Effects of Alcohol Availability, Access to Alcohol, and Naltrexone on Self-Reported Craving and Patterns of Drinking in Response to an Alcohol-Cue Availability Procedure

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ABSTRACT. Objective: Craving has long been cited by patients and providers as a principal construct in alcohol use disorders and an essential target for treatment. The goal of the current study was to examine the effects of alcohol availability (20% vs. 80% availability), access to alcohol (“open” vs. “locked” trials), and medication (oral naltrexone [Revia] vs. placebo) on self-reported craving and two behavioral measures of drinking (latency of attempt to access alcohol, amount of alcohol consumed when access permitted) in response to an alcohol-cue availability procedure. **Method:** Non-treatment-seeking, alcohol-dependent men and women ($N = 58$) self-referred for an alcohol administration study and were administered a modified alcohol-cue availability procedure under two medication conditions (naltrexone, placebo) using a within-subjects, repeated-measures design. **Results:** Analyses demonstrated that the

experimental manipulations used in this study had differential effects on craving and patterns of drinking. Specifically, reduced availability of alcohol (i.e., when alcohol was available in only 20% as opposed to 80% of trials) resulted in greater amounts of alcohol consumed per open trial; the unanticipated blocking of access to alcohol (i.e., a “locked” trial during the 80% availability condition) triggered more rapid attempts to obtain alcohol on subsequent trials. Naltrexone, relative to placebo, was associated with significant reductions in cravings for alcohol. **Conclusions:** Taken together, these findings offer partial support for the cognitive processing model and reinforce the utility of evaluating both self-report and behavioral indicators of motivation to drink in studies designed to identify factors associated with the construct of craving. (*J. Stud. Alcohol Drugs*, 73, 205–215, 2012)

PSYCHOLOGICAL, BEHAVIORAL, and neurobiological theories of substance dependence implicate craving as contributing to the development, maintenance, and re-emergence of problem drinking (Bottlender and Soyka, 2004; Tiffany, 1990; Verheul et al., 1999). Many psychosocial treatments for alcohol dependence, including cognitive-behavioral coping skills therapy (Longabaugh and Morgenstern, 1999) and Twelve-Step Facilitation (Nowinski et al., 1994), emphasize the development of coping strategies designed to reduce and manage cravings. Further, psychopharmacological interventions (e.g., opioid antagonists) for alcoholism are often designed to target neurobiological mechanisms of craving (Leggio, 2009; Swift, 1999).

Although craving has long been cited as a major contributor to relapse (Jellinek, 1960; Ludwig and Wikler, 1974; Pavlick et al., 2009), the research is equivocal (Lowman et al., 2000). Some studies suggest that craving predicts immediate drinking (Leeman et al., 2009) and relapse following treatment (Anton et al., 1996; Bottlender and Soyka, 2004), whereas others do not (Junghanns et al., 2005; Kiefer et al., 2005). There is evidence that psychosocial (e.g., cue exposure with coping skills; Monti et al., 1993) and pharmacological (e.g., oral naltrexone [Revia]; Monti et al., 1999) treatments explicitly designed to decrease craving result in reduced drinking; however, craving is rarely cited by patients as the primary reason for posttreatment relapse (Miller and Gold, 1994).

Discrepant findings may be because of differences in baseline levels of craving. Moderate to severe levels of craving may be present in only 50%–75% of alcohol-dependent individuals (Yoon et al., 2006, 2011). Further, naltrexone, an opioid antagonist with demonstrated efficacy as a short-term treatment (Srisurapanont and Jarusuraisin, 2005), is more

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effective in patients reporting higher pretreatment cravings (Jaffe et al., 1996; Monterosso et al., 2001). High-dose naltrexone significantly reduced craving and improved drinking outcomes in alcoholics reporting moderate to severe levels of pretreatment craving (Yoon et al., 2011). Thus, craving may be an important target for intervention among individuals with significant pretreatment cravings.

The primarily subjective experience of craving has also led to wide discrepancies in the conceptualization, modeling, and assessment of this construct (Connolly et al., 2009; Lowman et al., 2000; Pavlick et al., 2009; Shiffman, 2000; Sinha, 2009). It has been suggested that assessment of craving should extend beyond self-report measures to include behavioral indicators of drinking motivation (Rosenberg, 2009). Despite the lack of consensus, craving remains an important focus in the conceptualization of addictive behaviors (de Bruijn et al., 2005) as epitomized by the proposed inclusion of craving as a diagnostic criterion for alcohol use disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2010).

The cue-reactivity paradigm has enhanced empirical investigations of the effects of craving on drinking behavior and provided insight into factors that contribute to the onset and magnitude of craving for alcohol (Drummond, 2000). Within cognitive-behavioral theories, two major models describe how perceived alcohol availability (i.e., presence of alcohol-related cues) may affect craving. Classical conditioning models posit that, over repeated exposures and pairings, the presence of cues signaling the availability of alcohol (i.e., conditioned stimulus cues) leads to increased cravings (i.e., conditioned response; Robinson and Berridge, 1993; Stewart et al., 1984; Wise and Bozarth, 1987). These models also predict that the absence of cues signaling availability (i.e., belief alcohol is not available) will lead to reductions in cravings (Wertz and Sayette, 2001).

In contrast, the cognitive processing model (CPM; Tiffany, 1990) asserts that cravings for alcohol are strongest when an individual believes that alcohol is not available (i.e., when cues are absent or when access is denied). A central tenet of CPM is that alcoholics develop ritualized behaviors across repeated drinking episodes, which result in the automation of actions involved in the acquisition and consumption of alcohol (Tiffany, 1990). As ritualistic drinking behaviors become increasingly automatic, they become less dependent on intention/motivation. Accordingly, it is only when automatic behaviors are impeded (i.e., access is blocked), that nonautomatic behaviors dependent on intention/motivation are engaged and craving occurs.

Investigations of craving in smokers generally support classical conditioning models of dependence, with craving for cigarettes strongest when smoking cues are present (e.g., Carter and Tiffany, 2001; Dols et al., 2000). Similarly, lower ratings of cravings in hospitalized, abstinent-seeking drug

users are interpreted as supportive of classical conditioning models based on the premise that they were driven by the belief that drugs were not available (Wertz and Sayette, 2001). Data from alcohol studies have been less consistent. For example, although urges to drink alcohol are higher when alcohol is not available in heavy drinkers (MacKillop and Lisman, 2005), the availability of alcohol does not have a significant impact on self-reported cravings in an alcohol-dependent sample (Davidson et al., 2003).

A number of potential explanations for inconsistent findings exist. First, compared with other drugs of abuse (e.g., nicotine, heroin), the magnitude of cravings elicited for alcohol is smaller in cue reactivity studies (Carter and Tiffany, 1999). Given small effect sizes, choice of study design may affect the ability to identify meaningful differences between conditions. Although there are methodological reasons for selecting either between- or within-subjects designs, within-subjects designs reduce variability in outcome measures, thereby increasing sensitivity for detecting meaningful differences. Second, the strength of the effect of cue exposure on cravings may be influenced by severity of alcohol dependence. According to CPM, cravings for alcohol when access is blocked are strongest in individuals for whom ritualistic drinking behaviors are most automated (i.e., those most dependent; Tiffany, 1990). Third, differences in craving assessment (single- vs. multiple-item scales; self-report vs. behavioral measures) may affect outcomes. Although some studies rely on a single-item self-report indicator of craving, multiple-item (Connolly et al., 2009) and behavioral (Sayette et al., 2000) measures should be used whenever possible. Fourth, differences in stimulus cues, availability of alcohol, and restriction of access to alcohol across studies may each have significant effects on cravings.

This study was designed to investigate the effects of a modified version of the alcohol-cue availability paradigm (Carter and Tiffany, 2001) on craving and behavioral measures of drinking in a sample of non-treatment-seeking, alcohol-dependent individuals. The study incorporated a within-subjects design, in which both self-reported craving and drinking behaviors were examined across two levels of alcohol availability (80% vs. 20% "open" trials). The effect of the most recent attempt to access alcohol (i.e., open vs. locked trial) on these outcomes also was examined. Given evidence that opioid antagonists are effective at reducing cravings, this paradigm was evaluated within subjects comparing naltrexone with placebo.

Method

Recruitment, screening, and testing procedures were approved by the institutional review board at Indiana University and conducted in accordance with the guidelines for the administration of alcohol to humans published by the National Institute on Alcohol Abuse and Alcoholism (2005).

Participants

Inclusion/exclusion criteria and screening. Individuals who regularly drank five or more alcoholic beverages were targeted for recruitment for an alcohol administration study through print advertisements. Interested callers completed a telephone screening process to confirm willingness to consume one of three brands of light beer (alcohol by volume = .042) and basic inclusion/exclusion criteria. Those who passed the telephone screen were scheduled for an initial appointment to determine eligibility. Informed consent was obtained after participants provided a negative breath sample for alcohol. Eligibility was restricted to individuals ages 21–65 years who reported at least one drinking episode in the 7 days before the assessment, met current diagnostic criteria for alcohol dependence (DSM-IV-TR; American Psychiatric Association, 2000), and had neither received nor were interested in receiving alcohol treatment in the past year.

Exclusion criteria consisted of contraindications to the ingestion of alcohol or naltrexone or the presence of factors that would interfere with the ability to complete the study. Specific exclusion criteria included elevated liver enzymes; positive urine toxicology screen for cocaine, opiates, amphetamines, benzodiazepines, or barbiturates; use in the previous 30 days of prescription medications that might influence study outcomes (e.g., psychotropics); diagnosis of dependence on any substance other than caffeine or nicotine; evidence of serious risk of withdrawal (score > 8 on the revised Clinical Institute Withdrawal Assessment for Alcohol Scale [CIWA-Ar; Sullivan et al., 1989]); and court order prohibiting consumption of alcohol. Women who were pregnant or breast-feeding were excluded. Individuals who provided a positive breath sample for alcohol were excluded from participation on that day and disqualified from the study if they tested positive for alcohol during any subsequent session.

A total of 252 individuals passed the telephone screen, provided informed consent, and were scheduled for the initial eligibility appointment. Of those, 177 were ruled ineligible: 27.7% did not meet alcohol dependence diagnosis, 16.9% failed the urine drug screen, 14.7% were medical exclusions (laboratory result, medical disorder, and/or prescription medication), 9.0% had exclusionary psychiatric diagnoses/symptoms, 6.8% were deemed at significant risk for withdrawal, 5.1% provided two positive alcohol breath tests, 4.5% were noncompliant with screening procedures, 2.3% were lost to follow-up, 1.1% were excluded based on familiarity with the testing protocol through participation in a prior study, and 11.9% were excluded for multiple criteria. Three eligible participants were not enrolled because of study completion. The remaining 72 participants were enrolled and completed Day 1 as described below. Fifty-eight participants completed

the entire 17-day study protocol and were included in the analyses.

Sample characteristics. The average age of participants was 37.8 years ($SD = 9.4$; range: 21–56), and men comprised 71% of the sample. Sixty percent were African American, and 31% were White; there was one Asian American and one “other” participant. Sixteen percent did not graduate from high school, 29% completed high school, and 55% reported some postsecondary training. Twenty-six percent were employed full time, 21% were employed part time, 48% were unemployed, and one participant each reported being a student, homemaker, or on disability. The majority (89.7%) identified at least one first- or second-degree relative with alcohol dependence. Eighty-one percent were current smokers. The mean group score on the Alcohol Dependence Scale (ADS; Skinner and Horn, 1984) was 13.1 ($SD = 7.4$; range: 1–34). CIWA-Ar scores ranged from 0 to 6 ($M = 1.4$, $SD = 1.6$). In the 30 days before screening, participants endorsed drinking on 24.6 days ($SD = 5.2$; range: 10–30; 82.1% of possible days) and consumed 10.3 drinks per drinking episode ($SD = 5.2$; range: 3.9–27.3). Participants reported drinking heavily (five or more drinks for men, four or more for women) on 20.3 of the previous 30 days ($SD = 8.3$; range: 0–30; 81.2% of drinking days).

Screening measures and procedure

Breath alcohol tests were obtained via the Alco-Sensor IV Intoximeter (Intoximeters Inc., St. Louis, MO) to ensure zero breath alcohol concentration (BrAC) before each session. Volunteers were administered the Substance Use Disorders Module of the Structured Clinical Interview for the DSM-IV Axis I Disorders (First et al., 1996) by trained and supervised research personnel to establish the diagnosis of alcohol dependence and rule out a dependence diagnosis for substances other than caffeine or nicotine. The CIWA-Ar was administered to ascertain risk of withdrawal during each session, with scores greater than 8 resulting in exclusion. Participants provided their medical history as well as blood and urine samples for analysis of liver enzymes (SGOT, SGPT, and γ GGT) and to detect the presence of drugs. Women were administered a urine pregnancy test during the screening and before each testing session. Medical history, CIWA-Ar scores, and results of blood and urine screens were reviewed by study physicians to determine eligibility.

Baseline participant characteristics

Severity of alcohol dependence. The 25-item ADS (Skinner and Horn, 1984) has demonstrated reliability and was used to assess severity of alcohol dependence.

Patterns of drinking. Daily quantities of alcohol use were evaluated for the 30 days before the baseline screening session and for the days between sessions using

	80% Availability Condition															
Trial #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Access	<i>a</i>	O	O ^a	O	O ^a	L ^a	O	O	O ^a	L ^a	O	O ^a	O	O ^a	L ^a	O
Assessment	BL	–	BG	–	I	U	–	–	I	U	–	BG	–	I	U	–

	20% Availability Condition															
Trial #	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	
Access	L	L ^a	L	L ^a	O ^a	L	L	L ^a	O ^a	L	L ^a	L	L ^a	O ^a	L	
Assessment	–	BG	–	I	U	–	–	I	U	–	BG	–	I	U	–	

FIGURE 1. Pictorial representation of sample assessment schedule for craving across open and locked access trials in both 80% and 20% availability conditions. Notes: Order of 80% and 20% availability conditions was randomly assigned between participants and counterbalanced within participants across assessment sessions. In the 80% availability condition, 12 of the 15 trials were open access (O); in the 20% availability condition, 12 of the 15 trials were locked access (L). BL = baseline ($n = 1$; pre-manipulation of availability) assessment; I = assessment following an identical block of trials ($n = 6$); U = assessment following an unexpected trial ($n = 6$); BG = assessment following a bogus trial inserted to reduce the likelihood that ratings would serve as a cue the trial condition was about to change ($n = 4$). ^aTrials during which assessment of craving occurred.

the gold-standard, episodic-based, semistructured Timeline Followback interview (Sobell and Sobell, 1992).

Outcome measures

Self-reported craving. Four items were used to measure craving: (a) I want to use alcohol right now, (b) I have an urge to drink now, (c) it would be great to use alcohol now, and (d) nothing would be better than drinking right now. Items were derived from analyses of the 47-item Alcohol Craving Questionnaire (Singleton et al., 1995) and have been used as an indicator of craving in cue-availability testing (Pratt and Davidson, 2009). Ratings for each item were based on a 7-point Likert scale with response options ranging from *strongly disagree* (1) to *strongly agree* (7) and averaged to form a single craving score for each trial. Craving was evaluated on 17 of the 30 trials during each testing session (Figure 1). Internal consistency for the four-item measure was excellent under both naltrexone ($\alpha = .982$) and placebo ($\alpha = .979$) testing conditions.

Latency. Alcohol-seeking behavior was defined as the physical act of attempting to access alcohol, and latency was measured in milliseconds between the provision of the cue indicating the presence of alcohol and the attempted opening of the window to access alcohol.

Alcohol consumption. The amount of alcohol consumed on open trials (when access to alcohol was permitted) was obtained by weighing the alcohol cue before and after each trial using a Navigator scale (N1B110; Ohaus, Pine Brook, NJ), which provides measurements accurate to 0.1 g.

Procedure

Study design. A within-subjects protocol was designed to examine the effects of naltrexone, proportion of alcohol availability (available in 80% vs. 20% of trials), and the result of the most recent attempt to access alcohol (open vs. locked trial) on craving ratings and drinking behaviors in a sample of non-treatment-seeking, alcohol-dependent participants. The order of assessments for each participant was randomly determined and counterbalanced by medication and alcohol availability conditions. Participants and researchers conducting the sessions were blinded to medication condition. Each experimental session lasted approximately 35 minutes, contained 30 trials (15 each under 20%- and 80%-availability conditions), and was completed on the ninth day of medication dosing.

Day 1: Initial laboratory and medication visit. The initial laboratory assessment was scheduled within 3–10 days of screening. During this session, participants provided

daily drinking data for the preceding 30 days via Timeline Followback, completed the ADS, and were administered a half-dose of medication (25 mg naltrexone or placebo) to minimize likelihood of side effects. Participants were given a vial containing seven additional full doses of the medication (50 mg naltrexone or placebo) with instructions to take the medication in the morning during Days 2–8. Information regarding the typical side effects of naltrexone was provided. Participants were scheduled for two experimental sessions (Day 9 and Day 17) and instructed to fast from food and alcohol after midnight before these appointments. Between visits, staff called participants to confirm medication adherence, query for side effects, and provide reminders of scheduled appointments and fasting requirements.

Day 9: First alcohol-cue availability test. Participants arrived on Day 9 at 9:00 A.M., were administered their ninth dose of medication, provided daily drinking data for Days 2–8, and consumed a standardized light breakfast to control for food intake. Three hours after the medication dose (at approximately noon) participants completed the alcohol-cue availability procedure and then ate lunch. Participants were allowed to smoke before and after the alcohol-cue availability procedure. BrAC was monitored, and once BrAC fell below .02 g/dl, participants were provided with a half-dose of the second medication (25 mg naltrexone or placebo) and a vial containing seven additional doses (50 mg naltrexone or placebo for Days 10–16) and were paid \$50. Between-session telephone calls were placed to confirm medication adherence, query for side effects, and provide reminders of the scheduled appointments and fasting requirements.

Day 17: Second alcohol-cue availability test. The testing protocol for Day 17 was identical to Day 9. After BrAC fell below .02 g/dl, all participants received personalized feedback comparing their drinking behavior with the patterns of a social-drinking population and were provided with information about potential harm they might experience based on current drinking levels. No participants expressed interest in treatment. Each participant received \$100.

Alcohol-cue availability procedure. Testing occurred in a private room with a chair and table containing the cue box, computer keyboard, monitor, and headphones through which the stimulus tones were presented. A clear sliding glass window was used to separate the participant from the alcohol cue, and a second, opaque sliding glass window was used to block the cue from view to allow for measurements/refreshing the beverage. After participants were fitted with the headphones and were situated within comfortable reach of the cue box and computer keyboard by the dominant hand, chair placement was marked and participants were instructed to not move the chair during testing. Trials were guided by instructions displayed on the monitor, and white noise was played through the headphones to reduce distraction. A series of eight practice trials with a water cue were used to orient

the participant to the procedure and promote discrimination between two stimulus tones: One signaled the participant to open the window on the cue box to access the beverage, and the second signaled the participant to return his or her attention to the computer monitor. After the training trials, the alcohol-cue availability procedure began.

All trials began with the presentation of the following instructions on the monitor: “Look at the window and think about what you see.” Through the window, chilled beer poured into a 20-oz. glass was visible. After 14 seconds, a tone prompted the participant to return attention to the monitor and provide craving ratings. Once ratings were completed, the following instructions were displayed: “Please wait for the tone and then try to open the window.” Participants were instructed to always attempt to open the window when they heard the tone, and if the window opened (“open” trial) to always drink as much as they desired. After drinking, participants were instructed to return the beverage to the cue box and shut the window so that measurements could be taken and the alcohol cue refreshed outside the view of participants. If the window would not open (“locked” trial), participants were signaled to return attention to the monitor in anticipation of the next trial. Because participants were unaware in advance whether a trial would be “open” or “locked,” the effects of each trial on the outcome variables (craving, latency, and quantity) were based on data obtained during the subsequent trial.

Results

Preliminary analyses

Examination of group differences. No significant differences in ADS or CIWA scores, proportion of current smokers, or patterns of drinking were observed by race (African American vs. White) ($ps > .24$). Women ($M = 24.1$, $SD = 5.5$) did report more frequent heavy drinking episodes than men ($M = 18.7$, $SD = 8.9$) at baseline, $F(1, 56) = 5.28$, $p = .025$. No other gender differences broached statistical significance ($ps > .19$). Participants who received placebo first had statistically lower CIWA-Ar scores at baseline ($M = 0.93$, $SD = 1.11$) than those who received naltrexone first ($M = 1.93$, $SD = 1.88$), $F(1, 56) = 6.10$, $p = .017$, although both scores are far below the threshold for withdrawal risk (8), suggesting the difference is not clinically meaningful. No significant group differences were observed by order of availability ($ps > .11$).

Changes in drinking across assessment time points. A 2 (gender) $\times$ 2 (drug administration: placebo vs. naltrexone first), mixed-model, repeated measures multivariate analyses of variance examined potential changes in percentage of drinking days, typical quantity of alcohol consumed per drinking day (quantity), and

TABLE 1. Simple bivariate correlations between self-reported craving ratings, latency, and typical amount of alcohol consumed with Alcohol Dependence Scale scores, CIWA-Ar scores, and number of drinks consumed in past week by medication condition

Variable	Craving		Amount consumed		Latency	
	Naltrexone	Placebo	Naltrexone	Placebo	Naltrexone	Placebo
Craving	—	—	—	—	—	—
Amount consumed	.31*	.38**	—	—	—	—
Latency	.01	-.01	.06	-.14	—	—
Alcohol Dependence Scale	.16	.08	.11	-.01	.19	.16
CIWA-Ar score	.09	.01	-.00	-.11	.21	.07
No. of drinks consumed past week	.26*	.29*	-.03	.13	.25	-.12

Notes: CIWA-Ar = revised Clinical Institute Withdrawal Assessment for Alcohol Scale.

* $p < .05$; ** $p < .01$.

percentage of drinking days that were heavy drinking days between assessment time points. There were no significant multivariate (or univariate) interactions ($ps > .33$) or significant multivariate (or univariate) main effects of gender ($p = .21$) or drug administration ($p = .46$), suggesting that differences in drinking patterns occurred independent of these variables.

A significant multivariate main effect of assessment time point, $F(9, 46) = 8.93$, $p < .001$, demonstrated that drinking patterns changed significantly over time. Follow-up univariate analyses revealed a reduction in percentage of drinking days from baseline (30 days before screening; 82.1%) to the week between screening and the initial laboratory/medication visit ($M = 7.4$ days; 69.2%), which was maintained during the first week of medication before

the first testing session ($M = 7.5$ days; 59.0%) and through the second week of medication preceding the second testing session ($M = 7.6$ days; 60.3%), $F(3, 162) = 18.49$, $p < .001$. Similar reductions were observed for quantity of alcohol consumed from baseline ($M = 10.34$ drinks, $SD = 5.23$) to initial laboratory visit ($M = 8.71$, $SD = 5.62$), through the first ($M = 6.96$, $SD = 4.48$) and second testing sessions ($M = 6.40$, $SD = 4.11$), $F(3, 162) = 11.65$, $p < .001$. There was also a significant reduction in percentage of heavy drinking days across time points (81.2%, 69.0%, 63.0%, and 58.1% for baseline, the initial laboratory visit, the first testing session, and the second testing session, respectively), $F(3, 162) = 7.20$, $p < .001$. Tests of within-subjects contrasts confirmed these reductions were linear (all $ps < .001$), and follow-up univariate tests demonstrated that significant

FIGURE 2. Change in latency scores following unexpected access ("open" trial during 20% availability) or unexpected denial of access ("locked" trial during 80% availability) to alcohol. Notes: Lower latency values represent a more rapid attempt to access alcohol. Reduction in latency following unexpected access to alcohol ("open" trial during 20% availability) or unexpected restricted access to alcohol ("locked" trial during 80% availability) was statistically significant at $p < .01$.

TABLE 2. Means and distribution statistics for self-reported craving ratings, latency, and typical amount of alcohol consumed by medication (naltrexone vs. placebo), alcohol cue availability (80% vs. 20%), and access to cue (locked vs. open) conditions

Variable	<i>M</i>	<i>SD</i>	Min.	Max.	Skewness (<i>SE</i> = .314)	Kurtosis (<i>SE</i> = .618)
Medication						
Craving, ^a 1–7*						
Naltrexone	3.14	1.59	1.00	6.70	0.45	-0.65
Placebo	3.60	1.68	1.00	7.00	0.17	-0.86
Latency, ms						
Naltrexone	2,207	604	1,287	4,165	1.05	1.79
Placebo	2,149	565	1,177	4,079	1.02	1.54
Amount, g						
Naltrexone	1.62	0.78	0.31	3.46	0.45	-0.28
Placebo	1.84	0.95	0.05	4.24	0.65	0.64
Availability						
Craving, ^a 1–7						
80%	3.27	1.51	1.00	6.50	0.35	-0.61
20%	3.48	1.56	1.00	7.00	0.32	-0.44
Latency, ms						
80%	2,172	646	1,181	4,970	1.60	5.22
20%	2,121	536	1,318	3,846	1.05	1.78
Amount, g***						
80%	1.62	0.74	0.19	3.64	0.44	0.04
20%	2.16	1.03	0.49	5.48	1.05	1.83
Access						
Craving, ^a 1–7						
Locked	3.40	1.47	1.00	6.75	0.41	-0.48
Open	3.35	1.44	1.00	6.75	0.52	-0.13
Latency, ms**						
Locked	2,120	570	1,289	4,434	1.49	4.33
Open	2,173	600	1,211	4,322	1.12	2.26

Notes: Asterisks identify significant main effects of experimental manipulations on means. ^a1 indicates low craving; 7 indicates high craving.

* $p < .05$; ** $p < .01$; *** $p < .001$.

reductions occurred before the initiation of medication for percentage of drinking days, $F(1, 54) = 13.10$, $p = .001$; quantity, $F(1, 54) = 4.87$, $p = .032$; and percentage of heavy drinking days, $F(1, 54) = 6.55$, $p = .013$.

Correlations. Associations between the outcome variables (cravings, latency, amount of alcohol consumed) and ADS, CIWA-Ar, and total number of drinks consumed in the past week were examined by medication condition through a series of bivariate correlations. Self-reported craving ratings were positively associated with the amount of alcohol consumed during the assessment sessions (naltrexone: $r = .31$, $p = .017$; placebo: $r = .38$, $p = .003$) and number of drinks consumed in the past week (naltrexone: $r = .26$, $p = .050$; placebo: $r = .29$, $p = .026$). No other correlations were statistically significant (Table 1).

Primary analyses

See Table 2 for means and distribution statistics of outcome variables by medication, alcohol cue availability, and access conditions. A 2 (medication: naltrexone vs. placebo) $\times$ 2 (alcohol cue availability: 80% vs. 20%) $\times$ 2 (access: locked vs. open) within-subjects repeated measures multivariate analyses of variance examined main and

interactive effects of these manipulations on self-reported cravings and latency to access alcohol. Analyses revealed that the three-way ($p = .73$), Medication $\times$ Availability ($p = .84$), and Medication $\times$ Access ($p = .57$) multivariate interactions all failed to reach statistical significance. The multivariate Availability $\times$ Access interaction was statistically significant, $F(2, 56) = 5.80$, $p = .005$, with follow-up univariate analyses demonstrating a significant interaction for latency, $F(1, 57) = 10.52$, $p = .002$. Specifically, the occurrence of an “unexpected” trial (i.e., “locked” trial during 80% availability or “open” trial during 20% availability) produced a significant reduction in latency to attempt to access alcohol on the subsequent trial (Figure 2). Further, the reduction in latency following an unexpected “locked” trial during 80% availability ($M = 219$ ms, $SD = 433$) was more pronounced than the reduction in latency observed following an unexpected “open” trial during 20% availability ($M = 59$ ms, $SD = 391$), suggesting that participants were more strongly behaviorally motivated to acquire alcohol following unexpected denial of access. The univariate availability by access interaction on craving ratings was nonsignificant ($p = .13$).

The multivariate main effect of medication was also significant, $F(2, 56) = 6.35$, $p = .003$, with follow-up

FIGURE 3. Difference in typical quantity of alcohol consumed in 20% and 80% availability conditions for naltrexone assessment, placebo assessment, and total. Notes: Difference in typical amount of alcohol consumed between 20% and 80% availability conditions was statistically significant at $p < .001$.

univariate analyses demonstrating a difference in self-reported craving ratings between naltrexone ($M = 3.14$, $SD = 1.59$) and placebo ($M = 3.60$, $SD = 1.68$) sessions, $F(1, 57) = 5.41$, $p = .024$. There was no main effect of medication on latency ($p = .21$). The multivariate main effect of access (open vs. locked) failed to reach statistical significance, $F(2, 56) = 2.95$, $p = .061$. Latency of response was slightly faster following locked trials ($M = 2,120$ ms, $SD = 570$) compared with open trials ($M = 2,173$, $SD = 600$), $F(1, 57) = 4.32$, $p = .042$, despite the availability by access interaction previously described. Access to the alcohol cue did not affect self-report craving ratings on the subsequent trial ($p = .18$).

A second 2 (medication: naltrexone vs. placebo) $\times$ 2 (alcohol cue availability: 80% vs. 20%) repeated measures analysis of variance examined main and interactive effects on the amount of alcohol consumed per open trial. Access to the alcohol cue was not included in this analysis because alcohol could be consumed only during open trials. The Medication $\times$ Availability interaction was not significant ($p = .36$). A nonsignificant trend was noted, suggesting modestly reduced levels of consumption during the naltrexone testing condition ($M = 1.62$ g, $SD = 0.78$) compared with placebo ($M = 1.84$ g, $SD = 0.95$), $F(1, 57) = 3.76$, $p = .058$. Alcohol cue availability, however, was significantly associated with the amount consumed per open trial, $F(1, 57) = 37.18$, $p < .001$, with participants consuming more when alcohol was available only 20% of the time ($M = 2.16$ g, $SD = 1.03$) relative to when it was available on 80% of the trials ($M = 1.62$ g, $SD = 0.74$; Figure 3).

Discussion

The goal of this study was to examine the effects of a modified alcohol-cue availability paradigm on multiple indicators of motivation to drink in a sample of non-treatment-seeking, alcohol-dependent individuals. A within-subjects design was used to examine the effects of naltrexone, differences in perceived availability of alcohol (80% vs. 20% of trials), and unexpected changes in access to alcohol ("open" trial during 20% availability vs. "locked" trial during 80% availability) on self-reported craving and behavioral patterns of drinking (latency of attempt to access alcohol and amount consumed when access permitted).

The availability of alcohol had a significant effect on the amount of beer consumed when drinking was permitted. Specifically, heavy drinkers consumed significantly more alcohol during open trials when alcohol was available only 20% of the time than they did when alcohol was available 80% of the time. In addition, the unexpected denial of access to alcohol (i.e., a "locked" trial in the 80% availability condition) was associated with a nearly 10% faster attempt to acquire beer in the subsequent trial. Of note, these findings were observed under both naltrexone and placebo treatment conditions and occurred in the absence of a corresponding change in self-reported craving. These findings are consistent with CPM and demonstrate that specific behavioral indicators of motivation to drink may be influenced by the perceived unavailability (quantity) and unexpected restriction of access to alcohol (latency).

Ingestion of naltrexone for 9 days was associated with a significant reduction in self-reported craving ratings and a nonsignificant trend toward reduced quantity of alcohol consumed during the trials. There were no observed effects of naltrexone on patterns of drinking outside of the laboratory; however, naltrexone-induced changes in drinking are often not reported during the early stages of treatment. Further, the unexpected reductions in drinking observed before the initiation of medication treatment (a possible iatrogenic effect of the baseline assessment) may have obscured any potential benefits of naltrexone.

No evidence was obtained to support the CPM hypothesis that the magnitude of the effect of alcohol cue exposure on cravings would be determined by degree of alcohol dependence within this sample of heavy drinkers. Neither degree of alcohol dependence nor risk of alcohol withdrawal was correlated with craving, latency, or consumption outcomes in this study. The number of drinks consumed in the preceding week was modestly correlated with craving ratings across both medication conditions. Although this pattern of results does not refute the CPM of craving, it does suggest that within a restricted range of heavy drinking alcohol-dependent men and women, most recent drinking history may be a better predictor of self-reported craving in response to alcohol cues than degree of alcohol dependence.

The absence of consistent effects of the experimental manipulations on self-reported craving and behavioral indicators of motivation to drink mirrors the variability reported within the craving literature. Although each experimental manipulation had a significant effect (reduced access to alcohol led to increased consumption on "open" trials, unexpected denied access to alcohol led to more rapid attempts to acquire beer, and naltrexone was associated with lower self-reported craving), none of the manipulations affected multiple presumed indicators of desire/motivation to drink. Further, self-reported craving was only modestly correlated with the amount of alcohol consumed, and the speed with which participants attempted to access alcohol was not associated with either craving ratings or the amount consumed.

Methodological limitations may have contributed to the observed findings. First, in an effort to balance thoroughness of craving assessment with response burden given the multiple trials on which ratings were made ($n = 17$ per testing session), a four-item self-report measure was used. Although it is possible that the manipulations of perceived availability and restricted access to alcohol affect drinking behaviors but not craving, this negative finding may also reflect a limitation of this craving measure. Although this measure was sensitive to the effects of naltrexone treatment, recent studies provide evidence that craving comprises multiple factors, and truncated measures are assessing only part of the construct (Connolly et al., 2009; Kramer et al., 2010). Future research efforts may benefit from the

administration of more comprehensive, yet brief assessments of craving (e.g., the eight-item Alcohol Urge Questionnaire; Bohn et al., 1995).

Second, the use of latency in milliseconds from the presentation of the stimulus cue indicating beer may be available for consumption to the actual behavioral attempt to access the alcohol is subject to criticism given the variety of cognitive (e.g., motivation, expectancies) and physical (e.g., distance to target, factors affecting mobility) variables that may have influenced the speed of this behavioral outcome. Despite this limitation, latency of alcohol-seeking behavior was sensitive to experimental manipulations of access, suggesting that future research would benefit from the use of behavioral outcomes designed to reduce this variability.

Third, the structured and artificial nature of the testing sessions reduces the extent to which these findings may generalize to real-world drinking behavior. To the extent possible, future investigations would benefit from the use of paradigms that more closely mimic natural drinking situations. Finally, although the high prevalence of smokers in this study (81%) precluded an examination of the influence of smoker status on these experimental manipulations, future studies would benefit from a systematic examination of the impact of nicotine dependence on cravings induced by this paradigm.

In sum, these results offer partial support for the CPM of craving and reinforce the utility of evaluating both self-report and behavioral indicators of motivation to drink in studies designed to identify factors associated with craving. Further, this study demonstrates the utility of the alcohol-cue availability paradigm in examining predictors of self-report and behavioral indicators of motivation to drink. In addition to replicating these findings with other alcohol-dependent samples, future efforts to expand this research to individuals with both alcohol and nicotine dependence as well as non-alcohol-dependent, heavy drinking populations are warranted and will provide an improved understanding of the development of alcohol cravings.

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