivalence about smoking (i.e., increased desire to quit smoking *and* an increased difficulty in remaining abstinent; Griffin & Sayette, 2008). This study also found FACS data to reveal unique information about self-regulation failures outside of the laboratory, not otherwise available *via* self-report (see also Wilson et al., 2013).

While we were unable to find any PPC alcohol studies testing the ambivalence model of craving, there are some recent alcohol studies that bear on this issue. For instance, in the context of cue exposure therapy in an outpatient alcohol treatment center, Smith-Hoerter et al. (2004) coded verbatim patient verbal reactions to an in vivo alcohol cue and found evidence of both approach and avoidance inclinations (although no such analyses occurred for a neutral cue). Moreover, inpatients with alcohol dependence, but not social drinkers, showed a bias away from alcohol-related pictorial stimuli in the context of a dot probe task (Townshend & Duka, 2007). Schlauch et al. (2015) also used this ambivalence framework to probe competing approach and avoidance inclinations in response to pictorial alcohol cues in detoxified inpatients with alcohol dependence and found that high ambivalence (high approach and high avoidance) was associated with heavier drinking and more negative consequences. Finally, among a sample of alcohol-dependent patients who were nearing the end of inpatient detoxification treatment, Field et al. (2017) found that strong automatic alcohol avoidance tendencies during alcohol cue presentations (i.e., faster movement of a manikin away from alcohol pictures) predicted worse drinking outcomes 4 and 6 months after discharge from treatment, while self-reported approach and avoidance inclinations for alcohol did not predict drinking outcomes.

These intriguing findings suggest that future studies probing the ambivalence model of alcohol craving are warranted. For instance, studies using multimodal assessment techniques to assess cigarette cravings (e.g., FACS, eye tracking, event-related potentials, and time to respond to craving items) detected meaningful covariation among such measures during strong craving states (e.g., Creswell & Skrzynski, 2021; Germeroth et al., 2015; Piasecki et al., 2017; Sayette et al., 2003), and it might also be fruitful to incorporate non-verbal measures of approach/avoidance inclinations and affect when studying ambivalence for alcohol. These non-verbal measures may also reveal information not otherwise available with self-report and perhaps better predict relapse (e.g., Creswell et al., 2018; Piper & Curtin, 2006).

Overall, this body of work shows that in addition to negative emotional states, individuals at times can experience positive affect-related craving states or even affectively ambivalent states, and that these craving-related shifts in emotions may be linked to drug use. Future studies are needed to better understand the emotional tone of alcohol craving, as well as studies identifying factors linked to positive, negative, or affectively ambivalent craving states. Perceived drug use opportunity is one such factor that appears to be key, both in influencing whether cravings are linked to positive or negative affect as well as affecting the strength of the craving response. As noted above, conducting alcohol cue exposure studies in the context of a perceived ability to drink alcohol in individuals with alcohol dependence creates unique challenges, but such studies are likely needed to provoke powerful craving states in this population so that conceptual questions about craving can be fruitfully asked.

Insight into cravings: cold-to-hot empathy gap

Finally, in addition to in-the-moment shifts in cognition and emotion during the throes of a craving episode, there is smoking research that suggests another important mechanism that may underlie the link between craving and subsequent drug use. Research using a PPC approach with smokers has examined whether individuals have insight into the strength and motivational force of their own future craving states. Individuals in an affectively neutral "cold" state often underestimate the impact of being in an affectively charged "hot" state in their own future behavior (i.e., the cold-to-hot-empathy gap; Loewenstein, 1999). Consistent with this proposition, smokers in a cold, low-craving state, but not those in a high, peak-craving state, underpredicted the monetary value of smoking during a subsequent high, peak-craving state (Sayette et al., 2008). These findings suggest that smokers may not fully appreciate the powerful effects of craving when they currently are not craving. This lack of insight would appear to further undermine self-regulation efforts as individuals may enter high-risk situations erroneously believing that they will be able to resist smoking (Baker et al., 2004; Sayette & Creswell, 2016). Similar studies examining insight into alcohol cravings are indicated, especially given that emerging evidence suggests that, on average, individuals with alcohol dependence are less able to regulate their craving in response to cues compared to social drinkers (Naqvi et al., 2015).

CONCLUSION AND FUTURE DIRECTIONS

Craving is a core feature in nearly all models of addiction and lies at the heart of understanding motivation to use drugs. Interest in craving as a clinical construct has continued to flourish over the past two decades. Human alcohol craving studies during this time have tended to focus on craving as a dependent variable best assessed *via* self-report. This research has revealed that alcohol craving is a key construct vital to our understanding of alcohol use and relapse. Drawing on studies from the cigarette craving literature, we suggested ways to advance knowledge of mechanisms underlying alcohol craving. Specifically, we proposed inducing particularly strong alcohol craving states in order to investigate clinically meaningful cognitive and affective shifts as they unfold. To generate potent craving states, it may even be necessary to conduct cue exposure studies with patients with alcohol dependence in a hospital setting before the start of treatment (i.e., while participants are still drinking alcohol and at least believe that alcohol use will take place after cue exposure). It is under these strong craving states that questions about the impact of overpowering craving states described by leading researchers as critical to drug and alcohol use disorders (e.g., George & Koob, 2013; Volkow et al., 2010) can be addressed.

Our narrative review identified a handful of areas where smoking research might provide a roadmap for alcohol research. This list is by new means exhaustive. Future alcohol craving studies would likely benefit from consideration of several other factors. For instance, social contextual variables (e.g., solitary vs. social drinking) can predict alcohol use and misuse through different pathways (Creswell, 2021; Skrzynski & Creswell, 2020, 2021; Waddell et al., 2021), and social contexts may also be important to better understand alcohol cravings. Specifically, social drinking is linked to enhancing positive emotions and social experiences, and solitary drinking is linked to coping with negative emotions (Creswell, 2021). Consideration of the social context in which alcohol cravings are experienced might shed light on the emotional tone or strength of such cravings. For example, in an ecological momentary assessment study of adolescent frequent drinkers, alcohol craving was heightened during moments when adolescents were with their peers (Padovano & Miranda, 2021). Affect was not assessed, but it would be interesting to determine whether alcohol cravings experienced with friends might be linked to positive affect, or whether such cravings have some social utility. Indeed, smokers who were craving a cigarette with their friend physically present experienced a greater sense of similarity and felt closer to their friend than did craving smokers who were alone with their friend in another room (Dimoff et al., 2019). These studies suggest that cravings may be experienced differently based on whether an individual is alone or in a social setting, but this has largely been unexplored in alcohol craving research, as laboratory studies have evaluated craving almost exclusively among drinkers while they are alone. Future studies exploring how social contextual variables may influence alcohol cravings are indicated.

Furthermore, while self-reported urge measures ought to remain a critical method to assess craving, these rating scales may not fully capture the essence of craving states. Nonverbal approaches to assess cravings and other visceral states (e.g., emotions) often provide information that is unavailable *via* standard self-report rating scales (Creswell et al., 2018; Field et al., 2017; Griffin & Sayette, 2008; Piper & Curtin, 2006), suggesting that there is a need to expand the set of craving-related measures beyond traditional self-report rating scales (see also Perkins, 2009; Tiffany & Wray, 2009). For instance, we recently noted evidence for the utility of a nonverbal "visceral" measure of cigarette craving (squeezing a handheld dynamometer) that performed well during craving manipulation (i.e., detecting increases in urge following cue exposure, correlating with self-reported urge ratings, and predicting actual smoking behavior after cue exposure) (Creswell et al., 2019). Notably, this squeeze measure overcame an important shortcoming of traditional self-report measures (i.e., ceiling effects; see Sayette et al., 2001) by allowing participants to express their craving in an unbounded way. The squeeze measure of urge was also not reliant on language, making it particularly amenable to capturing internal drive states (like craving) that are visceral, nonverbal, and difficult to translate into symbolic systems (Schooler, 2002). Overall, novel alcohol craving measures that rely on different types of responding are needed to generate a more comprehensive, multimodal approach to assessment and to examine response covariation under different circumstances (e.g., Sayette et al., 2003). Efforts to develop and refine nonverbal approaches to craving assessment should remain a research priority.

In addition to novel craving assessment techniques, new technology will likely enable alcohol craving research to progress. For

instance, virtual reality and augmented reality (which is a rapidly emerging technology that superimposes digital images onto real-world scenes as viewed in real-time through a smartphone or other device, see Vinci et al., 2020) offers opportunities to create immersive and interactive environments so that alcohol cue exposure can be executed with lower risk since it does not require the actual presence of tempting alcoholic beverages. Use of these technologies seems especially promising in the context of cue exposure with individuals with alcohol dependence. Beyond clinical applications, these immersive applications provide an opportunity for researchers to present alcohol stimuli in a controlled way to individuals in their natural environment, perhaps generating more potent craving states than what can be induced in sterile laboratory settings, and allowing for a better understanding of craving-related cognitive and affect processing shifts as they occur in the real world. Future alcohol craving studies that incorporate virtual and augmented reality methods are needed.

In addition, studies are indicated to identify and confirm the role of individual difference variables that may influence the strength of alcohol cravings and the cognitive and affect-related shifts that occur during strong craving states. To date, there have been many individual difference variables identified that influence cue-induced cravings, but as noted above, future work must integrate these findings into a comprehensive model to better understand who is most susceptible to strong craving states. Variation in cue-induced craving levels are particularly important for these types of studies as uniformly strong craving states might obscure associations with individual difference factors. More diverse samples are also needed as the majority of human laboratory studies on alcohol craving to date have enrolled predominantly European American samples (Plebani et al., 2012). The ability to generalize alcohol study findings to more diverse populations has not been sufficiently addressed, and future studies are indicated. Finally, this review focused on human experimental alcohol craving work, but there other useful research designs (e.g., ecological momentary assessment; Moore et al., 2014; Serre et al., 2015) and topics (planned vs. unplanned drinking; Stevens et al., 2021) that are instrumental in better understanding alcohol craving.

In summary, much has been learned about craving as a clinical phenomenon in the past two decades. The purpose of this review is to stimulate additional alcohol craving research to investigate why and how alcohol cravings are clinically meaningful and to identify the circumstances in which alcohol cravings are particularly meaningful. A better conceptual understanding of alcohol cravings will almost certainly lead to more effective alcohol treatments.

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ENDNOTES

[1] The terms used to describe alcohol use disorders have changed throughout the years. This early work on craving used the term alcoholism. We use alcohol dependence in this article as most of the human alcohol cue exposure studies reviewed here used that term. At times, however, we use alcohol use disorder when that term is needed to more accurately describe a sample (e.g., when describing a study that included individuals with moderate to severe alcohol use disorder).

[2] It is worth noting that craving ratings that do not approach the maximum value on urge scales and are instead moderate in intensity might also be clinically meaningful (see Sayette & Tiffany, 2013).

[3] Research instead has focused on how acute alcohol intoxication affects time perception (see Nuyens et al., 2021 for a review).

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