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Reward, Relief and Habit Drinking: Initial Validation of a Brief Assessment Tool

Erica N. Grodin^{1,2}, Spencer Bujarski¹, Alexandra Venegas¹,
Wave-Ananda Baskerville¹, Steven J. Nieto¹, J. David Jentsch³,
and Lara A. Ray^{1,2,*}

¹Department of Psychology, University of California 1285 Franz Hall, Box 951563 Los Angeles, CA 90095, ²Department of Psychiatry and Biobehavioral Sciences University of California 760 Westwood Plaza Los Angeles, CA 90095, and ³Department of Psychology Binghamton University State University of New York PO Box 6000 Binghamton NY 13902

*Corresponding author: Psychology Department, University of California, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, USA. Tel: +310-794-5383; Fax: +310-206-5895; E-mail: lararay@psych.ucla.edu

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Abstract

Aims: Alcohol use disorder is highly heterogeneous. One approach to understanding this heterogeneity is the identification of drinker subtypes. A candidate classification consists of reward and relief subtypes. The current study examines a novel self-report measure of reward, relief, and habit drinking for its clinical correlates and subjective response (SR) to alcohol administration.

Methods: Non-treatment-seeking heavy drinkers ($n = 140$) completed the brief reward, relief, habit drinking scale (RRHDS). A subset of this sample ($n = 67$) completed an intravenous alcohol administration. Individuals were classified into drinker subtypes. A crowdsourced sample of heavy drinkers ($n = 187$) completed the RRHDS and a validated reward relief drinking scale to compare drinking classification results.

Results: The majority of the sample was classified as reward drinkers ($n = 100$), with fewer classified as relief ($n = 19$) and habit ($n = 21$) drinkers. Relief and habit drinkers reported greater tonic alcohol craving compared to reward drinkers. Reward drinkers endorsed drinking for enhancement, while relief drinkers endorsed drinking for coping. Regarding the alcohol administration, the groups differed in negative mood, such that relief/habit drinkers reported a decrease in negative mood during alcohol administration, compared to reward drinkers. The follow-up crowdsourcing study found a 62% agreement in reward drinker classification between measures and replicated the tonic craving findings.

Conclusions: Our findings suggest that reward drinkers are dissociable from relief/habit drinkers using the brief measure. However, relief and habit drinkers were not successfully differentiated, which suggests that these constructs may overlap phenotypically. Notably, measures of dysphoric mood were better at detecting group differences than measures capturing alcohol's rewarding effects.

INTRODUCTION

Alcohol use disorder (AUD) is a heterogeneous disorder, and for many years, the field has attempted to identify subgroups within AUD. Early efforts used data primarily derived from treatment-seeking populations to cluster individuals with AUD into subgroups based on several

criteria. Jellinek (1960) characterized five subtypes of problematic alcohol drinking based on etiological considerations, progression of alcohol use and resulting consequences of alcohol consumption. Cloninger *et al.* (1981) recommended the Type 1 versus Type 2 dichotomy based on age of onset of alcohol problems and personality

traits. Babor *et al.* (1992) also proposed two types of drinkers, Type A and Type B, who can primarily be distinguished based on age onset of alcohol problems, number of childhood risk factors, sex, socioeconomic status, psychological dysfunction, polysubstance use, chronic treatment history, familial history of alcoholism and life stress. Lesch and Walter (1996) characterized four subtypes based on biological, psychological and sociological dysfunction. More recently, Moss *et al.* (2007) used national substance abuse survey data from the 2001 to 2002 National Epidemiological Survey on Alcohol and Related Conditions (NESARC-II) to distinguish between five clusters of alcohol dependency based on age of onset of alcohol dependency, familial alcoholism, antisocial personality traits, endorsement of DSM-IV alcohol abuse criteria and comorbid psychiatric and substance use disorders. Although these proposed typologies enhanced our understanding of the various facets of AUD, there is still a lack of consensus about which approach can best advance the field (Leggio *et al.*, 2009).

Broadly speaking, the goal of classifying subgroups of patients with AUD is in the interest of providing more effective treatments that are tailored to common clinical features and putative pathophysiology. As such, attempts have been made to match behavioral treatments with specific alcohol drinking profiles. For example, using Babor's classification method, patients classified as Type A were shown to have better outcomes after group psychotherapy but do worse with coping skills training. Conversely, patients classified as Type B had better outcomes with coping skills training yet worse ones with interactional group therapy (Litt *et al.*, 1992). However, the lack of knowledge regarding other contributing factors to AUD may have led to the failure of large randomized clinical trials (i.e. Project MATCH) to target interventions to specific subgroups of alcohol-dependent patients (Project MATCH Research Group, 1997).

Recent efforts to identify discrete subgroups of patients with AUD have been informed by neurobiological models. Specifically, these neurobiological models of addiction have identified unique neural substrates underlying reward, relief and habit pathways. The allostatic model of addiction posits a heuristic framework that involves three stages of addiction: binge/intoxication, withdrawal/negative affect and preoccupation/intoxication stages (Koob and Le, 1997; Koob and Volkow, 2010; Koob, 2013). Initial alcohol use is characterized by positive reinforcement and impulsivity, such that alcohol's rewarding properties increase the likelihood of continued alcohol seeking and consumption (Wise, 1987). These initial features are mediated by both the dopaminergic and opioidergic activity within the ventral striatum (Volkow *et al.*, 2003; Gilman *et al.*, 2008; Mitchell *et al.*, 2012). In a subset of drinkers, repeated cycles of intoxication and withdrawal shift motivation to consume alcohol from positive reinforcement to negative reinforcement, wherein individuals drink alcohol to alleviate negative emotional states (Koob and Le Moal, 2005). The emergence of negative emotional states is mediated by neuroadaptations to stress systems in the extended amygdala (Koob and Kreek, 2007; Koob, 2008). Additionally, concurrent decreases in alcohol reward are associated with blunted dopaminergic activity in the ventral striatum (Koob and Bloom, 1988; Volkow *et al.*, 2007). Although the rewarding effects of alcohol diminish, alcohol-associated stimuli develop incentive-saliency via dopaminergic and glutamatergic signaling in the dorsal striatum, contributing to automaticity and habit learning (Robinson and Berridge, 1993; George and Koob, 2017). Over time, chronic alcohol consumption decreases executive functioning regulated by frontal lobe areas (Oscar-Berman and Marinković, 2007), leading to an overactive "Go" system that

drives craving and habits, and an underactive "Stop" system that inhibits these behaviors (Bechara *et al.*, 1999; Lobo and Nestler, 2011; Volkow and Morales, 2015; George and Koob, 2017). Taken together, compulsive alcohol drinking is the result of combined neuroadaptations in reward, stress, habit formation and executive function circuitry.

As with early efforts to classify AUD patients, neuroscience-informed clinical groupings are meant to inform treatment and personalize clinical care. Given that the initial stages of the addiction cycle are motivated by alcohol's ability to indirectly increase dopamine levels in brain reward pathways, it is reasonable to assume that a pharmacological treatment that diminishes alcohol reward would be a viable therapeutic option for AUD. Naltrexone, a mu opioid antagonist, blunts alcohol-induced dopamine release but is only modestly effective in treating AUD (O'Malley *et al.*, 1992; Volpicelli *et al.*, 1992; Bouza *et al.*, 2004). However, clinical responses to naltrexone are highly variable, which may be due, at least in part, to factors such as family history of alcoholism (King *et al.*, 1997; Rubio *et al.*, 2005; Krishnan-Sarin *et al.*, 2007) and variation in the OPRM1 gene (Oslin *et al.*, 2003; Ray and Hutchison, 2007; Anton *et al.*, 2008). Two recent studies have found that classifying individuals into reward and relief drinking subtypes impacts the effectiveness of pharmacological treatments for AUD (Roos *et al.*, 2017; Mann *et al.*, 2018). In the first study, individuals in the COMBINE study who were classified as high relief drinkers, defined as those who drink alcohol mainly to relieve negative affect, had better drinking outcomes when treated with the glutamatergic modulator acamprosate compared to placebo. There was no significant effect found for reward drinkers and naltrexone in improving drinking outcomes (Roos *et al.*, 2017). In contrast, Mann and colleagues utilized the PREDICT study sample and found that reward drinkers, defined as those who drink alcohol for its pleasurable/euphoric effects, benefited more from naltrexone in reducing heavy drinking compared to those treated with acamprosate (Mann *et al.*, 2018). The discrepancy between these two findings may be due to the differing protocols of the COMBINE and PREDICT studies, particularly in the duration of pre-randomization abstinence. In the COMBINE study, the majority of participants were abstinent for only a short period prior to study randomization, whereas in the PREDICT study, participants underwent a full medication detoxification protocol. These differences likely impacted glutamatergic neurotransmission, which has been hypothesized as acamprosate's mechanism of action (Holmes *et al.*, 2013; Mann *et al.*, 2018) and thereby limited the ability of Mann and colleagues to identify a relationship between relief drinking and acamprosate. Despite the contrasting medication findings, both studies reliably identified reward and relief AUD subtypes, which also replicates earlier work which classified reward and relief craving subtypes and identified specific clinical characteristics subserving them (Glockner-Rist *et al.*, 2013). However, for these clinical groups to be reliably identified, clinical instruments must be developed and validated. In the current context of healthcare, brief measures that can be easily administered are most likely to be adopted and to impact practice. To that end, this study examines a novel self-report measure of reward, relief and habit drinking developed a priori by our group and administered in a human laboratory study of non-treatment seeking problem drinkers (Bujarski *et al.*, 2018). In this report, we examine (a) the test-retest reliability of the new measure, (b) the clinical correlates of the three drinking subtypes and (c) patterns of subjective response (SR) to alcohol and self-administration of alcohol across the drinker subtypes. A follow-up study comprised of

a crowdsourcing-based survey was undertaken to explore the agreement between our approach to identifying reward/relief drinkers compared to the approach undertaken by Mann *et al.* (2018).

METHOD

Participants

This study was approved by the Institutional Review Board at University of California, Los Angeles (UCLA). Non-treatment-seeking heavy drinkers were recruited between April 2015 and August 2016 from the Los Angeles community through fliers and online advertisements. Initial eligibility screening was conducted via online and telephone surveys and was followed by an in-person screening session. After providing written informed consent, participants were breathalyzed, provided urine for toxicology screening and completed a battery of self-report questionnaires and interviews. All participants were required to have a breath alcohol content (BrAC) of 0 mg% and to test negative on a urine drug screen for all drugs (except cannabis). Female participants were required to test negative on a urine pregnancy test. A physical examination was performed to ensure medical eligibility. Full inclusion and exclusion criteria for the experimental alcohol administration procedures have been published elsewhere (Bujarski *et al.*, 2018). Participants were between the ages of 21 and 45 and were required to report drinking at (or above) heavy drinking guidelines (i.e. 14+ drinks/week for men or 7+ drinks/week for women).

Intravenous (IV) alcohol challenge and self-administration

Alcohol administration was conducted at the UCLA Clinical and Translational Research Center (CTRC). Detailed methodology can be found in (Bujarski *et al.*, 2018). Briefly, at intake, vitals, height and weight were measured and IV lines were placed by a registered nurse. Participants then completed baseline assessments. The alcohol infusion paradigm lasted 180 minutes. Study staff remained in the room to monitor the infusion, breathalyze the participant, take vital signs, administer questionnaires and answer questions but did not significantly engage with participants otherwise. To enable precise control over BrAC and to dissociate biobehavioral responses to alcohol from responses to cues, alcohol was administered IV (6% ethanol v/v in saline) using a physiologically based pharmacokinetic model implemented in the Computerized Alcohol Infusion System (CAIS (Plawecki *et al.*, 2008; Zimmermann *et al.*, 2008, 2013). During the alcohol challenge, participants were administered alcohol designed to reach target BrACs of 20, 40 and 60 mg%, each over 15 minutes. BrACs were clamped at each target level while participants completed questionnaires (~5 minutes). Participants began the self-administration paradigm immediately after reaching the 60 mg% time point. Participants could exert effort (by pressing an electronic button) to obtain additional “drinks” through the CAIS system, according to a log-linear progressive ratio schedule. Ratio requirements ranged from 20 responses (1st completion) to 3139 responses (20th completion). Each “drink” increased BrAC by 7.5 mg% over 2.5 minutes, followed by a descent of -1 mg%/min (Zimmermann *et al.*, 2008). A maximum BrAC safety limit was set at 120 mg%. If an infusion would exceed this limit, the response button was temporarily inactivated. Except for the first “drink”, participants were given no instruction with respect to their self-administration. After 180 minutes, the infusion ended and participants were instructed to wait until discharge. To ensure all participants were safe to discharge and to

disincentivize low-levels of self-administration for early discharge, all participants were informed that they would remain at the CTRC for at least 4 additional hours following alcohol self-administration regardless of their self-administration profile. Discharge occurred when participant BrAC fell below 40 mg% or 0 mg% if they were driving. Participants were permitted to leave earlier than the 4 additional hour time requirement if they reached discharge BrAC levels early. However, participants were not informed of the discharge options until after the self-administration protocol was complete to further reduce the confound of low-levels of self-administration due to a desired earlier discharge time.

Measures

The UCLA reward, relief, habit drinking scale (UCLA RRHDS). Reward, relief and habit drinking sub-types were assessed using a novel four-item self-report questionnaire (see Appendix 1). The first question asked participants to identify their primary reason for drinking alcohol (i.e. reward, relief or habit). The remaining questions asked participants to rate on a 1–7 scale how often they drank alcohol for its rewarding effects (i.e. to feel good), relief effects (i.e. reducing negative feelings) and out of habit (i.e. without thinking). Participants were classified into reward, relief and habit drinking sub-types based on their answers to questions 2–4, in which they rated how often they drank because of reward, relief or habit. Question 1 was used as a tie-breaker in cases where participants rated more than 1 dimension as the highest. The use of the tie-breaker question was required in 22% of the screening sample ($n = 31$) and 18% of the follow-up crowdsourcing sample ($n = 33$) to classify participants. Overall, there was a high level of consistency (93%) between participants’ self-identification of drinking type (i.e. question 1) and their highest frequency motive ratings (i.e. questions 2–4). This measure was assessed at the baseline visit and again at the eligibility physical visit. As the relief and habit drinking subtypes were largely indistinguishable in the larger screening sample (see Results) and previous research in this domain has only characterized reward and relief subtypes (Roos *et al.*, 2017; Mann *et al.*, 2018), the relief and habit subgroups were combined for analyses of the alcohol challenge experiment.

AUD severity measures. The Structured Clinical Interview for DSM-5 (SCID; adapted from (First *et al.*, 2015)) assessed for lifetime and current AUD. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) assessed for the alcohol withdrawal severity (Sullivan *et al.*, 1989). A 30-day timeline followback (TLFB) assessed drinking quantity and frequency (Sobell *et al.*, 1988). Participants also completed the alcohol dependency scale (ADS (Skinner and Allen, 1982)), the Alcohol Use Disorders Identification Test (AUDIT (Allen *et al.*, 1997)), the Drinkers Inventory of Consequences (DrINC-2r (Miller *et al.*, 1995)), the penn alcohol craving scale (PACS (Flannery *et al.*, 1999)), the obsessive compulsive drinking scale (OCDS (Anton, 2000)) and the Drinking Motives Questionnaire-Revised (Cooper, 1994).

Individual difference measures. Cigarette use and marijuana use were assessed using the TLFB (Sobell *et al.*, 1988). The Fagerstrom Test for Nicotine Dependence (FTND) assessed for nicotine dependence (Heatherton *et al.*, 1991). Depressive symptomatology was assessed via the beck depression inventory-II (BDI-II (Beck *et al.*, 1996)). Anxiety symptomatology was assessed using the state-trait anxiety

inventory (STAI (Spielberger, 2010)) and the Beck anxiety inventory (BAI (Beck *et al.*, 1988)).

SR measures. Based on previous factor analytic work, SR was assessed along four dimensions: stimulation/hedonia (stimulation), negative affect, sedation/motor intoxication (sedation) and craving (Bujarski *et al.*, 2015). Participants completed SR assessments at baseline, 20, 40 and 60 mg% time points during the challenge. Stimulation included the biphasic alcohol effects scale stimulation subscale (BAES (Martin *et al.*, 1993)) and the profile of mood states positive mood and vigor subscales (POMS (McNair *et al.*, 1992)). Sedation included the BAES sedation subscale and select items from the subjective high assessment scale (SHAS (Schuckit, 1984)); specifically items assessing feelings of floating, clumsiness and drunk were assessed (questions #11, 3, and 6 from the SHAS). Negative Affect included the POMS Negative Mood and Tension subscales. Craving was measured by the alcohol urge questionnaire (AUQ (Bohn *et al.*, 1995)). To incorporate multiple scales per SR domain, and equally weight scales with discrepant ranges, combined scores were computed within each SR domain by first Z-score transforming each measure across the entire challenge and then summing these scaled scores. These methods are consistent with our previous report from this study (Bujarski *et al.*, 2018).

Data analysis

All analyses were conducted in SPSS v. 24. Test-retest analyses were conducted on the reward, relief and habit measure using the sample that completed both the screening and eligibility physical visits ($n = 73$). The analysis of clinical characteristics of drinker subtypes used the entire screening sample ($n = 140$). Univariate analyses of variance (ANOVAs) were conducted to evaluate group differences. Post-hoc Tukey *t*-tests were conducted to evaluate the direction of differences between the reward, relief and habit groups. The analyses of SR and self-administration behavior only used the sample of participants who completed the alcohol infusion experimental session ($n = 67$). Repeated measures ANOVAs were conducted to identify group differences in SR to alcohol across four domains: stimulation, sedation, negative affect and craving. For each test, we were interested in the main effect of group (reward drinkers vs. relief/habit drinkers), the main effect of trial (i.e. baseline, 20, 40, and 60% time-points) and the group \times trial interaction. A series of analyses were conducted to evaluate the effect of drinking group (reward drinkers vs. relief/habit drinkers) on self-administration behavior. Regarding the self-administration outcomes, four domains were evaluated: total number of drinks self-administered, total number of button presses made, progressive ratio breakpoint, defined as the number of button presses in the last completed progressive ratio set, and maximum BrAC reached during the self-administration period. The number of button presses and progressive ratio breakpoint were log-transformed, as button-pressing requirements were generated from an exponential function and were not normally distributed. The self-administration domains were analyzed using *t*-tests. Given that this is an initial study designed to evaluate the newly developed measure, no *P*-value correction was implemented to account for multiple comparisons.

Follow-up study

In order to compare the UCLA RRHDS approach to identifying reward and relief drinkers to the approach taken by Mann *et al.*

(2018), we conducted an online survey using a crowdsourcing platform Amazon Mechanical Turk (MTurk). In doing so, we followed methodological recommendations by Strickland and Stoops (2019) and approached this survey as a complement to the human laboratory methods reported in this manuscript (Strickland and Stoops, 2018, 2019). The first step consisted of screening a large unselected sample of MTurk users ($n = 1000$) for their alcohol use based on the AUDIT. We then invited back individuals who scored ≥ 8 on the AUDIT, indicating a hazardous drinking pattern (Reinert and Allen, 2007) to complete a second series of questionnaires. The follow-up survey was comprised of the alcohol dependence scale (ADS), the UCLA RRHDS and the inventory of drinking situations ((IDS); (Davis *et al.*, 1987)), which was the primary instrument used by Mann *et al.* (2018) to classify reward/relief drinkers. As with the main study, the PACS and OCDS measures were also administered. Cross-tabulation analyses examined the agreement between the two methods in identifying reward drinkers. *T*-tests also compared reward/relief drinkers on the PACS, OCDS and ADS to replicate findings from the in-person assessment study.

RESULTS

Test-retest reliability of the UCLA RRHDS

For these analyses, a subset of individuals ($n = 73$) who completed the initial assessment were again given the UCLA RRHDS at the time of the physical exam required for medical clearance to the alcohol administration component of the study. On average, there were 10.83 ± 9.02 days between the completion of the reward, relief, habit measure conducted at the screening and physical exam (range = 2–48 days). First, we analyzed the test-retest reliability of the overall group identification. There was modest reliability of overall group identification; $\varphi_c = 0.53$, $P < 0.001$. We then assessed the test-retest reliability of each drinker sub-type. The reward drinker sub-type had strong reliability, 93% of individuals ($n = 50/54$) were classified as a reward drinker at baseline and at the physical. The relief and habit drinker sub-types were less reliable, 60% ($n = 6/10$) were classified as relief drinkers at both time-points, while only 33% ($n = 3/9$) were classified as habit drinkers at both time-points. Overall, 14 individuals were classified into different drinker sub-types at both time-points. Of this group, 12% ($n = 9$) were classified as relief or habit at the baseline visit and reward at the physical visit. The remaining individuals were classified as the following: reward at baseline, relief at physical ($n = 1$); reward at baseline, habit at physical ($n = 3$) and relief at baseline, habit at physical ($n = 1$). These results suggest that the reward-drinking subtype showed initial evidence of strong reliability, whereas the relief and habit drinking subtypes were not nearly as reliable, albeit with limited sample sizes.

Clinical correlates of drinker type

For these analyses, the full screening sample of 140 participants was included, because clinical characteristics were available on the full sample, whereas only a subset ($n = 67$) completed the alcohol administration procedures. The majority of the screening sample was classified as reward drinkers ($n = 100$; 71%), while 19 participants (14%) were classified as relief drinkers and 21 participants (15%) were classified as habit drinkers. The three groups did not differ on demographic characteristics (age, sex, cigarette smoking or cannabis use). Relief and habit drinkers had higher depressive symptomology and trait anxiety than reward drinkers. The groups did not differ on AUD severity, recent drinking behavior or dependence severity. Relief

Table 1. Clinical characteristics of reward, relief and habit drinkers

	Reward drinkers (<i>n</i> = 100)	Relief drinkers (<i>n</i> = 19)	Habit drinkers (<i>n</i> = 21)	Statistic	<i>P</i>	Effect size
Age	28.77 ± 6.50	30.42 ± 5.65	28.14 ± 5.20	<i>F</i> = 0.75	0.50	$\eta_p^2 = 0.01$
Sex (M/F)	51/49 (51/49%)	10/9 (53/47%)	9/12 (43/57%)	$\chi^2 = 0.52$	0.77	$\varphi = 0.06$
Cigarette smoker	43 (43%)	12 (63%)	9 (43%)	$\chi^2 = 2.70$	0.26	$\varphi = 0.14$
THC+	20 (20%)	2 (11%)	0 (0%)	$\chi^2 = 5.69$	0.06	$\varphi = 0.20$
BDI-II ^{a, b}	7.09 ± 7.32	11.34 ± 7.90	11.29 ± 11.89	<i>F</i> = 3.77	0.03	$\eta_p^2 = 0.05$
STAI Trait ^{a, b}	37.12 ± 9.28	47.42 ± 7.96	41.76 ± 10.01	<i>F</i> = 10.53	<0.001	$\eta_p^2 = 0.13$
STAI state	53.32 ± 2.96	52.53 ± 4.18	52.67 ± 3.75	<i>F</i> = 0.70	0.50	$\eta_p^2 = 0.01$
BAI ^a	4.83 ± 5.00	10.05 ± 9.74	7.52 ± 7/47	<i>F</i> = 6.42	0.002	$\eta_p^2 = 0.09$
AUD severity (none/mild/moderate/severe)	51/21/19/9	8/3/6/2	7/6/4/4	$\chi^2 = 4.95$	0.55	$\varphi = 0.19$
Total drinking days (TLFB)	16.25 ± 6.47	16.84 ± 6.44	19.05 ± 7.49	<i>F</i> = 1.55	0.22	$\eta_p^2 = 0.02$
Drinks per day (TLFB)	2.94 ± 2.13	2.83 ± 1.53	3.39 ± 2.70	<i>F</i> = 0.44	0.65	$\eta_p^2 = 0.01$
Drinks per week (TLFB)	20.56 ± 14.92	19.79 ± 10.72	23.70 ± 18.91	<i>F</i> = 0.44	0.65	$\eta_p^2 = 0.01$
Drinks per drinking day (TLFB)	5.41 ± 2.94	5.35 ± 2.94	5.01 ± 2.45	<i>F</i> = 0.17	0.85	$\eta_p^2 = 0.002$
Binge days (TLFB)	8.16 ± 6.66	8.79 ± 7.39	8.10 ± 7.30	<i>F</i> = 0.07	0.93	$\eta_p^2 = 0.001$
CIWA-Ar ^b	0.71 ± 1.36	1.16 ± 1.74	2.14 ± 3.09	<i>F</i> = 5.81	0.004	$\eta_p^2 = 0.08$
ADS	10.33 ± 5.56	12.37 ± 5.05	11.81 ± 5.87	<i>F</i> = 1.46	0.24	$\eta_p^2 = 0.02$
AUDIT	12.66 ± 6.13	14.95 ± 6.88	13.52 ± 7.06	<i>F</i> = 1.08	0.34	$\eta_p^2 = 0.02$
OCDS ^{a, b}	6.97 ± 4.22	9.95 ± 5.39	9.33 ± 5.48	<i>F</i> = 4.87	0.009	$\eta_p^2 = 0.07$
PACS ^a	7.59 ± 5.43	10.89 ± 5.59	9.95 ± 7.08	<i>F</i> = 3.58	0.03	$\eta_p^2 = 0.05$
Drinking motives—enhancement ^{a, b}	16.00 ± 4.49	13.58 ± 4.52	13.71 ± 4.65	<i>F</i> = 3.87	0.02	$\eta_p^2 = 0.05$
Drinking motives—social	16.69 ± 4.71	15.74 ± 5.24	15.67 ± 5.40	<i>F</i> = 0.59	0.56	$\eta_p^2 = 0.01$
Drinking motives—conform	7.31 ± 2.85	6.84 ± 2.46	8.48 ± 4.54	<i>F</i> = 1.61	0.20	$\eta_p^2 = 0.02$
Drinking motives—coping ^{a, c}	10.11 ± 4.08	15.37 ± 3.39	11.57 ± 5.21	<i>F</i> = 12.80	<0.001	$\eta_p^2 = 0.16$

^aReward and relief groups differ, *P* < 0.05.

^bReward and habit groups differ, *P* < 0.05.

^cRelief and habit groups differ, *P* < 0.05.

Characteristics that significantly differ between groups are displayed in bold type.

and habit drinkers had greater scores on alcohol craving measures (PACS and OCDS) than reward drinkers. Habit drinkers had significantly greater alcohol withdrawal symptoms than reward drinkers although all groups reported subclinical levels of withdrawal. The groups also differed on drinking motives. Reward drinkers were more likely to endorse drinking for enhancement motives, while relief drinkers were more likely to endorse drinking for coping motives. See Table 1 for complete results.

SR to alcohol by drinker type

For these analyses, only the subset of individuals who completed the experimental session (Bujarski *et al.*, 2018) were included (*n* = 67) and the relief and habit subgroups were combined. Forty-eight individuals (72%) were classified as reward drinkers, and 19 individuals (28%) were classified as relief/habit drinkers.

As previously reported (Bujarski *et al.*, 2018), across the sample, alcohol administration significantly increased ratings of stimulation (*F*(3,63) = 4.99, *P* = 0.002, $\eta_p^2 = 0.16$), sedation (*F*(3,63) = 14.21, *P* < 0.001, $\eta_p^2 = 0.40$) and craving for alcohol (*F*(3,63) = 10.84, *P* < 0.001, $\eta_p^2 = 0.34$), while it decreased ratings of negative mood (*F*(3,63) = 8.42, *P* < 0.001, $\eta_p^2 = 0.29$). Across the rising BrAC levels, there was a trend towards a main effect of group on sedation (*F*(1,65) = 3.65, *P* = 0.06, $\eta_p^2 = 0.05$), such that relief/habit drinkers reported greater levels of sedation than reward drinkers (Fig. 1b). There was also a significant interaction between group (reward drinker vs. relief/habit drinker) and rising BrAC (baseline, 20, 40,

and 60% target BrAC) for ratings of negative affect (*F*(3,63) = 2.70, *P* = 0.05, $\eta_p^2 = 0.11$), such that relief/habit drinkers reported high levels of negative affect at baseline and these sharply decreased upon alcohol administration (i.e. decrease from baseline to BrAC at 0.20 in the relief/habit group) (Fig. 1c). There was no significant main effect of group, nor a group × trial interaction, for ratings of stimulation or alcohol craving (*P*'s > 0.10; see Fig. 1).

Self-administration of alcohol by drinker type

For these analyses, only the subset of individuals included in the experimental session (Bujarski *et al.*, 2018) were included (*n* = 67). Four measures of self-administration were evaluated: number of drinks self-administered, total number of button presses, breakpoint and maximum BrAC reached. The reward and relief/habit drinking groups did not differ on any measure of self-administration (all *P*'s > 0.30; see Table 2).

Comparing approaches to identifying reward/relief drinkers

From the initial crowdsourcing sample (*n* = 1,000) screened for drinking levels, a total of 187 (*n* = 125 male, 67%) heavy drinkers (i.e. AUDIT ≥ 8) of an average age of 30.9 ± 7.98 completed the entire follow-up survey in MTurk. The sample reported drinking an average of 19 ± 11.18 standard drinks in the past week and had an average ADS score of 17.70 ± 9.27. Based on the IDS criteria for identifying reward drinkers, 131 (64.53%) of the sample was classified as reward

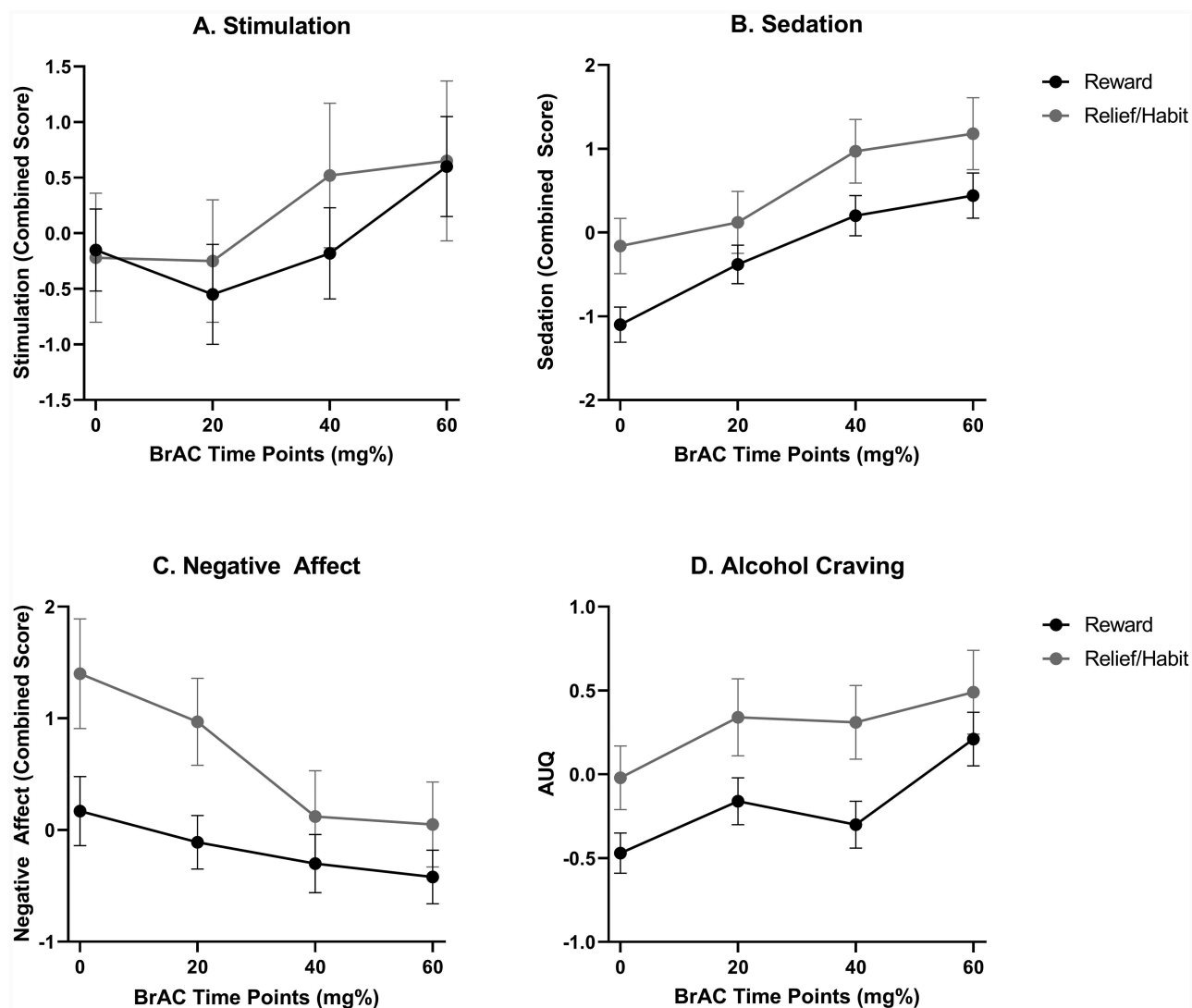


Fig. 1. SR to alcohol during the alcohol challenge, by group. (A) The stimulation outcome combined measures from the BAES stimulation, POMS Vigor and POMS positive mood subscales. There were no group differences in stimulation over the challenge. (B) The sedation outcome combined measures from the BAES Sedation and SHAS scales. There was a trend towards increased sedation in the relief/habit group compared to the reward group across the challenge. (C) The negative affect outcome combined measures from the POMS tension and negative mood subscales. There was an interaction between group and BrAC on negative affect, such that the reward/relief drinkers reported a large decrease in negative affect following alcohol administration, compared to reward drinkers. (D) Alcohol craving was measured using the AUC. There were no group differences on alcohol craving over the challenge.

Table 2. Alcohol self-administration by drinking type

	Reward ($n = 48$)	Relief + habit ($n = 19$)	Statistic	P	Effect size (Cohen's d)
Number of drinks	11.25 ± 4.84	9.84 ± 5.21	$t = 1.05$	0.30	0.28
Maximum BrAC	97.70 ± 21.09	91.79 ± 22.22	$t = 1.02$	0.31	0.27
Number of button presses (log transformed)	3.10 ± 0.82	2.92 ± 0.86	$t = 0.79$	0.63	0.21
Breakpoint (log transformed)	2.58 ± 0.56	2.42 ± 0.60	$t = 1.00$	0.66	0.28

drinker and the remaining 72 (35.47%) were relief drinkers. Based on the UCLA RRHDS, 142 (69.95%) individuals were classified as reward drinkers and 61 (30.05%) were relief drinkers. Habit drinkers identified on the UCLA RRHDS were excluded from these analyses given that habit was not assessed in the IDS. In order to examine the agreement between UCLA RRHDS and IDS, we conducted a cross-tabulation procedure and found that 126 (62.1%) drinkers

were identified as reward drinkers on both methods, whereas for the remaining 77 (38.9%) of drinkers, the UCLA RRHDS and IDS methods resulted in non-concordant classification.

Comparison between reward ($n = 119$) and relief ($n = 68$) drinkers identified by the UCLA RRHDS on the PACS, OCDS and ADS was undertaken to replicate the in-person assessment study. Results revealed group differences, such that relief drinkers

reported higher craving than reward drinkers on the OCDS [relief mean = 24.04 ± 7.54 ; reward mean = 16.54 ± 9.06], $t(185) = 5.78$, $P < 0.0001$. The same pattern emerged for the PACS [relief mean = 13.19 ± 4.88 ; reward mean = 9.93 ± 4.59], $t(185) = 4.56$, $P < 0.0001$. Unlike the main study, ADS scores were higher among relief drinkers compared to reward drinkers [relief mean = 20.07 ± 8.55 ; reward mean = 15.61 ± 9.42], $t(184) = 3.22$, $P < 0.01$.

DISCUSSION

This study sought to develop a brief measure designed to characterize drinking motivations into one of three primary categories, namely reward, relief and habit. To do so, clinical variables and alcohol administration variables were considered in groups comprised of reward, relief and habit drinkers. Regarding clinical variables, our findings suggest that, in this sample, relief and habit were not dissociable groups, yet both differed from the reward drinking group. Specifically, relief and habit drinkers reported higher levels of anxiety and depressive symptoms, higher levels of tonic craving and higher endorsement of drinking for coping motives than reward drinkers. Conversely, reward drinkers reported higher levels of drinking for enhancement motives, compared to relief/habit drinkers. Additionally, habit drinkers had greater withdrawal symptoms than reward drinkers. Our mood-related findings replicate earlier work characterizing reward and relief drinkers (Mann *et al.*, 2018), such that relief/habit drinkers report higher depressive symptomatology and higher trait anxiety. In further support of the current drinking classification, the groups differed on their self-reported drinking motives, such that reward drinkers endorsed drinking for enhancement (increase positive affect) while the relief group endorsed drinking to cope (decrease negative affect). In individuals with high coping motivation, negative affect induction increases automatic alcohol-approach associations, compared to individuals with low coping motivation (Ostafin and Brooks, 2011), which highlights the relief categorization of individuals with high coping motivation. Notably, however, the groups did not differ significantly on measures of alcohol use and AUD severity, suggesting that the distinction between reward and relief/habit drinkers represents a construct that is dissociable from AUD severity and drinking patterns. Importantly, the initial assessment of test-retest reliability suggested that only the reward drinker subtype benefited from strong reliability, whereas the relief and habit subtypes were clearly less reliable.

Regarding the experimental portion of the study, there were noteworthy group differences with regard to SRs to alcohol. Specifically, relief/habit drinkers reported a great decrease in negative mood during alcohol administration, as compared to reward drinkers. Moreover, there was a trend toward a main effect of drinker type on sedation, such that relief/habit drinkers reported higher sedation than reward drinkers. These effects were largely driven by baseline differences, suggesting that tonic levels of sedation may differentiate the two groups. Notably, the two groups did not differ on measures of self-administration during the self-administration phase of the task. This is somewhat consistent with our finding that the groups did not differ on clinical measures of AUD severity and alcohol use. Importantly, the self-administration phase of the task directly followed the alcohol challenge procedure, i.e. study participants had already received alcohol infusions up to a BrAC of 60 mg%. This methodology may have limited our ability to identify group differences in self-administration, as changes in negative mood and sedation had already occurred during the initial alcohol

exposure. Further, this initial alcohol exposure may have masked other group differences in self-administration that would be present if the paradigm was tested on individuals without a priming dose of alcohol. Overall, these results provide some support for the allostatic model (Koob and Le, 1997), as relief/habit drinkers appeared to be in the “withdrawal/negative affect” state prior to the administration of alcohol. However, we did not find experimental evidence to support the categorization of reward drinkers into the “binge/intoxication” state, i.e. there were no significant group differences on ratings of alcohol-induced stimulation throughout the challenge.

The clinical and experimental correlates of reward and relief/habit drinking may be used to facilitate a personalized medicine approach to AUD pharmacotherapy. In the current study, reward drinkers reported drinking to increase positive affect had lower levels of trait anxiety, depression symptomatology, withdrawal symptoms and less alcohol-induced sedation than relief drinkers. Thus, individuals classified as reward drinkers may respond better to pharmacotherapies targeting the positive rewarding effects of alcohol, such as naltrexone and nalmefene, which are both opioid antagonists. Indeed, in the PREDICT sample, reward drinkers who received naltrexone had a large reduction in the return to heavy drinking compared to those receiving placebo (Mann *et al.*, 2018). This approach has yet to be examined with nalmefene; however, given that nalmefene is structurally similar to naltrexone (Mason *et al.*, 1999), we would hypothesize that reward drinkers would show a positive response to nalmefene treatment on reductions in heavy drinking outcomes. In the current study, relief/habit drinkers reported drinking to reduce negative affect had significantly higher withdrawal symptoms, depressive symptoms and trait anxiety. Furthermore, the alcohol infusion resulted in a larger reduction in reports of negative affect in relief drinkers than reward drinkers. Therefore, relief/habit drinkers may respond better to medications designed to relieve the withdrawal and negative affect symptoms associated with chronic alcohol use, such as acamprosate and gabapentin. In the COMBINE study sample, high relief/moderate reward drinkers had better drinking outcomes when treated with acamprosate compared to placebo (Roos *et al.*, 2017). While the drinker subtype classification precision-medicine approach has not yet been applied to gabapentin, available evidence supports the potential use of this medication to treat relief/habit drinkers. Gabapentin, a GABA analog that acts on voltage-gated calcium channels (Hendrich *et al.*, 2008), has been shown to reduce alcohol-withdrawal symptoms (Myrick *et al.*, 2009). Furthermore, in individuals with high levels of alcohol withdrawal, such as was seen in relief/habit drinkers in the current study, treatment with gabapentin had higher percent days abstinent compared to placebo, whereas in individuals with low levels of alcohol withdrawal treatment with placebo produced better outcomes than treatment with gabapentin (Anton *et al.*, 2009). Finally, this drinking classification framework may be useful as novel medications are developed. For example, ibudilast, a neuroimmune modulator, has been shown to improve mood during alcohol and stress exposure, particularly in individuals who have higher depressive symptomatology (Ray *et al.*, 2017). These promising findings indicate that ibudilast may be more effective in relief/habit drinkers.

Notably, we were unable to differentiate relief and habit drinkers using the UCLA RRHDS. The role of habit in addiction has largely been studied with animal models (Vandaele and Janak, 2018). There has been significant interest in translating these preclinical findings into clinical substance use disorder populations. To that end, behavioral tasks have been developed to interrogate the construct of habit in substance using populations (Voon *et al.*, 2015; Ersche

et al., 2016; Luijten *et al.*, 2019) as well as its neural substrates (Sjoerds *et al.*, 2013; Sebold *et al.*, 2017; Grodin *et al.*, 2018). In a similar vein as the UCLA RRDHS instrument, a self-report questionnaire has recently been developed to capture habit-, reward- and fear-related motivations to drink (Piquet-Pessoa *et al.*, 2019). Habitual alcohol use was associated with a higher AUD severity, which corresponds to predictions from the addiction cycle model, where individuals with more severe AUD would have greater alcohol-induced neuroadaptations resulting in decreased executive control of goal-directed behavior. As we were unable to differentiate the relief and habit drinkers in the current study, it may be that a longer self-report measure or a behavioral task may be needed to fully capture habit drinkers and differentiate this group from relief drinkers.

Our measure of reward and relief/habit drinking patterns differs from previous work in several ways. The 30-item version of the Inventory of Drinking Situation (Annis *et al.*, 1987) used by Mann *et al.* (2018) categorizes reward and relief drinking profiles based on the frequency of *heavy drinking* in various *contexts* over the past year. In contrast, our four-item measure asks participants to identify their primary reason for drinking alcohol and how often they drink alcohol for reward, relief or out of habit. In order to directly examine how our measure relates to previous work, particularly that of Mann *et al.* (2018), we used a crowdsourcing approach to complement the present study and to identify heavy drinkers who could complete both assessments of reward/relief drinking as well as measures of craving and alcohol problems. Results indicated that the agreement (or reliability) between the two methods was 62%, which lies in the questionable range. This finding suggests only moderate overlap between the two approaches. Further, the crowdsourcing-based follow-up survey replicated the original finding that relief drinkers report greater tonic craving for alcohol while also suggesting that relief drinkers have higher ADS scores.

Taken together, our findings suggest that reward drinkers are dissociable from relief/habit drinkers using the brief measure developed by our group. However, relief and habit drinkers were not differentiated in our study, which suggests that these two constructs overlapped phenotypically, at least in this sample of non-treatment seeking heavy drinkers and individuals with AUD. In terms of group differences, clinical measures suggested that relief/habit drinkers experience more mood dysphoria, tonic craving and report drinking for coping while reward drinkers report drinking for enhancement. This supports the face-validity of the constructs, especially when no differences in AUD severity and alcohol use were observed. The experimental component of the study added to the dysphoria findings by suggesting that relief/habit drinkers were more likely to report sedation across the alcohol administration and to endorse greater decreases in negative mood as BrAC levels increased. It is notable that measures of dysphoric mood were better at detecting group differences in this study, than were measures capturing the rewarding and stimulant effects of alcohol.

These results should be considered in light of the study's strengths and limitations. Strengths include the combination of clinical and experimental variables, as well as an initial evaluation of test-retest reliability. Limitations include the relatively modest sample size, particularly in light of the disproportionate number of reward drinkers in this sample. The lack of strong reliability for the relief and habit subtypes may have been impacted by the relatively low numbers of drinkers identified in these categories, and large-scale studies of more diverse drinker groups are needed to fully evaluate this novel assessment tool. Further, about 20% of the sample in the initial

and follow-up studies required the use of a tie-breaker question (Question 1) to classify their drinker subtype, indicating that a sizeable minority of individuals endorsed drinking for reward, relief and/or habit equally. We recommend that future studies using the UCLA RRDHS expand the numerical range of the scale from 1–7 to 1–10 to allow for greater differentiation between drinker subtypes. Moreover, due to ethical considerations, this study only enrolled non-treatment-seeking individuals who were able to produce a 0 mg% BrAC reading at each study visit. These methodological limitations reduced our ability to recruit participants with moderate and severe AUD. Based on the addiction cycle model, we would hypothesize that individuals with moderate and severe AUD would be more likely to be classified as relief and habit drinkers; therefore, the lower enrollment of individuals with severe AUD may have limited our ability to identify relief and habit drinkers. Additionally, as this was a preliminary study of the reward relief measure, we did not include a correction for multiple comparisons. Therefore, the results in this study may include false positives and should be replicated in a larger sample. In conclusion, this study reports on a novel scale developed by our team to capture drinking subtype with an eye towards a brief and readily disseminable instrument that can inform treatment matching.

APPENDIX 1

UCLA RRDHS

- 1) Do you drink alcohol **primarily** because (please circle 1):
 1. It gives you a pleasant feeling (e.g. makes you feel good, excited, or confident)
 2. It reduces negative feelings (e.g. makes you feel less bad, sad, or nervous)
 3. It is a habit (e.g. without thinking about the effects of alcohol)
- 2) How often do you drink alcohol for the pleasant effects it has (e.g. makes you feel good, excited, or confident)?

Never	Half of the time	Always
1 ----- 2 ----- 3 ----- 4 ----- 5 ----- 6 ----- 7		
- 3) How often do you drink alcohol because it reduces negative feelings (e.g. makes you feel bad, sad, or nervous)?

Never	Half of the time	Always
1 ----- 2 ----- 3 ----- 4 ----- 5 ----- 6 ----- 7		
- 4) How often do you drink alcohol out of habit (e.g. without thinking about the effects of drinking)?

Never	Half of the time	Always
1 ----- 2 ----- 3 ----- 4 ----- 5 ----- 6 ----- 7		

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