Abbreviated Title: Lab/GMA drinking

Version Date: 2/16/2022

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Protocol #: 16-DA-N140

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Title: Effects of a new behavioral intervention on alcohol craving and drinking

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A. Précis

Objective: To evaluate alcohol memory retrieval-extinction, a novel behavioral procedure for reduction of craving and drinking, in problem drinkers.

Study population: We will collect evaluable data from up to 75 participants. Participants are evaluable if they complete geographical momentary assessment (GMA, described below). All participants will be adult alcohol drinkers (men: > 14 drinks/week or > 4 drinks/day; women: > 7 drinks/week or > 3 drinks/day) whose drinking scores as hazardous on the Alcohol Use Disorders Identification Test. Participants will not be seeking treatment for an alcohol-use disorder, be physiologically dependent on alcohol, or have other drug use disorders.

Design: A randomized study with three groups. Participants will use smartphones to provide geotagged reports of alcohol craving and drinking in daily life (GMA reports) before, between, and after a series of laboratory sessions. During sessions, participants will drink an alcoholic beverage (individualized to produce a 0.06 g/dL blood alcohol content) or a soft drink. Participants will then be repeatedly presented with alcohol- or soft-drink-associated cues without further drinking. These are the memory retrieval and extinction portions, respectively, of memory retrieval-extinction. Previous studies suggest this procedure can robustly reduce Pavlovian associations between cues and responses such as craving. The mechanism seems to involve memory reconsolidation, in which freshly retrieved associations (e.g., "drink cues and consumption → pleasant effects") become more vulnerable to disruption by extinction.

Three groups will be tested: (1) alcohol retrieval / alcohol extinction will be compared to (2) soft-drink retrieval / alcohol extinction and (3) alcohol retrieval / soft-drink extinction. Before and after retrieval-extinction, participants will be tested for alcohol craving and cue-induced physiological responses in laboratory sessions. Retrieval-extinction will be followed by 1 week of "follow-up" GMA reporting, with telephone contact 30 days thereafter.

Outcome parameters: The co-primary outcome measures are: self-reported alcohol craving in the laboratory sessions before and after retrieval-extinction, and GMA reports of alcohol craving and drinking. Daily-life responses are important because the version of retrieval-extinction we will be using, with retrieval induced by drinking alcohol itself, rather than alcohol cues alone, may be especially likely to have effects that generalize from the laboratory to daily life. Secondary outcome measures are: (1) self-reported alcohol craving and drinking at 30-day follow-up, (2) physiological reactivity during sessions, and (3) urine biomarkers for alcohol consumption.

B. Table of Contents

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List of abbreviations and acronyms:

AUD: alcohol-use disorder

CET: cue-exposure therapy

CR: conditioned response

CS: conditioned stimulus

EMA: ecological momentary assessment

GMA: geographical momentary assessment

GPS: global positioning system

US: unconditioned stimulus

VAS: visual-analog scale

C. Background

Cue-induced drug craving

Drug-associated environmental stimuli (i.e., cues) can significantly affect drug-abuse behaviors. Studies in laboratory animals show that presentation of drug cues can not only exacerbate ongoing drug self-administration (Goldberg & Tang, 1977; Alderson et al., 2000; Saunders & Robinson, 2010), but also reinstate drug seeking after periods of drug unavailability (reviewed by Bossert et al., 2013), even after a year (e.g., Ciccocioppo et al., 2004). Drug cues are also thought to contribute significantly to human substance-use disorders (SUDs) (Hyman, 2005). Significant behavioral, physiological, cognitive, and emotional effects of drug cues have been observed in people who use drugs (O'Brien et al., 1992; Field & Cox, 2008; Reynolds & Monti, 2013), and attenuating those effects has been recognized as an important goal in the development of better treatments (Taylor et al., 2009; Myers & Carlezon, 2010; Milton & Everitt, 2012).

One particularly important cue-elicited response is craving, the subjective desire for drug, which has long been a focus of clinical and scientific attention and has now been added to the DSM diagnostic criteria for substance-use disorders (Tiffany & Wray, 2012; Kavanagh et al., 2013; Haass-Koffler et al., 2014; Grant et al., 2015). This protocol focuses on cue-induced craving for alcohol and other effects of alcohol cues in drinkers. We chose to assess drinking rather than other drug use because (1) there is an extensive literature characterizing alcohol cue effects in drinkers (reviewed by Drummond, 2000; Reynolds & Monti, 2013) and (2) administering alcohol to human research participants in the laboratory raises fewer issues than administering most other abused drugs (NIAAA document "Administering Alcohol in Human Studies," Plebani et al., 2012)—and administering the drug is an essential component of the procedure we propose to test. The insights we gain into cue-induced craving for alcohol will likely be relevant to other drugs.

In people with alcohol-use disorders (AUDs), craving has been associated retrospectively and prospectively with greater rates of drinking (Yoon et al., 2006; Ramirez & Miranda, 2014; see also Fatseas et al., 2015) and greater motivation to drink (MacKillop et al., 2010; Amlung & MacKillop, 2014). Craving can also predict relapse during or after AUD treatment (Flannery et al., 1999; Oslin et al., 2009; Connolly et al., 2013; Papachristou et al., 2013). Finally, craving correlates with activity in brain areas implicated in associative learning and motivation (e.g., the ventral striatum; Schacht et al. 2013). Accordingly, interventions that target alcohol cue effects are considered an important component of AUD treatment. Craving reduction is not only an important concomitant of treatment response, but is itself an important clinical target (Tiffany & Wray, 2012; Reynolds & Monti, 2013; Enoch, 2014).

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Therapies based on reducing cue-induced responses: improving extinction training with memory retrieval beforehand

Cue-induced craving, like other effects of drug cues, follows the laws of Pavlovian learning: when alcohol (an unconditioned stimulus, US) is paired with initially "neutral" environmental stimuli, the neutral stimuli can become conditioned stimuli (CSs) capable of eliciting a variety of conditioned responses (CRs) such as craving. Like any CS-CR association, the association between cues and craving can be extinguished if the CS is presented repeatedly in the absence of the US (Blakey & Baker, 1980; Staiger & White, 1991; Staiger et al., 1999; Lee et al., 2007; MacKillop & Lisman, 2008). Extinction-based cue exposure therapies (CETs) are used in the treatment of other psychopathologies (e.g., anxiety disorders) but have not been widely adopted for substance-use disorders (Martin et al., 2010; Nic Dhonnchadha & Kantak, 2011). Some studies of alcohol CETs have produced promising results, with participants in CET groups showing, compared to control groups, less relapse, longer latencies to relapse, or less heavy drinking when they did drink (Monti et al., 1993; Drummond & Glautier, 1994; Sitharthan et al., 1997; Rohsenow et al., 2001). Other studies of CETs have not produced positive results or have not included sufficient information to evaluate their efficacy outside the laboratory, and it has been difficult to conclude overall that CETs are more effective than other types of treatment for AUDs (Conklin & Tiffany, 2002; Martin et al., 2010).

The limited success of CETs is not surprising when one considers what extinction really is. Extinction is new learning, not an erasure of prior learning. The content of the new learning appears to be *this association is no longer occurring in this context.* Accordingly, extinguished CRs can emerge again in several ways: (1) renewal, the return of CRs as the context changes, (2) reinstatement, the return of CRs upon re-exposure to the US, and (3) spontaneous recovery, the return of CRs as time passes. Laboratory studies of Pavlovian conditioning in human participants have demonstrated renewal (e.g. Collins & Brandon, 2002; Thewissen et al., 2006), reinstatement (Haaker et al., 2014), and spontaneous recovery (Corty & Coon, 1995). Each of these processes can produce enhancements of responding even when extinction training is initially successful (i.e., when it has produced significant decreases in responding), and together they show the limited scope of "standard" extinction training: behavior change depends on the particular circumstances (place, time, and drug-free state) under which extinction training is conducted.

Recent research suggests that the durability of extinction can be increased by a surprisingly simple manipulation: addition of a memory-retrieval experience shortly beforehand. In one striking demonstration, heroin addicts were given a brief "retrieval" presentation of heroin cues (on videotape, in

the absence of heroin) ten minutes before each actual extinction session (a longer period of exposure to paraphernalia and simulated heroin, again in the absence of heroin), and were found to have less cue reactivity than control participants 1, 30, and 180 days later (Xue et al., 2012). A clue as to the mechanism of this finding is that it depended on timing: one of the control groups underwent the same procedures as the experimental group, except that they saw the retrieval videotape six hours rather than ten minutes before each extinction session. For them, the retrieval had no measurable long-term effect. This suggests that the retrieval-extinction procedure works at least partly through a feature of memory processing called reconsolidation (Xue et al., 2012). Reconsolidation, which has now been extensively studied in both laboratory animals and humans, is the dynamic reprocessing of an established memory (i.e., a memory in long-term storage) (Alberini & Ledoux, 2013). When the content of an established memory is activated—brought out of long-term storage into working memory and/or conscious awareness—the memory can briefly become labile. It is more readily modified than if it had simply remained in long-term storage. A rough analogy would be opening a document that is stored on the hard drive of a computer. When the open document is resaved, the text of the document can be updated, or even erased, before the document is again stored with the same filename. (To be clear: we are using *memory* here to refer only to Pavlovian stimulus-response associations, not to narrative recollections of events.)

The version of the retrieval-extinction procedure that reduced heroin craving in the Xue et al. (2012) study uses only the CS (for example, a heroin videotape, not actual intoxication with heroin) for retrieval. This CS retrieval-extinction procedure has been shown in other human studies to reduce conditioned fear responses (Schiller et al., 2010; Oyarzun et al., 2012; Liu et al., 2014). Crucially, the procedure can work where "standard" extinction training without memory retrieval does not, such as: (1) in the establishment of an initial decrease in responding after extinction training (Xue et al., 2012), (2) in specific tests for the reinstatement of CRs (Oyarzun et al., 2012; Liu et al., 2014), and (3) with the passage of time and/or tests for spontaneous recovery of CRs (Schiller et al., 2010; Xue et al., 2012; Liu et al., 2014). The other major concern, renewal of the CR by a change in context, does not seem to have been tested in humans after CS retrieval-extinction, but has been tested in rats: CS retrieval-extinction reduces renewal of cocaine-trained responding in rats (Luo et al., 2015).

Initial excitement about CS retrieval-extinction has been tempered by discovery of its limitations. In rats trained to drink beer, the effects of CS retrieval-extinction depended on the type of test used to assess responsiveness: rats in the experimental group were not protected from (and were actually more vulnerable to) reacquisition of drinking in a progressive-ratio task where beer was again available (Millan

et al., 2013). This problem did not occur in cocaine-trained rats when the retrieval-extinction session was done with the US instead of just the CS—that is, when extinction was preceded one hour earlier by an injection of cocaine itself (Luo et al., 2015). This US version of retrieval-extinction showed several other advantages over the CS version. It reduced responding to CSs that had not been specifically targeted for extinction—a clear advantage for treatment of human drinkers whose years of experience with alcohol have established far too many CSs to be presented in laboratory extinction sessions. It also sped the process of extinction itself, and its effects were also more resistant to renewal, reinstatement, and the passage of time (Luo et al., 2015).

The US version of retrieval-extinction has been used successfully in healthy humans to prevent the return of a recently conditioned association between a visual stimulus and an electric shock (Liu et al., 2014). To our knowledge, it has not been tested in humans as an anticraving treatment.

The following table summarizes the expected advantages of US retrieval-extinction over older procedures:

Procedure	**Spontaneous recovery over time**	**Renewal by context change**	**Reinstatement by priming**	**Effects of cues that were not specifically extinguished**	**Responding in a progressive-ratio task**
Extinction alone	Not protected	Not protected	Not protected	Not protected	(no data)
CS retrieval-extinction	Protected	Protected	Protected	Not protected	Not protected
US retrieval-extinction	Protected	Protected	Protected	Protected	Protected

Geographical momentary assessment (GMA) of alcohol craving and drinking

Because one advantage of the US procedure is that its benefits should generalize from the laboratory to daily life, our study needs an outcome measure that can capture that. To that end, we will use real-time assessments of behavior and emotion on mobile electronic devices—a technique known as ecological momentary assessment (EMA) (e.g., Epstein et al., 2009), which we have expanded, with geolocation data, into geographical momentary assessment (GMA) (Epstein et al., 2014).

The use of EMA helps overcome the limitations of retrospective assessments, which may not adequately measure the dynamics of craving or accurately depict the relationships between craving and use (Tiffany & Wray, 2012; Kavanagh et al., 2013; Serre et al., 2015). Even once-daily reports may be subject to limitations such as forgetting, recall bias, and the state dependency of memory (Kirchner & Shiffman, 2013).

The use of EMA as a complement to laboratory assessments has been identified as an important future direction for research on cue reactivity (Reynolds & Monti, 2013). However, studies combining laboratory and field measures of the effects of alcohol cues have not been extensively pursued. Litt and colleagues (2000) first reported positive associations between the magnitude of cue-induced alcohol craving measured in the laboratory and the frequency of EMA reports of alcohol urges and drinking after discharge from treatment. Subsequently, Ramirez and Miranda (2014) reported significant associations between adolescent drinkers' alcohol craving in a laboratory session and their EMA reports of craving in response to alcohol cues in daily life. Combinations of laboratory sessions and EMA have been used in pharmacotherapy studies to find medication effects on alcohol craving and/or drinking (topiramate: Miranda et al., 2014b; naltrexone: Miranda et al., 2014a).

In completed and ongoing protocols (NIDA-IRP Protocols 020, 385, and 407), our section has used EMA successfully to study drug craving and use. In the EMA component of these studies, participants provided three types of reports via their handheld devices: (1) responses to random prompts, in which participants make reports throughout the day as the device sounds a randomly programmed alarm, (2) event-contingent reports, which are initiated by participants when they engage in a target behavior (e.g., use drug) or experience a target emotion (e.g., stress or craving), and (3) responses to non-random interval-based prompts, in which participants make reports after a given amount of time has passed or at a given time each day (e.g., before going to bed). Together, these different entries provide a comprehensive account of events that do or do not precede or follow drug craving and use.

We have also successfully combined EMA with geolocation information obtained from the global positioning system (GPS) to perform geographical momentary assessment (GMA) (e.g., Epstein et al., 2014). Using GMA, we have shown significant associations between drug craving and independently collected objective measures of neighborhood disorder and drug activity in the Baltimore city locations participants were moving through (Epstein et al., 2014). In the current study, we propose to use GMA because participants' mood and behavior can be readily compared to objective information about alcohol availability (e.g., the addresses of businesses with liquor permits) (Freisthler et al., 2014). Laboratory studies have shown that information about the availability of alcohol significantly affects cue-induced alcohol craving, although both more (MacKillop & Lisman, 2005) and less (Papachristou et al., 2012) craving has been observed when alcohol is unavailable vs. available.

Previously, we have used two separate devices, one for EMA and another for GPS data collection. We currently propose to use a single device, a smartphone, to collect both EMA and GPS data. GPS receiver chipsets have become ubiquitous in smartphones and, by combining GPS information

with information on the strength of signals obtained from cellular data networks and wireless internet data connections (i.e., assisted GPS), smartphones can provide accurate location information more quickly than standalone GPS units and in cases where GPS signals are attenuated (e.g., indoors, in urban areas with many tall buildings) (Zandbergen, 2009; Zandbergen & Barbeau, 2011).

Physiological responses to alcohol cues

In addition to craving, alcohol cues can produce changes in heart rate, blood pressure, salivation, skin temperature, and galvanic skin response (Carter & Tiffany, 1999; Monti et al., 1999; Szegedi et al., 2000; Reid et al., 2006; Fox et al., 2007; Hammarberg et al., 2009). These changes are another manifestation of the effects of associative learning with an alcohol US. Extinction training can reduce physiological responses to alcohol cues whether or not craving is reduced (e.g., Staiger & White, 1991; McCusker & Brown, 1995; Collins & Brandon, 2002), and physiological effects of alcohol cues can, in certain cases, predict treatment outcomes in situations where explicit craving ratings do not (Rohsenow et al., 1994; Garland et al., 2012). Thus, it is important for us to assess the effects of the retrieval-extinction procedure on cue-induced physiological responses. In heroin users, a heroin CS retrieval-extinction procedure reduced cue-induced changes in blood pressure as well as craving (Xue et al., 2012). We propose to collect physiological measures during the extinction component of the retrieval-extinction procedure in Sessions 2-5 and during the tests for renewal and reinstatement in Session 6 (described below).

Biomarkers for alcohol consumption

Although the real-time nature of EMA confers important advantages over retrospective assessments, EMA still has the limitations associated with self-report, such as socially desirable responding (Harrell, 1997). We plan to supplement EMA with the use of objective biomarkers of alcohol consumption, which are useful in both screening for heavy drinking and identifying relapse incidents (SAMHSA, 2012). Measurement of ethanol itself in breath or blood is appropriate for detecting ongoing intoxication or a single, recent bout of alcohol consumption. However, one breath or blood test for ethanol cannot establish typical consumption levels over time (e.g., chronic heavy drinking vs. an isolated incident), and the detection window for ethanol is only 10-12 hours after consumption (Jatlow & O'Malley, 2010), particularly in heavy drinkers, who can metabolize alcohol more rapidly than lighter drinkers (rates up to approximately 30 mg/dL/h, Winek & Murphy, 1984; Jones, 2010). Biomarkers can provide information about alcohol consumption outside of the intervals during which ethanol itself is detectable (SAMHSA, 2012). There is no single ideal biomarker for alcohol consumption, so the best measurements are obtained when several are combined (SAMHSA, 2012).

For our purpose, intermediate-term detection of recent drinking, we propose to use the biomarkers ethyl glucuronide (EtG) and ethyl sulfate (EtS) (SAMHSA, 2012). Although EtG alone can be used to detect drinking in an outpatient clinical population (McDonell et al., 2015), measuring both EtG and EtS reduces false positives caused by exposure to consumer products containing ethanol (e.g., hand sanitizers), and EtS is less subject to bacterial degradation than EtG (Ingall, 2012). Urine testing for EtG by immunoassay can detect heavy drinking for up to 5 days and light drinking for up to 2 days, with heavy drinking defined 4 or more drinks/day for men and 3 or more drinks/day for women (McDonell et al. 2015; see Jatlow and O'Malley 2010 for a similar estimate of duration based on mass spectrometry). Within this window, it may not be possible to distinguish recent moderate drinking from less recent heavier drinking (Ingall, 2012). Nonetheless, these detection windows are appropriate for our proposed study, in which participants make repeated, but not necessarily daily, visits to the laboratory over the course of several weeks.

We will measure EtG and EtS in urine. If new urine biomarkers for ethanol are discovered while we are running the protocol, we may measure those as well. We will also measure other substances in the urine samples (such as creatinine) that provide quality assurance for the biomarker measurements.

D. Study Objectives

The objective of this study is to test a novel behavioral intervention, US memory retrieval-extinction, for efficacy in attenuating cue-induced alcohol craving and drinking in problem drinkers.

Our co-primary objectives are to determine whether the retrieval-extinction procedure reduces (1) self-reported craving in response to alcohol cues presented in the laboratory and (2) EMA reports of alcohol craving and drinking in daily life. We have designated these as co-primary outcomes because laboratory data are more mechanistically informative and field data are more clinically relevant. We will assess self-reported craving during laboratory sessions conducted within and between four retrieval-extinction sessions, and then in tests for Pavlovian renewal and reinstatement that will follow the final retrieval-extinction session. We will assess changes in EMA reports before, between, and after the laboratory sessions. We hypothesize that, compared to the control groups, individuals receiving alcohol US retrieval-extinction will show reductions in craving (and possibly in drinking) over time. If we detect our hypothesized effects on the EMA measures alone, we will consider that sufficient evidence for the efficacy of the procedure. If we detect our hypothesized effects on the laboratory measures alone, we will consider that suggestive of possible efficacy, indicating that the procedure might need to be administered more intensively in future work.

Our secondary objectives are to test the effects of the retrieval-extinction procedure on (1) self-reported alcohol craving and drinking at the 30-day follow-up by telephone, (2) physiological responses to alcohol cues in the laboratory, and (3) biomarkers for alcohol consumption. We hypothesize that, compared to control groups, individuals receiving US retrieval-extinction will: report less alcohol craving and drinking at the 30-day follow-up telephone contact; have a reduction in physiological responses to cues; and have a reduction in biomarkers for alcohol consumption.

E. Study Design and Methods

1. Study overview

This is a 3-group, 6-session, randomized outpatient study in which drinkers are given access to a beverage that does or does not contain alcohol and are presented with cues that are or are not alcohol-related. For the US (unconditioned stimulus) version of the retrieval-extinction procedure, drinking provides the retrieval experience, which occurs before the cues are extinguished.

The three experimental groups are determined by whether the retrieval and/or extinction procedures involve alcohol versus control stimuli: (1) alcohol retrieval / alcohol extinction (experimental group) (2) soft-drink retrieval / alcohol extinction (control group A) and (3) alcohol retrieval / soft-drink extinction (control group B). Although soft drinks may have appetitive motivational properties of their own (Berns et al., 2001), we will use the soft drinks as inactive conditions as concerns craving for alcohol: the soft-drink retrieval condition is a no-alcohol retrieval condition, and the soft-drink extinction condition is a no-alcohol extinction condition. Using a soft drink rather than plain water allows for better matching of the sensory salience and caloric content of the alcoholic beverages, and by picking particular beverages (see below) we can minimize the potential for associative overlap between the soft drink and alcoholic beverages. We considered several other control groups, but practical considerations forced us to limit our choices to what was necessary for basic interpretability of the findings.

EMA/GMA data will be collected via smartphone throughout the study. After giving written informed consent in the first visit, participants will be trained to use smartphones for real-time self-report.

In the first laboratory session, scheduled as soon as possible after enrollment, participants will provide information needed for our development of personalized imagery scripts, which we will use in subsequent sessions to induce craving.

Approximately 7 days later, participants will have the first of four retrieval-extinction sessions in which they drink beverages and undergo cue exposure/extinction. These four sessions will be spaced at least 2 days apart from each other.

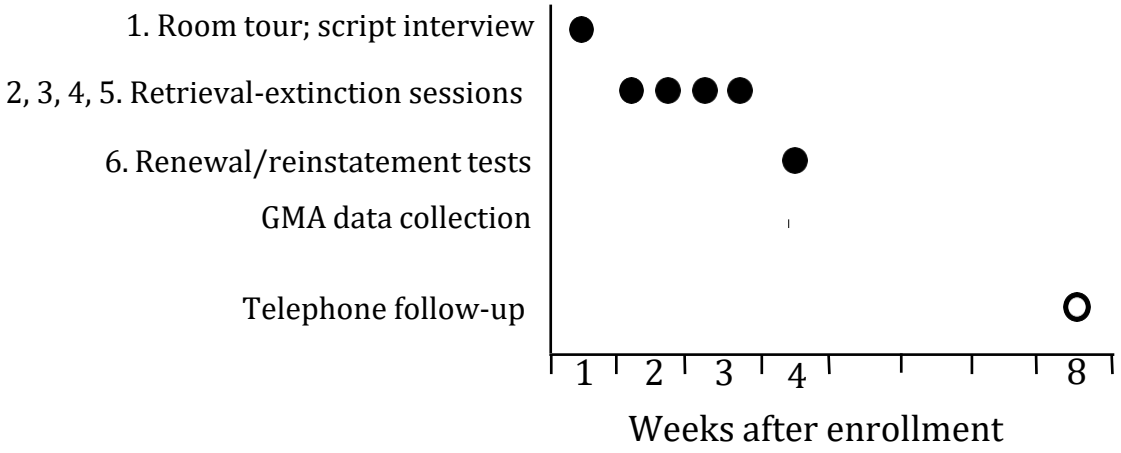
Approximately 7 days after the last retrieval-extinction session, we will test participants' responses to alcohol cues using two Pavlovian procedures, renewal and reinstatement, that have previously been used in studies of laboratory animals to differentiate the effects of retrieval-extinction from extinction alone (Luo et al., 2015). At this visit, participants will return their smartphones.

Each participant will receive a follow-up phone call approximately 30 days after his or her last visit.

The study will take each participant approximately 3 months to complete, depending on how close together sessions can be scheduled. Each type of session is described in more detail in the Study Procedures section.

2. Study procedures

Study Timeline



Session	Beverage	EmptyPackaging	CueScript	Drinking
2-5. Retrieval	**X**	**X**	-	**X**
2-5. Extinction	**X**	**X**	**X**	-
6. Renewal, same room	**X**	**X**	**X**	-
6. Renewal, different room	**X**	**X**	**X**	-
6. Reinstatement, same room	**X**	-	-	**X**

Experimental groups and randomization

As we mentioned above, we needed to limit the number of groups for practical reasons. Participants will be randomized to one of three groups: (1) alcohol retrieval / alcohol extinction, (2) soft-drink retrieval / alcohol extinction, and (3) alcohol retrieval / soft-drink extinction. The use of these two control groups (groups 2 and 3) assesses whether the retrieval-extinction procedure requires both its retrieval component and its extinction component. Group 2 represents a traditional CET approach, with

no relevant retrieval procedure. Group 3 controls for mere alcohol exposure in the laboratory, which has actually been shown to have some effect on subsequent drinking (Hodgson & Rankin, 1976; Modell et al., 1993; Pratt & Davidson, 2005).

Randomization will be stratified by sex and by the type of alcoholic beverage (beer, wine, or distilled spirits) that will be served in the laboratory sessions, as determined by questionnaire and consultation with the participant, as described below. Blinding is not practical with our manipulations. To reduce expectancy effects, we will not specifically inform participants about the number or nature of the experimental groups; the consent form will make clear that there is at least one control condition but will not be more explicit than that. In the follow-up phone call, after collection of the last outcome measures, we will explain the three-group design of the study and debrief participants about their perceptions of the study. This delay of disclosure will itself be disclosed in the consent form.

Description of laboratory sessions

Overview of laboratory sessions

Sessions will be scheduled to begin at approximately 12:00 pm. Participants will be asked to abstain from drinking alcohol and using any illicit or over-the-counter drugs for at least 24 hours before the session. On arrival at each session, participants will provide a breath sample for measurement of blood alcohol content (BAC) and a urine sample.

Participants will be told that they may be observed when giving urine samples. There are two ways in which a participant's urine collection will be observed. First, urine sample collection will be observed at random, with each collection from each participant having an equal chance of being observed. Second, urine collection will be observed if a participant attempts to tamper with the collection. Criteria for determinination of tampering are derived from the Direct Observation Procedures published by the US Department of Transportation's Office of Drug and Alcohol Policy and Compliance (https://www.transportation.gov/sites/dot.gov/files/docs/ODAPC%20DOTs_Direct_Observation_Procedures_Instruction_Sheet_August312009.pdf). Attempted tampering is indicated if a participant provides a sample with unusual characteristics (e.g., color, odor, temperature) or if a staff member sees a participant display paraphernalia or conduct used to tamper with urine collection. Paraphernalia include tubing, prosthetics, pre-prepared liquid samples, or substances to be added to urine to affect screening results. Conduct includes attempts to dilute, substitute, or adulterate samples or behavior that facilitates the use of paraphernalia to dilute, substitute, or adulterate samples (e.g., bringing bags, cases, or heavy coats into the sample collection area when instructed not to). When there is evidence of tampering, that sample will not be accepted. The participant will be required to provide a urine sample under observation to continue

with the session, and all of that participant's subsequent urine collection will be performed under observation.

If BAC is >0, the session will be rescheduled; participants for whom this happens more than twice will be discharged from the study. Urine samples will be used for pregnancy testing for female participants and for measuring biomarkers for alcohol consumption for all participants. Participants will be rescheduled if they are intoxicated by alcohol or any other drug upon arrival, as assessed by a field sobriety test (described below); participants for whom this happens more than twice will be discharged from the study. All participants will also have a urine drug screen performed, but, because drug use *per se* is not exclusionary, we will use the urine results only to help us interpret signs of intoxication. In sessions that involve participants drinking an experimental beverage, participants will be weighed to allow us to calculate their BMIs and the volume of beverage they should be served in the session. To reduce variability in alcohol metabolism caused by food consumption, all participants will be asked to eat a light meal before arriving at the laboratory. Food will be provided on arrival if needed. To control for nonspecific effects of thirst, plain water will be available to participants during sessions (Litt et al., 2000). Tobacco/nicotine deprivation state can also affect alcohol craving and drinking (Palfai et al., 2000; McKee et al., 2008), so participants will be allowed periodic breaks to use tobacco if desired. At the end of each session that involves drinking an experimental beverage, participants will provide breath samples and will be released when their BAC is ≤ 0.01 g/dL, measured twice 20 minutes apart. All participants will be offered transportation to and from the laboratory by taxi and/or with payment for public transportation fares for all sessions that involve drinking an experimental beverage, as described in more detail in the Compensation section below.

a. Session 1:

Session 1 will occur after screening and will typically begin immediately after the participant gives written informed consent for the study.

Introduction to the laboratory: We will show participants the rooms where subsequent experimental events will take place. This limits the effects of novelty on participants' responses in subsequent sessions (Collins & Brandon, 2002). The rooms will be designed to be distinguishable from one another, but emotionally neutral and not evocative of alcohol. To document that, we will ask participants to spend 5 min in each room and to write down as many different features of the room (e.g., wall color, furniture) as possible in 1 min and to rate the room on 100 mm visual analog scales (VAS) of (1) pleasantness ("This room is a pleasant place to be"; 0 = "very unpleasant," 100 = "very pleasant") and (2) relatedness to alcohol ("This room makes me think about drinking alcohol"; 0 = "not at all," 100 =

"more than anything else"). After viewing and rating the final room, participants will be asked to complete a VAS scale evaluating the rooms' similarity to one another ("The rooms I was in are different from each other"; 0 = "very similar," 100 = "very different"). Copies of the VAS's are included in the Appendix. Order of presentation of the rooms will be counterbalanced across participants. If a participant gives a rating that is beyond the midpoint of the scale in the unexpected direction, we will ask the participant about it and try to change the relevant features of the rooms. If that does not solve the problem, we will still run sessions with the participant, but, in analyzing the study results, we will perform sensitivity analyses in which we see whether omitting that participant's data changes our findings.

After seeing the rooms, participants will complete the following questionnaires:

- "Most frequently consumed alcoholic beverage" questionnaire: developed in-house for this study, this questionnaire asks participants about the alcoholic beverage they drank most frequently in the previous 90 days: the kind of beverage (i.e., beer, wine, liquor), as well as the commercial brand and style of presentation (i.e., how the beverage was most frequently served).
- Soft-drink preference questionnaire: developed in-house for this study, this questionnaire presents a list of beverages that do not contain alcohol or caffeine. For each beverage, participants are asked to rate: (1) familiarity, (2) liking, and (3) how frequently they have drunk it in conjunction with alcohol (i.e., as a mixer or chaser).
- PhenX Toolkit Alcohol Specific Intermediate Phenotypes (ver. 13.1, www.phenxtoolkit.org): includes questionnaires on current alcohol craving, alcohol motives and expectancies, and acute subjective effects of alcohol.
- Penn Alcohol Craving Scale (Flannery et al., 1999): assesses alcohol craving on a week's timescale, providing a retrospective measure of craving.
- Readiness to Change Questionnaire (Rollnick et al., 1992): assesses participants in terms of the "stages of change" (precontemplation, contemplation, action) regarding self-perceived excesses in drinking.
- Brief Situational Confidence Questionnaire (Breslin et al., 2000): measures participants' confidence in their ability to resist drinking in different types of risky situation (e.g., social pressure, physical discomfort).
- Plymouth Sensory Imagery Questionnaire (Andrade et al., 2014): measures the vividness of participants' ability to form mental images, in several sensory modalities.

- Neighborhood Environment Walkability Scale (NEWS) (Saelens et al., 2003): an 82-item survey assessing types of residences, proximity to stores and facilities, access to services, aesthetic quality, safety from traffic and crime, and neighborhood satisfaction.
- Behavioral Inhibition System / Behavioral Activation System Scales (Carver & White, 1994): assesses reward processing in terms of appetitive motivation, which is based on the pursuit of reward, versus aversive motivation, which is based on the avoidance of punishment or nonreward.

Session 1: Cue-script development: We will collect information for developing personalized sets of alcohol-associated stimuli to be used in Sessions 2-6. Imagery scripts will be developed adapting the methods of Sinha and colleagues (2003), which we have previously used to study food craving and eating (protocol 475). Participants will be asked to identify and describe (1) a pleasant personal situation that involved drinking alcohol (alcohol-related script) and (2) a pleasant personal situation that did not involve drinking alcohol (alcohol-unrelated script). We will avoid use of situations with strong negative emotional valence and/or stressful content (e.g., being cited for driving under the influence), both of which can affect alcohol craving (Rubonis et al., 1994; Willner et al., 1998; Fox et al., 2007; Ray, 2011).

The details required for the imagery scripts include physical and interpersonal context, verbal and cognitive attributions regarding people involved (including themselves), and physiological and bodily sensations experienced in the situation. We will write the information into a narrative and read it onto an audio recording for use in subsequent sessions with that participant. Each recorded script will last approximately 2 minutes.

To reduce variability in concentration and imagery ability, all participants will be trained in imagery visualization and trained to do 10 minutes of progressive muscle relaxation. The imagery training involves visualizing commonplace scenes presented by the script-development interviewer. The scenes are neutral and non-emotional in content, such as reading a magazine.

As a manipulation check, before being presented to the participants, each script will be evaluated by 1-2 experimenter(s) not involved in its generation. The evaluator(s) will rate the scripts on Likert scales (attached in Appendix) for alcohol-relatedness and emotional content. If an alcohol-related script scores below 3 on the 5-point Likert scale on alcohol-relatedness and/or scores above 3 on negative emotions, it will be revised. If an alcohol-unrelated script scores above 2 on the 5-point Likert scale on alcohol-relatedness and/or scores above 3 on negative emotions, it will be revised. Script revision will occur either (1) in Session 1 itself or (2) by telephone contact or in a separate laboratory visit scheduled to occur between Session 1 and Session 2. If it is needed, telephone contact or laboratory visit will be used only for script revision. We expect that, by working with the experimenter in the initial script

development session, most participants will generate an acceptable script without the need for revisions. If revisions are required, we expect that most can be made by telephone, and so we expect the use of the additional lab visit to be rare. The addition lab visit for script revision is not included in the numbering of subsequent sessions. In our prior studies, we have never needed to revise a script.

The session will last approximately one hour. At the beginning and end of the session, participants will rate their alcohol craving using a one-item alcohol craving VAS adapted from that of MacKillop and Lisman (2008): "I want an alcoholic drink right now"; 0 = "I don't want an alcoholic drink at all," 100 = "I *really* want an alcoholic drink." This urge scale will be used to measure craving during the extinction sessions. This same scale will be used for measuring craving during the extinction procedures, renewal test, and reinstatement conducted subsequently (described below). We are using a one-item VAS measure for craving because, in our prior studies, we have usually been better able to detect manipulation effects with these straightforward measures than with multi-item assessments of craving, and there may be good theoretical reasons for that (McGrath, 2005). We will measure craving for soft drinks using a similar VAS except references to alcoholic drinks are replaced by references to soft drinks. The alcohol and soft-drink craving scales are provided in the Appendix.

Before the end-of-session rating, participants will be given a 10-minute period with instructions to initiate progressive muscle relaxation and to focus on deep breathing. The relaxation procedure will be repeated until participants report not feeling stress and craving greater than pre-interview levels. Participants will then be discharged.

Initiation of GMA: During Session 1, participants will each be issued a smartphone. We will show them how to use the phone for EMA entries and ask them to make several practice entries (which will not be used in data analysis). We will explain the automatic collection of location information by the smartphone's GPS chipset. They will be shown how to charge the phone. They will be asked to keep the phone on and to carry it at all times.

GMA data will be transferred wirelessly from participants' phones to servers located at the NIDA BRC under a secure communications system developed by the NIDA Biomedical Informatics Section. Transfers will be scheduled to occur automatically at least twice a day. Participants will not have to visit the laboratory for these data transfers. If the remote transfers fail, we can manually initiate a wireless transfer when participants make their regularly scheduled laboratory visits. If that fails, we will swap out the participant's phone so that the NIDA Biomedical Informatics Section can try to recover the data.

We describe the content of EMA questionnaires in a separate section below, after the description of the sessions.

b. Sessions 2-5: Retrieval-extinction sessions

BAC will be checked at the start of each session and will need to be 0.00% to proceed. Session 2 will be scheduled 2-3 days after Session 1, with 2-3 days separating each subsequent session. Under unusual circumstances, sessions might be separated by up to 10 days. Unusual circumstances would include, for example, staff shortages or unforeseeable participant emergencies that combine with Federal holidays or weather events. We expect such scheduling to be rare and will not present it in the consent form as an option. Participants will be terminated from the study as unable or unwilling to complete study measures if they cannot schedule a retrieval-extinction session within this 10 day window.

At the beginning of Session 2, participants will complete a timeline follow-back calendar (Sobell et al., 1979; Sobell et al., 1996a) covering the time between Session 1 and Session 2 to provide a retrospective report of drinking at "baseline" for comparison with that week's GMA reports. At the beginning of Session 3-5, participants will report on their drinking in the time since their previous experimental session.

Retrieval: Participants will be placed in one of the two rooms they visited in Session 1. They will first complete a rating of their craving for alcohol and soft drinks. They will then be provided with either a beverage that contains alcohol (alcohol retrieval condition) or does not (soft-drink retrieval condition). The alcohol-containing beverage will be selected based on the types (beer, wine, spirit) and brands (commercial packaging) of beverages consumed in the previous 90 days, assessed by the "most frequently consumed alcoholic beverage" questionnaire. The participant's most frequently consumed beverage will typically be chosen for use during experimental sessions, but we will also discuss the results of the questionnaire with each participant to determine what he/she considers "typical" liked drinks for him/herself. A different beverage (i.e., not the most frequently consumed beverage) may be chosen from among these typical drinks if the participant's most frequently consumed beverage is not easily commercially available (e.g., is homemade or not in current production) or not practicable for attaining the study's target BAC in the time available for drinking in the session (e.g., a beverage that has a very low concentration of alcohol that would require a participant with a large volume of distribution rapidly to consume large volumes of liquid). The goal is to arrive with the participant at a beverage that (1) is acceptable to him/her to drink in the quantity required in the time available in the session and (2) provides a stimulus that is specific enough to the experience of the particular participants to be effective for memory retrieval and producing craving (Staiger & White, 1991). The soft drink will be based on participants' reports collected in Session 1 of typical nonalcoholic beverages consumed and liked,

screened by the experimenters to exclude caffeinated beverages and beverages commonly used by particular participants as mixers for alcohol.

Participants will be given a volume of alcoholic beverage necessary to produce a BAC of 0.06 ± 0.01 g/dL. We will adjust the amount of alcohol administered to attain this BAC based on equations by Brick (2006, Formula 14). Participants will be weighed at the beginning of each session for determination of total body water (Brick 2006, Formula 10), which is needed for the alcohol dose adjustment. Participants who do not reach the expected BAC will proceed with the rest of the session, but when we analyze the study data, we will perform sensitivity analyses in which we see whether omitting their data changes the conclusions.

The volume of soft drink we give will be adjusted for each participant to match the caloric content of the participant's preferred alcoholic beverage.

To enhance retrieval, participants will be given their beverage along with an empty commercial package for that beverage; for example, Budweiser beer served in a pint glass along with an empty Budweiser can for alcohol retrieval, or Tropicana orange juice served in a tumbler alongside an empty Tropicana carton for soft-drink retrieval. To help standardize BAC during the subsequent extinction training, we will limit the time participants are given to finish the beverage, to a maximum of 40 min. The time each participant takes to finish the beverage will be recorded. If a participant finishes the beverage in less than 40 min, the extinction procedure can begin (i.e., we will not wait for the full 40 min to pass before initiating extinction). Before and 30 min after drinking, participants will complete the PhenX Measure: Acute Subjective Response to Substances questionnaire.

If a participant cannot or will not drink the whole beverage, we will measure the volume of beverage remaining undrunk. Participants who drink ≥ 66% of the initial volume will be allowed to continue with the session. Participant who drink less will be considered not to have completed the retrieval procedure and will not proceed to the extinction procedure. Instead, they will be asked to wait for discharge from the laboratory, using the procedures for release described below. Given a failure to complete retrieval, a retrieval-extinction session can be rescheduled once; participants who do not complete the beverage second time will be discharged from the protocol.

A number of previous human studies have used a fixed dose of alcohol that produces BAC of approximately 0.06-0.07 g/dL. Doses in that range (0.5-0.65 g/kg) are considered "moderate" (Rose et al., 2014). Their effects are detectable by participants (Chutuape & de Wit, 1994; Rose & Duka, 2006) and are rated as "liked" (Chutuape & de Wit, 1994). They have been used successfully in studies of the effects of alcohol priming/preloading on several behavioral and subjective endpoints: hypothetical and

actual alcohol choice (de Wit & Chutuape, 1993; Chutuape & de Wit, 1994; Rose & Duka, 2006), food consumption (Rose et al., 2015), alcohol craving (see also Rankin et al., 1983; Christiansen et al., 2013; Rose et al., 2014), and cognitive and psychomotor test performance (Fillmore et al., 1998; Fillmore & Rush, 2001; Rose & Duka, 2006; Christiansen et al., 2013; Rose et al., 2014).

Extinction: The extinction procedure will begin 30 min after the end of the retrieval procedure to allow for alcohol absorption and distribution. Our intention is for the extinction procedure to occur when participants have a recent memory of alcohol intoxication, such that the temporal window of reconsolidation for that type of memory is open. Participants will spend the 30-min in the same room, to allow for the initiation of physiological monitoring (described below), and, to fill the time, participants will watch a series of short videos (Schiller et al. 2012). Videos will be drawn from the popular (approx. (3 million subscribers) online science and technology video series SciShow and screened for emotional and drug-use content. Participants may be asked to answer a series of brief, open-ended questions about the videos. The list of videos to be used and the list of questions to be asked are provided in the Appendix. At the end of the 30 min, participants will provide a breath sample for determination of BAC, and then the extinction procedure will begin.

During extinction, participants will listen to audio recordings of the imagery scripts developed in Session 1. Participants receiving alcohol extinction will listen to their alcohol-related script; participants receiving soft-drink extinction will listen to their alcohol-unrelated script. Participants will also be given their preferred beverage along with empty commercial packaging; these will be the same during extinction as they were during retrieval, but during extinction, participants will not drink.

For all participants, cues will be presented in 5-min blocks: audio imagery scripts for 2 min, beverage exposure for 3 min. Once per min during the 3 min of beverage exposure, the participant will be instructed to take the glass in hand, raise it to his or her nose, and inhale its scent. Participants who drink any of the beverage during the extinction procedure will be discharged from the protocol.

There will be five blocks of cue presentation per session, with 5 min between blocks. In the time between blocks, the cues will be obscured from participants' view. Participants will fill out the one-item alcohol craving VAS if needed and will then be instructed to relax until the next block of cues. The alcohol craving VAS will be given three times during the extinction session: (1) immediately before the first block of cues, (2) immediately after the first block of cues, and (3) immediately after the fifth, final block of cues. The rating taken before the first block will be used to determine whether the beverage itself increased craving (Christiansen et al., 2013; Rose et al., 2014). To check that participants were successfully attending to the cues, following the last urge scale, participants may be asked brief open-

ended questions about the session (e.g., "Tell me about what you did in today's session…"). Participants will then be allowed to remain in the room and to relax for 20 min, at which point physiological monitoring will be ended, yielding a total extinction time of 65 min. During this period, participants will be given instructions to initiate progressive muscle relaxation and to focus on deep breathing, as after the script generation procedure. If participants are still feeling craving or otherwise "triggered" by the cues at the end of this period, they will receive counseling.

Finally, participants will be asked to relax in a third, neutral room of the laboratory where their BAC will be checked every 20 minutes until ≤ .01%. Participants may be released from the laboratory when their Pre-discharge sobriety test is within normal limits and their BAC is ≤ .01%. A copy of the sobriety test is included in the Appendix.

Our decision to use four separate extinction sessions was based on data from previous studies, which showed that by the fourth session of extinction, craving for alcohol had decreased either to the point of not being different from that of neutral-beverage control participants, or by > 50%, or by reaching an asymptote such that additional sessions produced no further consistent declines craving (Blakey & Baker, 1980; Staiger & White, 1991; Staiger et al., 1999; MacKillop & Lisman, 2008). It is possible that US exposure (alcohol drinking for memory retrieval) will itself facilitate extinction (Luo et al., 2015). We believe that it is important to attempt to conduct a sufficient number of extinction sessions to allow the soft-drink retrieval / alcohol extinction group, as well as the alcohol retrieval / alcohol extinction group, to achieve a significant attenuation of cue effects.

c. Session 6: Post-treatment effects of cues in the laboratory

Participants will return their smartphones at the beginning of this visit. They will also complete a timeline follow-back calendar (Sobell et al., 1979; Sobell et al., 1996a) covering the time between Session 5 and Session 6 to provide a retrospective report of "post-extinction" drinking for comparison with that week's GMA reports.

In the session, all participants will be presented with alcohol cues and an alcohol-containing beverage (i.e., regardless of their previous group assignment to receive only a soft drink or soft-drink cues). Cue-induced craving and physiological changes will be measured in response to two procedures known to enhance responding after Pavlovian extinction procedures (Todd et al., 2014) and to differentiate the effects of extinction with or without prior memory retrieval in laboratory animals (Luo et al., 2015): (1) a renewal procedure, in which the extinguished response may reappear because the CS is presented in a new context and (2) a reinstatement procedure, in which the extinguished response may

reappear because the US has been reintroduced to create a "priming" effect. Each participant will undergo both the renewal and reinstatement procedures, in that order, in one session.

Renewal-test procedures: We will use a within-participant renewal procedure based on that of Thewissen and colleagues (2006), who studied renewal of cue-elicited cigarette craving. Participants will be given alcohol cues in both the same room in which they underwent retrieval-extinction (the extinction-concordant room) and a different room (an extinction-discordant room). The identities of the rooms, and the order of their presentation in the renewal test, will be counterbalanced across participants within each group. Renewal is indicated by significantly greater cue reactivity in the extinction-discordant room than the extinction-concordant room. This is a proxy measure for the clinical problem of patients' renewed craving after returning from the extinction setting to an outside environment (although, in our protocol, we will be attempting to assess that directly with GMA as well).

In the renewal procedure, participants will not be given an experimental beverage. Instead, in each room, they will rate their alcohol and soft-drink craving before and after a single block of alcohol cues, to be presented the same way as in the extinction sessions. In each room, physiological monitoring will begin 10 minutes before cue presentation and will continue for 5 minutes after the end of the craving ratings. This abbreviated schedule, compared to physiological monitoring used during the extinction procedure, is needed to allow for the tests to be completed in a timely manner with participants travelling between the two experimental rooms and spending time in a third, neutral room of the laboratory in between (described below).

BAC will be checked at the start of the session at will need to be 0.00% to proceed. Between their time in the first and second rooms, participants will spend 30 min in a third, neutral room and will be given a distractor: they will watch a series of short videos that have been screened for emotional and drug-use content and afterwards answer brief questions about their content. Videos will be drawn from the popular (approx. 3 million subscribers) online science and technology video series SciShow. The list of videos to be used and the list of questions to be asked are provided in the Appendix. The distractor is intended to limit carryover effects from cue presentation in the first room to the second (Reynolds & Monti, 2013). After completion of the renewal test, to limit carryover from the renewal procedure to the subsequent reinstatement procedure, participants will be returned to the neutral room for 30 min to complete the distractor task for a second time with a fresh video.

Reinstatement-test procedure: We know of no prior explicit demonstrations of the reinstatement of extinguished drug-conditioned responses in human laboratory studies, but reinstatement has been documented in human studies of fear conditioning (Haaker et al., 2014).

After the second distractor, all participants will be returned to the extinction-concordant room for the reinstatement procedure. Physiological monitoring will begin, and 10 min later, participants will rate their alcohol and soft-drink craving. They will then be given their experimental soft drink, which they will have 40 min to drink. 30 min later, they will again rate their alcohol and soft-drink craving. Then, they will be given their experimental alcoholic beverage, which they will have 40 min to drink. 30 min later, their BAC will be measured by breathalyzer, and they will again rate their alcohol and soft-drink craving. Reinstatement is indicated by greater craving after the alcoholic beverage than after the soft drink.

For reinstatement, the presentation of the alcoholic beverage and soft drink will be similar to the retrieval portion of the retrieval-extinction sessions: each beverage will be served to the participant as he/she typically consumes it along with its empty commercial packaging. However, we will present smaller volumes of beverage for reinstatement compared with retrieval. Participants will be served the volume of alcoholic beverage needed to give a dose of 0.3 g/kg absolute alcohol. In comparison, we estimate that participants will receive 0.5-0.6 g/kg absolute alcohol in retrieval, with exact doses varying according to each participant's body composition to produce the target 0.06 g/dL BAC for retrieval. The volume of soft drink served in reinstatement will be matched to the calories in the alcoholic beverage served and will, thus, also be smaller than in retrieval. In previous research, 0.3 g/kg alcohol has been used successfully to study alcohol craving following alcohol consumption in non-dependent drinkers (Hutchison et al. 2001; McKee et al. 2009; Schoenmakers et al. 2008; Udo et al. 2013), and studies in laboratory rodents also show that smaller amounts of alcohol can prime alcohol-seeking behavior, compared to the amounts of alcohol consumed during animals' self-administration training (e.g., Perry & McNally 2013). We believe the reduced beverage volumes used in reinstatement will allow us to observe a significant effect of alcohol while maintaining the comfort of participants, who are being asked to drink two beverages back-to-back in reinstatement, compared with the one beverage used for retrieval.

Participants will then be allowed to remain in the room and to relax for 20 min, at which point physiological monitoring will be ended. During this period, participants will be given instructions to initiate progressive muscle relaxation and to focus on deep breathing, as after the script generation procedure.

Finally, participants will be asked to relax in the third, neutral room of the laboratory where their BAC will be checked every 20 minutes until ≤ .01%. Participants may be released from the laboratory when their Pre-discharge sobriety test is within normal limits and their BAC is ≤ .01%.

<u>d.</u> Follow-up phone call

Approximately 30 days after the final laboratory session, we will call the participant to conduct a timeline follow-back calendar (Sobell et al., 1979; Sobell et al., 1996a) and to administer the Penn Alcohol Craving Scale (Flannery et al., 1999). We will then disclose the design of the study to them, explain which experimental group they were in, and debrief them about their perceptions of the study (e.g., whether they had known that they were in a control group or the intervention group).

Following the experimental debriefing, the participant will be asked to speak to a master's-degree-level counselor about his or her drinking behavior. The counselor will provide advice consistent with participants' AUDIT scores (Babor et al. 2001, p. 20) and, when appropriate, referrals to treatment programs and support groups for alcohol-use disorders.

The same advice will be given to study candidates who score in the same range (8-15) on the AUDIT but who are disqualified from study participation for other reasons, such as not endorsing any AUDIT items beyond the first three. This would be done by screening staff toward the end of screening, rather than in a post-study follow-up.

Physiological monitoring during Session 2-6

We will continuously measure heart rate, blood pressure, skin conductance, and skin temperature during the extinction procedures in Sessions 2-5 and during the tests for renewal and reinstatement in Session 6. We will use these measurements to assess changes in participants' physiological responses to the alcohol and soft-drink cues within and between sessions. Physiological measurements will be obtained using a standard laboratory physiological monitoring system: a BIOPAC or Coulbourn Instruments LabLinc noninvasive blood pressure amplifier with CNAP Monitor arm and finger cuffs plus fingertip-mounted skin temperature and conductance sensors . We have used these systems to measure participants' physiological responses to drug and stress cues (NIDA IRP protocols 020, 475).

Geographical Momentary Assessment (GMA) data collection

GMA data collection will begin with the issuing of a smartphone in Session 1 and conclude at the beginning of Session 6, the final laboratory visit. Before being issued a smartphone, each participant will have an instructional session in which the assessment items and smartphone operation are explained.

EMA Entries

Participants will make the following types of entries:

<u>Event-contingent (EC) entries:</u>

Drinking: We will tell participants to make an entry whenever they drink alcohol. We will use a questioning strategy similar to the one used successfully by Piasecki and colleagues (2014): participants will make an entry as soon as they finish their first drink of any drinking episode, and the smartphone will

then automatically prompt them 30, 90, and 150 minutes later to ask about any subsequent drinks, unless the participant indicates that he or she is going to bed. The list of questions will be short to keep compliance as easy as possible. The main thing of interest, apart from the rate and volume of drinking, is the extent to which the participant feels that the drinking episode is ill-timed or excessive.

Craving: We will tell participants to make an entry whenever they feel a craving, urge, or temptation to drink. Our use of all three terms is meant to capture the full range of the experience; we will tell participants to report even mild or fleeting temptations or wishes.

Random-prompt (RP) entries:

Three times per day, the smartphones will issue random prompts for participants to report their mood, activities, and degree of craving, with particular emphasis on recent encounters with any alcohol-related cues. (We will not ask participants to initiate an EC entry after every encounter with an alcohol-related cue because that seems likely to make them hypervigilant, changing the behaviors we are trying to assess.)

At each RP, we will ask whether the participant has had an unreported drink in the past hour. If the participant answers yes, the questions asked in a "drink" EC entry will be asked immediately following the RP, and the post-drink follow-up assessments (30, 90, and 150 minutes later) will be given as well.

Hours for RPs will be adjustable in accordance with participant's typical sleep/wake schedule; participants will also be able to turn off random prompting for a limited amount of time each day, to be used in settings where receiving a prompt would be disruptive (such as driving or religious services).

Measurement of blood alcohol concentration via breath (BAC):

For sessions 2-6, BAC will be measured at the start of each session and must be 0.00 to proceed. BAC will be measured again every 20 minutes after the last study procedure of the session until it comes down to ≤0.01, at which point, if the pre-discharge sobriety test is within normal limits, the participant can be discharged home.

3. Follow-up/termination procedures

Follow-up will be done by phone approximately 30 days after the final laboratory session, as described above. The follow-up phone call will terminate the participant's enrollment in the study.

F. Inclusion and Exclusion Criteria

The enrollment target for the protocol is 100 (at least 75 of whom we anticipate will complete all 6 study visits). We will enroll drinkers who report some problems or concerns with their own patterns of

drinking (via their scores on the Alcohol Use Disorders Identification Test, described below), because in that population, reductions in cue-induced craving or drinking will constitute a benefit. Measuring those outcomes in lighter drinkers would have little clear meaning. However, we will not enroll drinkers who need or are seeking treatment for an alcohol-use disorder, because giving them alcohol in the laboratory would raise greater ethical issues. Our choice of population keeps us well within the guidelines laid out in the NIAAA document "Administering Alcohol in Human Studies" <http://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm>. We expect to have little trouble finding problem drinkers who are not treatment seekers: two large surveys have shown a 12-month point prevalence of approximately 10% for problem drinking (Sobell et al., 1996b). In the same surveys, more than 75% of respondents with prior drinking problems had recovered with no formal treatment or support-group involvement, usually returning to moderate drinking (Sobell et al., 1996b).

Thus, our target population consists of generally healthy people who feel that they ought to reduce their drinking somewhat, in the same way that other generally healthy people might feel that they ought to reduce their coffee or snack-food consumption. In all these instances, the desire to reduce consumption does not equate to a desire or need for formal treatment or support-group involvement. There is no published questionnaire designed to identify members of our target population, so we are operationalizing the "ought to reduce" component primarily in terms of a minimum score on the Alcohol Use Disorders Identification Test (AUDIT), operationalizing the "not treatment-needing " component primarily in terms of a maximum score on the AUDIT and the history and physical examination, and operationalizing the "not treatment-seeking" component in terms of study applicants' responses to a specific written question ("Seeking Treatment / Seeking Abstinence" Questionnaire in the protocol appendix). When the MAI, or other staff involved in screening, suspects that a study applicant has a drinking problem more severe than the screening data overtly indicate, we will err on the side of caution by recommending treatment instead of enrolling the applicant. We will also discontinue sessions and recommend treatment for anyone whose need or desire for treatment emerges during the study.

Study candidates who score between 8 and 15 on the AUDIT but are disqualified for some other reason will, before they leave screening, be given the same advice and referrals that are given to people who have participated (see the section on follow-up phone calls for participants, page 23).

1. Inclusion criteria

(1) age between 21 and 65 years inclusive;

(2) Drinking at high levels for at least 10 different weeks during the last 90 days. High-level drinking for a given week can be either of the following:

a) For women, more than 3 drinks on any single day that week, or more than 7 drinks that week;

b) For men, more than 4 drinks on any single day that week, or more than 14 drinks that week;

(3) a score ≥ 8 and ≤ 15 on the self-report version of the Alcohol Use Disorders Identification Test (AUDIT), with endorsement of at least one item other than 1-3, because 1-3 assess only consumption, not concern or consequences;

(4) self-report of liking or having neutral feelings about the sight and smell of alcoholic beverages;

(5) for women, practicing an effective method of birth control before entry and throughout the study (or postmenopausal for at least one year, or surgically sterile); negative urine pregnancy test at each visit. Effective methods of birth control are those approved by the Food and Drug Administration (FDA) used as described in the FDA Birth Control Guide (http://www.fda.gov/downloads/forconsumers/byaudience/forwomen/freepublications/ucm517406.pdf). These methods are: (1) intrauterine device (IUD) copper; (2) IUD with progestin; (3) implantable rod; (4) contraceptive shot/injection; (5) oral contraceptives (combined pill, progestin-only pill, or extended/continuous-use combined pill); (6) contraceptive patch; (7) vaginal contraceptive ring; (8) diaphragm with spermicide; (9) sponge with spermicide; (10) cervical cap with spermicide; (11) male condom; (12) female condom; (13) male partner with a vasectomy. Abstinence from sexual intercourse is also an effective method of birth control.

2. Exclusion criteria

(1) risk of alcohol withdrawal, as determined by any of the following: a score ≥ 8 on the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) following a negative breath test for alcohol (i.e., BAC of 0.0), lifetime history of delirium tremens or seizures (related to alcohol or not), endorsement of a "drinking to avoid withdrawal" symptom on the SCID or M.I.N.I. (M.I.N.I. Section I, "Alcohol Use Disorder," items k1 and/or k2 answered affirmatively with counselor's evaluation to verify that symptoms indicated in item k1 are related to the individual's cutting down on drinking and/or the response to item k2 refers to withdrawal symptoms and not hangover); or physician's judgment.

(2) currently trying to quit drinking, or planning to quit or reduce alcohol drinking via formal treatment or support-group attendance in the next six months;

(3) for women: pregnancy, breastfeeding, or planning to become pregnant during the experiment;

(4) current liver disease or dysfunction, assessed by physical examination and medical history; and hepatitis C, chronic hepatitis B, or other current liver disease or dysfunction as assessed by physical examination and medical history or as reflected in blood levels more than 5 times the upper limit of normal in any of the following: aspartate transaminase (AST), alanine transaminase (ALT), or gamma-glutamyltransferase (GGT)

(5) any other medical illness or condition that in the judgment of the investigators is incompatible with alcohol consumption;

(6) current use of prescription or over-the-counter medications or herbal products for which drinking alcohol is strictly prohibited. When the metabolic half-life of the medication/product is known, we will require at least 7 half-lives to have elapsed before any session involving alcohol consumption. If the half-life is not known (as might be the case for some herbal preparations), we will require at least 7 days to have elapsed since the last use before any session involving alcohol consumption;

(7) substance-use disorder for any drug(s) other than alcohol or nicotine in the previous 12 months;

(8) past or present diagnosis of bipolar disorder or any psychotic disorder; any history of suicide attempt or current suicidal ideation; present diagnosis of uncontrolled or untreated mood or anxiety disorder;

(9) cognitive impairment severe enough to preclude informed consent or valid self-report

G. Clinical and Laboratory Methods

These are described in section E.

H. Collection and Storage of Human Specimens or Data

Electronic data will be stored on the NIDA IRP's secure, password-protected electronic medical-records system (Human Research Information System; HuRIS). Paper records will be stored in the Archway research space under double lock in an area not accessible to individuals who are not part of the study staff (BRC building; room number 01B605). After the study is completed and data have been analyzed, the paper records will be stored at an NIH-approved commercial facility for the storage of sensitive data until approval for their disposal has been given.

Stored biological specimens will be kept in a secure freezer in the Archway's NIDA freezer room until they are analyzed (BRC building; room 01B405). Specimens that are not used up in the analyses will be saved, but will not be used for any purpose not described in the protocol without prior IRB approval.

Urine samples will be kept in a secure freezer in the Archway's NIDA freezer room until they are analyzed (BRC building; room 01B405) and tracked by barcode. Those that are not used up in the analyses will be disposed of after the study. They will not be used for any purpose not described in the protocol without prior IRB approval. Any unplanned loss or destruction of the samples will be reported by the PI to the IRB.

I. Statistical Analysis

1. Outcome measures

Primary: (1) self-reported alcohol craving during the laboratory sessions, (2) GMA reports of alcohol craving and drinking.

Secondary: (1) self-reported alcohol craving and drinking at the 30-day follow-up, (2) heart rate during laboratory sessions and GMA collection periods, and (3) biomarkers for drinking, detected in urine samples collected during laboratory sessions.

2. Analysis of study outcomes

There are two ways in which we are performing multiple tests of statistical significance. First, we have two co-primary outcomes: a lab measure and an ambulatory measure. This design is actually conservative, because we will not consider US retrieval-extinction fully successful if it affects only the first outcome (protection from renewal/reinstatement in a lab setting) without affecting the second outcome (changes in daily-life behavior).

Second, we need to compare our experimental group to each of the two control groups—we expect the control groups to be similar to each other. If the experimental group differs from only one of the control groups, we will have to conclude that the effect of US retrieval-extinction did not actually require both retrieval and extinction, and thus worked via some unexpected mechanism. Although we might ultimately need to perform the two comparisons separately to explore unexpected findings, our main planned analysis is a single test of the joint hypothesis that the experimental group differs simultaneously from both control groups.

Our specific tests will be as follows.

Co-primary outcome 1: Protection from renewal/reinstatement of craving in session 6. We will analyze this in a linear regression model so we can control for a continuous covariate: each participant's mean level of craving in prior sessions (along with any person-level covariates that improve the fit of the model). To test the joint hypothesis that the extinction-retrieval group differs simultaneously from both control groups, we will dummy-code the 3-level predictor Group using two variables: Control Group A (0,1) and Control Group B (0,1), thereby making our intervention group the reference level. We will then perform a Wald test of the joint significance of the two Control Group predictors, maintaining an alpha of .05.

The dependent variable will be operationalized in terms of participants' ratings of alcohol craving in the renewal procedure and the reinstatement procedure from session 6. For each participant, we will generate a summary measure of renewal susceptibility (or, for separate analyses, reinstatement susceptibility) using within-session scores from session 6. For renewal, the score will be calculated as:

(pre-to-post-cue craving change in discordant room) *minus*
(pre-to-post-cue craving change in concordant room)

For reinstatement, the score will be calculated as:

(pre-to-post-cue craving change after alcohol) *minus*
(pre-to-post-cue craving change after soft drink)

Co-primary outcome 2: Reduction of craving and drinking in daily life. This will be analyzed in multilevel models, with the dependent variable operationalized in terms of participants' changes in alcohol craving and alcohol drinking in GMA reports after the four extinction-retrieval sessions, controlling for any preexisting differences. Because we cannot predict the time course of differential changes, our main analyses here will omit GMA data from the period when the four extinction-retrieval sessions are occurring. The dependent variable will be daily frequency of craving reports (or, in a separate analysis, daily number of drinks); the independent variables will be coded the same way as in the models for co-primary outcome 1, with experimental group (3 levels) dummy-coded so the experimental group is the reference level and a Wald test of joint significance can assess whether the experimental group differs simultaneously from both control groups. The continuous covariate will be each participant's overall frequency of craving or drinking during the baseline week of GMA.

Depending on the distribution of the dependent variable, we will use either general linear mixed models (e.g., SAS Proc Mixed) or generalized linear mixed models (e.g., SAS Proc Glimmix or SAS Proc NLMixed)—each of which provides a repeated-measures analysis that can handle missing days or early dropout and can accommodate person-level covariates, which will be included if they improve the fit of the model. These models use maximum-likelihood estimation and allow for specification of an

autoregressive error structure (which can be tested against alternative error structures to provide the best-fitting model). In supplementary analyses, we will examine the time course of any differences that emerge during the period when the four extinction-retrieval sessions are occurring.

Secondary outcomes: Most of the other laboratory measures, such as self-reported craving and drinking at the 30-day follow-up visit, urine biomarkers for drinking, and heart-rate responses to cues, will be analyzed by an ANCOVA approach similar to the one used for the co-primary outcome measure 1. Analysis of the GPS component of the GMA data will be more exploratory, but will include testing for group differences in susceptibility to alcohol craving as a function of nearness to bars and liquor stores—a possible reflection of cue reactivity.

3. Criteria for significance

Findings will be considered statistically significant at $p \leq .05$, two-tailed, with trends noted at $p \leq .10$.

J. Required Sample Size

We checked prior human studies to find likely effect sizes. For subjective drug craving, the difference between retrieval-extinction participants and control participants had a Cohen *d* of 1.12 (Xue et al., 2012, figure 3b, change scores for craving on day 4). In a prior human study on reinstatement of physiological reactivity to an extinguished (fear) cue, the difference between retrieval-extinction participants and control participants had a Cohen *d* of 1.11 (Liu et al., 2014, figure 1). These are large effects. We are powering our study for detection of effects that might be smaller. We used the module "Linear multiple regression: R-squared increase" in G*Power to determine what we could achieve with a realistic sample size. With evaluable data from 75 participants (25 in each of our 3 groups), we will have power of .80 to detect a Cohen f^2 as small as 0.13 on a test of the joint hypothesis that the intervention group differs simultaneously from both control groups in a linear regression model that also contains a covariate for baseline, at a two-tailed alpha of .05. An f^2 of .13 is approximately equivalent to a Cohen *d* of .61—conventionally considered a medium-sized effect. Despite the large effects seen in the prior studies, we think it is prudent to have power to detect a medium one.

Participants who drop out or are withdrawn from the study will be replaced. We anticipate that we will need to enroll 100 participants in order to have 75 complete the study.

K. Plans for Enrollment at Multiple Sites

Not applicable.

L. Human Subjects Protection Plan

1. The responsibilities of investigators

Responsibilities and qualifications of investigators are given in the protocol appendix.

2. The names of investigators who will obtain informed consent

- David H. Epstein, Ph.D.
- Karran Phillips, MD, MSc
- Jeremiah Bertz, Ph.D.
- Kenzie L. Preston, Ph.D.
- Louise Glezen, MS
- Brenda Curtis, PhD
- Edith Vargo, MD

Non-FTE staff members will explain the consent form to participants under the direct supervision of a federal employee (FTE) who will sign the consent form.

3. Rationale for subject selection based on gender/ethnic/race categories at risk

Participant selection will be equitable, without regard to nationality, race, religion, or creed. The anticipated racial/ethnic distribution will reflect that of the local community and drug-using population. According to 2010 census data, the population of Baltimore City was 63.7% black, 29.6% White, 2.3% Asian, and 0.4% American Indian/Alaskan Native. In the 2010 Census, 4.2% of respondents stated they were of Hispanic or Latino origin (US Census Bureau, accessed at www.quickfacts.census.gov, last revised 12/23/2011).

The inclusion and exclusion criteria were chosen to maximize generalizability while minimizing risk to participants. We chose an upper limit on age (65) to reduce the variability in responses to alcohol that might be associated with age, but we set this limit high enough so that it will most likely not disqualify any study applicants.

APPROVED STUDY POPULATION						
	FEMALE ENROLL-MENT	MALE ENROLL-MENT	**TOTAL** ENROLL-MENT	FEMALE COMPLETERS	MALE COMPLETERS	**TOTAL** COMPLETERS
APPROVED CEILING	33	67	100	25	50	75

NIH TARGETED/PLANNED ENROLLMENT

ETHNIC CATEGORY	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	1	3	4**
Not Hispanic or Latino	32	64	96
Ethnic Category: Total of All Subjects*	33	67	100*
RACIAL CATEGORIES			
American Indian/Alaska Native	0	1	1
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	21	43	64
White	11	22	33
Other	0	0	0
Racial Categories: Total of All Subjects*	33	67	100*

*The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: total of All

4. Recruitment plan

Recruiting

Recruitment through the NIDA Office of the Clinical Director will be done by the NIDA-IRP recruitment contractor, MMG, and under certain circumstances, materials may be developed by other contractors as well. Alternatively, we may develop our own ads or contract these services ourselves. All advertising methods will comply with the most current regulations (NIH and OHSRP SOPs and guidelines, as well as FDA guidelines for FDA-regulated research) and the NIDA policy on recruitment materials.

The recruitment contractor may alter the ads in minor ways without prospective IRB review and approval; see below for a list of these types of changes. Other than that, modifications to these materials will be submitted to the IRB for approval as protocol amendments.

The following changes may be made to recruitment materials with no prospective review and approval by the IRB:

- Contact phone numbers

- Color change to graphics
- Overall size, but all content will be increased or decreased proportionately
- Addition of tear-off phone number tags to an approved ad or flyer
- Color or font of the text, but any color change will replace all the text of a certain color. No new emphasis will be created.

All of these changes will be made to the most recently approved recruitment materials and submitted to the IRB annually at the time of continuing review.

Screening methods

Screening for this study will be conducted under protocol 06-DA-N415. Data from participants who enroll in this protocol and collected under protocol 06-DA-N415 will be shared and analyzed as part of this protocol.

The following measures will determine study eligibility:

Screening	**Medical**
(1) a 90-day timeline follow-back calendar for alcohol use	(1) medical history and physical examination,
(2) the Alcohol Use Disorders Identification Test (AUDIT),	(2) breath sample for measurement of blood alcohol level;
(3) the Addiction Severity Index (ASI),	(3) urine sample for drug testing and, for females, pregnancy testing
(4) Structured Clinical Interview for DSM Disorders (SCID) with counselor's evaluation or Mini International Neuropsychiatric Interview (M.I.N.I.)	(4) blood sample for the following laboratory tests: (a) NIDA chemistry 2 panel, (b) serum magnesium (Mg^{++}), (c) complete blood count with differential (CBC w/diff), (d) hepatitis B surface antigen, with reflex hepB panel if positive, and (e) hepatitis C antibody.
(5) the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar),	

Observation of urine collection for screening under protocol 06-DA-N415 will follow the same procedures as observation of urine collection in the 6 laboratory visits in this protocol: urine collection for screening will be observed at random and if a participant provides a sample with attempted tampering.

Abbreviated Title: Lab/GMA drinking

Version Date: 2/16/2022

Consent documents and process

Participants applying for the study and meeting its eligibility criteria will be asked to give informed consent. Consent will be obtained only by the investigators and coinvestigators named on this protocol, all of whom have completed NIH's electronic course in human-research ethics, and all of whom are qualified to answer questions about the study. Any study candidate who has questions or concerns about medical aspects of the study will be offered a chance to talk with the study physician before signing consent. After the consent form is read to or by the applicant, he/she will take and sign a 12-item quiz to ensure that he/she understands the protocol. The quiz may be done on paper or electronically in CDW/HuRIS. A score of 80% will be considered passing; if the score is lower than that, the quiz will be readministered once. The process will be documented in the CDW by the investigator who obtains consent. The consent form contains all required elements. Participants may sign the consent form on paper or electronically in CDW/HuRIS. Regardless of consent method, participants will be given hardcopies of their signed consent forms.

5. Justification for exclusion of vulnerable populations

Justification for the exclusion of children under 18 including neonates

Children under 18 will not be included because many of the measures to be administered in this study are not validated for use with children. Furthermore, it is illegal to administer alcohol to individuals under the age of 18.

Justification for the exclusion of pregnant women and human fetuses

A safe threshold for fetal alcohol exposure has not been established ("Administering Alcohol in Human Studies" <http://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm>). Therefore, pregnant women and human fetuses will not be included.

Justification for the exclusion of other vulnerable populations

Individuals who are cognitively impaired to the extent that they cannot give informed consent or cannot give self-reports appropriately will be excluded. Self-report is a central outcome measure; including participants who cannot do it would invalidate the study. Including participants who cannot give informed consent cannot be justified for this study.

6. Evaluation of Risks/Discomforts and Benefits ratio

This study is more than minimal risk. The risks to participants are generally small and transient, and are outweighed by the potential benefits for treatment of substance-use disorders.

Potential benefits

Direct benefits:

Participants are not expected to receive any direct benefit.

Indirect benefits:

The generalizable knowledge gained may benefit society by providing data on a potential intervention for substance use disorders.

Potential risks

Risks associated with alcohol consumption:

There are physical, psychological, and social risks associated with alcohol consumption (Wood & Sher, 2000). Physical risks include gastrointestinal distress, headache, flushing reactions; psychological risks include unwanted or excessive intoxication, embarrassment from impaired performance or disinhibited behavior; social risks include behavioral disinhibition leading to socially inappropriate action, censure from those who believe it is morally wrong to consume alcohol (e.g., for religious reasons), and legal sanctions (e.g., for public intoxication or driving while intoxicated).

Risks associated with cue exposure:

Alcohol cue presentation during the laboratory sessions is meant to cause craving for alcohol. Participants may experience stress and/or negative affect during these sessions, or may object to the eliciting of emotions by an experimental manipulation. The risk and discomfort with these procedures is related to their intended effects.

Risks associated with urine collection:

Participants may experience embarrassment from being observed while giving urine samples; this risk is minimized by having the observation always occur through a one-way mirror, by a staff member of the same sex as the participant.

Risks associated with GMA data collection:

Carrying the portable electronic devices may be a burden to participants. There is a risk of loss of confidentiality associated with carrying information on alcohol use on and location on smartphones. Carrying these devices may increase the likelihood of being robbed.

Other inconveniences:

Participants will need to spend time in the laboratory, including time for the experimental procedures and time BAC to return to a safe level. Participants will be compensated for their time (see Compensation section for details).

Alternative treatments and procedures

This protocol will not provide treatment for drinking problems and is not intended for people who want or need such treatment. Participants or study applicants who indicate a desire for treatment at any point, or who, in the investigators' judgment, need treatment, will be referred for treatment rather than being enrolled or continued in the protocol.

Procedures for protecting against or minimizing any potential risks

Protecting against or minimizing risks associated with alcohol consumption:

We will not serve alcohol to people who do not drink regularly in their daily lives. We will not include those seeking treatment for their alcohol use, and we will not serve alcohol to people who are seeking to become alcohol abstinent on their own (i.e., without participation in a formal treatment program). Participants will have access to a limited amount of alcohol in each session, and the amount of alcohol available in each session is similar to or less than what participants report typically consuming on their own. When presented with an alcohol-containing beverage, participants will not be pressured to drink more of the beverage, or to drink it more rapidly than they wish to. Physical and psychological risks are also minimized by the availability of both medical staff and trained psychological counselors. Participants will be able to contact medical staff and counselors during and between laboratory visits. Social risks are minimized by (1) the safeguarding of personally identifiable information according to standard NIH policies, which are designed to prevent breach of privacy at a level considered sufficient for sensitive healthcare data, and (2) requesting that participants remain in the laboratory until their BAC has fallen to an acceptable level and until participants can pass a pre-discharge sobriety test.

Protecting against or minimizing risks associated with cue exposure:

Responses will be closely monitored and managed during and after the challenge sessions by trained staff. Participants will be debriefed, and standard CBT techniques for coping with cravings will be used when necessary.

Protecting against or minimizing risks associated with urine collection:

Any observation of urine collection will be performed through a one-way mirror by a staff member who is the same sex as the participant.

Protecting against or minimizing risks associated with GMA data collection:

We will reduce the burden of carrying the portable electronic devices by providing participants carrying cases with belt clips. The risk of loss of confidentiality associated with carrying information on alcohol use on and location on smartphones will be minimized because the smartphones will have only coded identification numbers on them and will be password-protected. Many people now carry electronic devices, including smartphones, every day, and so it is not likely that the risk of robbery is substantially increased over the usual risks. We have issued smartphones or handheld computers to approximately 300 participants in prior studies without having encountered this problem. Similarly, all cell phones in the state of Maryland are now required to have position-tracking devices; therefore, risks from location tracking are similar to those of using a standard cell phone. All information we collect will be protected under an NIH-issued Certificate of Confidentiality.

Provisions for ensuring that necessary medical or professional intervention is available

Medical intervention will be provided by the Medical Advisory Investigator or nursing staff associated with the Treatment Section. Participants will also have access to trained psychological counselors. Participants will be able to contact medical staff and counselors during and between laboratory visits.

7. Subject monitoring

Parameters to be monitored

BAC will be measured at the start of sessions 2-6 and then every 20 min after completion of study session tasks until BAC ≤0.01% and participant may be discharged home by taxi or public transportation as described in "Study design" above.

Criteria for individual subject withdrawal

A participant will be withdrawn from the study if he or she:

- so requests, or withdraws consent.
- misses and does not reschedule any of the study visits.
- is unable or unwilling to complete study measures.
- does not complete at least 75% of GMA entries in two consecutive weeks.
- loses or damages two GMA smartphones.
- arrives at session with a BAL > 0 in more than two sessions
- develops any exclusionary condition or medical problem for which, in the MAI's medical judgment, it is in the participant's best interest to be withdrawn from the study.
- develops any other conditions for which, in the investigators' opinion and following adequate safety review, it is in the participant's best interest to be withdrawn from the study.
- becomes or is found to be pregnant or unwilling to practice required contraception.
- shows an emergence or worsening of clinically significant psychiatric symptoms such as psychosis, low mood, suicidal ideation or behavior, anxiety, agitation, or disorientation.

8. Conflicts of interest

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts of interest to report.

M. Protection of Participants' Privacy and Confidentiality

1. Methods used to identify and contact potential participants

Identification and contacting of potential participants will occur according to the recruiting plan described in this protocol.

2. Settings in which an individual will interact with an investigator

During laboratory visits, research activities will be conducted in private rooms located in restricted-access areas of the NIDA BRC. Outside of the laboratory visits, participants can contact

investigators by telephone. Investigators will not initiate contact with participants outside of the laboratory visits unless a need arises to give new safety information or notify participants of an unexpected need to reschedule a visit.

3. Appropriateness of all personnel present for research activities

Only those personnel needed for the conduct of research activities will be present for research activities.

4. Methods used to obtain information about subjects and the nature of the requested information

Methods used to obtain information about subjects

Information about participants will be collected by self-report, by interview with an investigator, or through the collection of biological samples (blood, urine).

The nature of the requested information

The requested information is necessary for the successful conduct of the study or the interpretation of its results. It consists of: (1) information necessary to individualize the experimental tasks used during the laboratory sessions, (2) the study's primary and secondary outcome measures, (3) demographic information that could affect the study's outcome measures, or (4) other information about the participant that could affect the study's outcome measures. In the latter case, this information consists of measures of psychological processes related to drinking alcohol or soft-drinks or obtaining other rewards, home environment, or mental imagery, which are essential features of the laboratory sessions and/or GMA data collection.

5. Information that may be obtained about individuals other than those enrolled in the study

We will not obtain identifiable private information about individuals other than those enrolled in the study. For demographic purposes, three study questionnaires ask about members of participants' families: (1) participants are asked whether they are married, (2) participants are asked about their total family income, (3) participants are asked about their family history of alcohol use. In all cases, the other individuals are identified only in relation to the enrolled participant and by the type of relation (e.g., sister, cousin). We will not collect the other individuals' names, dates of birth, addresses past or present, social security numbers, biometric information, or other identifiable private information. Individuals who are not enrolled in the study are not human subjects.

6. Justification for the amount of personal information required

The amount of personal information required is appropriate. Only the personal information needed for the successful conduct of the study or the interpretation of its results is collected.

N. Study Agents/Interventions

Only commercially produced and packaged alcohol and soft-drink beverages will be used. The beverages will be chosen based on participants' preferences and regularly consumed beverages to maximize the relevance of the study procedures to the participants' normal alcohol consumption patterns.

There is no gene therapy and no FDA-regulated device or drug in this study.

O. Plan for Reporting Unanticipated Problems and Adverse Events

Reportable events will be tracked and submitted to the IRB as outlined in Policy 801.

P. Data and Safety Monitoring

1. Data and safety will be monitored by the Principal investigator and MAI.
2. A DSMB is not necessary for this study, which is unblinded and occurring at a single site.

a. Monitoring mechanism: The Principal Investigator is responsible for data and safety monitoring, and will work with the MAI to examine the adverse event data for safety concerns. The Lead Associate Investigator and Associate Investigators on the project will examine data for integrity and report to the PI.

b. Frequency: Data will be examined once a year at the time of the continuing review. Adverse event data will be examined as new events occur weekly.

c. Criteria for stopping the study: We will stop the study after we complete data collection from our target number of completers (n=75). We will stop the study sooner than that if there are more than 10 SAEs that are probably or 5 SAEs that are definitely attributed to study participation.

d. Advanced plans for interim/futility analyses: Interim analyses will not be conducted.

e. Information to be monitored:

1. *Participant Safety:* We will continually monitor adverse events for serious situations. Yearly, we will conduct an assessment of all adverse events to understand the risks that may be associated with the study.

2. *Study Demographics*: We will monitor recruiting and enrollment data to assure the consistency of our efforts with enrolling a diverse population representative of Baltimore City and its surrounding counties.

3. *Data Quality*: We will review the data at the completion of each of the first 5 participants and at the end of completion of each 10 participants thereafter for data integrity as it relates to primary outcome measures.

f. Communication: The Lead Associate Investigator and Associate Investigators will bring safety and data integrity concerns to the PI. Safety and data integrity concerns will be immediately brought to the attention of the IRB and the Clinical Director via problem reports.

Q. Clinical Monitoring Plan

Not applicable.

R. Data/Records Management

For medical records and research data: All participants' records generated by the NIDA/IRP staff will be accessible to authorized NIDA/IRP staff only and will be kept in locked files or password-protected electronic files (i.e., NIDA/IRP's Clinical Data Warehouse; CDW, a Microsoft SQL Server database). Data will be kept in password-protected computers. All data forms will be identified by ARC number; participant names and ARC numbers will not appear together on paper forms except where mandated by federal or NIH policy (as on signed consent forms). The key that links ARC numbers with participants' names will be kept by the principal investigator in a locked filing cabinet in a locked room.

For stored samples: Samples will be stored using codes that we assign. Samples will be kept in freezers in a restricted-access area of the BRC. All access to that part of the BRC requires an NIH badge and is automatically logged. Samples may be used for other research projects with participant's written consent. The samples will be coded with non-identifying information and the code kept at NIDA.

No clinically usable genotype data will be generated during the course of this study and no Clinical Laboratory Improvement Act-certified (CLIA-certified) genotyping acceptable for diagnostic or insurance purposes will be performed.

A Certificate of Confidentiality will be obtained prior to initiation of the study. To the extent legally possible, NIDA/IRP will not release participants' information without participants' explicit consent. However, in the event of a medical emergency, pertinent information will be provided to attending physicians.

1. Quality assurance

To ensure the validity and integrity of the data, the majority of data will be collected directly by participant self-entry into computers, and we will create and use

checklists and standard operating procedure (SOP) manuals for data collection.

2. Relationship to other protocols

Data from participants who enroll in this protocol and that was collected through screening under protocol 06-DA-N415 will be shared and analyzed as part of this protocol. It is expected that behavioral and physiological data obtained from this protocol may be combined and/or compared with those obtained in other IRP protocols. Additionally, behavioral, physiological, and genetic data obtained from other IRP protocols may be combined and/or compared with those obtained in this protocol. This will allow us to better understand commonalities and differences in genotypes and phenotypes across different drug-using cohorts and healthy controls.

3. Data-sharing description

We share information with researchers outside the NIH in two ways. Most commonly, we have specific partnerships with other researchers. Also, we may put data into one or more scientific databases, where it is stored along with information from other studies. Researchers can then study the information combined from many studies to learn even more about health and disease.

We will share some protocol data with our scientific research partners inside or outside the NIH. Research partners outside the NIH sign an agreement with the NIH to share data. This agreement indicates the type of data that can be shared and what can be done with those data.

Some health information collected under this protocol may be placed into one or more scientific databases after it has been stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. A researcher who wants to study the information must apply to the database and be approved. Researchers with an approved study may be able to see and use the data from this protocol, along with that from many other studies. We do not expect any direct benefits for participants resulting from in the use of protocol data and information, though new discoveries that may help other people could occur. The Principal Investigator is open to answering any questions about how this data may be used.

Participants may stop participating in this study at any time. They may subsequently decide to withdraw permission for the use of their individual data, specimens and health information for additional or future research at any time. If they choose, we will destroy their data. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

4. Technology transfer

There are no Technology Transfer agreements needed for this study.

S. Compensation

Volunteers will be compensated for time and research-related inconveniences. All participants will be offered at the experimenters' expense either a taxi ride to and from the laboratory or payment for public transportation fares for all sessions involving drinking an experimental beverage. For public transportation fare payments, we will request receipts from participants documenting their fares and pay participants for the indicated amounts. Participants may, however, be using longer-term or multi-ride electronic pass systems (e.g., monthly unlimited ride cards) that do not provide ride-by-ride tickets or receipts with ride-by-ride pricing information. If participants do not possess individual receipts, we will provide payments to cover the cost of a 1-day pass or 1 round trip fare on each public transportation system used by the participant. An experimenter will establish the transportation systems used in discussion with participants about their routes, verified by transportation schedules, maps, and/or route planners showing the connections between participants' point of origin and the BRC. Transportation by taxi and public transportation payments may be combined to provide rides by taxi to/from public transportation service locations (e.g., train stations).

Amount of compensation (hourly rate, inconvenience units and maximum for study):

1. Session 1: 5 hours, compensated at $20/hour, for a total of $100.00
2. Sessions 2-5: 6 . 0 hours, compensated at $20/hour, for a total of $120.00 per session
3. Session 6: 8.5 hours, compensated at $20/hour, for a total of $170.00
4. Compensation for GMA data collection: $80.00 for answering ≥ 82.0% of random prompts, $100.00 for return of the smartphone in working condition
5. Follow-up contact by telephone: 1 hour, compensated at $20/hour, for a total of $20.00
6. If a participants' first cue script development session does not produce appropriate material (described above), he/she will be asked revise or replace the material either by telephone contact or by returning to the laboratory on a separate day. This will take ≤ 1hour, and participants will be compensated $20.00 for doing so (not included in total compensation amount below).
7. If a blood draw for any visit is unsuccessful due to technical, processing, or laboratory error, a participant may be asked to return on a separate day for repeat draw and will be compensated $20 (not included in total compensation amount below).

The total amount of compensation if the participant completes all experimental events is $950.00. The total maximum compensation does not include compensation for imagery script revision or repeat blood draw if needed.

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