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# Incubation of Alcohol Craving as it Naturally Occurs in a Developmentally Diverse Sample of Dependent and Non-Dependent Drinkers

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## Abstract

Longer periods of abstinence are shown to enhance response to alcohol cues among alcohol-dependent animals[1–4] and humans[5,6], a phenomenon described as "incubation of craving." The present work examined the effects of days since last drink on general craving and alcohol-cued craving as it occurs in daily life and explored whether effects were influenced by age and dependence.

**Methods—**Three samples were combined to include 266 drinkers ranging in age from 14 to 67 years recruited from the community; about half (59.4%) met criteria for alcohol dependence. Drinkers used handheld electronic devices to rate their subjective alcohol craving (assessed as "urge to drink") and situational context (e.g., presence of visible alcohol cues) at non-drinking times in daily life, with days since last alcohol use culled from timeline follow-back interviews and real-world reports.

**Results—**Drinkers at the lower end of the age range in this sample reported greater intensification of craving with more days of continuous abstinence than drinkers at the upper end of the age range. Age was not related to incubation of cue-elicited craving, in specific, however. For drinkers with dependence, craving when in the presence of visible alcohol cues intensified with more days of continuous abstinence, suggesting craving incubation.

**Conclusions—**This study builds from important foundational work to demonstrate that incubation of cue-elicited craving occurs in dependent drinkers and applies regardless of age. Inasmuch as craving is a motivational drive that maintains alcohol use[7], understanding factors that influence craving in daily life holds promise for improving clinical care.

### Keywords

Incubation of craving; Alcohol dependence; Ecological momentary assessment; Abstinence; Cue reactivity

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Author Contributions

RM was responsible for the parent study design, concept, and implementation. RM and HTP conceptualized and designed the present analysis. HTP conducted analyses and drafted the manuscript. RM assisted with interpretation of findings and provided critical revision of the manuscript. Both authors reviewed and approved the final version for publication.

## Introduction

Craving is an urge, want, or sense of compulsion to use alcohol or other drugs. Its importance for understanding substance misuse is evident by its inclusion as a diagnostic criterion for substance use disorders (SUDs), both by the World Health Organization[8] and American Psychiatric Association[9], its primacy as a treatment target[10], and its centrality to most contemporary theories of addiction[11,12]. Incubation of alcohol-cued craving, or progressive intensification of craving when presented with alcohol or drug cues during longer periods of non-use, is one potential mechanism prompting unplanned use or relapse[13]. The present investigation builds from prior work to examine whether craving elicited by the presence of visible alcohol cues in the natural environment is heightened with more days since the last drink, i.e., incubation of craving. Moreover, this study explores whether craving incubation is shown across age and among both dependent and non-dependent drinkers.

Over three decades ago, it was proposed that environmental cues could trigger intense drug craving after withdrawal had abated and that cue-elicited craving did not decay over time, as was previously assumed[14]. In the years since, time-honored animal analogues, i.e., drug self-administration and conditioned place preference, repeatedly demonstrated that removing access to drugs does not extinguish cue-elicited craving, but, rather, that dependent animals exhibit time-dependent heightening of cue-elicited drug-seeking for drugs and alcohol[1–4,15]. Recent human laboratory studies extended this work to adults with dependence, showing intensified cue-elicited craving over time for cigarettes, methamphetamine, cocaine, and alcohol[5,6,16–18]. Most recently, neural cue reactivity was examined among men with alcohol dependence, comparing cue-elicited mesolimbic neural activation after controlled abstinence to activation after voluntary psychosocial and/or naltrexone treatment[6]. This study demonstrated incubation of craving, and, moreover, that incubation predicted reduced treatment response and relapse risk[6].

Studies exploring influences on craving earlier in the individual's drinking history, as alcohol use and misuse progresses, are needed[19]. Adolescents are different from adults in many ways that may alter their craving patterns. Alcohol consumption increases during the transition from adolescence to emerging adulthood in both animals[20] and humans[21]. Adolescents also show greater acute tolerance to alcohol and relative insensitivity to negative effects and hypersensitivity to the social and rewarding effects[20,22]. Yet, adolescents with dependence tend to go longer without drinking than adults with dependence, which may be due to differences in alcohol access and could influence craving[23]. Although craving can emerge early in a person's drinking history[24], most studies focus on drinkers already ensnared in a pattern of pathological use[25]. This limited understanding of craving across age is notable given the recognized etiological importance of early drinking for developing alcohol use disorder (AUD) later in life[26,27]. Indeed, analogues for alcohol craving in adolescent animals predict alcohol pathology as the animals mature[28]. Further, mounting human studies with adolescent drinkers show that exposure to *in vivo* or pictorial alcohol cues in the laboratory elicit craving, especially among those with more alcohol-related problems[24,29–31].

Overall, considerable preclinical evidence, and emerging support from laboratory investigations, opposes the view that cue-elicited craving decays after initial withdrawal, but rather suggests that vulnerability to conditioned craving progressively intensifies for some time, abating only after a period of weeks to months[13,17,32]. Yet, with few exceptions, incubation of craving has been tested under conditions of artificially imposed or forced abstinence. In human studies to date, one paid smokers to abstain from cigarettes for randomly assigned periods[16], and others restricted access to methamphetamine or alcohol in inpatient settings[5,6,17]. Thus, it remains unknown whether reactivity to alcohol cues heightens, abates, or stabilizes during periods of naturalistic periods without drinking. Moreover, age- or dependence-related developmental trends in incubation of craving have not been explored.

One way to address existing gaps in our understanding of cue-elicited craving is to extend findings from the laboratory to real-world settings with ecological momentary assessment (EMA). EMA affords the ability to determine how craving is impacted by individual differences, such as the drinker's age and AUD, in combination with environmental characteristics, such as the presence of visible alcohol cues. Inasmuch as craving is influenced by environmental context[33], it is important to extend laboratory findings to drinkers' usual settings. EMA studies show that alcohol craving is a common antecedent of drinking, particularly among heavy drinkers or those with alcohol-related problems[24,34]. EMA studies also demonstrate greater cue-elicited craving among drinkers with more problems or AUD[24,35,36].

The present investigation sought to understand the effects of not drinking on alcohol craving as it naturally occurs in a developmentally diverse sample of dependent and non-dependent drinkers. In doing so, we aimed to extend preclinical findings to humans and extend human laboratory findings to the natural conditions under which periods without drinking and alcohol craving exist. Craving and the presence or absence of visible alcohol cues in the natural environment were assessed via a custom EMA application implemented on a handheld electronic device or smartphone that prompted drinkers to report their current craving at randomly sampled times as they carried out their usual activities of daily life. Participants were engaged in their normal drinking patterns during the data collection period, and we monitored spontaneous variations in days of consistent abstinence. We expected the data to support "incubation of craving," i.e., moderation of cue-induced craving by days since last drink, such that reactivity to visible alcohol cues at non-drinking times in daily life would be heightened with more days of continuous abstinence. We expected to see craving incubation among dependent drinkers and explored the effect among non-dependent drinkers. Last, given known differences in drinking frequency patterns among adolescent and adult drinkers, even those with dependence[23], we also explored age effects on incubation of cue-elicited craving and craving more generally, regardless of the presence of visible alcohol cues.

## Materials and Methods

### Participants

The present analysis incorporates data from three separate studies conducted by our research group between 1998 and 2015. Participants ($N$=266) were recruited from the community for randomized, placebo-controlled trials of medications for treating alcohol use disorder[36,37]. All data were from pre-randomization monitoring periods during which participants were not assigned to a medication condition and were not taking study medication. Together, the three samples include participants ranging in age from 14 to 67 years, allowing a test of age-related differences in craving. Eligibility criteria were similar across studies, with some differences (Table 1). Across all studies, participants were required to be able to read simple English for EMA purposes.

Exclusion criteria were also similar across studies, with most differences based on specific medical screening criteria to ensure safety while taking the study medication in the larger trials. Potential participants were excluded for medical conditions or medications that were contraindicated with the study medications (i.e., naltrexone for Studies 1 and 3; topiramate for Study 2). All studies excluded females who were pregnant, nursing, or would not use a reliable method of birth control (e.g., condom). Across all studies, individuals with a history of clinically significant alcohol withdrawal, as measured using the Clinical Institute Withdrawal Assessment for Alcohol-revised,[38] were excluded from participation. All studies excluded those currently in treatment for alcohol problems. Studies 1 and 2 excluded those with a history of treatment in the 30 days before enrollment, seeking formal alcohol treatment, or living with someone who was actively participating in the study, whereas Study 3 excluded those seeking formal treatment for alcohol or drug use, or any lifetime history of treatment, or living with any person who had ever participated in the study. Potential participants who were actively psychotic or suicidal or were exhibiting symptoms of alcohol withdrawal were not eligible.

### Procedures

All studies followed the same recruitment, screening, and medical screening procedures during the baseline period. For all studies, volunteers completed an initial telephone screening; those who appeared eligible were invited for an in-person screening. Consent was obtained from participants who were ≥18 years of age, and in the case of minors, parents provided permission and minors provided assent. Participants were provided with handheld electronic devices and were taught to use our EMA program. Self-report and interview assessments were administered in a baseline session, after which participants completed a several-day EMA monitoring period prior to randomization to the larger trials.

### Individual Difference Measures

**Demographic and clinical characteristics—**Participants completed baseline assessments of demographic and clinical characteristics, including age, biological sex, race, and ethnicity. AUD diagnoses were derived using age-appropriate structured diagnostic interviews, i.e., Kiddie Schedule for Affective Disorders for School-Age Children[39] or

Structured Clinical Interview for DSM-IV Axis 1 Disorders[40]. Responses were coded to indicate DSM-IV-TR alcohol dependence (1) or not (0).

**Alcohol use—**Drinking at baseline was assessed using the 90-day Timeline Follow-Back interview (TLFB).[41] TLFB completed at the end of the premedication EMA period identified any missing EMA drinking data. TLFB was also used to calculate the covariate baseline percent drinking days.

## EMA Measures

Similar EMA protocols were followed in all studies. Participants completed assessments upon waking (morning reports), before and after consuming alcoholic drinks (drink reports), and in response to audible prompts (random assessments) delivered throughout the day except when sleeping or otherwise unable to respond (e.g., driving). The primary focus of this investigation is craving data collected during random assessments at non-drinking times, with daily drinking levels derived from morning reports. Data from drink reports and from random assessments occurring after drinking were excluded to avoid the confounding effects of alcohol intoxication.

### Morning Reports

**Days Abstinent:** Alcohol use during the EMA monitoring period was assessed at morning reports, with missing data culled from the TLFB. Every morning upon waking, participants indicated the type of alcohol and number of standard drinks consumed the previous day. A combination of EMA and TLFB data identified the number of days of continuous abstinence for each day of the EMA monitoring period.

### Random Prompts

**Craving:** Craving was assessed with a widely used[24,42] single-item measure of urge to drink on an 11-point visual analog scale from 0 (no urge) to 10 (strongest ever). Daily average craving was calculated for all random prompts on non-drinking days, and only those random prompts preceding drinking on drinking days were included in analyses.

**Presence of Visible Alcohol Cues:** Participants identified whether alcohol cues were directly visible. Specifically, in Studies 1 and 2, the question stem stated, “Is alcohol visible?” with response options including direct *in vivo* (e.g., bottle, glass) and other (e.g., TV, ad, store) visible alcohol cues, as well as an option to indicate the absence of any visible alcohol cues. In Study 3, the question stem simply stated, “Alcohol cues?” and response options included only presence of visible alcohol cues (e.g., TV, ad) or the absence of any visible alcohol cues. Responses were dichotomized to indicate the presence of *in vivo* or other visible alcohol cues (1) or absence of visible alcohol cues (0).

**Contextual Covariates:** The EMA software recorded date and time of each entry. Weekend status was defined as 6 p.m. on Friday through 6 p.m. on Sunday and dichotomized into weekend (1) or not (0). Time of day was represented by four categories (i.e., 6-h blocks starting from midnight) with 6 p.m. to midnight serving as the reference category. Additionally, locations were recorded and subsequently merged into six representative

categories as follows: *work/school* (school or work); *social setting* (friend's house, other's house, or party); *public place* (public place, outside, inside, restaurant, club, bar, liquor store, or Brown visit); *vehicle* (car, bus, or other transportation); *other* (elsewhere or other); *residence* (home or dorm). Residence served as the reference category. Finally, participants recorded who accompanied them at the time of each entry to identify whether participants were with others (1) or alone (0).

### Analytic Plan

Analyses were performed with SAS 9.4 (SAS Institute Inc., 2002–2012). First, study descriptive characteristics were compared with Tukey-Kramer and chi-square tests. Next, two-level, random-intercept mixed models accounted for the nesting of EMA reports within participants and varying number of reports per participant. For all mixed-model analyses, we used REML estimation, between-within degrees of freedom, and an unstructured covariance matrix which does not impose any relation among the EMA reports. Among various potential approaches for handling missing outcome data (e.g., multiple imputation, last value carried forward), we prefer maximum likelihood (in this case restricted maximum likelihood) estimation. In SAS PROC MIXED, REML estimation still reduces the sample size of the analyzed dataset consistent with missing outcome data, but "borrows" information from the reports where the outcome is available. REML uses this information to account for uncertainty in the calculation of effect estimates and standard errors.

The intraclass correlation (ICC) is the ratio of participant-level to overall variance, providing an estimate of the extent to which variability in craving was due to stable, participant-level influences or fluctuating, EMA-level influences. Participant-level continuous variables were sample-mean centered, and EMA-level continuous variables were person-mean centered. Reference categories for categorical predictors are noted in tables. Additional covariates were included to test whether effects were better accounted for by other putative influences on craving. Participant-level covariates were gender, race, and baseline percent drinking days. EMA-level covariates were time of day, weekend status, presence of others, and location.

Initial mixed models evaluated participant-level influences on craving (i.e., study, age, and dependence). EMA-level influences of presence of visible alcohol cues and number of days abstinent were evaluated, accounting for participant-level averages. Whether the effect of days abstinent varied by age was tested via inclusion of a cross-level interactive effect of days abstinent and age. Incubation of craving was tested via inclusion of a three-way interactive effect of days abstinent and presence of visible alcohol cues and dependence. Significant interactive effects were probed via plotting least squared means.

## Results

### Descriptive Information

Participants ranged in age from 14 to 67 ($M$=25; SD=9.8). The majority were White (84.8%) or Black (8.0%), and met criteria for alcohol dependence (59.4%). Overall, drinking levels were high, with most participants drinking on half of the days at baseline (50.8% drinking

days; SD=23.4), and during EMA (55.3% drinking days; SD=39.7). Heavy drinking occurred on about one-third of days at baseline (31.6%; SD = 22.6), and during EMA (33.3%; SD=47.1). EMA data were collected on 1573 social days (i.e., calendar days recoded so that reports made after midnight but before retiring for the evening corresponded to the previous day), totaling 4304 non-drinking random prompt reports, and averaging 17.16 reports per person (SD=8.12; range=1–42). Each person contributed reports on 6.88 days, on average (SD=2.03; range=1–14), and, on average, 3.50 reports were completed per day (SD=1.74; range=1–9).

Samples did not differ in terms of biological sex, $\chi^2(2, N=266)=1.78$, $p=.410$, or alcohol dependence, $\chi^2(2, N=266)=1.71$, $p=.425$ (Table 2). Racial and ethnic distributions were different across studies, however, $\chi^2(10, N=266)=32.06$, $p<.001$, and $\chi^2(2, N=266)=27.09$, $p<.001$, respectively, with less diversity in Study 3. Study 3 participants were also older by design, $F(2,263)=33.2$, $p<.001$, whereas post-hoc analyses did not indicate age differences between Studies 1 and 2, 95%CI *M*difference (−1.9, 7.0). Similarly, Study 3 participants drank at higher levels, both at baseline and during EMA (Table 2).

## Days Abstinent

Days since last standard drink (collected via EMA and TLFB) ranged from 0 to 26 ($M=1.42$, SD=3.12). There were 116 (of 1573) days where days since last drink could not be determined from TLFB or EMA data, reflecting 7.4% of days. Age was included in mixed models as a sample-centered, continuous predictor, but grouped by meaningful age categories for descriptive purposes. Underage participants (<21) reported periods of abstinence that were, on average, two days longer than emerging adults (21–24), *M*difference=2.17, $p<.001$, and adults (25+), *M*difference=2.60, $p<.001$, and emerging adults reported periods of abstinence that were, on average, almost half a day longer than adults, *M*difference=0.43, $p<.001$. The range of number of days abstinent also varied considerably between age groups, with underage drinkers reporting from 0 to 26 days abstinent ($M=2.94$, SD=4.55), whereas emerging adults reported from 0 to 15 days abstinent ($M=0.77$, SD=1.52), and adults reported from 0 to 4 days abstinent (with one outlying data point at 16 days of abstinence) ($M=0.34$, SD=1.13).

## Relation of Age, Dependence, Days Abstinent, and Presence of Alcohol Cues with Craving

Nearly all participants ($n = 257$; 96.6%) reported more than zero craving at one or more EMA reports during the monitoring window. Of the nine participants who never reported craving, none were from Study 1, six were from Study 2, and three were from Study 3. Overall, participants reported more than zero craving in 64.2% of random-prompt EMA entries. The intraclass correlation was .33, indicating significant variability in craving due to both participant-level, stable characteristics (33%) and momentary, fluctuating influences on craving levels (67%). Table 3 presents results of main effects of focal study variables on craving. In support of our expectations, age was not related to craving, neither alone, $b=0.02$, SE=0.01, $p=.138$, nor when accounting for the effects of study, dependence, days since last drink, and presence of visible alcohol cues, $b=0.0007$, SE=0.01, $p=.955$. As expected, dependence was associated with greater craving, $p<.001$. Contextual effects, i.e., periods of abstinence and being in the presence of visible cues, were also associated with heightened

craving, *p*s<.001. The person-level counterpart of abstinence was not significant, *p*=.613, suggesting the effect was not due to having longer periods of abstinence, on average. In contrast, being in the presence of visible alcohol cues more often, on average, related to higher craving, *b*=1.20, SE=0.43, *p* = .006. In interactive models, the presence of visible alcohol cues did not moderate the association of age, dependence, or days since last drink with craving, *p*s = .431, .983, and .310. Thus, age, dependence, and days since last drink were associated with craving, more generally (as shown in Table 3), but not cue-elicited craving, in specific.

## Incubation of Alcohol-Cued Craving

In support of our hypothesis, longer periods without drinking elicited the greatest craving when in the presence of visible alcohol cues among dependent drinkers, *b*=0.38, SE=0.15, *p*=.009 (Table 4). This effect remained significant when accounting for additional covariates, *b*= 0.40, SE=0.14, *p*=.004. Least squares means illustrate how cue-elicited craving is heightened with more days of abstinence among drinkers with dependence (Figure 1). This effect did not appear to be developmentally linked, i.e., incubation did not differ across age, *b*=−0.02, SE=0.02, *p*=.446.

## Age Moderates the Influence of Abstinence on Craving

Although age did not alter the relation of abstinence on cue-elicited craving, age was related to the association of abstinence and craving more generally. Specifically, at the lower end of the age range in this analysis, more days since the last drinking day was associated with heightened craving in the natural environment, regardless of the presence of visible alcohol cues, *b*=− 0.01, SE=0.004, *p*=.01 (Table 5). This effect remained significant when removing the nonsignificant interactive effects of age with dependence and age with presence of visible cues, and when accounting for additional covariates, *b*=−0.009, SE=0.004, *p*=.028. The interactive effect of age and days abstinent was depicted through graphing the Least squares means by underage (<21), emerging adult (21–24) and adult (25+) drinkers (Figure 2).

## Missing Data

We used all reports where outcome (craving) data were available (*n* = 4304). Taking a step back in our data, there were 1040 reports where a report was started and no craving data was provided, increasing the number of available reports to 5344. Almost all of these (98.9%) were from Study 3, which was due, at least in part, to additional features of the custom EMA program in Studies 1 and 2 that prevented skipping questions. Removing reports with missing data for the craving outcome removed one participant (*n* = 151 rather than 152 for Study 3), reflecting .007% of the sample, which is not likely to introduce bias. In all, however, removing missing craving reports eliminated 19.5% of our data, which is arguably not negligible. Importantly, when we use the dataset with missing outcome values (*n* = 5344) and REML, there was minimal change to the parameter estimates, and the significance values of our focal tests did not change.

### Sensitivity Analysis

Although 0–26 days of continuous abstinence were reported across the full age range of the combined samples, days abstinent was truncated among participants aged 25+. Sensitivity analyses were conducted to restrict the sample to only those EMA reports where ≤4 abstinent days were reported. Results were the same. Additionally, the focal days-abstinent variable was only assessed daily, whereas the outcome of craving was assessed, on average, four times per day. In the primary analysis, multiple reports of craving were retained so that EMA covariates at each report (e.g., location, presence of visible cues) could be included. Sensitivity analyses were conducted aggregating the craving outcome to the daily level. Results were the same.

## Discussion

Addiction manifests as a cluster of connected biobehavioral expressions, for example, craving and inability to control use[43]. Understanding how alcohol craving functions in daily life across age and alcohol pathology is key to verifying its relevance as a diagnostic criterion, clinical target, and theoretical marker of AUD development. The weight of existing evidence supports the following assertions: (1) adolescents are not like adults in their drinking patterns or outcomes, (2) both adolescents and adults report alcohol craving, (3) alcohol cues elicit craving, and (4) drinkers with dependence crave more. The present study sought to demonstrate incubation of cue-elicited craving, i.e., a phenomenon where longer periods of abstinence among animals or humans enhances response to alcohol cues[5,32], in drinkers' natural environments. We found, first, that age was not related to cue-induced craving, but being in the presence of visible alcohol cues and having a diagnosis of alcohol dependence are. Next, this work offers evidence for incubation of craving in drinkers' natural settings during periods without drinking. For drinkers with dependence, craving was heightened the most when in the presence of visible cues and after having gone more days without drinking.

A question asked, by researchers and lay people alike, is, "*Do adolescents really crave alcohol?"* If you ask a clinician this question, their response will be a resounding, *"Yes, of course they do."* Indeed, in the human laboratory, adolescents crave when presented with alcohol *in vivo* or pictorial cues[29–31], and ecological momentary assessment studies show that adolescents report craving in their daily lives[36,44]. Further, our prior work with a subset of the present samples suggests that levels of alcohol craving reported while drinking in the natural environment may be similar for adolescents and adults[37]. Yet, less research among adolescent drinkers, relative to emerging adult or adults, may explain why the relevance of craving across the lower end of the age range is still a matter of some debate. In the present analysis, age alone was not related to craving outside of drinking episodes in daily life, suggesting that craving when not drinking may also be experienced by adolescents and adults alike.

That incubation of craving was found only for drinkers with dependence in this analysis must be viewed as preliminary. One potential mechanism of this finding may be differences among drinkers with and without dependence in motivation or intention to set drinking limits or otherwise purposively restrict alcohol consumption. It is possible that drinkers with

dependence were actively attempting to reduce their alcohol consumption or abstain from drinking, thereby promoting higher craving, whereas those without dependence were not imposing limits on their drinking, and therefore had no reason to crave alcohol. On balance, drinkers in these studies were not in formal treatment, and therefore all participants may have been engaging in typical drinking patterns without intentions to set limits. Future research is needed to carefully consider and test whether drinkers without dependence would show craving incubation under conditions of restricted access to alcohol.

We did not find the same moderating influence of age on cue-elicited craving with longer periods of abstinence, suggesting that age was not a proxy for dependence. Although cue-elicited craving incubation operated similarly across age, the effect of days abstinent on craving, more generally, was moderated by age. This result reiterates a key consideration for all investigations into AUD development: Adolescents are not adults[23]. In addition to physical, cognitive, emotional, and alcohol-response differences, adolescent drinkers, unlike adults, have limited access to alcohol. As a result, their drinking is often necessarily opportunistic, restricted to times when they are without supervision and with access to alcohol. The sporadic and opportunistic nature of drinking among adolescents is reflected in the present sample, with underage participants reporting longer periods without drinking, and more variability in the number of days since last drink, than drinkers who can legally buy alcohol. Thus, during periods of abstinence, going longer without drinking may produce more craving in underage drinkers because legal drinkers, barring monetary or other restrictions, have access to alcohol.

In the present investigation, two-thirds (67%) of the variability in craving was due to momentary influences, such as situational context or cues, rather than characteristics of the person. In aggregate, drinkers who were in the presence of visible alcohol cues more often did tend to report higher levels of craving, overall, but these averages did not overshadow in-the-moment elevations in craving at non-drinking times when alcohol was present. This finding suggests that deviations in situational context contributed to heightened cue-elicited craving. Through a clinical lens, this finding suggests that craving may emerge the strongest when deviating from a typical routine. It is important to note, as well, that participants in this analysis were not enrolled in formal treatment and were not forced or expected to go without drinking alcohol. Although alcohol dependence was associated with greater craving, overall, at least some alcohol craving was reported by nearly all participants (97%). Thus, while craving is related to drinking and alcohol problems, it was still a common experience for drinkers in this sample.

Individuals with alcohol dependence may be told that the earliest days of recovery are the most difficult, and that their craving should subside if they remain abstinent for long enough. Yet, animal models suggest that craving is enhanced by periods when the craved substance is not available[1–3]. It is also common for problem drinkers to have extended periods without drinking followed by a return to previous drinking patterns[45]. Among the factors thought to underlie prolonged relapse is conditioned alcohol craving brought forth by the presence of alcohol or other cues associated with drinking, i.e., cue-elicited craving[46]. Given the strong clinical relevance of cue-induced craving, our understanding of the time course of reactivity to alcohol cues with progressive abstinence in humans has been grossly insufficient.

Our naturalistic study builds from a small group of studies testing incubation in humans[5,6,16,17]. Bedi and colleagues (2011) provided monetary incentives to smokers for abstaining from nicotine for randomly assigned periods (i.e., 7, 14, or 35 days), with abstinence biochemically verified daily[16]. Between and within-groups tests showed that cue-elicited craving increased with longer abstinence periods for some craving indices and did not decrease with abstinence for any craving index, thus providing evidence for incubation of nicotine craving[16]. Li and colleagues (2014) applied a similar paradigm for individuals with alcohol dependence during a 1 to 3-month inpatient hospital admission. Alcohol access was restricted for the full duration of stay, groups were randomly assigned to be tested at 7, 14, 30, or 60 days after withdrawal, and a final group was tested at all timepoints. Importantly, Li and colleagues provided evidence for progressive increases in cue-elicited alcohol craving with longer periods of continuous abstinence, while also showing progressive decreases in withdrawal symptomatology for up to 60 days post detoxification[5]; this finding suggests that withdrawal symptomatology is not the mechanism driving incubation in humans.

The current work adds an evaluation of craving incubation in drinkers' daily lives, across 266 drinkers aged 14 to 67, and showed evidence for the craving incubation phenotype among dependent drinkers. Building from prior studies, we monitored spontaneous variations in days of continuous abstinence as participants engaged in their normal drinking patterns, which is reflected in our limited range of days since last drink. It is noteworthy that we observed evidence of craving incubation in a time period that is considerably shorter than in prior work. In our study, duration of abstinence and other key variables, such as the presence of naturally occurring visible alcohol cues, was not standardized across participants or randomly assigned. Recent innovations in Cue Reactivity Ecological Momentary Assessment (CREMA) offer potential for experimentally determining the presence or absence of visible substance-use cues in the natural environment[47]. Manipulating pictorial cue presentation via a standardized paradigm implemented on a smartphone, together with assessing situational contextual cues in daily life, is a new method offering the advantage of experimental control for data collected in real-word settings.

Other important limitations should be considered when interpreting our findings. First, data were culled from three separate studies that were not run simultaneously. Differences in eligibility criteria based on drinking frequency across studies was reflective of known age differences in drinking patterns. Although covariates including study, age, gender, race, and baseline percent drinking days did not change our pattern of significant findings, the potential for recruitment bias must be acknowledged. In relation, data remain cross-sectional with regard to age and thus subject to cohort effects. Longitudinal studies exploring the effects of age and AUD when following drinkers over time are needed. Next, to limit participant burden, craving was assessed through a single-item measure of "urge to drink," which, although widely used,[24,42] is only one potential operationalization of craving. Last, our ability to use other in-depth assessments of alcohol-use severity and other alcohol-related problems in addition to the KSADS and TLFB was limited due to differences in measures across studies. These limitations notwithstanding, the size and age range of the combined EMA data are noteworthy strengths. In addition, evaluating incubation of craving in drinkers' daily lives, across naturally occurring periods without drinking, is novel and

important for understanding how alcohol cues heighten craving to maintain substance misuse.

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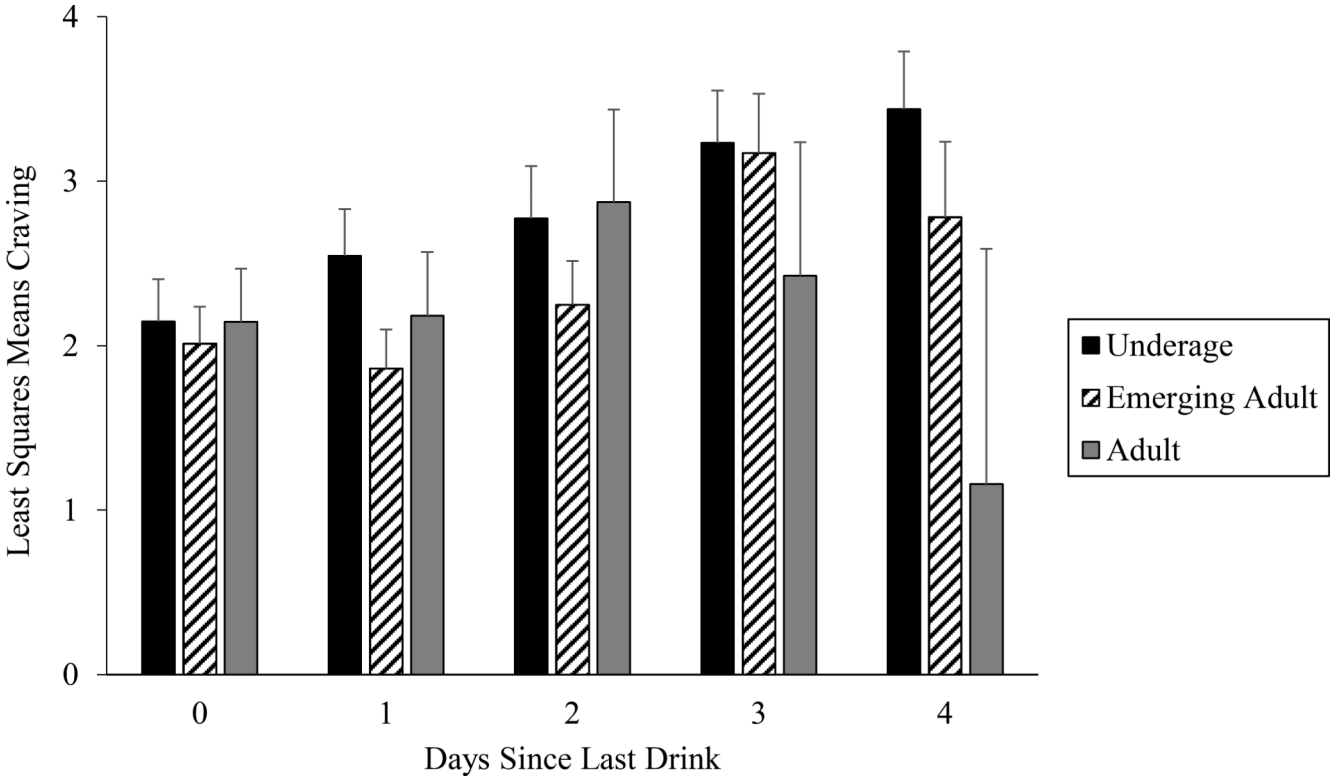


**Figure 1.**
Least squares means (and standard error bars) for craving by age group and days since last standard drink. Covariates included study, dependence, average days since last drink, average presence of visible alcohol cues, and presence of visible alcohol cues.

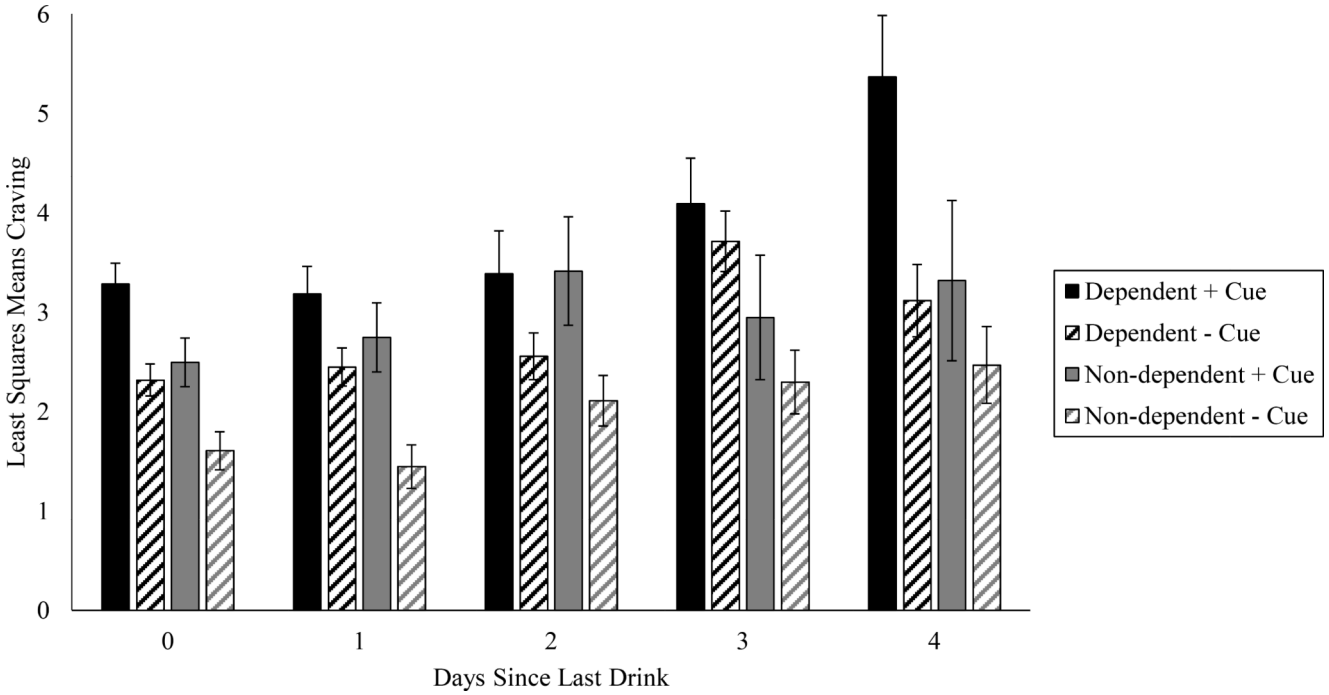


**Figure 2.**

Least squares means (and standard error bars) showing incubation of craving whereby cue-elicited craving increases with more days since last standard drink among drinkers with dependence. Covariates included study, age, average days since last drink, and average presence of visible alcohol cues.

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**Table 1.**

Summary of Inclusion Criteria and Ecological Momentary Assessment Report Details by Study

| | Study | | |
|---|---|---|---|
| | **1** | **2** | **3** |
| Inclusion criteria | | | |
| Age (years) | 15 to 19 | 14 to 24 | 21 to 67 |
| Drinking frequency, *i.e., occasions per week in past 30 days* | 2+ | 2+ | 4+ |
| Frequency of heavy drinking, *i.e., occasions per week in past 30 days; heavy drinking defined as >6/>4 drinks for men/women* | None required | None required | 2+ |
| Interest in reducing alcohol use | Not explicitly listed in inclusion criteria | Yes | Not explicitly listed in inclusion criteria |
| Able to read simple English, *i.e., to respond to questions on the device* | Yes | Yes | Yes |
| Ecological Momentary Assessment random prompt report details | | | |
| Delivery schedule | Once in each 3-hr block per day stopped when in “sleep” mode, and not overlapping with drink reports | Once in each 3-hr block per day stopped when in “sleep” mode, and not overlapping with drink reports | Scheduled as 5 on average per day, stopped when in “sleep” mode, and not overlapping with drink reports |
| Delay maximum | 20 min | 20 min | 20 min |
| Suspension maximum | 7 hr | 7 hr | 2 hr |
| Maximum time to start a response (or delay) before marked as missed[a] | 2 min | 2 min | 2 min |

Note.

[a]Once an audible prompt was delivered, participants must have acknowledged it within 2 min, or it was marked as a missed report. They could choose to either delay their response for up to 20 minutes or complete the report immediately. Once a response was initiated, participants could complete the report at their own pace; however, reports were designed to be brief and take less than 90 seconds.

**Table 2.**

Summary of Descriptive Statistics by Study

| | Study | | | |
|---|---|---|---|---|
| **Variable** | **1 (*n* = 29)** | **2 (*n* = 86)** | **3 (*n* = 151)** | **Overall (*N* = 266)** |
| Age | | | | |
| Observed Range | 15 – 19 | 14 – 24 | 21 – 67 | 14 – 67 |
| *M* (*SD*) | 18.2 (1.1)[a] | 20.7 (2.1)[b] | 28.8 (11.5)[a,b] | 25.0 (9.8) |
| Sex, # (%) female | 16 (55.2) | 42 (48.8) | 65 (43.1) | 123 (46.2) |
| Race, # (%) | | | | |
| White | 20 (71.4) | 63 (75.0) | 140 (92.7) | 223 (84.8) |
| Black | 3 (10.7) | 12 (14.3) | 6 (3.4) | 21 (8.0) |
| Native Hawaiian or Pacific Islander | 1 (3.4) | 0 (0.0) | 1 (0.7) | 2 (0.8) |
| Asian | 3 (10.7) | 4 (4.8) | 0 (0.0) | 7 (2.7) |
| American Indian or Native Alaskan | 1 (3.4) | 3 (3.6) | 0 (0.0) | 4 (1.5) |
| Other | 0 (0.0) | 2 (2.4) | 4 (2.7) | 6 (2.3) |
| Hispanic, # (%) | 5 (17.2)[a] | 18 (20.9)[b] | 2 (1.3)[a,b] | 25 (9.5) |
| Alcohol Dependence, # (%) | 14 (48.3) | 53 (61.6) | 91 (60.3) | 158 (59.4) |
| Baseline drinking levels | | | | |
| % drinking days, *M* (*SD*) | 28.0 (16.7)[a] | 34.9 (20.1)[b] | 64.4 (16.1)[a,b] | 50.8 (23.4) |
| % heavy drinking days, *M* (*SD*) | 15.3 (18.3)[a] | 14.0 (13.2)[b] | 44.7 (18.3)[a,b] | 31.6 (22.6) |
| Drinking in monitoring period | | | | |
| % drinking days, *M* (*SD*) | 37.6 (38.6)[a] | 37.5 (48.5)[b] | 71.5 (45.2)[a,b] | 55.3 (39.7) |
| % heavy drinking days, *M* (*SD*) | 21.7 (41.3)[a] | 11.3 (31.7)[a] | 51.8 (50.0)[a] | 33.3 (47.1) |
| Included monitoring days | | | | |
| Observed range | 5 – 13 | 1 – 14 | 1 – 8 | 1 – 14 |
| *M* (*SD*) | 7.1 (1.5) | 7.7 (2.1)[a] | 6.2 (4.0)[a] | 6.9 (2.0) |

Note: Race percentages are based on available data; three participants chose not to report their race. Baseline drinking levels are derived from the 90-day Timeline Follow-Back interview. Drinking during the EMA monitoring period is derived from morning reports.

[a]Common superscripts indicate column means that are significantly different from each other. Racial category differences across studies are not depicted with superscripts due to small cell sizes invalidating results of the reduced $\chi^2$ test.

**Table 3.**

Estimates [and 95% Confidence Intervals] from Random-Intercept Mixed Models Relating Participant Age, Dependence, Presence of Visible Alcohol Cues and Days of Continuous Abstinence to Alcohol Craving

| | *Est.* | LCL | UCL | *p* |
|---|---|---|---|---|
| Intercept | 2.49 | [2.12, | 2.86] | < .001 |
| Level-2 Effects | | | | |
| Study 2 | − 0.97 | [− 1.46, | − 0.49] | < .001 |
| Study 1 | − 0.52 | [− 1.20, | 0.17] | .139 |
| *Study 3 (Reference)* | | | | |
| Age | 0.00 | [− 0.02, | 0.02] | .956 |
| Dependence *(No dependence = reference)* | 0.75 | [0.36, | 1.15] | < .001 |
| Average Days Since Last Drink | 0.02 | [− 0.06, | 0.10] | .613 |
| Average Presence of Visible Alcohol Cues | 1.19 | [0.35, | 2.04] | .006 |
| Level-1 Effects | | | | |
| Days Since Last Drink | 0.18 | [0.13, | 0.23] | < .001 |
| *Presence of Visible Alcohol Cues (Alcohol is not present = reference)* | 0.92 | [0.71, | 1.12] | < .001 |
| Intercept (Level-2) Variance | 2.07 | [1.64, | 2.51] | < .001 |
| Error (Level-1) Variance | 4.84 | [4.62, | 5.06] | < .001 |
| Fit Statistics | | | | |
| Model Deviance (−2LL) | 18294.8 | | | |
| AIC | 18298.8 | | | |
| BIC | 18305.9 | | | |

*Note.* −2LL = −2 Log Likelihood. AIC = Akaike Information Criterion. BIC = Bayesian Information Criterion. Model Deviance (−2LL) for the null (unconditional means) model was 19673.2, AIC = 19677.2, BIC = 19684.4.

**Table 4.**

Estimates [and 95% Confidence Intervals] from Random-Intercept Mixed Models Testing "Incubation of Craving"

| | *Est.* | LCL | UCL | *p* |
|---|---|---|---|---|
| Intercept | 2.479 | [2.12, | 2.86] | < .001 |
| Level-2 Effects | | | | |
| Study 2 | − 0.98 | [− 1.46, | − 0.49] | < .001 |
| Study 1 | − 0.54 | [− 1.22, | 0.15] | .125 |
| *Study 3 (Reference)* | | | | |
| Age | 0.00 | [− 0.02, | 0.02] | .953 |
| Dependence *(No dependence = reference)* | 0.73 | [0.33, | 1.14] | < .001 |
| Average Days Since Last Drink | 0.02 | [− 0.06, | 0.10] | .605 |
| Average Presence of Visible Alcohol Cues | 1.14 | [0.30, | 2.01] | .011 |
| Level-1 Effects | | | | |
| Days Since Last Drink | 0.16 | [0.09, | 0.24] | < .001 |
| Presence of Visible Alcohol Cues *(Cues are not present = reference)* | 0.84 | [0.54, | 1.15] | < .001 |
| Interactive Effects | | | | |
| Presence of Cues × Dependence | 0.10 | [− 0.31, | 0.51] | .628 |
| Presence of Cues × Days Since Last Drink | − 0.06 | [− 0.23, | 0.12] | .515 |
| Dependence × Days Since Last Drink | 0.01 | [− 0.11, | 0.13] | .916 |
| Presence of Cues × Dependence × Days Since Last Drink | 0.38 | [0.10, | 0.67] | .009 |
| Intercept (Level-2) Variance | 2.07 | [1.64, | 2.51] | < .001 |
| Error (Level-1) Variance | 4.83 | [4.61, | 5.05] | < .001 |
| Fit Statistics | | | | |
| Model Deviance (−2LL) | 18295.1 | | | |
| AIC | 18299.1 | | | |
| BIC | 18306.2 | | | |

*Note.* −2LL = −2 Log Likelihood. AIC = Akaike Information Criterion. BIC = Bayesian Information Criterion. Model Deviance (−2LL) for the null (unconditional means) model was 19673.2, AIC = 19677.2, BIC = 19684.4.

**Table 5.**

Estimates [and 95% Confidence Intervals] from Random-Intercept Mixed Models Testing Age Effects

| | *Est.* | LCL | UCL | *p* |
|---|---|---|---|---|
| Intercept | 2.49 | [2.12, | 2.86] | < .001 |
| Level-2 Effects | | | | |
| Study 2 | − 0.97 | [− 1.45, | − 0.49] | < .001 |
| Study 1 | − 0.52 | [− 1.20, | 0.17] | .140 |
| *Study 3 (Reference)* | | | | |
| Age | 0.00 | [− 0.04, | 0.03] | .942 |
| Dependence *(No dependence = reference)* | 0.75 | [0.35, | 1.15] | < .001 |
| Average Days Since Last Drink | 0.02 | [− 0.06, | 0.10] | .619 |
| Average Presence of Visible Alcohol Cues | 1.20 | [0.35, | 2.04] | .006 |
| Level-1 Effects | | | | |
| Days Since Last Drink | 0.15 | [0.10, | 0.21] | < .001 |
| Presence of Visible Alcohol Cues *(Alcohol is not present = reference)* | 0.93 | [0.72, | 1.14] | < .001 |
| Cross-level interactions | | | | |
| Age × Dependence | 0.00 | [− 0.04, | 0.05] | .877 |
| Age × Days Since Last Drink | − 0.01 | [− 0.02, | − 0.002] | .017 |
| Age × Presence of Visible Alcohol Cues | 0.01 | [− 0.02, | 0.05] | .475 |
| Intercept (Level-2) Variance | 2.08 | [1.65, | 2.52] | < .001 |
| Error (Level-1) Variance | 4.83 | [4.62, | 5.05] | < .001 |
| Fit Statistics | | | | |
| Model Deviance (−2LL) | 18309.7 | | | |
| AIC | 18313.7 | | | |
| BIC | 18320.8 | | | |

*Note.* −2LL = −2 Log Likelihood. AIC = Akaike Information Criterion. BIC = Bayesian Information Criterion. Model Deviance (−2LL) for the null (unconditional means) model was 19673.2, AIC = 19677.2, BIC = 19684.4.