Addictive Behaviors Reports 7 (2018) 71–74

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

Relationship between tonic and phasic craving for alcohol

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ARTICLE INFO

Keywords:
Alcohol
Craving
Assessment

ABSTRACT

Background: Multiple measures are utilized to assess alcohol craving, often interchangeably. Little is known about the relationship between tonic and phasic craving. This study fills this gap in the literature by examining the association between tonic levels of alcohol craving and phasic craving for alcohol that is provoked by alcohol administration.

Methods: Forty-three non-treatment seeking problem drinkers underwent an initial interview and two laboratory testing sessions, where either alcohol or a saline placebo was administered intravenously. Tonic craving was assessed via the Penn Alcohol Craving Scale (PACS) and Obsessive Compulsive Drinking Scale (OCDS) at the initial interview. Phasic craving was assessed during the laboratory sessions (i.e., alcohol and saline administrations, single blinded) at baseline and at 3 subsequent breath alcohol concentrations (0.02, 0.04, and 0.06 g/dl).

Results: There was a main effect of PACS in predicting phasic craving across both saline and alcohol administration conditions ($p < 0.05$). The OCDS was predictive of phasic craving when alcohol, but not saline, was administered ($p = 0.058$); the obsessive subscale ($p = 0.01$), but not the compulsive subscale ($p > 0.10$), predicted phasic craving during alcohol, as compared to saline administration.

Conclusion: In sum, tonic craving captured by the OCDS was predictive of phasic craving during alcohol administration whereas the PACS more generally captured the increase in phasic craving. Therefore, these measures of tonic craving may function differently in capturing the experience of phasic craving. Implications for the utilization of the PACS and OCDS as well as assessments of craving in alcoholism research are discussed.

1. Introduction

The phenomenon of craving for substances of abuse has been long recognized (Drummond, 2001; Jellinek et al., 1955), however, understanding of the clinical utility of craving has grown increasingly over the past generation. Though definitions vary, craving has broadly been defined as a desire or strong urge to use a substance (Flannery et al., 2001). Craving has been implicated in multiple domains, including prognosis, intervention target, clinical outcome, and notably has been included as a diagnostic criterion in the latest iteration of the Diagnostic and Statistical Manual of Mental Disorders (Hasin et al., 2013; Tiffany & Wray, 2012). However, the experience of craving varies widely both between and within individuals due to a host of factors including severity of alcohol use, environmental factors, heightened stress, and withdrawal (Drummond, 2001; Haass-Koffler, Leggio, & Kenna, 2014).

Various methods of assessing alcohol craving have been developed. Self-report measures of subjective craving capture either longer-term, *tonic* craving or in the moment, provoked, *phasic* craving (Ray, Courtney, Bacio, & MacKillop, 2013). Tonic measures of craving are, by nature, retrospective and capture a general subjective experience of craving over a prescribed time period when craving has not been provoked (Ray, Courtney, et al., 2013). Tonic craving has been predictive of drinking and treatment outcomes (Bottlender & Soyka, 2004; Flannery, Poole, Gallop, & Volpicelli, 2003; Oslin, Cary, Slaymaker, Colleran, & Blow, 2009). The Penn Alcohol Craving Scale (PACS) is a 5-item measure assessing frequency and severity of craving over the previous week (Flannery, Volpicelli, & Pettinati, 1999). The PACS benefits from asking specifically about duration and frequency of craving, whereas most other measures assess intensity of craving alone, producing a "composite" craving score (Tiffany & Wray, 2012). Alternatively, the Obsessive Compulsive Drinking Scale (OCDS) is a 14-item measure of alcohol related urges and thoughts that produces two subscales, obsessive and compulsive (Anton, Moak, & Latham, 1995). The OCDS is based on the notion that alcohol use disorders (AUD) are akin to obsessive compulsive disorders and thus assesses severity of alcohol-related urges, obsessive thoughts, and compulsive alcohol use over a

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https://doi.org/10.1016/j.abrep.2018.03.001
Received 11 November 2017; Received in revised form 11 March 2018; Accepted 11 March 2018
Available online 12 March 2018

specified timeframe. The OCDS has high reliability and convergent validity with other measures of craving, AUD, and alcohol consumption (Bohn, Barton, & Barron, 1996; Connor, Jack, Feeney, & Young, 2008; Kranzler, Mulgrew, Modesto-Lowe, & Burleson, 1999; Moak, Anton, & Latham, 1998; Ray, Courtney, et al., 2013).

Phasic measures of alcohol craving, on the other hand, assess in vivo, current, state-levels of subjective craving for alcohol. Phasic craving is often the result of provocation, for example during laboratory cue-exposure paradigms, and has been shown to predict drinking outcomes (Drummond & Glautier, 1994; Litt, Cooney, & Morse, 2000). This dynamic state of craving may fluctuate based on a number of factors, such as the presence of alcohol related cues or ingestion of alcohol itself (Ray, Courtney, et al., 2013). The 8-item Alcohol Urge Questionnaire (AUQ; Bohn, Krahn, & Staehler, 1995) assesses an individual's severity of craving at the given moment and is frequently used in laboratory based paradigms that include a craving provocation (e.g. MacKillop, 2006; O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002; Ray & Hutchison, 2007).

While alcohol craving research has a long history in the field, the relationship between tonic and phasic levels of craving for alcohol, within the individual, remain poorly understood. This study seeks to advance the literature by comparing tonic (i.e., PACS and OCDS) and phasic (i.e., craving during controlled alcohol and saline administration in the laboratory) craving for alcohol in a sample of non-treatment seeking drinkers. We hypothesize that tonic craving will predict phasic craving in the laboratory in response to alcohol administration but not the saline control condition. The rationale for the hypotheses is that to the extent tonic and phasic craving are related conceptually, there should be an association between those assessments within individuals tested in our study for tonic (i.e., self-reported craving over a longer time frame) and phasic (i.e., craving directly induced by alcohol administration) craving.

2. Methods

2.1. Participants

A total of 295 problem drinkers from the greater Los Angeles community completed the in-person screening visit where inclusion criteria were: (1) 21–65 years of age; (2) endorse problems related to alcohol use; (3) report drinking ≥48 drinks per month; (4) meet DSM-IV criteria for alcohol dependence (current, defined as past year). Exclusion criteria were: (1) currently in or seeking treatment for alcohol problems; (2) report no alcohol use in the past three weeks; (3) history of major psychiatric disorder (e.g. psychosis); (4) Clinical Institute Withdrawal Assessment (CIWA-Ar; Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989) score ≥ 10. Of those, a subset of 43 individuals were selected for an alcohol administration study based on a genetic polymorphism of the mu opioid receptor (*OPRM1*) gene (Ray, Bujarski, et al., 2013); twenty-three of these participants were AA homozygotes and the remaining twenty were G-allele carriers. Sample demographics are presented in Table 1.

2.2. Procedures

Participants responded to online and print advertising by calling the laboratory to complete a telephone interview. Eligible participants were invited to an in-person assessment where they provided written informed consent and completed individual differences measures. Participants then completed a physical examination. Eligible participants were invited to complete two infusion visits, saline and alcohol, which were completed in randomized, blind, counterbalanced order at least one week apart (Ray, Bujarski, et al., 2013).

When participants arrived for infusion sessions, they were breathalyzed to confirm a breath alcohol concentration (BrAC) of 0.00 g/dl and regular smokers were allowed to have a cigarette. In order to mitigate variability in blood alcohol concentration observed between individuals, a 5% ethanol solution was administered intravenously using a formula accounting for sex and weight (Ray, Bujarski, et al., 2013). Upon reaching each target BrAC, 0.02, 0.04, and 0.06 g/dl, the infusion rate was reduced in half to maintain constant BrAC level while participants completed a series of measures. During the saline infusion visit, measures were administered at 0, 18, 43, and 75 min during the saline infusion, to mirror the approximate time points at which target BrACs were reached in the alcohol administration session. When participants reached a BrAC ≤0.02 g/dl they were permitted to leave (0.00 g/dl if driving).

Table 1
Demographic, substance, and mood variables of the sample (n = 43).

Demographics	
Age (SD, range)	29.3 (9.5, 21–51)
% Male (N)	74.4 (32)
% Caucasian (N)	69.8 (30)
Substance use variables	
Drinks per drinking day (SD)	7.1 (2.9)
Drinking days (SD)[a]	19.2 (7.5)
Total number DSM-IV AUD symptoms (SD)	6.5 (2.3)
CIWA (SD)	5.6 (4.4)
% Daily smokers (N)	32.56 (14)
FTND (SD)	2.2 (2.8)
Alcohol craving	
PACS (SD)	15.0 (6.2)
OCDS (SD)	20.6 (9.2)
OCDS-Obsessive (SD)	8.8 (5.2)
OCDS-Compulsive (SD)	11.8 (4.7)
Mood variables	
BDI (SD)	18.9 (12.8)
BAI (SD)	15.7 (12.5)

[a] Drinking days was assessed using the past 30-day TLFB interview

2.3. Measures

At the screening visit, a master's level clinician administered the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995), past 30-day Timeline Follow-Back interview (Sobell, Sobell, Klajner, Pavan, & Basian, 1986), and the CIWA-Ar (Sullivan et al., 1989). Self-report measures included: a demographics questionnaire, the Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1993), the Beck Anxiety Inventory (BAI; Beck & Steer, 1993), and the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).To assess tonic craving, the PACS (assessing past week craving; Flannery et al., 1999) and the OCDS (assessing past year craving; Anton et al., 1995) were completed. During the infusion visits, the AUQ (Bohn et al., 1995) was completed as each target BrAC (or matched time point) was reached.

2.4. Data analysis plan

Linear regression models were formulated using PROC Mixed in SAS 9.3, first for the PACS and secondly the OCDS and the two subscales, where the dependent measure was mean phasic craving, as assessed by the AUQ. All models were designed with individual intercepts, allowing for random intercepts, where the within subject variables, BrAC and Alcohol condition, were Level 1 fixed variables and tonic craving was a Level 2 variable. Covariates tested in all models included *OPRM1* status, smoking status, BDI, BAI and sex, however, none were significant. The models examined *BrAC*, which was used as 4-level, within subject indicator of *time* (baseline was time-point zero, BrAC = 0.02 g/dl was considered time-point 1, etc.), *alcohol condition* (alcohol versus saline), and *tonic craving* (PACS, OCDS, subscales), and their *interactions*. The three-way interaction was then removed from the model if not significant.

Table 2
Alcohol administration models pertaining to the tonic craving models predicting phasic craving in the laboratory.

	PACS		*OCDS*	
	F	*p*	F	*p*
Alcohol	**12.14**	< 0.01	0.62	0.43
Time	0.67	0.57	0.88	0.45
PACS	**4.37**	0.04	1.27	0.27
Alcohol * time	0.43	0.73	0.06	0.98
Tonic craving * alcohol	1.66	0.20	**3.63**	0.057
Tonic craving * time	1.14	0.33	1.41	0.24
Tonic craving * alcohol * time	0.11	0.95	0.49	0.69
Alcohol	**12.13**	< 0.001	0.62	0.43
Time	0.67	0.57	0.88	0.45
Tonic craving	**4.37**	0.04	1.27	0.27
Alcohol * time	1.84	0.14	1.91	0.13
Tonic craving * alcohol	1.66	0.20	**3.62**	0.058
Tonic craving * time	1.14	0.33	1.39	0.24
Alcohol	**35.34**	< 0.001	**35.46**	< 0.001
Time	**19.58**	< 0.001	**19.58**	< 0.001
Tonic craving	**4.37**	0.04	1.25	0.27

Note: Bolded items signify $p < 0.05$. Alcohol refers to alcohol or placebo administration. Time refers to BrAC levels (0.00, 0.02, 0.04, 0.06 g/dl). Tonic Craving is assessed via the PACS or OCDS.

3. Results

AUQ scores were greater when participants received alcohol compared to placebo, supporting a main effect of alcohol administration on phasic levels of craving ($p < 0.05$; Ray, Bujarski, et al., 2013). Results for the PACS indicated that tonic craving by the PACS had a significant simple effect (β = 0.06, SE = 0.03, $p = 0.04$), such that regardless of alcohol condition higher PACS scores predict higher AUQ scores (Table 2). There were also simple effects of alcohol condition and time such that AUQ scores were higher when alcohol was administered compared to saline and as BrAC increased.

Models using the OCDS as an indicator of tonic craving revealed a trend level interaction of OCDS × condition (F = 3.62, $p = 0.058$). To further investigate this effect, the model was tested in each condition. Results indicate the OCDS was predictive of phasic craving during the alcohol administration (β = 0.05, SE = 0.03, $p = 0.05$) but not during saline (β = 0.02, SE = 0.03, $p > 0.10$). In probing OCDS subscales, results indicated that the obsessive subscale was driving these effects such that there was a significant interaction of obsessive subscale with condition (F = 6.17, $p = 0.01$) such that craving was predictive of phasic craving during alcohol administration (β = 0.11, SE = 0.05, $p = 0.02$) but not during saline (β = 0.04, SE = 0.05, $p > 0.10$). These effects were not observed for the compulsive subscale of the OCDS (F = 0.75, $p > 0.10$).

4. Discussion

Despite the long recognition of alcohol craving as a critical phenomenon in AUD, little is known about the relationship between tonic and phasic craving levels. Results from this study indicated that the PACS did not predict phasic craving in response to alcohol administration. However, there was a main effect of PACS such that higher tonic craving was predictive of higher phasic craving, regardless of whether alcohol or saline was administered. On the other hand, the OCDS was predictive of phasic craving when alcohol was administered, but not during the saline administration; similarly, the Obsessive subscale, but not the Compulsive subscale, was predictive of phasic craving when alcohol was administered. Thus, tonic craving, as assessed by the OCDS, may be more sensitive to phasic craving that is provoked by alcohol administration (but not saline), whereas the PACS appears to generally predict increased phasic craving, regardless of presence of alcohol. These findings suggest that these measures of tonic craving may function differently.

Overall, the OCDS is based on the theory that addictive disorders are similar to obsessive-compulsive disorders and focuses on alcohol related cognitions and urges. Such cognitions, measured by the obsessive subscale, may be heightened when alcohol is present. However, data are mixed regarding the concurrent validity of the OCDS. One study of alcohol dependent patients did not find any relation of the OCDS to other measures of alcohol use (Connor et al., 2008). Additionally, Kranzler et al. (1999) questioned the predictive validity of the OCDS as it did not strongly predict drinking after completion of a pharmacotherapy trial. In contrast, the PACS has shown unique prognostic utility in predicting number of standard drinks after treatment, above the effects of the AUQ (Flannery et al., 2003). In this study, higher PACS score generally predicted higher phasic response but such response was not different based on alcohol condition, perhaps speaking to the general ability of this measure to capture a broader dimension of craving.

The relationship between tonic and phasic craving is clinically relevant as both types of craving have shown to predict drinking behaviors. Interventions targeting tonic craving may in turn dampen phasic response to alcohol administration or cues, thus assessing craving in multidimensional fashion and accounting for combined phasic and tonic effects appears warranted. To that end, a recent human laboratory study found that a novel neuroimmune medication (ibudilast) reduced tonic craving compared to placebo (captured by the PACS) yet there were no medication effects on alcohol- or cue-induced phasic craving (Ray et al., 2017). This serves to illustrate the complex clinical interplay between tonic and phasic craving and its treatment implications.

These results should be interpreted in light of study strengths and limitations. Strengths include the experimental manipulation where participants completed both alcohol and placebo administration sessions. Limitations include the small sample size and the fact that craving could have been dampened during the infusion due to lack of other cues (e.g. taste, visual). Future studies should examine relationships between tonic and phasic craving using other craving provocations, such as cue and stress exposure paradigms. Though participants were included based on *OPRM1* status, which has been related to subjective response, data regarding the association of this polymorphism to craving has been mixed (Ray, 2011; Ray, Bujarski, et al., 2013) and inclusion as a covariate did not impact the findings presented herein. Though it appears craving has a strong genetic component (Enoch, 2013; Kimura & Higuchi, 2011), it is unlikely the experience of craving is attributable to a single genetic variant. Lastly, the intersection between tonic and phasic craving assessments could be further elucidated using ecological momentary assessment (EMA) approaches. In conclusion, this study provides an initial evaluation of the association between tonic and phasic subjective craving for alcohol in the clinic and in the laboratory and finds that while the association was significant, it is clear that most of the variance between tonic and phasic measures of alcohol craving are non-shared.

Funding: This study was supported by grants from ABRMF, the Foundation for Alcohol Research, and the UCLA Clinical and Translational Science Institute.

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