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.