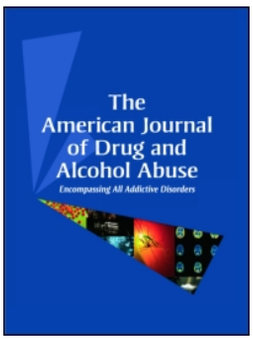

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ORIGINAL ARTICLE

Comparing alcohol cue-reactivity in treatment-seekers versus non-treatment-seekers with alcohol use disorder

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ABSTRACT

Background: Recent studies have examined the distinction between treatment-seekers and non-treatment-seekers with alcohol use disorder (AUD) with a focus on treatment development.
Objectives: To advance our understanding of treatment-seeking in clinical research for AUD, this study compares treatment-seekers to non-treatment-seekers with AUD on alcohol cue-reactivity (CR).
Methods: A community sample (N = 65, 40% female) of treatment-seeking (n = 32, 40.6% female) and non-treatment-seeking individuals (n = 33, 39.4% female) with a *DSM-5* diagnosis of moderate-to-severe AUD completed a laboratory CR paradigm. Analyses compared the two groups on subjective alcohol craving, heart rate, and blood pressure after the presentation of water cues and alcohol cues.
Results: Mixed-design analyses of variance revealed a main effect of treatment-seeking status (i.e., group; p = .02), such that treatment-seekers reported higher levels of subjective craving across both water (p = .04) and alcohol (p = .03) cue types. However, analyses did not support a group × cue type interaction effect (p = .9), indicating that treatment-seekers were not more cue-reactive. Group differences in craving were no longer significant when controlling for AUD severity. On blood pressure and heart rate, there was no significant effect of cue type, group, or cue type × group (p's > 0.13).
Conclusion: These findings suggest that while treatment-seekers report higher levels of subjective craving than non-treatment-seekers, they are not more cue-reactive. Under the framework of medications development, we interpret these null findings to indicate that non-treatment seeking samples may be informative about CR and therefore, medication-induced effects on CR.

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Alcohol; craving; cue-reactivity; treatment-seeking; behavioral pharmacology

Introduction

Alcohol use disorder (AUD) is a chronic, relapsing condition, characterized by continued use despite harmful medical, psychological, and social consequences. Despite AUD being highly prevalent, treatment rates remain remarkably low. Among those with 12-month and lifetime diagnoses of AUD, only 7.7% and 19.8%, respectively, sought treatment from 2012–2013 (1). Furthermore, it has been estimated that there is an average lag of approximately 8 years between the age of onset and age at first treatment (2). Greater severity of substance use disorders is a predominant factor associated with treatment-seeking (3,4) and individuals with current AUD are more likely to endorse a desire for AUD treatment if they are older, female, report higher levels of social impairments, and failed efforts to stop or cut down on drinking (5–7). Similarly, it has been demonstrated that treatment-seekers with AUD have higher rates of negative social consequences and higher levels of drug use and psychiatric severity, than non-treatment-seekers (8). Taken together, these studies not only identify specific traits that differ across these two samples, but also highlight their clinical significance.

The distinction between treatment-seekers and non-treatment-seekers with AUD is pertinent in both research and clinical contexts and is particularly important in AUD treatment development. For instance, behavioral pharmacology trials represent a necessary first step in establishing preliminary safety and efficacy of novel medications and are largely conducted in non-treatment-seeking samples (9). However, it is often observed that findings from human laboratory studies do not consistently and reliably carry over in clinical trials (10,11). Although the exact cause of discrepant findings between human laboratory studies and randomized controlled trials remains ambiguous, one plausible explanation is that treatment-seekers respond differently to medications

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for AUD than non-treatment-seekers. This hypothesis is supported by the nicotine and tobacco literature, which suggests that motivation to quit smoking significantly influences the efficacy of medications for smoking cessation, such that nicotine replacement therapy (i.e., nicotine patch), was found to increase abstinence in treatment-seekers, but had no significant effect in those who were not currently seeking treatment (12,13). Moreover, our group (6) and others (7) have recently identified a host of clinical variables that distinguish treatment-seekers from non-treatment-seekers, including tonic craving. As such, examining possibly inherent differences between treatment-seeking and non-treatment-seeking samples in terms of experimental and clinical paradigms for AUD is warranted.

The cue-reactivity (CR) paradigm was developed to evaluate the urge to drink in response to alcohol-related stimuli, as alcohol cue-exposure in the laboratory can mimic real-world situations in which alcohol is readily available, artificially inducing a conditioned response to alcohol cues (14). This response is a viable target to AUD treatment, as cue-induced alcohol craving has been shown to be predictive of treatment outcome (14). Studies have used CR in the context of treatment and found that salivary response to alcohol cues during detoxification predicted a higher frequency of drinking days during the 3-month follow-up (15)However, given that human laboratory CR trials have been comprised of non-treatment-seeking samples, the inclusion of (and comparison to) treatment-seekers is a necessary next step in this line of research.

To that end, the present study compared treatment-seekers to non-treatment-seekers with AUD on a human laboratory assessment of alcohol CR. Based on the finding that treatment-seekers report higher levels of tonic craving (6), we hypothesized that treatment-seekers would display higher levels of alcohol CR compared to non-treatment-seekers, over and above the effects of AUD severity. Lastly, exploratory analyses considered a dichotomous definition of craver versus non-craver, as proposed by Mason and colleagues (16).

Participants and methods

Participants

A community sample of treatment-seeking and non-treatment-seeking individuals reporting current problems associated with alcohol use was enrolled in the study (N = 65). Inclusion criteria for the study were: (i) age between 21 and 50 years; (ii) fluency in the English language; and (iii) meet current (past 3-month) *DSM-5* diagnostic criteria for moderate or severe AUD. Exclusion criteria were: (i) currently in treatment for alcohol use or history of treatment in the 30 days preceding the study visit; (ii) lifetime *DSM-5* diagnostic criteria for a bipolar or psychotic disorder; (iii) positive urine toxicology screen for any drug (other than cannabis), as measured by Medimpex United Inc. 10 panel drug test; (iv) blood alcohol concentration (BAC) of 0.000 g/dl at the time of the study visit, as measured by the Dräger Inc. Alcotest® 6510; (v) score of 10 or higher on the Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar (17);) and (vi) current use of psychoactive medications. The two groups of treatment-seekers (n = 32) and non-treatment-seekers (n = 33) were identified on the basis of their self-reported desire for treatment, as indicated by their answer to the following question: "For this study, we are looking for people who are seeking treatment for their alcohol use (would like help with treatment planning) as well as people who are not. Which category best describes you?" Their indication of treatment-seeker or non-treatment-seeker informed their participation in the study as described below.

Screening procedures and measures

All study procedures were approved by the University of California, Los Angeles Institutional Review Board, and all participants provided written informed consent after receiving a full explanation of the study procedures. Participants were recruited via online and print advertisements. Interested individuals called the laboratory and completed a phone interview for preliminary eligibility.

Following telephone screening procedures, eligible participants completed one in-person screening/assessment visit, lasting approximately 1 hour. This assessment visit was comprised of individual differences measures, including questionnaires designed to assess demographics, past-month substance use, AUD severity, baseline craving, and readiness to change drinking patterns. The following measures were administered: (1) *Timeline Follow-Back* (TLFB; (18)); (2) *Alcohol Dependence Scale* (ADS; (19)); (3) *Obsessive Compulsive Drinking Scale* (OCDS; (20); (4) *Penn Alcohol Craving Scale* (PACS; (21)); (5) *Stages of Change Readiness and Treatment Eagerness Scale* (SOCRATES; (22)); and (6) *Contemplation Ladder* (23).

A total of 314 individuals completed a screening interview over the phone, of which 113 individuals were eligible and came to the laboratory for an in-person screening visit. Of the 113 individuals evaluated in person, 65 of them were deemed eligible for the study. Reasons for exclusion after the in-person assessment included not meeting diagnostic criteria for

moderate-to-severe AUD, BAC greater than 0.000 g/dl, and testing positive on the urine toxicology screen for drugs other than marijuana. Immediately following the in-person assessment, eligible participants (N = 65) completed an alcohol cue-exposure session. After the cue exposure, all participants discussed their responses to the alcohol cues with a trained counselor. Treatment-seekers also completed a treatment planning session with the counselor, in which treatment options were discussed. A summary of screening and experimental procedures is provided in Figure 1.

Alcohol cue-reactivity (CR) procedures and measures

Alcohol CR followed well-established procedures (24,25). Sessions began with a 3-minute relaxation period. Then, participants held and smelled a glass of water for three minutes to control for the effects of simple exposure to any potable liquid. Next, participants held and smelled a glass of their preferred alcoholic beverage and were asked to recall sensory and psychological memories associated with their alcohol use (e.g., how one typically feels right before beginning to drink, one's mood prior to drinking, the location in which one typically drinks, and with whom one typically drinks). Order was not counterbalanced, due to carryover effects that are known to occur (24). Participants who self-identified as cigarette smokers were allowed a smoke break 15 minutes prior to and immediately after the CR assessment to avoid the potential confounding effects of nicotine withdrawal. The following measures were collected before and after the presentation of the water and alcohol cues during the CR procedure:

Alcohol urge questionnaire

The Alcohol Urge Questionnaire (AUQ (26);) is an 8-item scale in which subjects rated their craving for alcohol at the present moment. Participants rated their urge to drink prior to beginning the alcohol CR procedure, after the presentation of the water cue, and after the presentation of the alcohol cue, on an 11-point Likert scale ranging from "strongly disagree" to "strongly agree." The AUQ has demonstrated high internal consistency in alcohol human laboratory studies (27).

Physiological indicators

Vital signs including heart rate and blood pressure were measured using an Omron BP785N Automatic Blood Pressure Monitor. Vital signs were not measured continuously during each period of the CR procedure, but instead were measured before beginning the procedure, once following the presentation of the water cue, and once more following the presentation of the alcohol cue, resulting in three measures of physiological reactivity. Given that we used a single time-point recording method, there was no tool for checking for motion artifacts.

Treatment planning session

All participants who completed the CR paradigm met with a trained study counselor, supervised by a licensed clinical psychologist to discuss their responses to the alcohol cues. Those who self-identified as treatment-seeking participated in a treatment planning session with the study counselor. The counseling session followed standardized procedures developed for this study. The counselor began by providing the participant with feedback on answers to the various

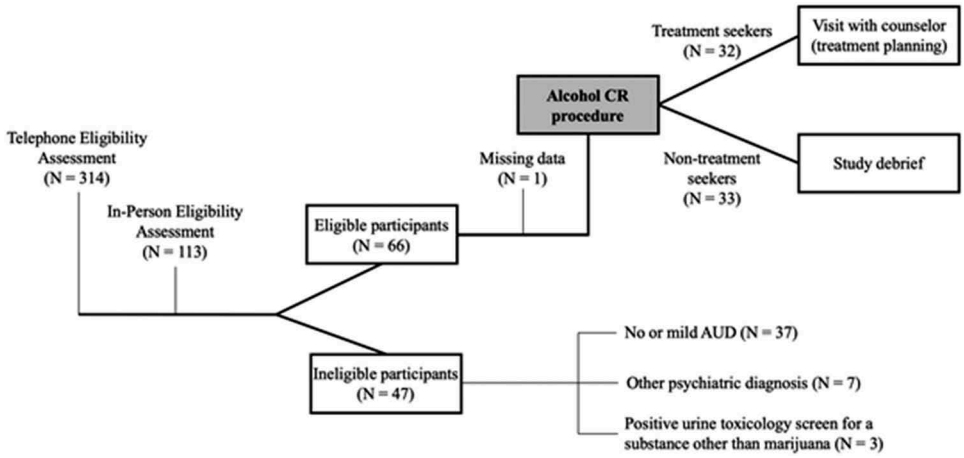

Figure 1. Overview of screening and experimental procedures.

questionnaires from the screening portion of the visit (drinking and drug use patterns, AUD diagnosis, family history of alcohol use, and withdrawal and depressive symptoms). Next, the counselor reviewed the participant's history of alcohol treatment and sought to identify barriers to treatment access. Lastly, the counselor reviewed treatment options with the participant, including the participant's primary care provider, self-help groups, and local clinics. The counselor provided all participants with the "Rethinking Drinking" (28) pamphlet and addressed any questions or concerns.

Power analysis

Given that no preliminary data were available for effect size estimation, the current study was powered to detect a medium effect size (Cohen's d = 0.50). A power analysis was conducted according to Cohen's guidelines to determine the sample size needed to achieve a power ≥ 0.80 (i.e., 80%) at an alpha level of 0.05. Using the program G*Power version 3.1.2 and selecting the repeated measures analysis of variance (ANOVA), between-subjects design, with alpha = 0.05 and f = 0.25, we arrived at a total of 64 participants (32 treatment-seekers and 32 non-treatment-seekers).

Data analysis plan

A series of mixed-design (repeated-by-between-subjects) analyses were conducted using PROC GLM in SAS Statistical Software Version 9.4 (SAS Institute, Inc., Cary, N.C.). Specifically, we conducted general linear model analyses in which group (treatment-seeker versus non-treatment-seeker) was a two-level between-subjects factor and cue (water cue versus alcohol cue) was a two-level within-subjects factor. The dependent measures were alcohol craving, as measured by self-reported craving on the AUQ (primary outcome), and physiological response to cues (secondary outcome: heart rate and blood pressure). Based on clinical differences reported between treatment-seekers and non-treatment-seekers (6,7), subsequent analyses compared treatment-seekers to non-treatment-seekers on cue-induced subjective craving after adjusting for age and ADS score.

Exploratory analyses

We sought to explore whether treatment-seekers were more likely to be classified as "cravers" than non-treatment-seekers. To do so, we followed the classification proposed by Mason and colleagues (16), whereby an individual was considered cue-reactive if his or her "strength of craving" score was one standard deviation greater for alcohol than for water cues on the Visual Analog Scale (VAS), corresponding to an increase of 3 VAS rating scale points. In the present study, an individual was considered cue-reactive if his or her craving rating per the AUQ was at least 6 points or higher for alcohol than for water cues. To test the dichotomous craving variable, we conducted a chi-square test to examine whether treatment-seekers were more likely to be classified as cravers than non-treatment-seekers.

Results

Sample characteristics

Sixty-five participants who completed the entire study were included in the statistical analyses reported herein. Sample characteristics are reported in Table 1, including alcohol use quantity and frequency, baseline levels of craving, and AUD severity. As shown in Table 1, of the 65 participants enrolled in the study, 40% (n = 26) met current diagnostic criteria for moderate AUD, whereas 60% (n = 39) met diagnostic criteria for severe AUD.

As shown in Table 1, analyses comparing treatment-seekers and non-treatment-seekers on demographic and clinical variables revealed that treatment-seekers were older, had higher OCDS and PACS scores (p's < 0.05), marginally higher ADS scores (p < .053), and were more likely to report cigarette smoking (p < .05).

As expected, given the treatment-seeking construct itself, treatment-seekers reported significantly higher levels of motivation for change, as indexed by higher readiness to change (i.e., a higher score on the Contemplation Ladder), greater recognition of alcohol problems and lower ambivalence subscales on the SOCRATES (p's < 0.05).

Effect of treatment-seeking status on alcohol cue reactivity

Cue-induced subjective craving

Analyses revealed a main effect of cue type on cue-induced subjective craving, such that levels of self-reported subjective craving (i.e., AUQ score) were higher following the presentation of alcohol cues than after the presentation of water cues (F(1, 64) = 35.0, p < .0001). Analyses also revealed a main effect of group (defined as treatment-seeking status; F(1, 63) = 5.3, p < .05), such that treatment-seekers displayed higher levels of subjective craving than non-treatment-seekers following both the water and alcohol cues. However, analyses did not yield a group × cue type interaction effect (F(1, 63) = 0.03, p = .86). These results are presented in Figure 2.

Table 1. Sample characteristics and group differences.

Variable[a]	Treatment-Seekers (n = 32) *M*(SD) or *n*(%)	Non-treatment-Seekers (n = 33) *M*(SD) or *n*(%)	Full Sample (N = 65) *M*(SD) or *n*(%)	*t* or χ^2	*p*
Age	37.28 (7.78)	30.94 (8.42)	34.06 (8.65)	−3.15	.002*
Gender					
Female (%)	13 (40.6%)	13 (39.4%)	26 (40.0%)	0.010	.92
Hispanic/Latino					
Yes (%)	9 (28.1%)	6 (18.2%)	15 (23.1%)	0.91	.34
ADS[b]	20.22 (8.42)	16.18 (6.80)	18.17 (8.40)	−1.98	.054
OCDS[c]	20.25 (8.97)	15.33 (7.52)	17.75 (8.57)	−2.40	.02*
Baseline AUQ[d]	18.06 (12.12)	13.27 (10.77)	15.63 (11.62)	−1.69	.098
CIWA-Ar[e]	1.06 (2.14)	1.27 (2.52)	1.17 (2.32)	0.36	.72
PACS[f]	18.91 (7.10)	13.94 (6.84)	16.38 (7.35)	−2.87	0.006*
SOCRATES[g]: Recognition	25.91 (5.88)	19.79 (6.46)	22.80 (6.86)	−3.40	<.001*
SOCRATES[g]: Ambivalence	15.84 (3.45)	12.42 (3.22)	14.11 (3.73)	−4.13	<.001*
SOCRATES[g]: Taking Steps	25.19 (8.86)	22.88 (6.94)	24.02 (7.96)	−1.17	.25
Contemplation Ladder	6.59 (2.14)	5.18 (2.53)	5.88 (2.43)	−2.43	.02*
AUD Diagnosis[h]					
Moderate (%)	12 (37.5%)	14 (42.4%)	26 (40.0%)	0.16	.69
Severe (%)	20 (62.5%)	19 (57.6%)	39 (60.0%)		
Drinking Days[i]	24.31 (7.52)	20.58 (8.80)	22.42 (8.35)	−1.84	.070
Drinks/Drinking Day[i]	7.72 (5.62)	6.09 (4.15)	6.89 (4.96)	−1.33	.19
Binge Drinking Days[i]	14.31 (10.26)	11.52 (9.17)	12.89 (9.75)	−1.16	.25
Smoker					
Yes (%)	24 (75.0%)	17. (51.5%)	41 (63.1%)	3.85	.0498
Cannabis user[i]					
Yes (%)	16 (50.0%)	22 (66.7%)	38 (58.5%)	1.86	.17
BDI-II[j]	15.25 (11.83)	17.97 (11.30)	16.63 (11.55)	0.95	.35
BAI[k]	15.31 (13.11)	12.18 (9.73)	13.72 (11.54)	−1.09	.28

[a]Standard deviations appear within parentheses for continuous variables. Percent of group (i.e., treatment-seekers or non-treatment-seekers) appear within parentheses for categorical variables.
[b]Alcohol Dependence Scale (ADS)
[c]Obsessive Compulsive Drinking Scale (OCDS)
[d]Alcohol Urge Questionnaire (AUQ)
[e]Clinical Institute Withdrawal Assessment for Alcohol – Revised (CIWA-Ar)
[f]Penn Alcohol Craving Scale (PACS)
[g]The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES)
[h]Current (past 3 months) Alcohol Use Disorder (17) assessed by the Structured Clinical Interview DSM-5 (SCID-5).
[i]Assessed by Timeline Follow Back (TLFB) interview for the past 30 days.
[j]Beck Depression Inventory – II (BDI-II)
[k]Beck Anxiety Inventory (BAI)
*Asterisks denote statistically significant differences between groups (*p's* < 0.05).

There were observed group differences with regard to age and ADS score (Table 1), such that treatment-seekers were significantly older ($p < .05$) and reported marginally greater ADS scores ($p < .053$), which was expected given prior research. Both of these variables were tested as covariates in separate mixed-design ANCOVA models. When comparing treatment-seekers to non-treatment-seekers on cue-induced subjective craving, adjusting for both of these variables in separate models, the effect of treatment-seeking status was no longer significant after controlling for ADS score ($p = .13$); however, the effect of treatment-seeking still remained after controlling for age ($p < .05$). This finding suggests that treatment-seeking status and measures of AUD severity overlapped in this sample, despite our efforts to match groups on severity.

Cue-induced heart rate and blood pressure

Difference scores for measures of heart rate and blood pressure were calculated by subtracting the values obtained during the relaxation period from the values obtained following the presentation of the water and alcohol cues, respectively. ANOVAs did not reveal significant effects of cue on any physiological indicators of cue-reactivity, including cue-induced heart rate ($F(1, 64) = 0$, $p = .97$), systolic blood pressure ($F(1, 64) = 2.4$, $p = .13$), or diastolic blood pressure ($F(1, 64) = 0$, $p = .95$). Similarly, although analyses yielded a significant effect of group on cue-induced heart rate ($F(1, 63) = 4.1$, $p < .05$), they did not yield any significant effects of group on systolic blood pressure ($F(1, 63) = 0.7$, $p = .42$) or diastolic blood pressure ($F(1, 63) = 0.04$, $p = .84$). Lastly, there were no significant group × cue interaction effects on cue-induced heart rate ($F(1, 63) = 0.3$, $p = .61$), systolic blood pressure ($F(1, 63) = 1.0$, $p = .33$), or diastolic blood pressure ($F(1, 63) = 0.2$, $p = .63$).

Exploratory analyses

Across groups, 41.5% ($n = 27$; 14 non-treatment-seekers, 13 treatment-seekers) of individuals were considered to be cue-reactive. Chi-square analyses comparing the

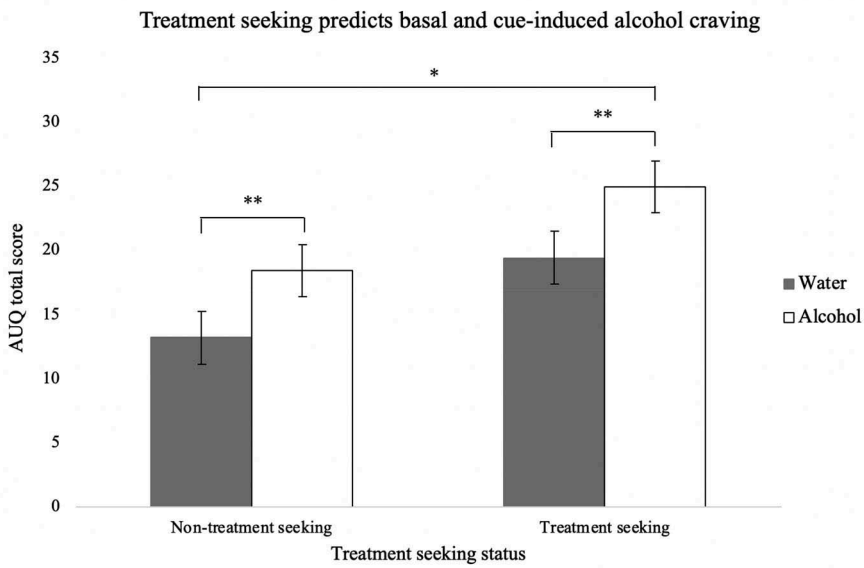

Figure 2. Subjective craving scores (Alcohol Urge Questionnaire; AUQ), presented with standard errors, following water and alcohol cue presentation. Double asterisks denote a significant main effect of cue, such that individuals reported significantly higher rates of craving following the alcohol cue compared to the water cue ($p < .0001$). Single asterisks denote a significant effect of group, indicating that treatment-seekers displayed higher levels of subjective craving following both the water and alcohol cues ($p = .02$).

probability across the 2 × 2 model (cue-reactive versus non-cue reactive; treatment-seeking versus non-treatment-seeking), indicated that there were no significant differences in the likelihood of being classified as cue-reactive between groups, such that treatment-seekers were no more likely to be considered cue-reactive than non-treatment-seekers (χ^2 (1, $n = 65$) = 0.02, $p = .88$).

Discussion

Results generally provided evidence for higher levels of self-reported alcohol craving in treatment-seekers than non-treatment-seekers. However, there was no evidence that treatment-seekers were more cue-reactive, contrary to our initial hypothesis. Instead, treatment-seekers displayed elevated levels of craving at baseline and following the presentation of both the water and alcohol cues and there was no support for a group × cue interaction effect. Furthermore, after adjusting for AUD severity and measures of tonic craving (e.g., PACS, OCDS), the effect of treatment-seeking status was no longer significant, suggesting that group differences in AUD severity may explain the higher craving scores that were observed in treatment-seekers. Although we attempted to match these groups on AUD severity by only including participants with moderate-to-severe AUD, group differences in other measures of AUD severity were observed. Those clinical differences in turn are consistent with previous findings of greater AUD severity among treatment-seeking individuals (6,7).

In terms of physiological indicators of cue-induced craving, no indices yielded significant effects of either cue or group, such that cue-induced heart rate and blood pressure remained relatively constant across both water and alcohol cues, as well as across treatment-seeking status. The procedures employed in the present study resulted in three discrete measurements of physiological indicators of craving. Our approach consisted of a single time-point recording, as opposed to continuous long-range assessment, which may pose a limitation in that the largest physiological effect was likely not captured within the present paradigm. These methods may explain the largely null findings with regard to cue-induced heart rate and blood pressure.

Despite potential limitations of this procedure, the results obtained are in line with the mixed evidence regarding physiological reactivity and its role in subjective craving. While there is evidence suggesting that the exposure to alcohol cues increases craving and associated physiological arousal in abstinent alcohol dependent individuals and social drinkers (29–31), there is mixed evidence with regard to the effect of alcohol-related cues on physiological indices (32–34). Furthermore, some work has shown that physiological cue-reactivity is only moderately correlated with subjective craving (35–37), if at all (38). It is plausible that subjective response represents a more reliable indicator of craving than

the physiological measurements employed in this study, which might explain these nonsignificant findings.

Regarding the exploratory aims, analyses reflect alternative ways in which the field has dealt with the construct of cue-reactivity (i.e., craver versus non-craver). Exploratory analyses suggested that categorizing individuals as cravers or non-cravers, as recommended by Mason and colleagues (16), produced the same results such that treatment-seekers were no more likely to be classified as cue-cravers than non-treatment-seekers.

The present study must be interpreted in light of its strengths and limitations. Strengths include that this study was one of original data collection with the a-priori aims of comparing these two groups. Extensive efforts were made to match the two groups on severity by only allowing those with moderate-to-severe AUD to participate. Additionally, offering a treatment-planning session to ensure commitment to the treatment process was a strength which allowed participants' involvement in the study to be matched by their stated desire for treatment. Lastly, the exclusion of polysubstance users on the basis of clinical assessments and toxicology data also bolstered the internal validity of the study as it applies to sample with a primary diagnosis of AUD. Study limitations include the fact that we did not offer a full treatment program such that the full range of treatment-seekers may not have participated in our study. It is possible that treatment-seekers exhibiting the most severe range of symptoms were not well represented. The fact that the sample was not fully matched on AUD severity also represents a limitation, which we sought to address statistically by adding relevant covariates to our models.

In conclusion, our study found that although treatment-seekers reported higher levels of alcohol craving during the CR procedure, they were not significantly more reactive to alcohol cues than non-treatment-seekers. Results from the present study have implications for medications development and behavioral pharmacology for AUD. Specifically, these findings suggest that studies of non-treatment-seekers on cue-reactivity may be translatable to treatment-seeking samples. In other words, while clinical differences between treatment-seekers and non-treatment-seekers for AUD have been recently identified (6,7), such differences do not seem to extend to cue-reactivity per se. Nonetheless, whether individuals who are treatment-seeking (or who are motivated to change their drinking) are more responsive to medications for AUD than non-treatment-seekers are remains an open question, not addressed in this study. More research is needed to further investigate the differences between these groups in the context of pharmacotherapy studies and determine their differential response to AUD medications targeting cue-induced craving.

Disclosure statement

Neither author has any conflicts of interests to disclose.

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