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Subjective Response and Self-Administration of Alcohol: Implications for Alcoholism Etiology

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Subjective Response and Self-Administration of Alcohol: Implications for Alcoholism Etiology

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Psychology

by

Spencer Evan Bujarski

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ABSTRACT OF THE DISSERTATION

Subjective Response and Self-Administration of Alcohol: Implications for Alcoholism Etiology

by

Spencer Evan Bujarski

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2017

Professor Lara Allison Ray, Chair

The biobehavioral effects of alcohol have emerged as central components of alcoholism etiology in both clinical and preclinical research. To understand the biology of alcohol use disorder (AUD) preclinical researchers have developed animal models of drug and alcohol addiction, however, the translational applicability of these models is often assumed by face validity. The overarching aim of this dissertation is to advance a human laboratory framework for translating the preclinically derived Allostatic Model, and Incentive Salience Theory (IST) to clinical samples.

Despite the central role subjective responses to alcohol (SR) in several etiological theories, relatively little is known about its structure. Therefore, prior to leveraging SR as a translational phenotype, Paper I examined the factor structure of SR using data from a large and well-controlled alcohol challenge study. Results suggested a 4-factor solution to SR along the domains of

Stimulation/Hedonia, Negative Affect, Sedation/Motor Intoxication, and Craving/Motivation capturing positive reward, negative reward, punishment and subjective motivation respectively. This

paper offers a synthesis of multiple SR measures and provides recommendations for consolidating these measures into four meaningful and interrelated constructs.

In Paper II, predictions from the Allostatic Model regarding a transition from positive reinforcement to negative reinforcement in alcohol dependence were tested. Heavy drinking participants representing a range of AUD severity completed a novel alcohol administration paradigm designed to capture domains of alcohol reward and reinforcement via a standardized alcohol challenge and progressive ratio self-administration. Validating the laboratory paradigm, AUD predicted greater alcohol craving, and greater alcohol reinforcement. Furthermore, craving during the challenge robustly predicted subsequent reinforcement behavior. These data however, provided evidence for neither a transition *from* positively reinforced alcohol use, nor a transition *to* negative reinforcement. AUD severity did not predict stimulation/hedonia, and hedonic responses didn't predict self-administration regardless of AUD severity. While AUD severity was associated with greater basal negative affect, alleviation of negative affect by alcohol did not differ by AUD severity and negative affect did not predict self-administration at any level of AUD severity. Sedative response however did predict lower reinforcement behavior consistent with the Differentiator and Low-Level of Response models derived in human laboratory research. This study thus represented a novel approach to translating predictions from the Allostatic Model to a clinical sample. While the experimental paradigm did meaningfully capture domains of alcohol reward and reinforcement, hypotheses regarding allostatic processes were generally not supported.

In Paper III, hypotheses from the Incentive Sensitization Theory were tested in terms of the dissociation between alcohol liking and wanting, and the role of incentive salience in motivating alcohol consumption. Overall the hypotheses based on IST were not supported. AUD severity predicted neither subjective liking nor wanting during the alcohol challenge, and these variables remained highly correlated across AUD severity. Utilizing an alcohol dot probe measure of attentional bias, AUD severity did not predict greater incentive salience, and incentive salience variables did not predict reinforcement. Of note however, these data were consistent with recent evidence suggesting the dot probe tasks may be unreliable. Therefore, it is possible that these null results are a consequence of poor reliability for the

incentive salience measure. Thus, by examining a behavioral measure of incentive salience in addition to subjective liking and wanting, this paper advanced a more complete framework for translating IST to clinical populations, and highlighted the need for accurate behavioral measures of incentive salience in humans.

In order to optimally benefit from the precision of preclinical research, it is necessary to establish that preclinical models accurately map onto key aspects of human AUD. Together these three papers advance a novel human laboratory framework for translating preclinical models of addiction to clinical samples. Factor analytic work validated SR as a translational phenotype capturing key aspects of reward and punishment. The novel experimental paradigm in Papers II and III captured variations in both alcohol reward and reinforcement and found results which were consistent with prominent human laboratory models of alcoholism risk. Conversely however, few of our hypotheses derived from the Allostatic Model or Incentive Sensitization Theory were supported highlighting the need for increased reverse translation efforts to promote consilience between preclinical and human subjects research. Ultimately, determining whether preclinical theories of alcoholism etiology accurately capture pathological processes in humans suffering from AUD is essential to fully understanding alcoholism etiology and developing efficacious treatments to alleviate the sizeable human cost of alcohol addiction.

The dissertation of Spencer Evan Bujarski is approved.

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Paper 1 of the dissertation is:

Bujarski, S., Hutchison, K.E., Roche, D.J.O. & Ray, L.A. (2015) Factor Structure of Subjective Responses to Alcohol in Light and Heavy Drinkers. Alcoholism: Clinical and Experimental Research. 39(7), 1193-1202.

Dr. Lara Ray served as the study sponsor on the project

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DISSERTATION INTRODUCTION

Alcohol use disorder (AUD) is characterized by a cluster of behavioral and physical symptoms involving prolonged and maladaptive alcohol use despite impairment in daily life functioning and/or psychological distress. AUD is among the most prevalent and costly psychiatric disorders with a past year prevalence of approximately 8% (Compton, Thomas, Stinson, & Grant, 2007; Grant et al., 2004; Merikangas & McClair, 2012) and an estimated economic toll of $180 billion per year (Rehm et al., 2009). However, despite high prevalence rates and substantial economic burden, scientific consensus regarding the etiology of AUD is lacking.

Both researchers and clinicians alike have long recognized AUD as a chronic and relapsing condition, strongly influenced by individual genetic and psychosocial factors (Kendler, Prescott, Neale, & Pedersen, 1997, p. 199; Ray, 2012; Verhulst, Neale, & Kendler, 2015). Several prominent and well-supported theories of alcoholism etiology developed in both preclinical and clinical research have identified the biobehavioral response to alcohol as an integral component for alcoholism risk and disease progression (e.g. King, Roche, & Rueger, 2011; Koob & Le Moal, 1997; Newlin & Thomson, 1990; Ray, Bujarski, & Roche, 2016; Robinson & Berridge, 1993; Schuckit, 1984).

While addiction research of all kinds is striving to explain human psychopathology, human subjects research is fundamentally limited in terms of experimental control and biological precision. Thus, preclinical researchers have sought to develop and refine paradigms which simulate addiction in animals. These preclinical paradigms have generated considerable insight into the biology of drug and alcohol addiction; however, the translational applicability of preclinical models is often assumed by face validity (e.g. through producing in "addicted" rodents high levels of free-access alcohol consumption, physiological withdrawal, or alcohol reinforcement that is insensitive to cost). Few studies to date have directly tested whether the predictions of preclinical neuroscience theories accurately predict human behavior. The overarching aim of this dissertation therefore is to develop a translational human laboratory framework and test the behavioral predictions from two prominent preclinical models of alcoholism

etiology: the Allostatic Model proposed by Koob & Le Moal (1997) and the Incentive Salience Theory proposed by Robinson & Berridge, (1993). This dissertation is structured in three connected papers.

Paper I: Factor Structure of Subjective Responses to Alcohol in Light and Heavy Drinkers

Subjective responses to alcohol (SR), or the biobehavioral effects of alcohol, are integral components of both preclinical and clinical theories of alcoholism etiology (Bujarski & Ray, 2016; Morean & Corbin, 2010; Quinn & Fromme, 2011; Ray et al., 2016). In spite of SR's apparent etiological role, relatively little is known about the factor structure of SR (Lutz & Childs, 2017; Ray, MacKillop, Leventhal, & Hutchison, 2009). Therefore, prior to leveraging SR as a translational phenotype, Paper I examined the psychological structure of SR using data from a large and well-controlled alcohol challenge study (Bujarski, Hutchison, Prause, & Ray, 2015). It was hypothesized that these data would replicate the 3-factor model of SR comprising domains of Stimulation, Sedation, and Negative Affect (Ray et al., 2009) with the addition of a fourth dimension of Craving. Analyses confirmed these hypotheses and thus and offered a synthesis of the SR construct that was used as a translational phenotype in subsequent papers.

Paper II and Paper III present the results of a new study which was developed to test behavioral predictions derived from the Allostatic Model (Paper II) and Incentive Sensitization Theory (Paper III) in a sample of heavy drinkers.

Paper II: Testing the Transition from Positive to Negative Reinforcement in Alcoholism: Application of a Novel Experimental Paradigm in a Clinical Sample

Paper II leveraged a novel human laboratory paradigm, which was designed to capture alcohol reward and reinforcement, to test translational predictions derived from the Allostatic Model (Koob & Kreek, 2007; Koob & Le Moal, 1997, 2008). The Allostatic Model characterizes addiction in terms of a cycle of progressive neuroadaptation that produces blunted hedonic responses to drug administration (i.e. blunted positive reinforcement) and a dysphoric state in abstinence leading to enhanced negative reinforcement in late-stage dependence. To test this hypothesized transition from positive to negative reinforcement in humans, heavy drinking participants with a range of AUD severity (sub-clinical heavy

drinkers through severe AUD) completed an intravenous alcohol administration paradigm that included a standardized alcohol challenge (target BAC = 60mg%) followed by progressive ratio self-administration. Participants self-reported SR during the alcohol challenge captured domains of alcohol reward, and self-administration behavior captured reinforcement. Analyses examined the effects of AUD severity in terms of (1) SR during the challenge, (2) motivated alcohol reinforcement during self-administration, and (3) the relationship between dimensions of SR and reinforcement capturing whether the function of SR in promoting alcohol motivation differs as a function of AUD severity. Based on allostatic processes, it was hypothesized that hedonic SR will predict reinforcement among lower severity AUD, whereas the negative affect would predict reinforcement behavior among severe AUD.

Paper III: Testing the Incentive Salience of Alcohol Cues as a Determinant of Alcohol Reinforcement in a Clinical Sample

The Incentive Sensitization Theory suggests that drug liking and wanting are neurobiologically dissociable, and that addiction is the result of sensitization in the neurobiological systems responsible for attributing incentive salience of drugs and drug-paired cues (Robinson & Berridge, 1993, 2001, 2008). Thus, IST proposes that liking and wanting for alcohol become increasingly dissociated as AUD progresses, and that attribution of incentive salience leads to compulsive drinking despite reduced hedonic reward. To test IST in a clinical sample, participants reported on their subjective liking and wanting throughout the alcohol challenge and completed an alcohol dot probe task at baseline and 60mg% timepoints which measured the ability of alcohol cues to orient attention, a central component of incentive salience (Duka & Townshend, 2004; Miller & Fillmore, 2010; Robinson & Berridge, 2008; Townshend & Duka, 2001). Analyses examined the effects of AUD severity on alcohol liking and wanting and tested whether incentive salience mediated the association between AUD severity and alcohol reinforcement. Based on IST it was hypothesized that AUD severity would predict greater alcohol wanting, but not liking, and would predict lower correlations between liking and wanting. It was also hypothesized that incentive salience would mediate the relationship between AUD severity and self-administration.

Overarching Goal

In order for researchers and society to optimally benefit from the precision of preclinical addiction research, it is necessary to establish that preclinical models accurately capture key aspects of human addictive pathology. Together these three papers serve to advance a novel human laboratory framework for translating preclinical models of addiction to clinical samples. Ultimately, the goal of this translational approach is to either validate preclinical neuroscience theories *vis a vis* human alcoholism, or promote refinement of preclinical paradigms so as to more accurately model human addiction.

PAPER I – Subjective Response Factors

Factor Structure of Subjective Responses to Alcohol in Light and Heavy Drinkers

Bujarski, S., Hutchison, K.E., Roche, D.J.O. & Ray, L.A. (2015) Factor Structure of Subjective Responses to Alcohol in Light and Heavy Drinkers. Alcoholism: Clinical and Experimental Research. 39(7), 1193-1202.

Abstract

Background: Subjective responses to alcohol (SR) have been implicated in alcoholism etiology, yet less is known about the latent factor structure of alcohol responses. The aim of this study is to examine the factor structure of SR using a battery of self-report measures during a controlled alcohol challenge.

Methods: Non-treatment seeking drinkers (N = 242) completed an intravenous alcohol challenge including the following SR measures: Biphasic Alcohol Effects Scale, Subjective High Assessment Scale, Profile of Mood States, Alcohol Urge Questionnaire, and single items assessing alcohol 'Liking,' and 'Wanting.' Ascending limb target Breath Alcohol Concentrations were 0.02, 0.04 and 0.06, and descending limb target was 0.04 g/dl. Exploratory factor analyses were conducted separately on estimates of mean and dose responses on the ascending limb and on descending limb data. To examine the generalizability of this factor structure these analyses were repeated in heavy drinkers (≥14 drinks/week for men, ≥7 for women; n = 132) and light drinkers (i.e. non-heavy drinkers; n = 110).

Results: In the full sample, a 4-factor solution was supported for ascending limb mean and dose responses and descending limb data representing the following SR domains: Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect. This 4-factor solution was replicated in heavy drinkers. In light drinkers however, SR was better summarized by a 3-factor solution where ascending mean and descending limb responses consisted of Stimulation/Hedonia, Craving/Motivation and a general negative valence factor, and dose responses consisted of a general positive valence factor, Sedation/Motor Intoxication and Negative Affect.

Conclusions: These findings suggest that SR represents a multifaceted construct with consistent factor structure across both ascending and descending limbs. Further, as drinking levels escalate more defined Craving/Motivation and negative valence dimensions may emerge. Longitudinal studies examining these constructs are needed to further our understanding of SR as potentially sensitive to alcohol-induced neuroadaptation.

Introduction

The acute subjective responses to alcohol (SR) are biphasic in nature (Earleywine, 1994; Earleywine & Martin, 1993; Martin et al., 1993), with individuals reporting stimulatory and hedonic subjective effects as breath alcohol content (BrAC) rises or is at a peak (King, de Wit, et al., 2011; Roche et al., 2014), and largely sedative and aversive effects as BrAC declines (Newlin & Thomson, 1990; Ray et al., 2009). While this pattern of SR has been characterized across numerous acute alcohol administration studies, individual SR has been shown to be highly variable and sensitive to a multitude of factors, including the alcohol dose that was administered and risk factors for development of an alcohol use disorder (AUD; King, de Wit, et al., 2011; Quinn & Fromme, 2011). In turn, the direction and magnitude of an individual's SR may play a significant role in their future alcohol use and risk for the development of an AUD. For example, in the laboratory, greater stimulatory and hedonic SR is associated with increased alcohol preference and self-administration (Corbin, Gearhardt, & Fromme, 2008; de Wit & Doty, 1994), whereas greater sedative and aversive SR, or reduced stimulatory and hedonic SR, are associated with decreased alcohol consumption and preference (Chutuape & de Wit, 1994; de Wit, Pierri, & Johanson, 1989). Furthermore, sons of alcohol dependent individuals (versus controls) display a reduced sedative/aversive SR in the laboratory (Schuckit, 1984) and this SR is predictive of future AUD development, independent of the risk conveyed by family history of alcoholism (Schuckit & Smith, 1996; Schuckit, Smith, & Kalmijn, 2004b). Further, heavy drinkers, compared to light drinkers, display greater stimulatory and hedonic SR during the rising BrAC limb and reduced sedative SR during the declining BrAC limb, a pattern which was predictive of future increases in binge drinking and the number of AUD symptoms (King, de Wit, et al., 2011; King et al., 2014; Roche et al., 2014). Given the variability in SR and its importance to understanding the development of AUD, clearly characterizing the nature and measurement of SR is a high research priority.

While SR has been well characterized and is relatively stable within individual samples of at-risk drinkers (Roche et al., 2014; Schuckit & Smith, 1996), there is little consilience on SR across studies or between different populations of at-risk drinkers. As a result, the role of independent dimensions of SR in

the development in AUD remains under debate (King, Roche, et al., 2011; Newlin & Renton, 2010; Schuckit, 2011). Both heightened and attenuated responses to alcohol have been theorized to contribute to AUD development among young adults with family history of the disorder or who regularly binge drink (King, de Wit, et al., 2011; King et al., 2014; Newlin & Renton, 2010; Newlin & Thomson, 1990; Quinn & Fromme, 2011; Schuckit, 2011; Schuckit & Smith, 1996). These seemingly paradoxical theories on the relationship between SR and AUD development have been speculated to be due to several methodological inconsistencies, including the use of multiple and disparate SR measures across alcohol administration studies (King, Roche, et al., 2011; Ray et al., 2009, 2010). For example, a seminal series of studies by Schuckit and colleagues has indicated that reduced SR, as measured by the Subjective High Assessment Scale (SHAS), is highly predictive of future AUD development (Schuckit & Smith, 1996; Schuckit et al., 2004b). However, the SHAS appears to best describe "maximum terrible feelings" in response to alcohol (Schuckit, 1985; Schuckit & Gold, 1988) or to be most strongly related to the sedative effects of alcohol (Ray et al., 2009, 2010). Thus, the aforementioned series of studies may have only characterized the role of the aversive or sedative SR in AUD development without considering the contribution of the hedonic and stimulatory dimensions of SR. This is relevant, as the degree of stimulatory and hedonic SR is predictive of AUD symptomatology in heavy drinkers (King, de Wit, et al., 2011; King et al., 2014) and the positively reinforcing effects of alcohol are prominent in theories of AUD development (Newlin & Thomson, 1990). Yet, while the King and colleagues experiments used multiple measures to ensure the assessment of stimulating, sedating, and hedonic components of the SR, they did not include the SHAS, rendering the comparison and synthesizing of findings with the Schuckit studies difficult.

While the concurrent use of multiple measures certainly provides a more comprehensive assessment of individual differences in SR, they also raise issues regarding how to best define the core constructs of SR and may even complicate the integration of findings in the alcohol administration literature because of the ambiguity of the relationship between the SR measures (Ray et al., 2009, 2010). A more parsimonious conceptual understanding of the multiple dimensions encompassing SR would help advance and integrate the seemingly paradoxical SR literature. To that end, a previous study by our group

(Ray et al., 2009) assessed SR across the rising BrAC limb during an alcohol administration study in a sample of heavy drinkers and examined the latent factor structure of SR as indexed by three commonly used measures: the Subjective High Assessment Scale (SHAS; Schuckit, 1984), the Biphasic Alcohol Effects Scale (BAES: Martin et al., 1993), and the Profile of Mood States (POMS: McNair, Lorr, & Droppleman, 1971). Results revealed a three-factor model which captured the following dimensions of subjective intoxication: (a) stimulation and other pleasant effects indexed by the BAES Stimulation subscale and the POMS Positive Mood and Vigor subscales; (b) sedation and unpleasant effects indicated by the BAES Sedation and SHAS; and (c) alleviation of tension and negative mood indexed by the POMS Tension and Negative Mood. Findings from this study support the notion that different measures of SR uniquely assess domains of individual differences in the phenomenology of the construct, and that SR is multifaceted and should not be simply defined as either positive or negative on a single dimension. Rather, SR at moderate levels of alcohol dosing appears to have concomitant dimensions of positive reinforcement, negative reinforcement, and punishment (Ray et al., 2009).

To further our understanding of SR, the goal of the present study is to characterize the psychological structure of SR using exploratory factor analysis on a battery of self-report measures during a controlled intravenous alcohol challenge. To extend the results of our prior factor analytic work (Ray et al., 2009) and to determine whether the factor structure of SR differs as a function of drinking pattern, the current study included two groups of drinkers (i.e., heavy and light drinkers). Furthermore, we seek to expand the conceptualization of SR measurement beyond the SHAS, BAES, and POMS via inclusion of a commonly used measure alcohol craving, the Alcohol Urge Questionnaire (Bohn et al., 1995; MacKillop, 2006) and measures of alcohol 'Liking' and 'Wanting' based on incentive sensitization theory (King, de Wit, et al., 2011; King et al., 2014; Robinson & Berridge, 2001). These additions are important for the promotion of consilience across alcohol challenge studies as no previous research has empirically established the structural relationship between craving, 'Liking,' 'Wanting' and SR domains. Further we will examine the factor structure of these SR domains on both the ascending and descending limb of alcohol intoxication. We hypothesized that we would replicate the 3-factor model previously observed in

heavy drinkers (Ray et al., 2009) with the addition of a fourth craving dimension. Further, as dose-dependent increases in SR along the ascending limb have been reported (e.g. King, de Wit, et al., 2011; Ray et al., 2009) this study characterized the latent factor structure of ascending limb SR at both the level of mean response, and response to an escalating dose in addition to descending limb SR. In light of previous work validating the BAES across ascending and descending limbs (Rueger, McNamara, & King, 2009) we hypothesized that the factor structure of SR would be consistent across these three levels of analysis.

Methods

Participants

This study was approved by the Human Research Review Committee at the University of New Mexico. Non-treatment seeking drinkers (N = 242) were recruited from the community through fliers and advertisements targeting regular drinkers over the age of 21. In order to reduce the possibility of adverse events in the alcohol challenge, participants were required to be regular drinkers reporting at least 3 or more drinks (2 for women) twice per week. Participants with a history of depression with suicidal ideation or lifetime psychotic disorder were excluded. Based on their past 60-day drinking history, participants were split into two groups based on whether they were heavy drinkers (N = 132; i.e. ≥ 14 drinks per week for men, ≥ 7 for women; NIAAA, 1995) or light drinkers (N = 110; < 14 (7 for women) drinks per week).

Screening Procedure

Initial eligibility was conducted via telephone screening, and eligible participants were then invited to a laboratory session. Upon arriving to the laboratory, participants provided written informed consent, were breathalyzed (Alcosensor IV from Intoximeters, Inc.), provided urine for a drug screen, and completed a battery of self-report questionnaires and interviews. All participants were required to test negative on a urine drug screen (except marijuana) and to have a BrAC reading of zero, otherwise they were rescheduled. Female participants were required to test negative for pregnancy. This in-person

assessment visit took approximately 2 hours after which time eligible participants traveled with the experimenter to a university-based hospital for the alcohol administration procedure.

Alcohol Administration Paradigm

Alcohol was administered intravenously in order to assess participants' subjective response to alcohol as distinct from learned responses to alcohol cues, and to allow for precise experimental control over BrAC (Li, Yin, Crabb, O'Connor, & Ramchandani, 2001). Each participant was tested individually following an established infusion protocol (Ray, Bujarski, et al., 2013; Ray & Hutchison, 2004). Participants were seated in a recliner chair with an IV placed in their non-dominant arm. Alcohol was administered using a 5% alcohol solution. Participants were infused at a rate of 0.166 ml/min × body weight in kilograms (0.126 ml/min × body weight for females). The alcohol infusion started at half target rate, to ensure safety, and was then escalated to the full rate after 5 minutes of monitoring. BrAC was measured via breathalyzer every three to five minutes. Target ascending limb BrACs were 0.02, 0.04, and 0.06 g/dl. Upon reaching each target BrAC, infusion rates were reduced by half to maintain BrAC stable during testing (i.e. short-term clamping). Participants were told that they would receive alcohol but remained blinded to their BrAC throughout the experiment. The IV alcohol administration resulted in highly controlled BrAC levels at each assessment of the ascending limb: mean BrAC (SD): 0.020 (0.001), 0.040 (0.002), and 0.060 (0.002) g/dl. Participants took an average of 15.77 minutes to reach a BrAC of 0.02, 15.97 minutes (from assessment completion) to go from a BrAC of 0.02 to 0.04, and, 16.48 minutes to reach the last target BrAC of 0.06. Participants were maintained at each target BrACs for approximately 5-7 minutes while they completed self-reports of SR. After completion of the 0.06 assessments, the IV catheter was removed. Participants' BrAC was monitored via breathalyzer approximately every 5 minutes and participants completed one descending limb self-report battery (target BrAC 0.04 g/dl).

Measures

Alcohol Use Measures

The Timeline Follow-Back (TLFB) was administered in interview format to capture daily alcohol use over the 60 days prior to the visit (Sobell et al., 1988). Several indicators of alcohol use quantity and frequency were computed from the TLFB included drinks per drinking day (DPDD) and number of drinking days (Drinking Days). TLFB data were used to group participants based on their drinking pattern over the past 60 days (i.e., light vs. heavy drinking groups).

Subjective Response Measures

The following self-report measures were selected based on their frequent use in alcohol challenge research and were collected at the following BrAC time points: ascending 0.02, 0.04 and 0.06 g/dl and descending 0.04 g/dl. The Biphasic Alcohol Effects Scale (BAES) was used to capture self-reported feelings of stimulation and sedation in response to alcohol and is a reliable and valid measure (Erblich & Earleywine, 1995; Martin et al., 1993; Roche et al., 2014). In this sample, both BAES subscales were found to have excellent reliability at each BrAC time point (α's $\geq$ 0.83). The Subjective High Assessment Scale (SHAS) captured subjective feelings of alcohol intoxication. This measure was adapted from Schuckit (1984) and has been widely used in alcohol challenge studies (Ray et al., 2012, 2009). The SHAS was found to be highly reliable (α's $\geq$ 0.88). The Profile of Mood States (POMS) is a popular affect scale with four dimensions: positive mood, negative mood, vigor, and tension. This version of the POMS has been validated in the context of alcohol administration at the doses examined in the present study (Ray et al., 2009). The vigor and positive mood subscales were found to have good reliability at every time point (α's $\geq$ 0.85) and the tension and negative mood subscales had adequate internal-reliability (α's $\geq$ 0.61). The Alcohol Urge Questionnaire (AUQ) assesses state alcohol craving and has demonstrated high reliability in experimental studies including alcohol administration (Bohn et al., 1995; MacKillop, 2006). The AUQ was highly reliable (α's $\geq$ 0.84). Alcohol 'Liking' and 'Wanting' were assessed via single items from the Alcohol Rating Scale (Liking: "How much did you like the exposure to alcohol?"; Wanting: "Do you want to be infused with more alcohol?"; Hobbs et al., 2005). Both liking and wanting were rated on a 10-point Likert scale.

Data Analytic Strategy

In order to capture ascending limb subjective response to alcohol both at the level of mean response and across alcohol-dose, a series of linear multi-level random coefficient growth models were conducted on each SR variable. In these models, BrAC was centered at the 0.04 g/dl time point, and both intercepts and linear slopes along rising BrAC were estimated as random effects at the subject level. This analytic scheme is comparable to conducting an OLS regression in each subject with a mean centered predictor variable (BrAC), which produces an intercept value equal to the mean of the outcome, and a slope representing the linear effect of BrAC. This methodology thus allows for the estimation of individual participants' mean response (predicted value at the mean BrAC time point) and dose response (linear effect of an escalating alcohol dose) parameters, via empirical Bayesian estimation. This approach has been shown to be superior to conducting a series of ordinary linear regression in each subject independently, as it allows for parameter estimation with missing data, and utilizes data from all participants in parameter estimation, thus reducing the influence of random measurement error (Raudenbush & Bryk, 2001). These analytic procedures were selected for the following reasons: 1) To limit the number and redundancy of statistical tests. 2) Mean and dose-response variables represent more mathematically dissociable aspects of alcohol response (mean r = 0.39, versus 0.82 for individual time points), thus providing a stronger test of the true psychological structure of SR, particularly if a consistent factor structure is observed, and 3) To reduce the influence of random measurement error (Raudenbush & Bryk, 2001). Of note, the dose-response examined in this study is referring to the effect of a single escalating dose from a single alcohol administration. This is opposed to more traditional pharmacological dose studies where different doses are administered at separate sessions. All multilevel modeling was conducted using the lme function in the multilevel package (Bliese, 2008) in R version 2.13.1.

After these empirical Bayesian parameter estimates were computed for each subject, a series of exploratory factor analyses were conducted on the full sample to examine the latent factor structure of SR. Exploratory factor analysis was conducted using the fa function in the psych package (Revelle, 2014). A minimum residual extraction technique was used to minimize the risk of Heywood cases while still producing reliable indices of latent factor structure (Revelle, 2014) and the Scree test was used to

determine the number factors to extract (Velicer & Jackson, 1990). Oblique factor rotation via direct oblimin was used which allows factors to be correlated (Costello & Osborne, 2005). A factor loading threshold of 0.32 was used to determine item inclusion in a factor (Tabachnick & Fidell, 2001). While specific recommendations for adequate sample size in exploratory factor analysis have been contested in the statistics literature (e.g. Costello & Osborne, 2005), factor analyses performed in this study exceeded the canonical recommendation of ≥ 10 subjects per variable (B. S. Everitt, 1975).

Analytic procedures for descending limb data were nearly identical with a few exceptions. First, since descending limb data was only collected at a single time point, factor analytic techniques were applied to the SR raw data. Furthermore, owing to the lack of a clamping procedure on the descending limb, observed BrAC's at this time point were substantially more variable (SD = 0.007). Thus, only data from subjects with a measured BrAC ≥ 0.030 and ≤ 0.050 were included in the analyses (N = 200; 111 heavy drinkers and 89 light drinkers).

Results

Sample Characteristics

Sample characteristics are reported in **Table 1.** No differences were observed between drinking groups (i.e., light vs. heavy drinkers) in terms of demographic variables including cigarette smoking (*p's* ≥ 0.31). As expected, heavy drinkers reported greater drinking frequency and quantity and more alcohol related problems (*p's* < 0.001).

Ascending Limb Mean Response Factor Structure

For mean response over the ascending limb, examination of the Scree plot (**Figure 1A**) suggested a 4-factor solution for the full sample. These four factors cumulatively explained 73% of the variance in SR variables with each factor contributing a substantial amount of variance (21%, 18%, 18% and 15%). All items loaded ≥ 0.56 on their primary factor, and only one item, POMS Positive Mood, cross-loaded with both Factors 1 and 4 (loadings = 0.61 and -0.44 respectively).

As shown in **Table 2**, Factor 1 comprised the scales BAES Stimulation, POMS Positive Mood and POMS Vigor, suggesting that this factor represents a stimulatory and hedonic rewarding component

of SR. Factor 2 was indexed by the AUQ as well as the 'Liking' and 'Wanting' items, suggesting that it represents a craving or motivational component of subjective response to alcohol. Factor 3 was indexed by the BAES Sedation and the SHAS scales indicating that it represents the sedative and motor intoxication responses. Finally, Factor 4 was indicated by the POMS Tension and Negative Mood subscales as well as a negative loading of the POMS Positive Mood subscale suggesting that this factor represents a negative affect dimension. Factors were also found to correlate with one another (r-range -0.22 – 0.42, **Table 2**).

Ascending Limb Dose-Response Factor Structure

As with ascending limb mean response, examination of the Scree plot suggested a 4-factor solution for alcohol dose responses (**Figure 1B**). These 4 factors cumulatively explained 54% of the overall variance and each factor contributed a substantial amount of variance (17%, 16%, 12%, and 9%). All items loaded ≥ 0.33 on their respective factors. Each item loaded on one and only one factor.

The factor structure of ascending limb dose-responses was nearly identical to that observed for mean response (**Table 2**). Factor 1 comprised the BAES Stimulation and POMS Positive Mood and Vigor subscales. Factor 2 was indicated by the BAES Sedation subscale as well as the SHAS. Factor 3 was comprised by the AUQ, 'Liking' and 'Wanting.' Lastly, Factor 4 was comprised of the POMS Tension and Negative Mood subscales. Factors were also found to correlate with one another (r-range -0.10 – 0.31). These results revealed that, in the full sample, the factor structure of the ascending mean responses and the dose-responses were consistent, representing the four domains of: Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect.

Descending Limb Factor Structure

Four factors were also suggested for descending limb SR (**Figure 1C**). These factors cumulatively explained 71% of the overall variance and each factor contributed a significant amount of variance (20%, 19%, 17%, and 14%). Each item loaded ≥ 0.55 on their primary factor, though two items exhibited cross-loading. Specifically, POMS Positive Mood and POMS Negative Mood both loaded onto Factors 2 and 4 (**Table 3**).

The factor structure of descending limb alcohol responses was fully analogous to the results obtained for both mean and dose responses on the ascending limb (**Table 3**). Factor 1 comprised the BAES Stimulation and POMS Positive Mood and Vigor subscales. Factor 2 was indicated by the SHAS, the BAES Sedation, and the POMS Negative Mood subscales. Factor 3 was comprised of the AUQ, 'Liking' and 'Wanting.' Lastly, Factor 4 was comprised of the POMS Tension and Negative Mood subscales and negatively loading POMS Positive Mood. Factors were also found to correlate with one another (r-range -0.21 – 0.32). In sum, the factor structure of SR was found to be consistent across ascending and descending limbs representing the four domains of: Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect.

Factor Structure by Drinking Group

In order to examine whether the latent factor structure of alcohol responses was reliable across levels of drinking, the sample was split by weekly heavy drinking, followed by identical EFA procedures conducted in these groups separately.

The identified latent factor structure of alcohol response in heavy drinkers was fully analogous to that identified in the full sample (**Table 4**). Specifically, a 4 factor solution was suggested for ascending limb mean response with the 4 factors explaining 72% of the total variance with identical item clustering as with the full sample. A 4 factor solution was also suggested in terms of ascending limb dose-response and descending limb with identical item clustering as with the full sample (54% and 71% variance explained respectively). Thus, as with the full sample, in the heavy drinking subsample, alcohol responses at all levels of analysis were clustered into the 4 domains of Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect.

For light drinkers, a 3-factor solution was identified as the best solution for ascending limb mean response to alcohol (**Table 4**). These 3 factors explained 65% of the variance and each factor explained individually a substantial amount of variance (23%, 22%, and 20% respectively). In terms of mean response, Factors 1 and 3 were identical to the Stimulation/Hedonia and Craving/Motivation factors

identified in the full sample. The second factor however, was indexed by the BAES Sedation, SHAS, POMS Tension and POMS Negative Mood, suggesting a general negative valence dimension.

Three factors were also suggested for ascending limb dose response in light drinkers (51% variance explained; **Table 4**). In terms of alcohol dose response, the second and third factors were analogous to the Sedation/Intoxication and Negative Affect dimensions identified in the full sample. However, the first factor was comprised of the BAES stimulation, POMS Positive Mood, POMS Vigor, AUQ, 'Liking,' and 'Wanting' suggesting a general positive valence response dimension.

Among light drinkers, descending limb factor structure was nearly identical to that observed for ascending limb mean response. Specifically, three factors were observed (63% of variance explained) with a general negative valence Factor 1 indexed by the BAES Sedation, SHAS, and the POMS Tension and Negative Mood subscales. Factor 2 was indicated by the BAES Stimulation, POMS Positive Mood and Vigor subscales, and negative loading of the POMS Negative Mood subscale. Lastly, the third factor was comprised of the AUQ, 'Liking' and 'Wanting' and negative loading of the POMS Tension subscale.

Discussion

The goal of this study was to promote consilience in alcohol challenge research through examination of the latent factor structure of SR as assessed using a battery of commonly used self-report measures and during a highly controlled intravenous alcohol challenge. In these analyses we were able to replicate a 3-factor structure of SR reported previously using the BAES, SHAS, and POMS measures (Ray et al., 2009) along the ascending limb at the level of both mean and dose response. This study also aimed to extend this multidimensional model by incorporating assessments of alcohol craving, 'Liking' and 'Wanting' in the conceptual framework of subjective response. Our results revealed that these three measures comprised a fourth Craving/Motivation factor. The inclusion of these additional items provides valuable insight into the structure of SR through incorporating craving and motivational salience, which are key constructs in alcoholism and addiction etiology (Addolorato et al., 2005; de Wit, 2000; Drummond et al., 2000; Robinson and Berridge, 1993, 2001). It should be noted that this study assessed alcohol-induced craving as opposed to unprovoked or cue-induced craving. Together these results suggest

that SR is a multidimensional construct with four distinct domains representing Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect. Furthermore, we were able to validate this four-factor structure on the descending limb of alcohol intoxication, thus providing much needed insight regarding the parallelism of SR structure on ascending versus descending limb. These results suggest that future alcohol challenge studies should assess these four domains of SR to ensure full coverage of alcohol's subjective effects while reducing the number of redundant comparisons and perhaps increasing power to detect meaningful effects.

As a secondary aim, this study assessed the generalizability of this factor structure to different drinking groups. To achieve this goal, participants were dichotomized into light drinkers or heavy drinkers based on a threshold of 14 drinks (7 for women) per week (NIAAA, 1995). The 4-factor structure identified in the full sample was fully maintained in the subsample of heavy drinkers. In light drinkers however, a three-factor structure was observed. Specifically, in terms of ascending limb mean response and descending limb, sedation and negative affect loaded on a single negative valence factor, and in terms of dose-response stimulation and craving loaded on a single positive valence factor. Together these results suggest that heavy drinkers may experience greater dissociation in terms of subjective response, whereas light drinkers are more inclined to report global positive or negative responses to alcohol. Alternatively, tolerance and sensitization to the effects of alcohol may influence specific domains of alcohol response that would result in greater dissociation of SR constructs in heavy drinkers as compared to lighter drinkers. Further research is needed to validate and disentangle these potential effects.

While some of the results were direct replications of previous research by our group (Ray et al., 2009), alcohol 'Liking' was expected to load with stimulation and hedonic domains (Bice and Kiefer, 1990; Hobbs et al., 2005; Robinson and Berridge, 1993, 2001). In these data however, 'Liking' was found to load with the AUQ and 'Wanting' to a greater extent than stimulation and positive affect scales. In fact, alcohol 'Liking' was most highly correlated with 'Wanting' (mean response: $r = 0.71$; dose-response: $r = 0.39$, descending: $r = 0.65$). These results stand in opposition to the predictions of incentive sensitization theory which proposes that hedonic reward and motivational salience are both phenotypically and

neurobiologically dissociable constructs, particularly in dependence (Robinson and Berridge, 1993, 2001). The high correlation between 'Liking' and 'Wanting' in these data may be influenced by the assessment procedure. This and many other similar alcohol challenge studies have assessed these two constructs with single items within a common measure, and thus proximal in time. As a result, it is possible that responses on the 'Liking' item may contaminate the assessment of 'Wanting' as subjects may recall their answer to their enjoyment of the alcohol dose when responding whether they would want more alcohol (Podsakoff and Organ, 1986; Salancik and Pfeffer, 1977). Studies that have utilized different assessment techniques for 'Liking' and 'Wanting' have demonstrated greater dissociation between these constructs (Hobbs et al., 2005).

Alternatively, the high correlation between 'Liking' and 'Wanting' in this sample may reflect the possibility that liking and wanting are still closely linked in many drinkers. 'Liking' is a fairly vague measure as it may reference both hedonic reward or alleviation of negative affect, and thus may simply be a global assessment of whether the subject had a net positive experience with the alcohol and thus would like to continue that experience, which would be expressed via wanting more alcohol. Conversely, the detailed assessment of Stimulation/Hedonia may capture in a more refined phenotype uniquely measuring a subset of positive and invigorating responses to alcohol. Recent work by our group has lent support to this idea that stimulation and hedonic assessments are sensitive to alcoholism-related differences in the association between hedonic reward and motivational salience as proposed by the incentive sensitization model of addiction (Bujarski and Ray, 2014).

Recent scale construction work has argued that the BAES and the SHAS, do not adequately assess all four affective quadrants affected by alcohol consumption (i.e. high/low arousal × positive/negative valence; Morean et al., 2012, 2013). Thus, Morean et al (2013) have developed the four-factor Subjective Effects of Alcohol Scale (SEAS), which expands SR measures by assessing high arousal negative (e.g. "demanding," "rude," and "aggressive") and low arousal positive (e.g. "mellow," "relaxed," and "calm") domains. While the SEAS measure was not included in this study, our inclusion of the POMS invites comparison to the SEAS. Specifically, while the direction is reversed, the tension subscale

of the POMS contains identical items as the SEAS low arousal positive subscale (e.g. “calm,” and “relaxed”). Thus the tension subscale may be capturing a similar psychological construct as this SEAS subscale, though this proposition should be subjected to direct empirical investigation in future studies. However, while our data may have captured low arousal positive SR, no items in our data substantively overlapped with high arousal negative items.

This study and its findings should be interpreted in light of design strengths and limitations. Study strengths include the large sample size comprised of both light and heavy drinkers, the controlled alcohol administration methods, the reliance on multiple valid measures of subjective response to alcohol, and the analytic approach accounting for alcohol dosing, BrAC limb, and drinking pattern. Limitations include the moderate dose of alcohol, the lack of a saline or placebo control, and the lack of representation of more severe and chronic drinkers. As with all IV alcohol studies, this study sacrifices external validity for greater experimental control, and thus future research should validate the observed factor structure using more naturalistic designs (e.g. oral alcohol dosing). Lastly, while the timeframe of the alcohol administration was brief (~1.5hr) it is possible that acute sensitization and/or acute tolerance effects may have influenced the data and results.

In sum, this study extends alcohol challenge research by suggesting that SR is indeed a multifaceted construct, consistent with recent longitudinal work ascertaining its etiological contribution (King, de Wit, et al., 2011; King et al., 2014). Further, the observed distinction between light and heavy drinkers is consistent with the notion that alcohol exposure may alter the course of subjective response and this study suggest that heavy drinkers experience greater dissociation of SR dimensions as compared to light drinkers for whom alcohol’s effects may be more globally experienced as positive or negative. An important implication of this finding is that studies of SR in light drinkers may not translate effectively for heavy drinkers (and beyond) given that the structure of the core constructs differ. Future studies including more chronic alcohol users may reveal further structural differences in the SR constructs associated with level of alcohol use. Ultimately, longitudinal studies examining these constructs over the

course of drinking trajectories at the individual level are needed to further our understanding of SR as a dynamic construct that may be sensitive to neuroadaptation resulting from chronic alcohol intake.

Table 1

Sample characteristics and tests of drinking group differences.

	Light Drinkers (N = 110)	Heavy Drinkers (N = 132)	Statistical Test
Age	25.75 (4.04)	25.53 (4.32)	t = 0.41, $p = 0.68$
Sex (% Male)	65%	62%	X^2 (1) = 0.22, $p = 0.64$
Ethnicity (% White)	45%	52%	Fisher Exact $p = 0.31$
Education (years)	14.76 (2.49)	14.61 (2.21)	t = 0.48, $p = 0.63$
Cigarette Smoking Days (past 60)	20.03 (96.58)	21.53 (26.20)	t = 0.17, $p = 0.86$
DPDD	3.53 (1.61)	6.12 (2.80)	t = 8.60, $p < 0.001$
Drinking Days	16.27 (9.64)	32.89 (11.90)	t = 11.80, $p< 0.001$
Heavy Drinking Days	3.95 (4.47)	20.36 (11.90)	t = 13.68, $p < 0.001$
AUDIT	9.10 (4.33)	14.22 (5.04)	t = 8.41, $p < 0.001$

*Note: Ethnicity differences between groups were tested as a 5 level categorical variable and overall distribution of ethnicity was not found to differ between groups; however, for simplicity of presentation, only percent Caucasian is reported.

Table 2

Factor loadings and inter-factor correlations from the full sample. Significant factor loadings are bolded. In the full sample, a 4-factor solution was supported both for mean and dose responses representing the following SR domains: Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect.

	Ascending Limb Mean Response				**Ascending Limb Dose Response**			
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 1	Factor 2	Factor 3	Factor 4
BAES Stimulation	**0.75**	0.11	0.14	0.11	**0.48**	0.24	0.10	0.06
POMS Pos. Mood	**0.61**	0.02	0.18	**-0.44**	**0.63**	0.10	0.10	-0.17
POMS Vigor	**0.99**	-0.02	-0.08	0.04	**0.85**	-0.09	-0.06	0.04
AUQ	0.04	**0.56**	-0.04	0.09	0.18	0.12	**0.43**	-0.01
Liking	-0.02	**0.89**	0.09	-0.03	0.29	0.27	**0.38**	0.08
Wanting	0.02	**0.81**	-0.09	0.00	-0.06	-0.06	**0.85**	-0.01
BAES Sedation	0.01	-0.05	**0.94**	-0.01	-0.15	**0.74**	-0.07	-0.03
SHAS	0.00	0.10	**0.88**	0.07	0.05	**0.91**	0.01	0.02
POMS Tension	0.09	0.00	0.01	**0.90**	0.00	0.00	0.00	**0.87**
POMS Neg. Mood	-0.11	-0.06	0.20	**0.66**	-0.30	0.09	-0.02	**0.33**

	Inter-factor Correlations				Inter-factor Correlations			
		Factor 1	Factor 2	Factor 3		Factor 1	Factor 2	Factor 3
	Factor 2	0.33			Factor 2	0.14		
	Factor 3	0.29	0.42		Factor 3	0.31	0.22	
	Factor 4	-0.22	-0.11	0.21	Factor 4	-0.10	0.06	-0.10

Table 3

Descending limb factor loadings and inter-factor correlations from the full sample. Significant factor loadings are bolded. In the full sample, a 4-factor solution was supported descending limb alcohol responses representing the following SR domains: Stimulation/Hedonia, Craving/Motivation, Sedation/Motor Intoxication, and Negative Affect.

	Descending Limb			
	Factor 1	Factor 2	Factor 3	Factor 4
BAES Stimulation	**0.81**	0.10	0.07	0.08
POMS Pos. Mood	**0.56**	0.23	0.02	**-0.42**
POMS Vigor	**0.96**	-0.08	-0.01	0.02
AUQ	0.10	-0.03	**0.65**	0.23
Liking	0.06	0.18	**0.64**	-0.10
Wanting	-0.04	-0.04	**0.91**	-0.06
BAES Sedation	-0.04	**0.88**	0.00	0.00
SHAS	0.07	**0.90**	0.03	0.05
POMS Tension	0.07	0.03	-0.05	**0.88**
POMS Neg. Mood	-0.16	**0.34**	0.01	**0.55**

	Inter-factor Correlations		
	Factor 1	Factor 2	Factor 3
Factor 2	0.32		
Factor 3	0.27	0.31	
Factor 4	-0.21	0.19	-0.17

Table 4

Factor loadings and inter-factor correlations in light and heavy drinkers. Significant loadings are bolded. In heavy drinkers, the factor structure was analogous to the full sample. In light drinkers SR was better summarized by a 3-factor solution where mean responses consisted of Stimulation/Hedonia, Craving/Motivation and a general negative valence factor, and dose responses consisted of a general positive valence factor, Sedation/Motor Intoxication and Negative Affect.

Ascending Limb Mean Response

	Light Drinkers			Heavy Drinkers			
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 4
BAES Stimulation	**0.70**	0.27	0.09	**0.83**	0.09	0.05	0.11
POMS Pos. Mood	**0.84**	-0.11	0.09	**0.56**	0.22	0.02	**-0.52**
POMS Vigor	**0.93**	0.03	-0.13	**0.95**	-0.08	0.02	0.02
AUQ	-0.02	0.16	**0.53**	0.04	-0.09	**0.55**	0.08
Liking	0.00	0.04	**0.87**	-0.01	0.14	**0.84**	0.02
Wanting	-0.05	0.02	**0.82**	0.02	-0.10	**0.79**	-0.07
BAES Sedation	0.14	**0.83**	0.09	0.02	**0.93**	-0.03	-0.04
SHAS	-0.22	**0.60**	-0.28	-0.01	**0.87**	0.11	0.10
POMS Tension	-0.30	**0.58**	-0.20	0.12	0.02	-0.01	**0.93**
POMS Neg. Mood	0.10	**0.81**	0.22	-0.14	0.26	-0.08	**0.63**

Inter-factor Correlations			Inter-factor Correlations			
	Factor 1	Factor 2		Factor 1	Factor 2	Factor 3
Factor 2	0.15		Factor 2	0.26		
Factor 3	0.38	0.31	Factor 3	0.39	0.36	
			Factor 4	-0.23	0.15	-0.15

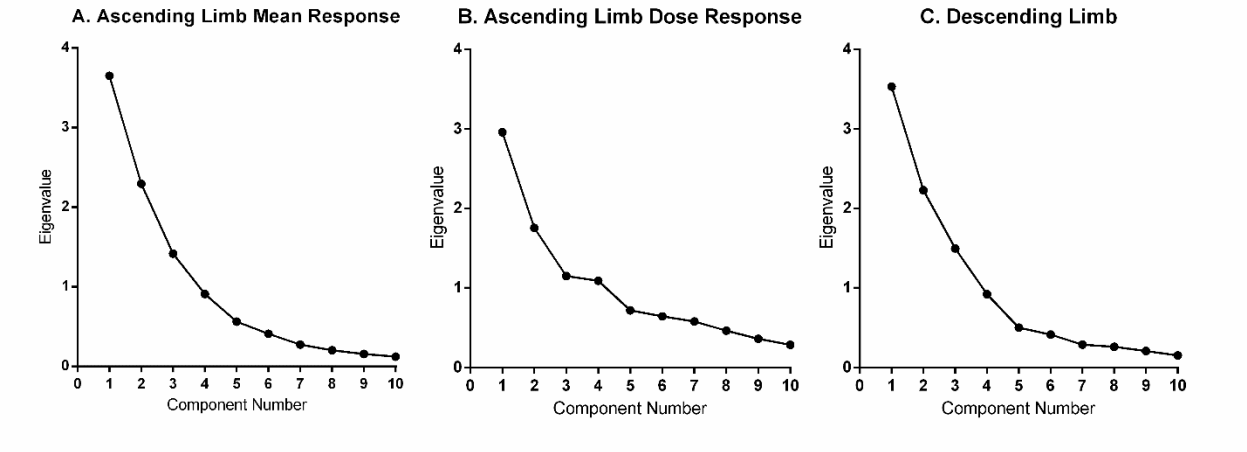
Ascending Limb Dose Response

	Light Drinkers			Heavy Drinkers			
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3	Factor 4
BAES Stimulation	**0.68**	0.03	0.11	0.29	**0.48**	0.10	0.13
POMS Pos. Mood	**0.55**	0.07	**-0.51**	0.10	**0.60**	0.10	0.03
POMS Vigor	**0.71**	-0.16	-0.11	-0.10	**0.85**	-0.06	-0.05
AUQ	**0.56**	0.10	0.14	0.03	0.02	**0.70**	-0.08
Liking	**0.63**	0.22	-0.04	0.29	0.17	**0.42**	-0.03
Wanting	**0.43**	0.06	-0.14	-0.08	-0.05	**0.78**	0.05
BAES Sedation	-0.15	**0.90**	-0.07	**0.68**	-0.15	-0.05	-0.02
SHAS	0.28	**0.79**	0.10	**0.89**	0.03	0.01	0.00
POMS Tension	0.19	-0.06	**0.60**	0.10	-0.02	-0.15	**0.33**
POMS Neg. Mood	-0.27	0.20	**0.48**	-0.01	0.00	0.00	**1.00**

Inter-factor Correlations			Inter-factor Correlations			
	Factor 1	Factor 2		Factor 1	Factor 2	Factor 3
Factor 2	0.21		Factor 2	0.09		
Factor 3	-0.30	0.07	Factor 3	0.21	0.25	
			Factor 4	0.03	-0.12	0.00

Figure 1

Scree plots of subjective responses to alcohol in the full sample in terms of (A) ascending limb mean response across the alcohol challenge, (B) change in response along an ascending limb alcohol dose, and (C) descending limb of the alcohol challenge.



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PAPER II – Positive and Negative Reinforcement

Testing the Transition from Positive to Negative Reinforcement in Alcoholism: Application of a Novel Experimental Paradigm in a Clinical Sample

Abstract

Background: Neuroscientific models of addiction developed in preclinical laboratories benefit from unparalleled neurobiological precision, however the degree to which these models map onto human psychopathology is unknown. The Allostatic Model, proposes that alcoholism is characterized by a transition from positive reinforcement in early alcohol use to abstinence-related dysphoria and negative reinforcement in late-stage dependence. The aim of this study is to test this transition in humans.

Methods: Heavy drinking participants representing a range of alcohol use disorder (AUD) severity completed a novel intravenous alcohol administration paradigm that included a standardized alcohol challenge (target BAC = 60mg%), followed by a progressive ratio self-administration paradigm. Participants reported on their subjective responses to alcohol (SR) during the challenge along the domains of stimulation/hedonia, negative affect, sedation, and alcohol craving. Analyses tested whether AUD severity predicted SR and/or self-administration, and whether the associations between SR and self-administration were moderated by AUD severity.

Results: AUD severity predicted greater alcohol craving and greater self-administration BAC curves. Furthermore, alcohol craving during the challenge robustly predicted self-administration. AUD severity did not predict stimulation, and stimulatory/hedonic responses did not predict self-administration regardless of AUD severity. AUD severity was associated with greater basal negative affect; however, alcohol-related alleviation of negative affect did not differ by AUD severity and negative affect did not predict self-administration. Self-reported sedation was punishing in that it predicted lower levels of self-administration.

Conclusions: This study represents a novel approach to translating neuroscientific theories developed in animal models to the human laboratory. Contrary to the Allostatic Model, these results supported neither a transition from positively reinforced alcohol consumption, nor a transition to negative reinforcement. These results were more consistent with models developed in human experimental laboratories including the Differentiator and Low Level of Response models of SR and AUD liability.

Introduction

Alcohol Use Disorder (AUD) is a highly prevalent and costly psychiatric disorder (Merikangas & McClair, 2012; Rehm et al., 2009), yet scientific consensus regarding etiology is lacking. Both researchers and clinicians alike have long recognized AUD as a chronic and relapsing condition, strongly influenced by both genetic and psychosocial factors (Kendler, Prescott, Neale, & Pedersen, 1997; Ray, 2012; Verhulst, Neale, & Kendler, 2015). Preclinical and human subjects research have identified the biobehavioral responses to alcohol as an integral component of alcoholism risk and disease progression (King, de Wit, McNamara, & Cao, 2011; Koob & Le Moal, 1997; Newlin & Thomson, 1990; Robinson & Berridge, 1993; Schuckit, 1984).

Though addiction research of all kinds aims to explain a human condition, human subjects research is limited in neurobiological precision and experimental control. Conversely, preclinical models allow researchers to measure biological function at a level of granularity wholly unattainable in human subjects. However, the degree to which preclinical models map onto human psychopathology is often evidenced by face validity. The aim of this study therefore, is to test the degree to which one prominent preclinical model of alcoholism etiology, the Allostatic Model (Koob & Kreek, 2007; Koob & Le Moal, 1997; Koob & Volkow, 2009) predicts the behavior and affective responses of human subjects in an experimental pharmacology design. The Allostatic Model was selected for translational investigation due to its focus on reward and reinforcement mechanisms in early vs. late stages of addiction. In this study, we advance a novel translational human laboratory approach to assessing the relationship between alcohol-induced reward and motivated alcohol reinforcement.

The Allostatic Model is based on the understanding that addiction involves both impulsivity and compulsivity. Impulsivity, or enhanced behavioral sensitivity to reward, is a well-established risk factor for addictive disorders generally (Courtney et al., 2012; de Wit, 2009; Jentsch et al., 2014; Verdejo-García, Lawrence, & Clark, 2008) and is mediated primarily by dopaminergic projections in midbrain (Buckholtz et al., 2010; Jentsch & Taylor, 1999; Johansen et al., 2009). Compulsivity on the other hand is characterized by aversive affective states which are alleviated by the compulsive behavior (American

Psychiatric Association, 2013; Carr, 1974), and persist even in the face of recurrent adverse consequences (Everitt & Robbins, 2005; Koob, 2009). Thus, impulsivity and compulsivity are associated with positive and negative reinforcement respectively (Koob & Volkow, 2009). The Allostatic Model also builds on opponent process theory by suggesting that repeated drug administration causes the opponent 'B' process, which counteracts the hedonic response to the drug (the 'A' process), to strengthen, whereas the 'A' process is blunted (Koob & Le Moal, 1997). The result of this neuroadaptation is blunted hedonic reward and positive reinforcement, yet persistent elevations in negative emotionality when the drug is not present, termed allostasis and enhanced negative reinforcement (Koob, 2004; Koob & Kreek, 2007; Koob & Le Moal, 1997; Koob & Volkow, 2009).

The Allostatic Model is supported primarily by chronic ethanol vapor paradigms in rodents which produce severe withdrawal symptoms, high levels of ethanol self-administration, high progressive ratio breakpoints, enhanced reinstatement, and reduced sensitivity to punishment (Deroche-Gamonet, Belin, & Piazza, 2004; Koob, 2009, 2009; Koob & Kreek, 2007; Koob & Le Moal, 1997; O'Dell, Roberts, Smith, & Koob, 2004; Vanderschuren & Everitt, 2004; Vengeliene, Celerier, Chaskiel, Penzo, & Spanagel, 2009). Diminished positive reinforcement in this dependence state is inferred through examination of reward thresholds using electrical stimulation techniques in the medial forebrain bundle (Koob, 2009; Koob & Kreek, 2007; Schulteis & Liu, 2006; Schulteis, Markou, Cole, & Koob, 1995). Concurrently to diminished reward, the Allostatic Model suggests that neuroadaptation in the extended amygdala (defined in Heimer & Alheid, 1991), primarily HPA-axis hyperfunctionality, produces prolonged negative affectivity in drug abstinence which serves to motivate drug seeking through negative reinforcement mechanisms (Koob, 2009, 2010, 2013, Koob & Le Moal, 2005, 2008).

Decades of alcohol challenge research in human subjects have demonstrated that individuals vary dramatically in their subjective responses to alcohol (SR) and that these differences affect alcoholism risk (King, de Wit, et al., 2011; King, McNamara, Hasin, & Cao, 2014; King, Roche, & Rueger, 2011; Schuckit, 1984; Schuckit & Smith, 1996). The relationship between SR and AUD is highlighted in two competing models. The Low Level of Response (LR) Model suggests that decreased sensitivity to

alcohol's subjective effects predicts AUD, because low responders need to consume more alcohol to reach desired subjective effects (Schuckit, 1984, 1994; Schuckit & Smith, 1996). Critically however, research has demonstrated that SR is a multi-dimensional construct comprised of stimulation/hedonia, sedation/motor intoxication, negative affect, and craving dimensions (Bujarski, Hutchison, Roche, & Ray, 2015; Ray, MacKillop, Leventhal, & Hutchison, 2009). The Differentiator Model dissociates stimulation and sedation and suggests that diminished sedation and/or enhanced stimulation responses predict future alcohol dependence.

Both the LR and Differentiator models have garnered considerable empirical support in terms of prospective prediction of AUD risk, associations with family history, and behavioral genetics, though both models share some limitations. With few exceptions (e.g. Bujarski, Hutchison, Prause, & Ray, 2015; Bujarski & Ray, 2014b; Hobbs, Remington, & Glautier, 2005), human subjects research has not examined whether the function of SR in promoting alcohol consumption is responsive to, or even causally related to the development of AUD. This gap in the literature is particularly salient as dynamic changes in the function of SR over AUD development is a central tenet of several prominent preclinical models of alcoholism etiology including the Allostatic Model (Koob & Le Moal, 1997) and Incentive Sensitization Theory (IST: Robinson & Berridge, 1993, 2001).

In two previous studies, we showed that stimulation/hedonia and craving are highly correlated among non-dependent heavy drinkers, whereas no stimulation-craving association was evidenced among alcohol dependent participants (Bujarski, Hutchison, Prause, et al., 2015; Bujarski & Ray, 2014b). These results were interpreted as consistent with the Allostatic Model insofar as the functional significance of hedonic reward in promoting craving appeared diminished in alcohol dependence. Of note however, neither study observed a relationship between negative affect and craving, which was hypothesized to be present in dependent participants. A primary limitation of these previous studies was the utilization of craving as a proxy endpoint for alcohol motivation and reinforcement.

This study examines whether SR predicts motivated alcohol self-administration and whether this relationship is moderated by AUD severity thus providing much needed insight about the function of SR

in alcohol reinforcement. Furthermore, this study advances an experimental framework for translating preclinical etiological models to the human laboratory. Individuals with a range of AUD severity (sub-clinical heavy drinkers through severe AUD) completed an IV alcohol administration session consisting of a standardized alcohol challenge followed by progressive ratio self-administration. Based on the Allostatic Model it was hypothesized that a strong relationship between stimulation and self-administration will be observed among low AUD severity, whereas no such association would be observed among severe AUD. Conversely, it was hypothesized that negative affect would be a stronger predictor of alcohol self-administration among more severe AUD participants. These two hypotheses would thus capture dependence-related blunting of positive reinforcement, and enhancement of negative reinforcement as determinants of alcohol consumption.

Methods

Participants and Screening Procedures

This study was approved by the Institutional Review Board at the University of California, Los Angeles. Non-treatment seeking drinkers were recruited for a study on responses to alcohol from the Los Angeles community through fliers and online advertisements. Participants could receive up to $270 for their participation.

Initial eligibility screening was conducted via online survey and a follow-up telephone screening interview. Eligible participants were then invited to 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 (see Measures below). All participants were required to have a BrAC of 0.000 g/dl, and test negative on a urine drug screen (except marijuana). Female participants were required to test negative for pregnancy.

Inclusion criteria for this study were: (1) age between 21 and 45, (2) Caucasian ethnicity (due to a secondary behavioral genetic aim not reported here), (3) fluency in English, (4) current heavy alcohol use of greater than 14 drinks per week for men, or 7 for women, (5) if female, not pregnant or lactating; and be willing to use a reliable method of birth control (e.g., condoms) during the study, and (6) weigh less

than 265 pounds to reduce the likelihood of exhausting the alcohol supply during the alcohol administration. Exclusion criteria included: (1) current, or recent (past 30 days) treatment seeking for alcohol use, (2) current DSM-5 diagnosis of substance use disorder other than nicotine, or alcohol, (3) lifetime DSM-5 diagnosis of moderate to severe substance use disorder other than nicotine, alcohol, or cannabis, (4) current or lifetime diagnosis of schizophrenia, bipolar disorder, or a psychotic disorder, (5) current major depressive disorder with suicidal ideation, (6) current use of non-prescription psychoactive drugs, other than marijuana, as determined by urine toxicology screen and/or self-report, (7) use of marijuana more than twice weekly, (8) clinically significant physical abnormalities as indicated by physical examination or clinically significant elevation on liver functioning tests on a comprehensive metabolic panel, (9) history of chronic medical conditions, such as: HIV, hepatitis, chronic liver disease, ulcer disease, seizure disorder, neurological disease, cardiac disease, obstructed bowel, hypertension, hyperthyroidism, or a circulatory disease, (10) current use of any psychoactive medications, such as antidepressants, mood stabilizers, sedatives, anxiolytics, seizure medications, pain killers, stimulants, antipsychotics, or depressants, (11) score $\geq$ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989), indicating clinically significant alcohol withdrawal requiring medical management, and (12) fear of, or adverse reactions to needle puncture.

Alcohol Administration Session

For the alcohol administration, participants arrived at the Clinical and Translational Research Center (CTRC) at UCLA at 10:30am at which time their vitals, height, and weight were measured, and they were provided with a standardized high caloric breakfast. IV lines were set by registered nurses at approximately 11:30am and, after participants acclimated to the IV lines, participants completed the baseline assessments (see below). The alcohol infusion paradigm began at approximately 12:00pm and lasted a total of 180 minutes. To ensure all participants were safe to discharge, and to disincentivize low-levels of self-administration for early discharge, all participants were required to remain at the CTRC for

at least 4-hours. Participants were discharged at approximately 7:00pm, or until their BAC fell below 40mg% if they were not driving, or zero if they were driving.

Throughout the infusion, participants were seated in a comfortable chair in a private room. Participants were not able to view the infusion pump or technician's screen. To control distractions participants could watch a movie (BBC's Planet Earth), or listen to music. Study staff remained in the room to monitor the infusion, take breathalyzer readings, take vital signs, administer questionnaires, and answer questions, but did not significantly engage with participants.

Alcohol Infusion Parameters

To enable precise control over BAC and to dissociate biobehavioral responses to alcohol from cue-induced responses, alcohol was administered intravenously (6% v/v EtOH in saline prepared by the UCLA Research Pharmacy) using a physiologically-based pharmacokinetic model implemented in the Computerized Alcohol Infusion System (CAIS; Plawecki, Han, Doerschuk, Ramchandani, & O'Connor, 2008; Zimmermann et al., 2008, 2009; Zimmermann, O'Connor, & Ramchandani, 2013). CAIS estimates arterial BAC pseudo-continuously (every 30 seconds) based on the alcohol infusion time course and individual subject characteristics including sex, age, height, weight, as well as observed breathalyzer values. The CAIS system was modified for this study in collaboration with Drs. Ramchandani, Stangl, and O'Connor to seamlessly combine two alcohol administration paradigms. During the Challenge, participants were administered alcohol doses designed to reach target BACs of 20, 40, and 60mg%. Each rise took 15 minutes, after which BAC's were clamped while participants completed self-report questionnaires, and had their heart rate and blood pressure measured (~5 min). This Challenge procedure closely mirrors alcohol challenge studies by our group (e.g. Bujarski, Hutchison, Prause, et al., 2015; Bujarski & Ray, 2014b; Ray & Hutchison, 2004, 2007).

Following the 60mg% timepoint questionnaires, participants were instructed to use the restroom, and then began Self-Administration. During Self-Administration, participants were permitted to work (button press) to obtain additional "drinks" through the CAIS system according to a progressive ratio schedule. All participants were required to complete one alcohol self-administration to familiarize

themselves with the procedure (participants had previously viewed a demonstration). The progressive ratio was log-linear and determined through simulations and pilot testing:

$$\text{Requirement}_i = 10 \times e^{0.3 \times Ratio_i} + 8 \times Ratio_i - 1$$

This progressive ratio equation resulted in a requirement schedule ranging from 20 responses at ratio 1 through 3139 responses at ratio 20. As is standard in CAIS, each "drink" was designed to increase BAC by 7.5 mg% over 2.5 minutes, followed by a decent of -1 mg%/min (Zimmermann et al., 2008, 2009, 2013). During the alcohol delivery, the response button became inactive. For safety reasons, a maximum BAC limit was set at 120mg%. If at any point during the experiment, the next infusion would exceed this threshold, the response button was temporarily inactivated. Except for the first "drink" requirement, participants were given no instruction with respect to how much they should self-administer. After 180 minutes, the alcohol infusion ended, the IV line was removed, and participants were provided with a lunch.

Measures

Alcohol Use Disorder Severity Measures: The Structured Clinical Interview for DSM-5 (SCID; adapted from First, 2005) was administered by Master's level clinicians under the supervision of a licensed clinical psychologist (LAR). The SCID assessed for lifetime and current (i.e. past 3-months) alcohol use disorder and the exclusionary psychiatric diagnoses. The CIWA-Ar assessed for the severity of withdrawal symptoms (Sullivan et al., 1989). Participants also completed a 30-day timeline follow-back (TLFB) to determine drinking quantity and frequency (Sobell, Sobell, Leo, & Cancilla, 1988). Participants completed the following alcohol-related measures: the Alcohol Dependency Scale (ADS; Skinner & Allen, 1982), the Alcohol Use Disorders Identification Test (AUDIT; Allen, Litten, Fertig, & Babor, 1997), the Drinkers Inventory of Consequences (DrINC-2r; Miller, Tonigan, & Longabaugh, 1995), the Penn Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999), and the Obsessive Compulsive Drinking Scale (OCDS; Anton, 2000).

Other Baseline Measures: Naturalistic cigarette, and marijuana use were assessed using the TLFB (Sobell et al., 1988). Family history of alcohol related problems was ascertained via a family tree

questionnaire (Mann, Sobell, Sobell, & Pavan, 1985). The Fagerstrom Test for Nicotine Dependence assessed for smoking status and dependency (Payne, Smith, McCracken, McSherry, & Antony, 1994). Depressive symptomatology was assessed via the Beck Depression Inventory – II (Beck, Steer, & Brown, 1996).

Subjective Response to Alcohol Measures: Based on previous factor analytic by our group, SR was assessed along the four domains of Stimulation/Hedonia (Stimulation), Negative Affect, Sedation/Motor Intoxication (Sedation), and Craving capturing the constructs of positive reward, negative reward, punishment, and subjective motivation respectively (Bujarski, Hutchison, Roche, et al., 2015; Ray et al., 2009). Stimulation was measured using the Biphasic Alcohol Effects Scale Stimulation subscale (BAES; Martin, Earleywine, Musty, Perrine, & Swift, 1993; Rueger, McNamara, & King, 2009) and the Profile of Mood States Positive Mood and Vigor subscales (POMS; McNair, Lorr, & Droppleman, 1992; Ray et al., 2009). Sedation was measured via the BAES Sedation subscale and the Subjective High Assessment Scale (SHAS; Schuckit, 1984). Negative Affect was measured via the POMS Negative Mood and Tension subscales. Craving was measured by the Alcohol Urge Questionnaire (AUQ; Bohn, Krahn, & Staehler, 1995; MacKillop, 2006). While a full factor analysis is beyond the scope of this paper, bivariate correlation matrices across these SR measures at each timepoint were consistent with the factor structure identified in previous work (see supplemental). Therefore, 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.

Data Analysis

All analyses were conducted in **R** version 3.3.0 using base functions unless otherwise noted (R Development Core Team, 2008). In order to minimize the influence of measurement noise, and limit the number of statistical tests and false positive risk, a principal component analysis using the **princomp** function was conducted on AUD severity variables to generate an AUD Severity factor score, which then served as the primary predictor variable for subsequent analyses.

The data analytic plan was broken into three sections. First, the effect of AUD Severity on SR during the Challenge was tested via a series of multilevel models using the **lme** function in the **multilevel** package (Bliese, 2013). Multilevel modeling was utilized due to the nested structure of the data where observations (Level 1) are nested in participants (Level 2). In each model, the SR dependent variable was predicted by Challenge BAC timepoint (coded 0 – 3), AUD Severity factor score, and their interaction. Intercepts and BAC effects were treated as random at Level 2. Results of all multilevel models were plotted using **ggplot2** (Wickham, 2009) through computing expected values.

Second, a series of multilevel models were conducted testing whether AUD Severity predicted self-administration BAC curves. In total, CAIS generate 13,323 BAC estimates, or 198.85 ± 19.61 per subject. These estimates were extremely highly autocorrelated with an average absolute change from one estimate to the next of 0.67 ± 0.49mg%, and an average lagged correlation of 0.999. To address this extreme autocorrelation, estimated BAC values during the Self-Administration were averaged over 10 minute bins resulting in 698 BAC observations, or 10.42 ± 0.97 per subject. Visual inspection confirmed that these binned averages closely approximated the raw BAC curves well (see supplemental materials) and the degree of autocorrelation was substantially reduced. Mean absolute difference between adjacent bins was 5.06 ± 4.50mg%, and the average lagged correlation was 0.968, which represented a substantial decrease ($Z = 50.85$, $p < 0.001$). A polynomial model-building approach was utilized with these binned BAC values to test BAC curves as a function of AUD Severity, with Δ-2LR tests on nested models to test for overall model fit. As models differed in their fixed effects, full information maximum likelihood estimation was used. Level-1 autocorrelation was expected to be substantial and was thus modeled in all BAC curve analyses using an AR(1) structure. In addition to AUD Severity, Sex, Age, and BDI were tested as potential predictors of BAC curves. If significant, these characteristics were explored as covariates to test robustness of AUD Severity effects.

Third, to test whether Challenge SR predicted self-administration, SR variables were entered as Level 2 predictors of BAC curves overall and as moderated by AUD Severity. Consistent with our previous work, SR indices for each subject were computed via Empirical Bayesian (EB) estimation within

the multilevel modeling framework (Bujarski, Hutchison, Roche, et al., 2015). Specifically, for each SR variable, we computed a Level, the expected value of SR at the 40mg% BAC time point (the middle post-baseline time point), and a Slope, the expected linear change in SR over the Challenge (illustrated in supplemental materials). This approach is superior to conducting an OLS regression on each subject separately in that it allows for parameter estimation with missing data and utilizes data from all participants in parameter estimation, thus reducing the influence of random measurement error (Raudenbush & Bryk, 2001). EB estimates of Level and Slope across all SR domains were found to meaningfully vary between participants, and the degree of correlation between Level and Slope within an SR domain were relatively modest (see supplemental materials). These EB estimates of SR Level and Slope were then entered as Level 2 moderators of BAC curves. The model building approach started with a fully interactive model based on the polynomial function determined in section 2, followed by singular trimming of nonsignificant predictors for parsimony.

Results

Sample Characteristics

A total of 140 participants completed the in-person screening visit, 67 of whom were eligible for and completed the alcohol administration session (recruitment flowchart shown in **Figure 1**). Sample characteristics for study completers by AUD diagnostic severity are reported in **Table 1.** AUD diagnostic severity was not associated with demographic characteristics including Age ($F(3,63) = 1.88$, $p = 0.141$) or Sex (Fisher Exact $p = 0.812$). AUD diagnostic severity was related to depressive symptomatology (BDI-II score: $F(3,63) = 4.85$, $p = 0.004$) and most alcohol-related variables except drinks per drinking day, binge drinking proportion, family history of alcohol related problems and AUD age of onset (see **Table 1**). AUD diagnostic severity was not associated with cigarettes per day ($F(3, 63) = 0.16$, $p = 0.924$), FTND score ($F(3, 25) = 0.29$, $p = 0.831$), or days of marijuana use ($F(3, 63) = 0.86$, $p = 0.466$).

AUD Severity Factor

In order to minimize the influence of measurement noise, and limit the number of statistical tests and false positive risk, a principal component analysis was conducted on the following AUD severity

variables: (1) current AUD symptom count and (2) lifetime AUD symptom count from the SCID, (3) drinks per week, (4) drinks per drinking day, (5) drinking days per month, and (6) proportion of binge drinking days from the TLFB, and the (7) ADS, (8) AUDIT, (9) CIWA-Ar, (10) OCDS, and (11) PACS. Principal component analysis revealed a single component solution which explained 53% of the variance with all variables loading ≥ 0.495 on the AUD Severity factor (additional details in supplemental materials). AUD Severity factor score served as the primary predictor of interest.

Alcohol Administration Overview

BAC curves estimated by CAIS are displayed in **Figure 2**. Average duration of the Challenge was 70.66 ± 5.20 minutes, and the Self-Administration was on average 100.42 ± 5.10 minutes. BAC's during the Challenge were well controlled across all three timepoints (17.34 ± 2.00, 38.71 ± 3.21, and 59.10 ± 4.19 mg%). The duration of each timepoint clamp varied due to the inclusion of additional assessments in the 60mg% time point ($F(2,198) = 103.7$, $p < 0.001$; 20mg%: 7.58 ± 2.19; 40mg%: 6.72 ± 1.51; 60mg%: 11.36 ± 2.17).

Subjective Response to the Alcohol Challenge

Stimulation increased over BAC during the Challenge (B = 0.28, SE = 0.11, t = 2.56, df = 200, $p = 0.011$, **Figure 3A**). AUD Severity did not predict Stimulation as a main effect (B = -0.05, SE = 0.13, t = -0.38, df = 65, $p = 0.705$), or as a moderator of BAC slopes (B = 0.00, SE = 0.05, t = 0.01, df = 199, $p = 0.992$). Sex, Age, and BDI were not associated with Stimulation (p's ≥ 0.153). Thus, while Stimulation increased over the Challenge, it was not affected by AUD severity, nor other subject characteristic.

Sedation increased over the Challenge (B = 0.51, SE = 0.07, t = 7.48, df = 200, $p < 0.001$, **Figure 3B**). Participants with greater AUD Severity reported greater Sedation (B = 0.21, SE = 0.07, t = 2.83, df = 65, $p = 0.006$). The AUD Severity × BAC interaction was not significant (B = -0.03, SE = 0.03, t = -0.87, df = 199, $p = 0.387$). No sex or age differences were observed for Sedation (p's ≥ 0.278). Greater depressive symptomatology was associated with greater Sedation overall (B = 0.33, SE = 0.10, t = 3.33, df = 65, $p = 0.002$), though the BDI × BAC interaction was nonsignificant (B = -0.01, SE = 0.04, t = -0.33, df = 199, $p = 0.742$). The AUD Severity effect was not robust to controlling for BDI score (B =

0.13, SE = 0.08, t = 1.65, df = 64, $p = 0.104$). Thus, Sedation generally increased over the Challenge, and participants with greater severity reported greater sedation, though this latter effect was no longer significant after controlling for depression.

Negative Affect decreased over rising BAC (B = -0.26, SE = 0.06, t = -4.06, df = 200, $p < 0.001$, **Figure 3C**), and participants with greater AUD severity reported greater Negative Affect (B = 0.27, SE = 0.09, t = 3.05, df = 65, $p = 0.003$). The AUD Severity × BAC interaction was not significant (B = 0.03, SE = 0.03, t = 1.02, df = 199, $p = 0.310$). Sex differences were not observed in terms of Negative Affect (p*'s* ≥ 0.579). Older participants trended towards greater Negative Affect (B = 0.06, SE = 0.03, t = 1.87, df = 65, $p = 0.066$), with no difference in BAC slope (B = 0.00, SE = 0.01, t = -0.45, df = 199, $p = 0.651$). The AUD Severity effect was robust to covarying for Age (B = 0.23, SE = 0.09, t = 2.51, df=64, $p = 0.015$). As expected, greater depressive symptomatology predicted greater Negative Affect (B = 0.50, SE = 0.11, t = 4.49, df = 65, $p < 0.001$), though no differences in BAC slopes were observed (B = -0.06, SE = 0.04, t = -1.52, df = 199, $p = 0.130$). The AUD Severity effect did not survive controlling for BDI score (B = 0.13, SE = 0.09, t = 1.41, df = 64, p = 0.164). In sum, Negative Affect decreased with rising BAC, and AUD severity was associated with greater negative affect, though the effect of AUD severity was not robust to controlling for depressive symptomatology.

Lastly, Craving increased over the Challenge (B = 0.20, SE = 0.03, t = 5.74, df = 200, $p < 0.001$, **Figure 3D**), and greater AUD severity predicted greater craving (B = 0.18, SE = 0.04, t = 4.05, df = 65, $p < 0.001$). The AUD Severity × BAC interaction was nonsignificant (B = 0.00, SE = 0.02, t = 0.18, df = 199, p = 0.859). Male participants reported overall greater levels of alcohol craving (B = -0.51, SE = 0.20, t = -2.55, df = 65, $p = 0.013$), with no change in BAC slope (B = 0.02, SE = 0.07, t = 0.23, df = 199, $p = 0.817$). BDI was also associated with Craving (B = 0.17, SE = 0.06, t = 2.60, df = 65, $p = 0.012$), with no change in slope (B = -0.01, SE = 0.02, t = -0.53, df = 199, $p = 0.599$). The effect of AUD Severity on alcohol craving was robust to controlling for Sex and BDI (p's ≤ 0.002). No effects of age were observed (p's ≥ 0.160). Thus, rising BAC and greater AUD Severity were both associated with increased craving for alcohol, and the effect of AUD Severity was robust to controlling for Sex and BDI score.

Point Indicators of Self-Administration

Participants self-administered 10.85 ± 4.95 'drinks' on average. The average breakpoint was 605.39 ± 472.71 and the average maximum BAC reached by participants was 96.03 ± 21.42. Contrary to our expectations, these single point indicators of self-administration were not predicted by AUD Severity (*p's* ≥ 0.163).

AUD Severity and Self-Administration

To improve statistical power and analyze self-administration at a finer resolution than single point indicators, analyses were conducted on self-administration BAC curves. Using a fully interactive model with increasing order polynomial Trial parameters (i.e. bin number) and AUD Severity, the final fixed effects model was determined to be a quartic polynomial curve (cubic vs. quartic model: Δ-2LR = 46.59, df = 7, $p < 0.001$; quartic vs quintic Δ-2LR = 10.01, df = 8, $p = 0.264$). All Trial parameters were significantly random at the subject level (Δ-2LR's ≥ 41.17, df = 5, *p's* < 0.001). The highest order AUD Severity × $Trial^4$ interaction was trimmed ($p = 0.363$). AUD Severity significantly moderated linear through cubic Trial terms (AUD Severity × Trial: B = 1.20, SE = 0.60, t = 1.99, df = 624, $p = 0.048$; AUD Severity × $Trial^2$: B = -0.23, SE = 0.10, t = -2.35, df = 624, $p = 0.019$; AUD Severity × $Trial^3$: B = 0.01, SE = 0.01, t = 2.27, df = 624, $p = 0.024$), such that AUD Severity was associated with greater self-administration BAC curves (**Figure 4** and supplemental table). The AR(1) φ coefficient in the final model was 0.670. Thus, by capitalizing on the greater resolution and statistical power of modeling BAC curves as opposed to single point indicators, these results suggest that greater AUD severity predicted greater levels of self-administration, though the effects are relatively modest as compared to the full range of BAC curves observed (see **Figure 2**).

Male participants had greater self-administration BAC curves. Sex moderated quadratic and cubic trial terms ($p \leq 0.048$), and, at a trend level, linear and quartic terms ($p = 0.068$, and 0.062 respectively). Age moderated the linear BAC Curve parameter at a trend level ($p = 0.081$). The moderating role of AUD Severity on BAC curves was largely unaffected by covarying for Sex (AUD Severity × Trial: $p = 0.088$; $Trial^2$: $p = 0.038$; $Trial^3$: $p = 0.039$) or Age (AUD Severity × Trial: $p = 0.066$; $Trial^2$: $p = 0.020$; $Trial^3$: $p =$

0.026). BDI did not predict BAC curves. Thus, while the effect of AUD Severity was modest, it was robust to controlling for sex and age differences. See supplemental details for full model results and figures.

Craving and Self-Administration

As expected, and lending construct validity to the paradigm and analytic methods, Craving Level strongly predicted BAC curves (**Figure 5**). Specifically, Craving Level predicted linear through cubic Trial parameters (Trial: B = 4.94, SE = 1.42, t = 3.48, df = 624, $p < 0.001$, $Trial^2$: B = -0.82, SE = 0.23, t = -3.52, df = 624, $p < 0.001$, $Trial^3$: B = 0.04, SE = 0.01, t = 3.14, df = 624, $p = 0.002$) and intercept (B = 4.28, SE = 0.94, t = 4.57, df = 64, $p < 0.001$). Interestingly, after accounting for Craving Level, AUD Severity was no longer a significant moderator of BAC curve parameters (*p's* ≥ 0.305) suggesting that Craving Level was a full mediator *vis a vis* AUD Severity and self-administration. The effect of Craving Level was not moderated by AUD Severity (*p's* ≥ 0.151), and controlling for Sex and Age did not affect these results. In sum, alcohol craving during the Challenge was a significant predictor of BAC curves, and appeared to fully mediate the effect of AUD Severity.

Craving Slope over the challenge also predicted BAC curves at the linear and quadratic level (Trial: B = 12.16, SE = 5.03, t = 2.42, df = 622, $p = 0.016$, $Trial^2$: B = -0.95, SE = 0.39, t = -2.44, df = 622, $p = 0.015$; see supplemental materials). In this model, the effect of AUD Severity was relatively unaffected, suggesting that Craving Slope is not a mediator of the relationship between AUD Severity and self-administration. No Craving Slope × AUD Severity × Trial interactions were significant (*p's* ≥ 0.158). Interestingly, when covarying for Sex differences, several Craving Slope × AUD Severity × Trial interactions were trending towards significant ($Trial^2$: $p = 0.094$; $Trial^3$: $p = 0.069$; $Trial^4$: $p = 0.088$) such that the effect of Craving Slope was marginally greater among those with lower levels of AUD Severity (see supplemental materials). Controlling for Age did not affect these results. In conclusion, Craving Slope over the alcohol challenge independently predicted self-administration.

Positive Reinforcement Mechanism

Stimulation Level did not predict BAC curves either as a main effect ($p = 0.429$), or as a moderator of BAC curve parameters (p's ≥ 0.360; for full results see supplemental materials). Furthermore, AUD Severity did not moderate the relationship between Stimulation Level and BAC curves (p's ≥ 0.604). Covarying for Sex and Age did not affect these results. Thus, contrary to our hypotheses, Stimulation Level did not predict self-administration regardless of AUD severity.

At a trend level, Stimulation Slope positively predict BAC levels as a main effect (B = 2.08, SE = 1.21, t = 1.72, df = 64, $p = 0.090$, **Figure 6**). All other effects of Stimulation Slope were non-significant. Stimulation Slope did not moderate any BAC curve parameters (p's ≥ 0.174; see supplemental materials). All AUD Severity × Stimulation Slope interactions were nonsignificant (p's ≥ 0.247). After accounting for sex differences, the trend-level effect of Stimulation Slope became non-significant (B = 1.62, SE = 1.19, t = 1.36, df = 63, p = 0.180). Controlling for Age had no effect on these results. Thus, greater alcohol-induced stimulation slope may have predicted greater self-administration, but this effect was small and not robust to controlling for sex differences.

Negative Reinforcement Mechanism

Negative Affect Level did not predict BAC curves as a main effect ($p = 0.658$), or moderator of Trial parameters ($p \geq 0.438$; for full results see supplemental materials). AUD Severity did not moderate the relationship between Negative Affect Level and BAC curves either overall ($p = 0.994$), or in interaction with Trial parameters (p's ≥ 0.432). These results were unaffected by covarying for Sex and Age. Contrary to our expectations, Negative Affect Level did not predict self-administration regardless of AUD Severity.

The Negative Affect Slope × AUD Severity was trending toward significant (B = 3.18, SE = 1.88, t = 1.69, df = 63, $p = 0.095$) such that greater reductions in negative affect (i.e. more negative slopes) predicted greater self-administration among less severe participants, whereas this trend was reversed among greater AUD Severity (**Figure 7**). No other interactions involving Negative Affect Slope approached significance (p's ≥ 0.405). The AUD Severity × Negative Affect Slope trend was not robust to controlling for sex differences (B = 2.65, SE = 1.83, t = 1.45, df = 62, p = 0.153). Controlling for Age

did not affect these results. As with negative affect level and contrary to our hypotheses, greater reductions in negative affect during the alcohol Challenge, did not predict greater self-administration among more severe participants.

Punishment Mechanism

Sedation Level moderated linear, quadratic and cubic Trial parameters (Trial: B = -2.28, SE = 0.88, t = -2.60, df = 621, $p = 0.010$; $Trial^2$: B = 0.41, SE = 0.14, t = 2.90, df = 621, $p = 0.004$, $Trial^3$: B = -0.02, SE = 0.01, t = -2.87, df = 621, $p = 0.004$) such that greater Sedation predicted lower BAC curves (**Figure 8**). AUD Severity did not moderate any of these effects ($p's \geq 0.256$). These results were unaffected by covarying for sex and age differences.

The results for Sedation Slope were fully analogous to Sedation Level. Sedation Slope predicted linear through cubic BAC curve parameters (Trial: B = -7.77, SE = 3.64, t = -2.13, df = 621, $p = 0.033$; $Trial^2$: B = 1.52, SE = 0.58, t = 2.62, df = 621, $p = 0.009$; $Trial^3$: B = -0.09, SE = 0.03, t = -2.75, df = 621, $p = 0.006$, see supplemental materials). AUD Severity was not a moderator of the relationship between Sedation Slope and BAC curve parameters ($p's \geq 0.455$). Controlling for Sex and Age did not alter these results. Thus, consistent with the Differentiator and LR models, lower sedative responses to alcohol were found to predict greater self-administration independent of AUD severity.

Discussion

The aim of this study was to develop a human laboratory paradigm to translate predictions from the Allostatic Model to clinical research in heavy drinkers with and without AUD. The Allostatic Model suggests that AUD is the result of neurobiological adaptation that diminishes positive reinforcement while simultaneously producing abstinence-related dysphoria and increasing negative reinforcement (Koob & Kreek, 2007; Koob & Le Moal, 1997; Koob & Volkow, 2009). In this study, we utilized a novel intravenous alcohol administration paradigm in humans that seamlessly incorporates standardized alcohol challenge methods with progressive ratio self-administration. The standardized alcohol challenge captured subjective responses to alcohol that are positively rewarding (i.e. hedonic responses), negatively rewarding (i.e. alleviation of negative affect), punishing (i.e. sedative responses), and motivating (i.e.

craving responses). Through incorporating a progressive ratio self-administration paradigm, we were able to test whether subjective responses to alcohol predicted self-administration behavior, thus capturing the relationships between reward and reinforcement central to allostatic processes.

As expected, severity of alcohol use and problems was predictive of greater alcohol craving across the alcohol challenge, and predicted greater motivation for alcohol consumption as measured by self-administration BAC curves. Further validating the paradigm, these data demonstrated a robust relationship between self-reported craving for alcohol during the challenge and subsequent reinforcement behavior. Interestingly, the "average" level of craving served as a full mediator of the observed association between AUD severity and self-administration, suggesting that AUD severity only predicted self-administration insofar as it predicted increased craving during the alcohol challenge. Conversely, alcohol-induced changes in craving predicted self-administration independently of AUD severity. These results suggest that individuals' craving reactivity to a priming dose of alcohol may represent an independent risk factor for escalated alcohol consumption and motivation.

In terms of positive reinforcement, our hypotheses that stimulating and hedonic responses to alcohol would predict self-administration to a greater degree among less severe participants were not supported. First, although stimulation and hedonic responses increased in the challenge, the severity of AUD did not affect reported levels of stimulation. Second, and more importantly for determining the relationship between hedonic responses and motivation, stimulation did not predict self-administration behavior, save for one trend-level effect which was not robust to sex differences. Furthermore, AUD severity did not predict a diminishing relationship between hedonic reward and reinforcement as we hypothesized. These results stand in contrast to our previous reports which found that the relationship between hedonic reward and alcohol craving was blunted in dependence as compared to non-dependent heavy drinking (Bujarski, Hutchison, Prause, et al., 2015; Bujarski & Ray, 2014b). However, one of the central limitations of these previous studies was the use of craving as a proxy endpoint for reinforcement, and thus our previous results may not generalize to actual motivated alcohol consumption in spite of

reliable relationships between craving and self-administration (Stangl et al., 2017; Wardell, Ramchandani, & Hendershot, 2015).

Regarding enhanced negative reinforcement, our hypotheses that negative affect would be a stronger predictor of alcohol self-administration among more severe AUD participants were only partially supported. AUD severity was associated with greater levels of depressive symptomatology ($r = 0.423$, $p < 0.001$), and negative affect during the challenge. However, alcohol's effects in alleviating negative affect was not influenced by AUD severity meaning greater negative reward was not observed in more severe AUD. Furthermore, but for one effect that was not robust to controlling for sex differences, negative affect did not predict reinforcement behavior and AUD severity had no effect on whether negative affect predicted self-administration. Thus, we did not observe negative reinforcement regardless of the severity of alcohol dependence.

While these negative affect findings are commensurate with our previous studies which found small or null effects with respect to craving (Bujarski, Hutchison, Prause, et al., 2015; Bujarski & Ray, 2014b), they appear inconsistent with a body of literature that has demonstrated robust relationships between negative affect and alcohol use both cross-sectionally (Bujarski & Ray, 2014a; Carpenter & Hasin, 1999; Greeley & Oei, 1999; Kessler et al., 1994; Prescott, Aggen, & Kendler, 2000) and prospectively (Jackson & Sher, 2003; Schmidt, Buckner, & Keough, 2007). Difference in granularity may explain these discrepant results. This study tested short term predictive relationships between state negative affect and alcohol self-administration in a highly-controlled laboratory setting. This contrasts with survey-based research testing the relationship between trait or trait-like mood and naturalistic alcohol consumption. These discrepant results could be explained if negative affect promoted alcohol consumption as a general, though maladaptive, coping strategy based on inaccurate, or exaggerated beliefs about the efficacy of alcohol in reducing negative affect (Carpenter & Hasin, 1999; Glöckner-Rist, Lémenager, & Mann, 2013). It is also possible that negative affect relief, particularly among individuals with severe AUD, occurs at much higher BACs than those examined in this study. Though our design precludes strong claims on this possibility, these data provide no evidence that simply consuming more

alcohol would result in a greater reduction in negative affect in severe AUD. Conversely, negative affect appeared to be more stable at greater AUD severity, though it is not a significant interaction.

In terms of sedating and intoxicating responses to alcohol, these results were partially consistent with the Differentiator and Low Level of Response Models which suggest that sedation is protective for future heavy drinking (King, de Wit, et al., 2011; Newlin & Thomson, 1990; Schuckit, 1984, 1994). Although sedation responses to the challenge increased with greater AUD severity (which ran counter to LR and Differentiator models), greater sedation during the alcohol challenge robustly predicted lower levels of reinforcement during self-administration. This result highlights that sedation is punishing insofar as greater sedation predicted reduced motivation for additional alcohol. The fact that this study recruited no light, or moderate drinkers may explain the counterintuitive findings regarding sedation responses during the challenge as most other studies compare lighter drinkers to heavy drinkers (Morean & Corbin, 2010; Quinn & Fromme, 2011).

In total, these data provided scant evidence for the Allostatic Model in a human laboratory paradigm. Contrary to our hypotheses of diminishing positive reinforcement in severe AUD, no differences in hedonic responses to alcohol were observed across AUD severity and AUD severity did not predict whether hedonic reward promoted reinforcement behavior. In terms of negative reinforcement, we did observe greater negative affect among more severe AUD, however, alleviation of negative affect during the challenge was not greater among more severe participants, and negative affect did not predict self-administration regardless of AUD severity. Thus, these data provide evidence for neither a transition *from* positively reinforced alcohol consumption, nor a transition *to* negative reinforcement. These null results stand in contrast to robust associations between craving and self-administration, and protective effects of sedation, both of which were observed in this study and are consistent with models derived in human subjects research.

This study should be interpreted in light of its strengths and weaknesses. The study benefits chiefly from a novel, highly controlled, and translational alcohol administration paradigm which measures alcohol reward and reinforcement, and isolates cue-reactivity. Limitations include the fact that

participants were required to be non-treatment seeking and able to produce a zero on a breathalyzer test. These exclusion criteria may have impeded our ability to recruit very severe AUD patients. While participants classified as severe per DSM-5 (American Psychiatric Association, 2013) were enrolled, this subgroup was considerably smaller than other groups, and generally represented the lower range of severe AUD with respect to symptom count (6.57 ± 0.79 symptoms). Ethical standards limit the recruitment of treatment-seeking participants in alcohol administration studies (Dolinsky & Babor, 1997; Enoch et al., 2009). However, the available data suggests that participation in alcohol administration studies does not increase naturalistic drinking, and in fact tends to decrease alcohol consumption (Pratt & Davidson, 2005; Sinha, Krishnan-Sarin, Farren, & O'Malley, 1999; Sommer et al., 2015). The ethanol vapor paradigm, which was used primarily to establish the Allostatic Model, induces very high levels of physiological dependence with severe withdrawal (Kantak & Luzzo, 2007; Macey, Schulteis, Heinrichs, & Koob, 1996). Therefore, it is possible that allostatic neuroadaptation occurs at very high levels of dependence which likely would be excluded from this study based on indication for medically managed detoxification and/or inability to produce a zero on a breathalyzer test (Sullivan et al., 1989). The substantial BAC curve ceiling effect, where 36% of participants were impacted by our safety threshold (120mg%), may also have affected out results. Lastly, though this study was cross-sectional in terms of AUD status, the Allostatic Model focuses on neuroadaptation and is thus necessarily longitudinal. King et al. (2016) recently showed SR to be fairly stable over 5 years; however, it is unknown whether the function of SR in promoting alcohol consumption is more or less dynamic than the SR magnitudes themselves. It is possible, for example, that participants who have developed moderate-to-severe AUD over the course of several years may still report high levels of stimulation/hedonia at follow-up, but their choices to consume large amounts of alcohol may be unrelated to these euphorigenic effects.

In conclusion, this study represents a novel approach to translating neuroscientific theories developed in animal models to the human laboratory. These data found that AUD severity predicted greater alcohol craving which in turn predicted self-administration. Furthermore, self-reported sedation was protective and predicted lower levels of self-administration. Conversely, little evidence for the

allostatic processes of diminished positive reinforcement and enhanced negative reinforcement in more severe AUD was observed. Taken together, these results were more consistent with the Differentiator and Low-Level of Response Models which were developed in human experimental laboratories. Further studies refining and enhancing this translational paradigm, for example through including affective manipulations to test the role of stress in reward and reinforcement are warranted. Longitudinal studies would enable researchers to test whether changes in reward and reinforcement are observed across AUD development within individuals. Lastly, given the severity of dependence induced by preclinical paradigms, recruitment of more severe AUD samples is necessary for a robust translational examination.

Table 1

Sample characteristics of study completers by current DSM-5 AUD severity.

	AUD Severity - Current				
Variable	None (n=29)	Mild (n=15)	Moderate (n=16)	Severe (n=7)	Test Statistic, p-value
Demographics					
Age	27.45 (6.49)	29.67 (6.64)	29.94 (5.92)	33.57 (7.02)	$F(3,63) = 1.88$, $p = 0.141$
Sex (% Female)	14 (48%)	7 (47%)	8 (50%)	2 (29%)	Fisher Exact $p = 0.812$
Beck Depression Inventory-II*	4.79 (4.79)	9.93 (9.45)	11.94 (8.96)	14.43 (10.31)	$F(3,63) = 4.06$, $p = 0.011$
Alcohol Use Variables					
Drinks per Week	18.91 (11.67)	18.71 (7.76)	25.56 (9.30)	34.12 (25.38)	$F(3,63) = 3.57$, $p = 0.019$
Drinks per Drinking Day	5.00 (2.57)	4.61 (1.80)	6.14 (2.69)	6.09 (3.38)	$F(3,63) = 1.31$, $p = 0.279$
Drinking Days (past 30)	16.45 (6.18)	18.27 (6.26)	19.06 (5.85)	23.14 (7.58)	$F(3,63) = 2.31$, $p = 0.085$
Binge Proportion	0.45 (0.31)	0.49 (0.29)	0.58 (0.33)	0.56 (0.29)	$F(3,63) = 0.70$, $p = 0.555$
ADS	8.34 (4.29)	10.73 (5.51)	13.25 (3.82)	18.57 (4.61)	$F(3,63) = 11.21$, $p < 0.001$
AUDIT	10.31 (4.23)	11.60 (3.22)	16.63 (4.00)	23.00 (6.22)	$F(3,63) = 21.36$, $p < 0.001$
CIWA	0.41 (0.63)	1.27 (1.39)	1.44 (1.26)	2.14 (2.54)	$F(3,63) = 4.83$, $p = 0.004$
OCDS	5.59 (2.16)	8.13 (2.61)	10.81 (3.83)	17.29 (6.24)	$F(3,63) = 26.94$, $p < 0.001$
PACS	6.93 (3.51)	9.07 (4.01)	11.81 (6.15)	18.14 (6.96)	$F(3,63) = 11.74$, $p < 0.001$
Family History Positive	11 (44%)	6 (46%)	9 (56%)	4 (57%)	Fisher Exact $p = 0.872$
Alcohol Use Disorder					
AUD Symptoms Lifetime	2.03 (1.70)	4.13 (2.00)	5.44 (1.36)	8.14 (1.46)	$F(3,63) = 31.40$, $p < 0.001$
AUD Age of Onset (n=53)	20.20 (2.43)	21.00 (3.76)	20.94 (4.89)	20.71 (4.23)	$F(3,49) = 0.13$, $p = 0.941$
AUD Symptoms Current	0.52 (0.51)	2.40 (0.51)	4.13 (0.34)	6.57 (0.79)	$F(3,63) = 350.5$, $p < 0.001$
AUD Severity Factor	-1.26 (1.09)	-0.05 (1.07)	1.57 (1.05)	4.14 (2.51)	$F(3,63) = 40.75$, $p < 0.001$

*Beck Depression Inventory-II scores were square-root transformed to improve normality for analyses.

Figure 1

Study Recruitment Overview

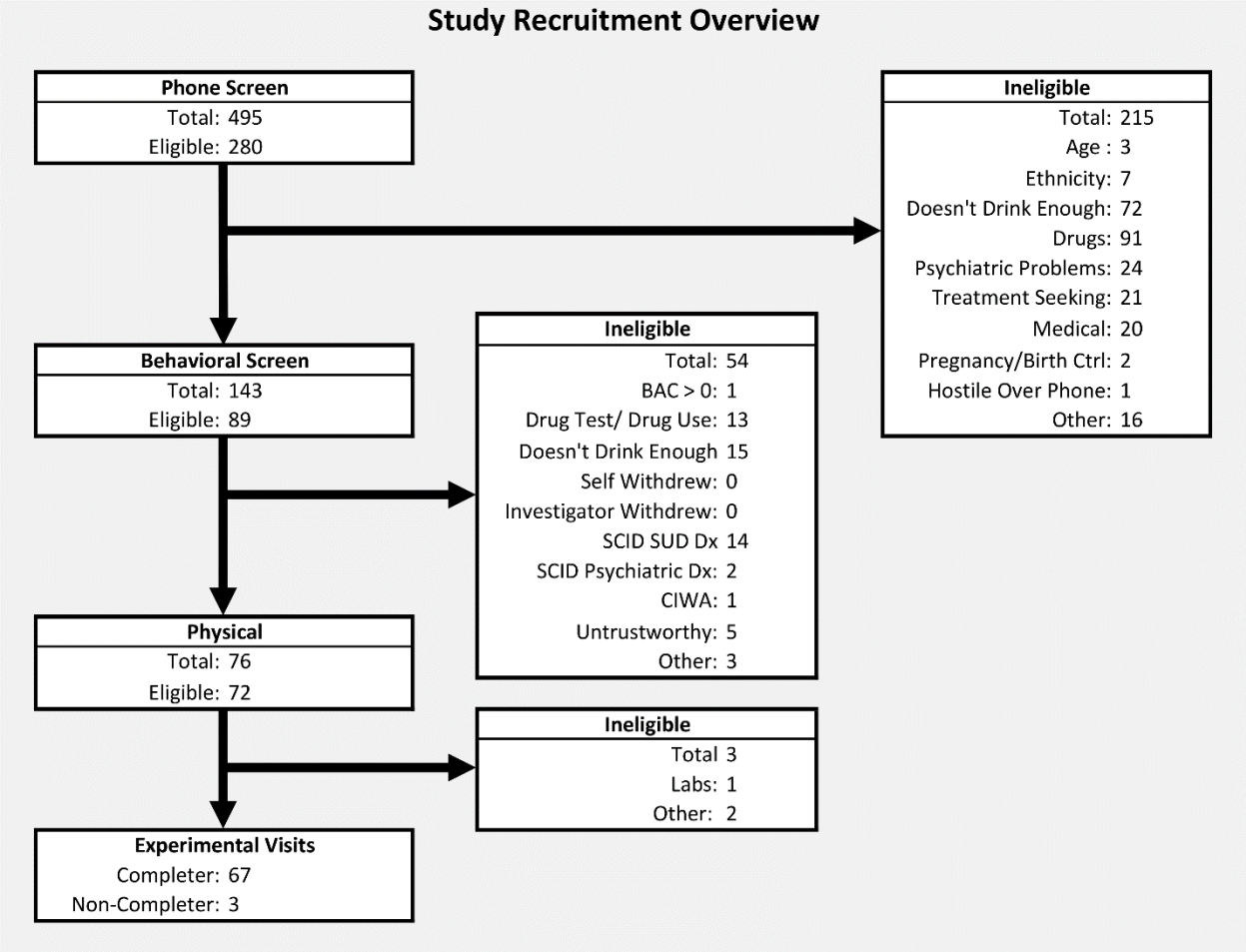


Figure 2

Individual BAC curves estimated using the PBPK model of alcohol pharmacokinetics implemented in the CAIS software package. The alcohol administration paradigm consisted of two components. The Alcohol Challenge, which lasted on average 70.66 (SD = 5.20) minutes, and the Alcohol Self-Administration paradigm, which lasted on average 100.42 (SD = 5.10) minutes.

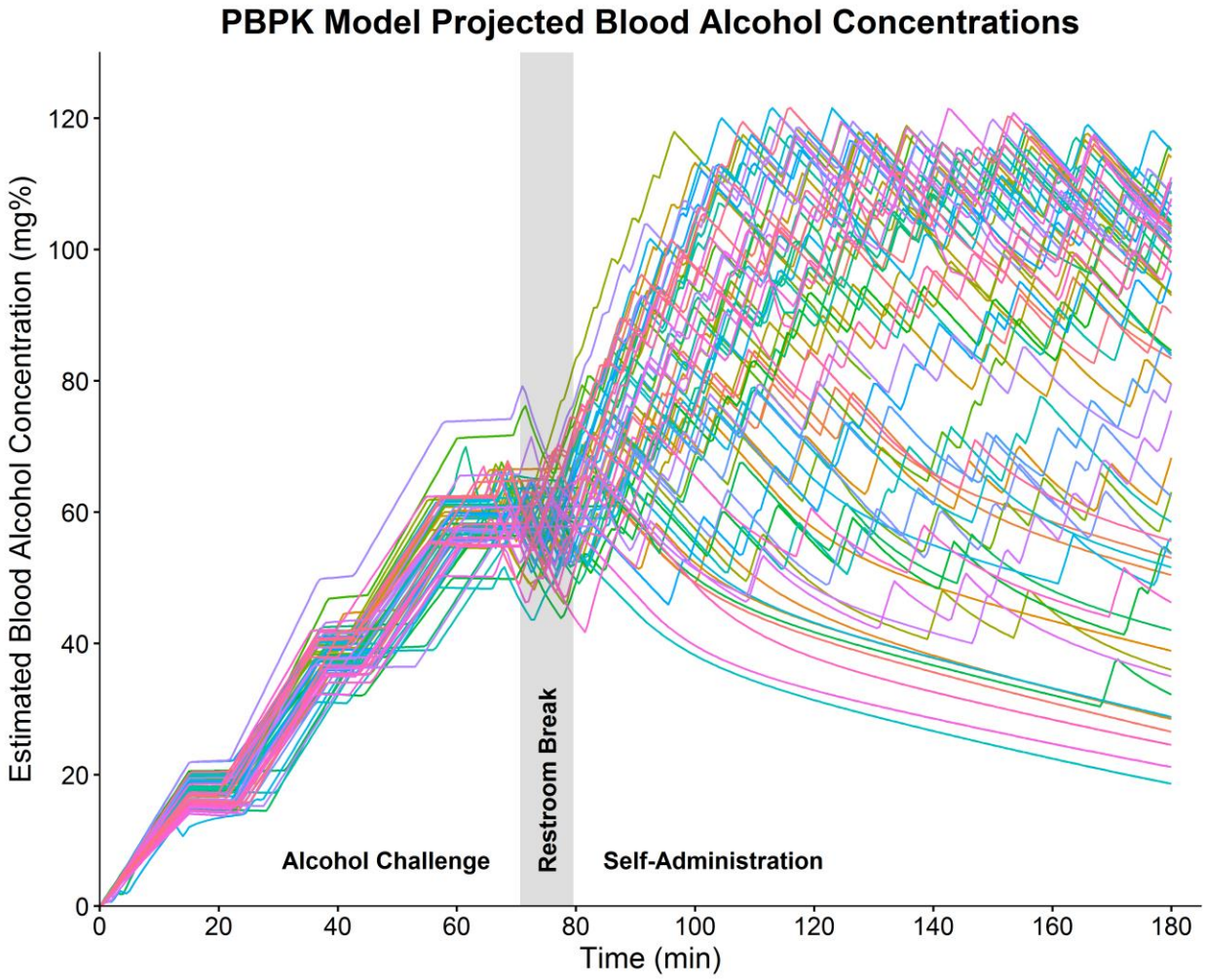


Figure 3

Magnitude of subjective responses to alcohol over the Challenge. Each graph represents the expected value of the subjective response variable estimated from a multilevel model including the predictors of AUD severity, BAC time point, and their interaction. (A) The Stimulation outcome was a combined outcome including the measures, BAES Stimulation, POMS Vigor, and POMS Positive Mood. (B) The Sedation outcome was combined from the BAES Sedation and SHAS scales. (C) Negative Affect combined POMS Tension and Negative Mood. (D) Alcohol craving was measured using the AUQ. The selected AUD Severity factor levels correspond to the mean values for participants who had no current AUD diagnosis (-1.26), mild AUD (-0.05), moderate AUD (1.57), and severe AUD (4.14).

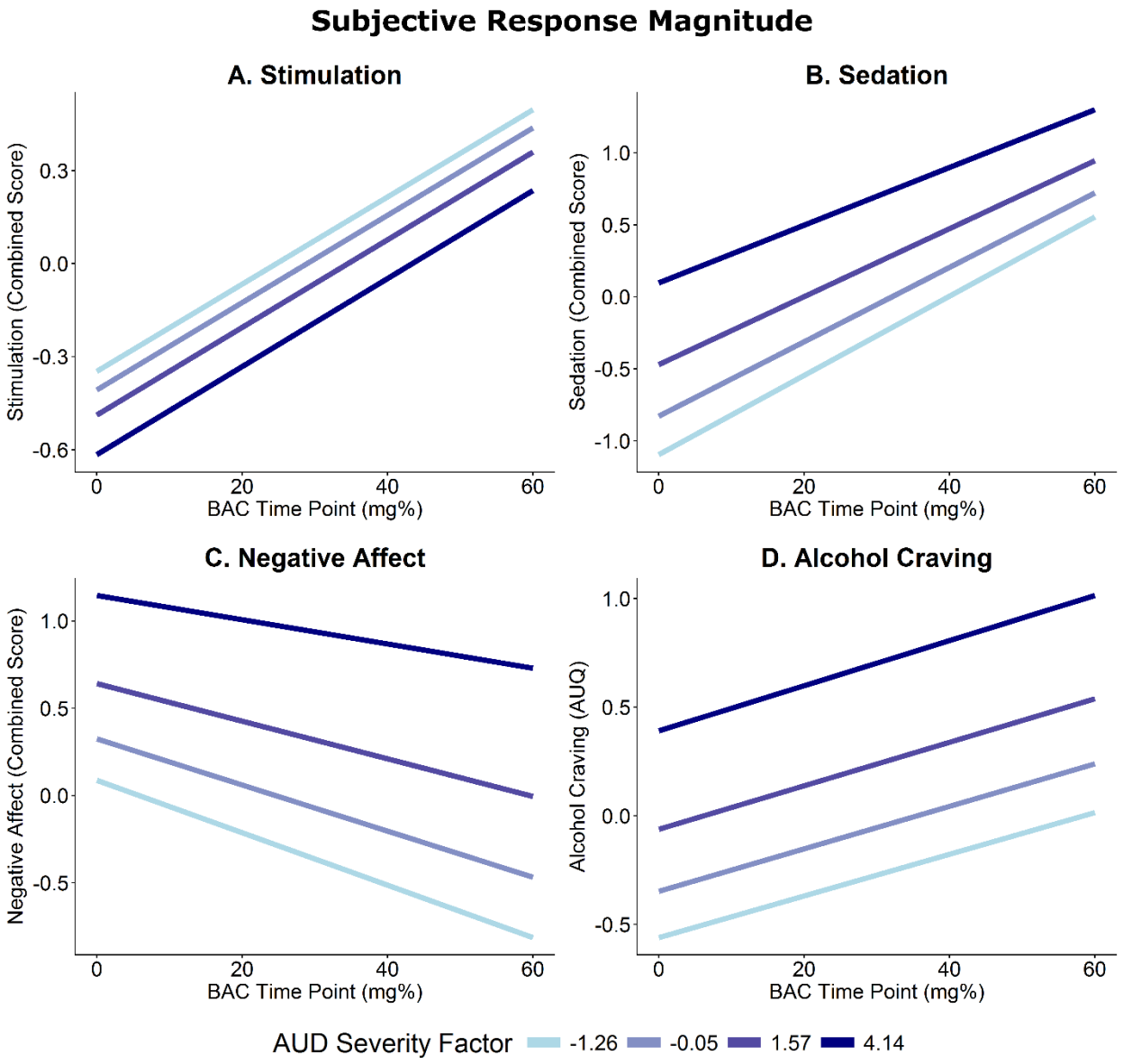


Figure 4

AUD Severity was found to predict greater BAC curves over the course of the alcohol self-administration. BAC levels were estimated by the CAIS software in 30 sec intervals, however for analyses, these estimated BAC values were averaged over 10 minute bins. The displayed lines represent the predicted values according to the final multilevel including a quartic time trend, AUD Severity factor score, and the interaction between AUD Severity and linear through cubic time terms. For display, the curves are shown with respect to minutes of self-administration as opposed to bin number. Displayed AUD severity factor levels correspond to average AUD Severity factor scores for participants with AUD diagnostic severity of None, Mild, Moderate, and Severe respectively.

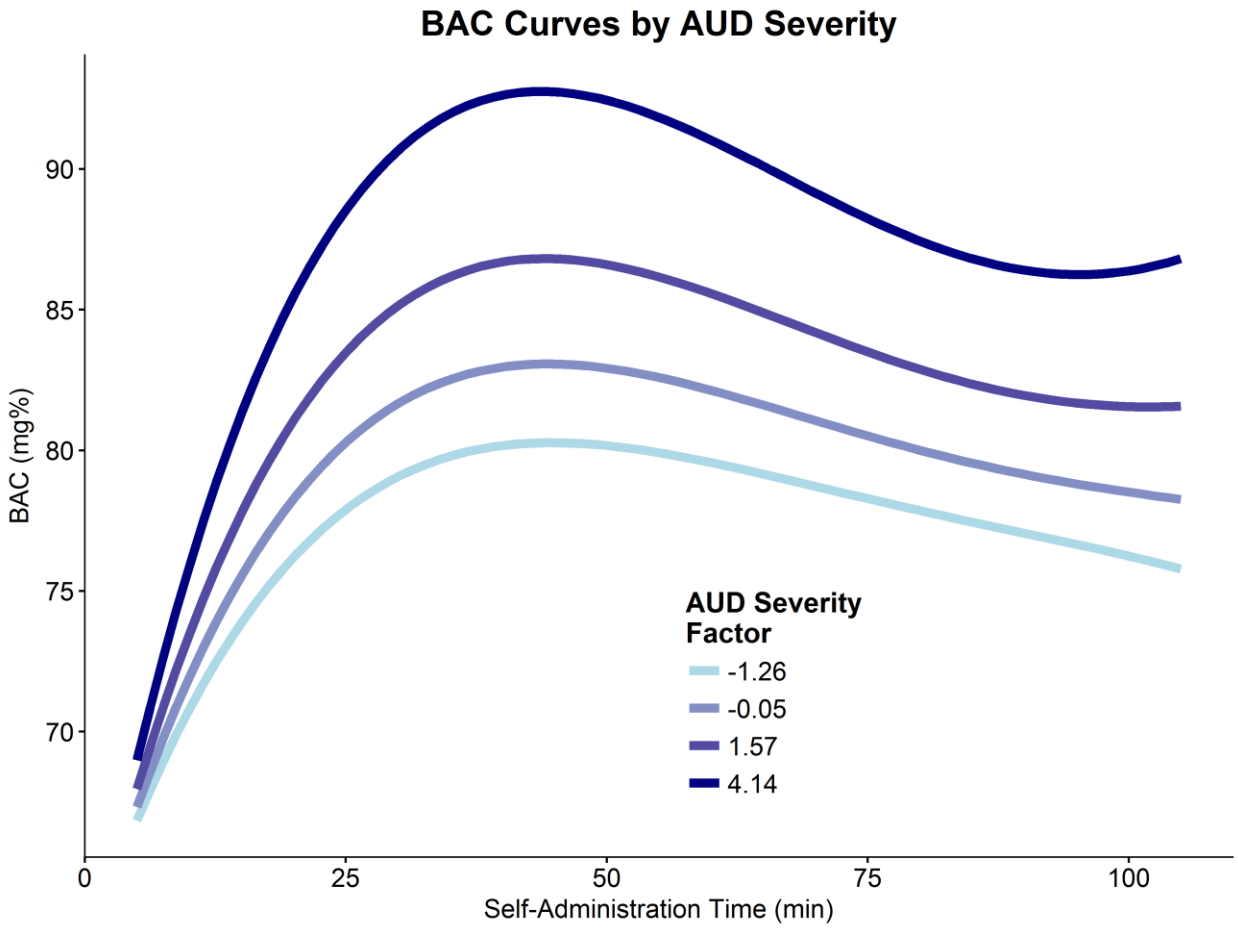


Figure 5

Final model with Craving Level and AUD Severity predicting BAC self-administration curves. Craving Level significantly predicted BAC curve parameters. After accounting for alcohol craving level, AUD Severity no longer predicted self-administration curves.

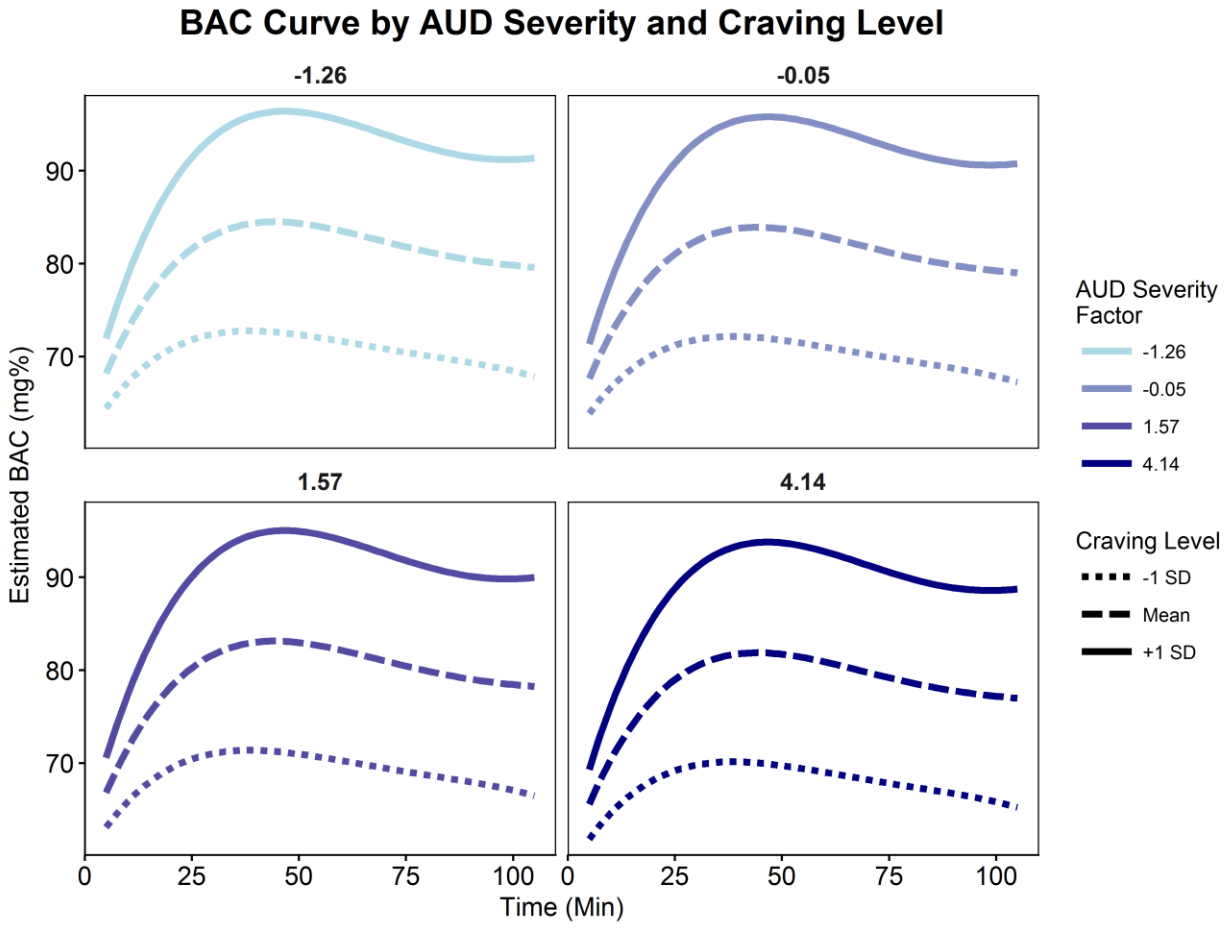


Figure 6

Final model with Stimulation Slope and AUD Severity predicting BAC curves. The main effect of Stimulation Slope was trending towards significant (p = 0.090), however it was not robust to controlling for sex differences

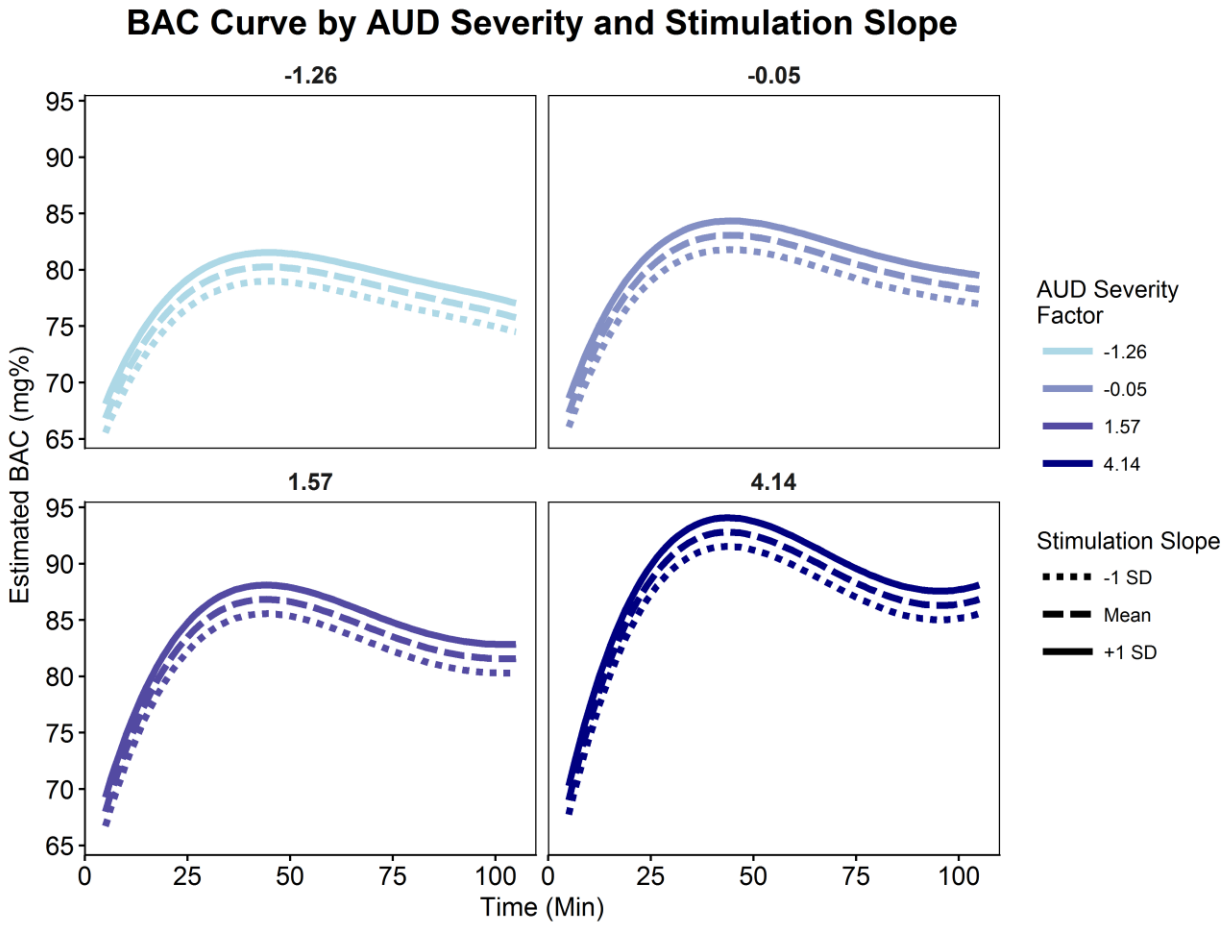


Figure 7

Final model with Negative Affect Slope and AUD Severity predicting BAC self-administration curves. The AUD Severity × Negative Affect Slope interaction was found to predict BAC curves overall at a trend level (p = 0.095), though this effect was not robust to controlling for sex differences. Of note, greater Negative Affect Slope means *less* alcohol-related reduction of negative affect.

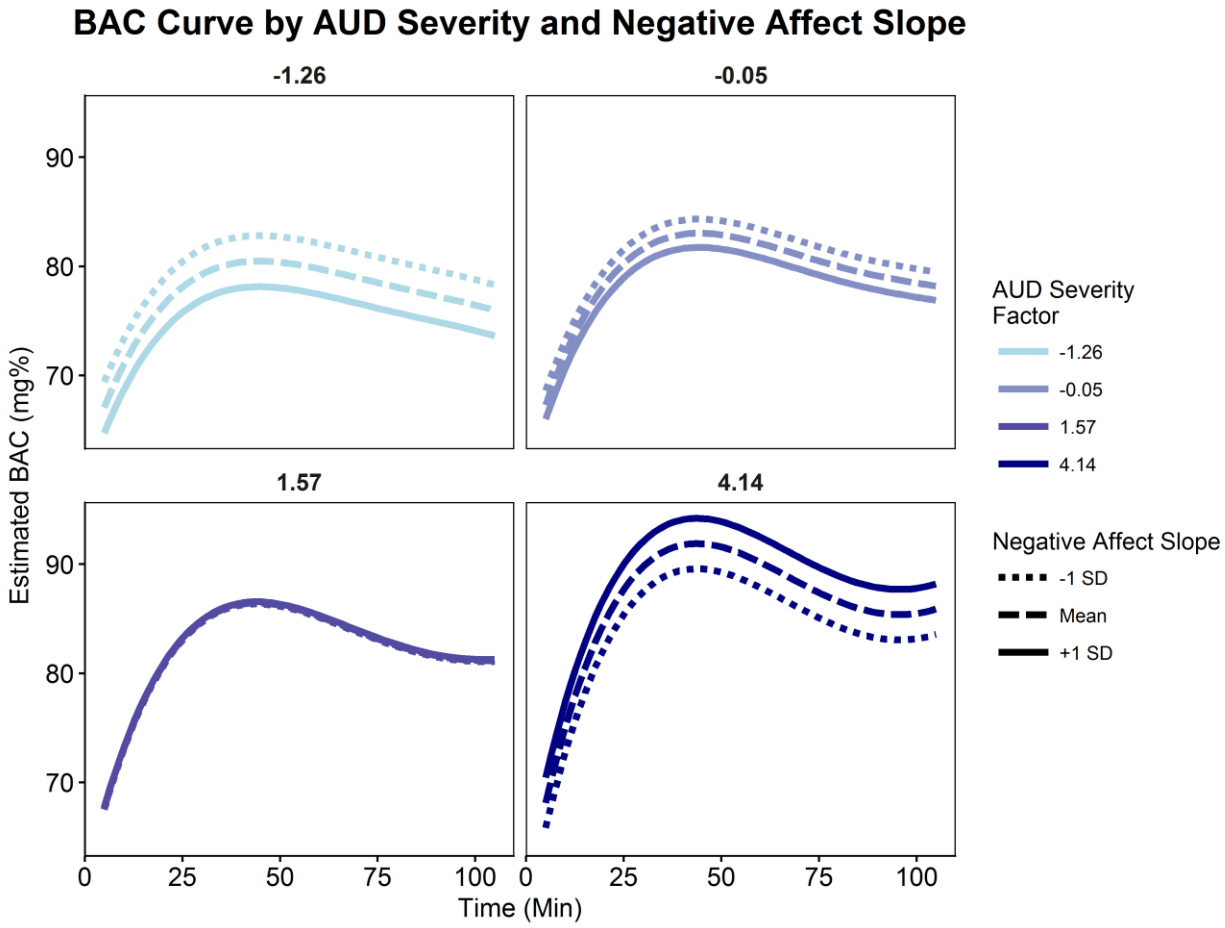
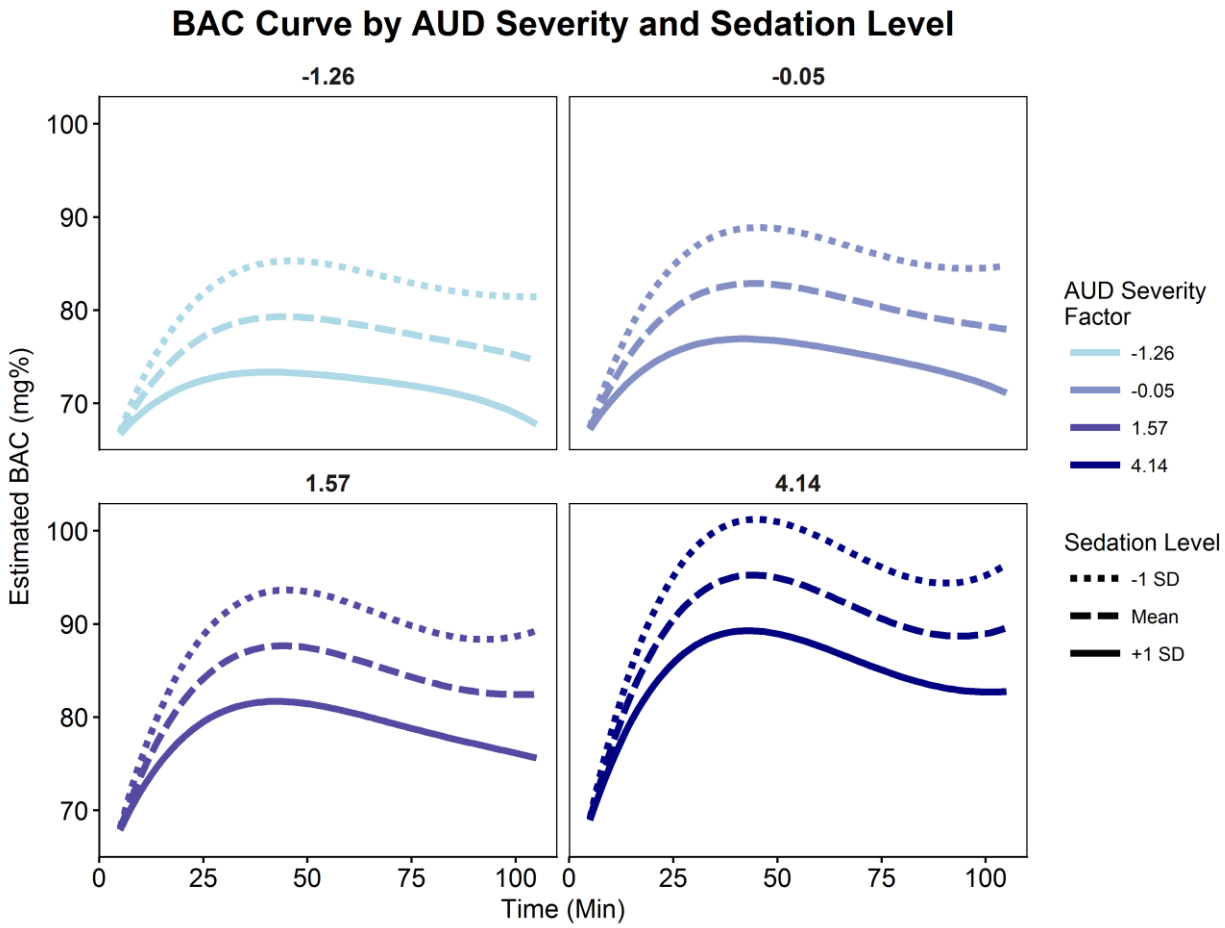


Figure 8

Final model with Sedation Level and AUD Severity predicting BAC self-administration curves. Sedation Level negatively predict BAC curves independent of AUD severity.



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Supplemental Materials

Bivariate correlations between subjective response measures during the alcohol Challenge

BASELINE

	BAES Stim.	POMS P. Mood	POMS Vig	AUQ	BAES Sed.	SHAS	POMS Tension
POMS P. Mood	0.666						
POMS Vig	0.768	0.791					
AUQ	0.004	-0.054	-0.056				
BAES Sed.	-0.440	-0.435	-0.537	0.215			
SHAS	-0.351	-0.309	-0.301	0.204	0.627		
POMS Tension	-0.354	-0.569	-0.414	0.330	0.336	0.432	
POMS N. Mood	-0.353	-0.530	-0.417	0.401	0.521	0.521	0.714

BAC = 20 mg%

	BAES Stim.	POMS P. Mood	POMS Vig	AUQ	BAES Sed.	SHAS	POMS Tension
POMS P. Mood	0.629						
POMS Vig	0.674	0.738					
AUQ	0.381	0.237	0.237				
BAES Sed.	-0.159	-0.261	-0.510	-0.058			
SHAS	0.073	-0.226	-0.229	0.049	0.647		
POMS Tension	-0.069	-0.452	-0.217	-0.067	0.159	0.263	
POMS N. Mood	-0.233	-0.440	-0.328	0.111	0.329	0.267	0.725

BAC = 40 mg%

	BAES Stim.	POMS P. Mood	POMS Vig	AUQ	BAES Sed.	SHAS	POMS Tension
POMS P. Mood	0.710						
POMS Vig	0.805	0.740					
AUQ	0.310	0.219	0.202				
BAES Sed.	-0.153	-0.217	-0.377	-0.064			
SHAS	0.310	0.061	0.132	0.235	0.517		
POMS Tension	-0.124	-0.364	-0.098	-0.046	0.159	0.274	
POMS N. Mood	-0.384	-0.521	-0.445	-0.026	0.294	0.186	0.725

BAC = 60mg%

	BAES Stim.	POMS P. Mood	POMS Vig	AUQ	BAES Sed.	SHAS	POMS Tension
POMS P. Mood	0.786						
POMS Vig	0.861	0.772					
AUQ	0.348	0.171	0.239				
BAES Sed.	-0.275	-0.240	-0.479	0.000			
SHAS	0.160	0.028	-0.062	0.266	0.604		
POMS Tension	-0.109	-0.403	-0.137	0.302	0.191	0.273	
POMS N. Mood	-0.403	-0.582	-0.458	0.136	0.379	0.212	0.705

Raw BAC curves estimated in the CAIS software (black) with average BAC values over 10 minute bins overlaid (blue). The binned BAC means track the full BAC curves well, while reducing the degree of autocorrelation and smoothing out the short-term spikes and dips with each self-administered infusion.

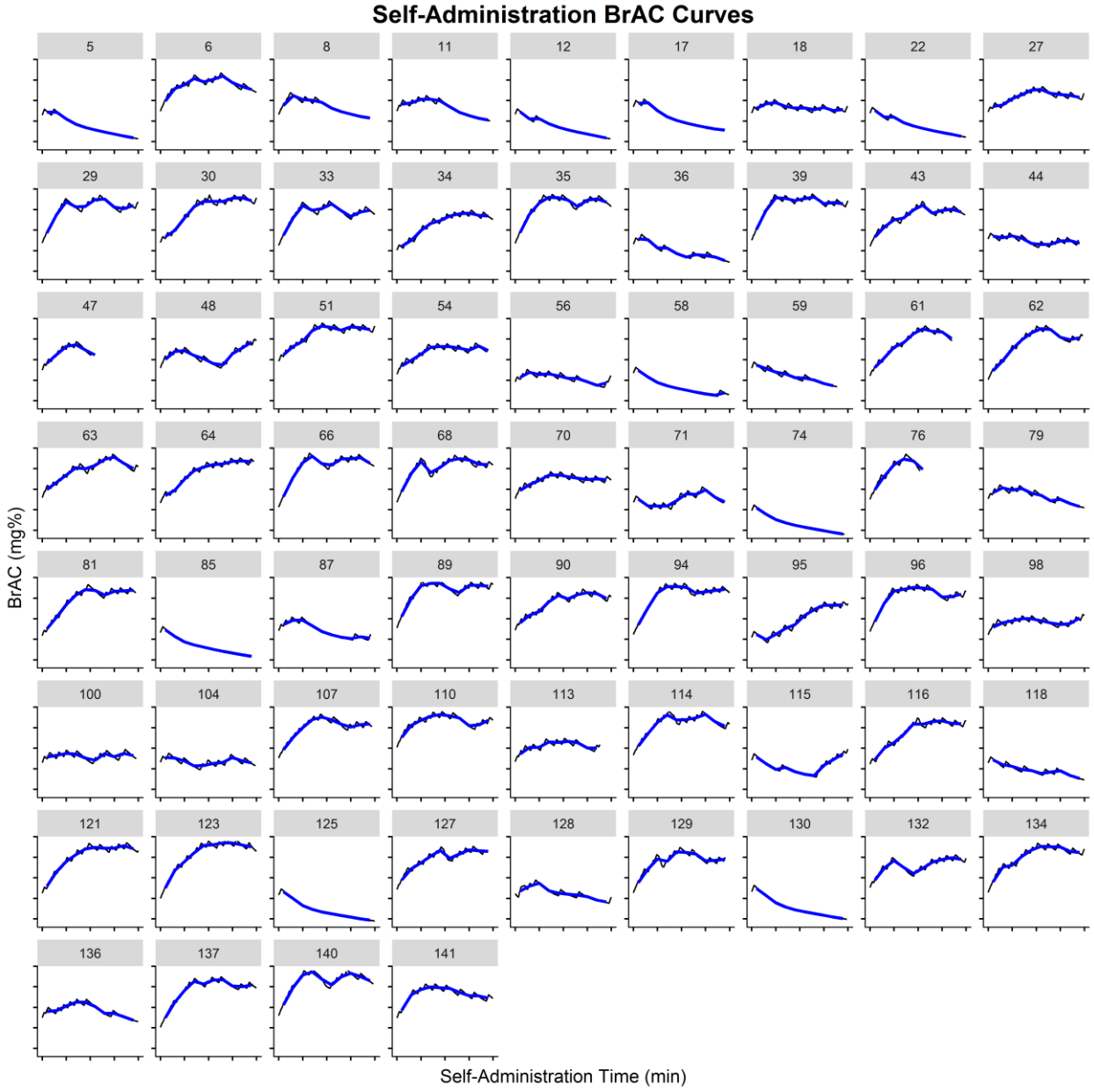
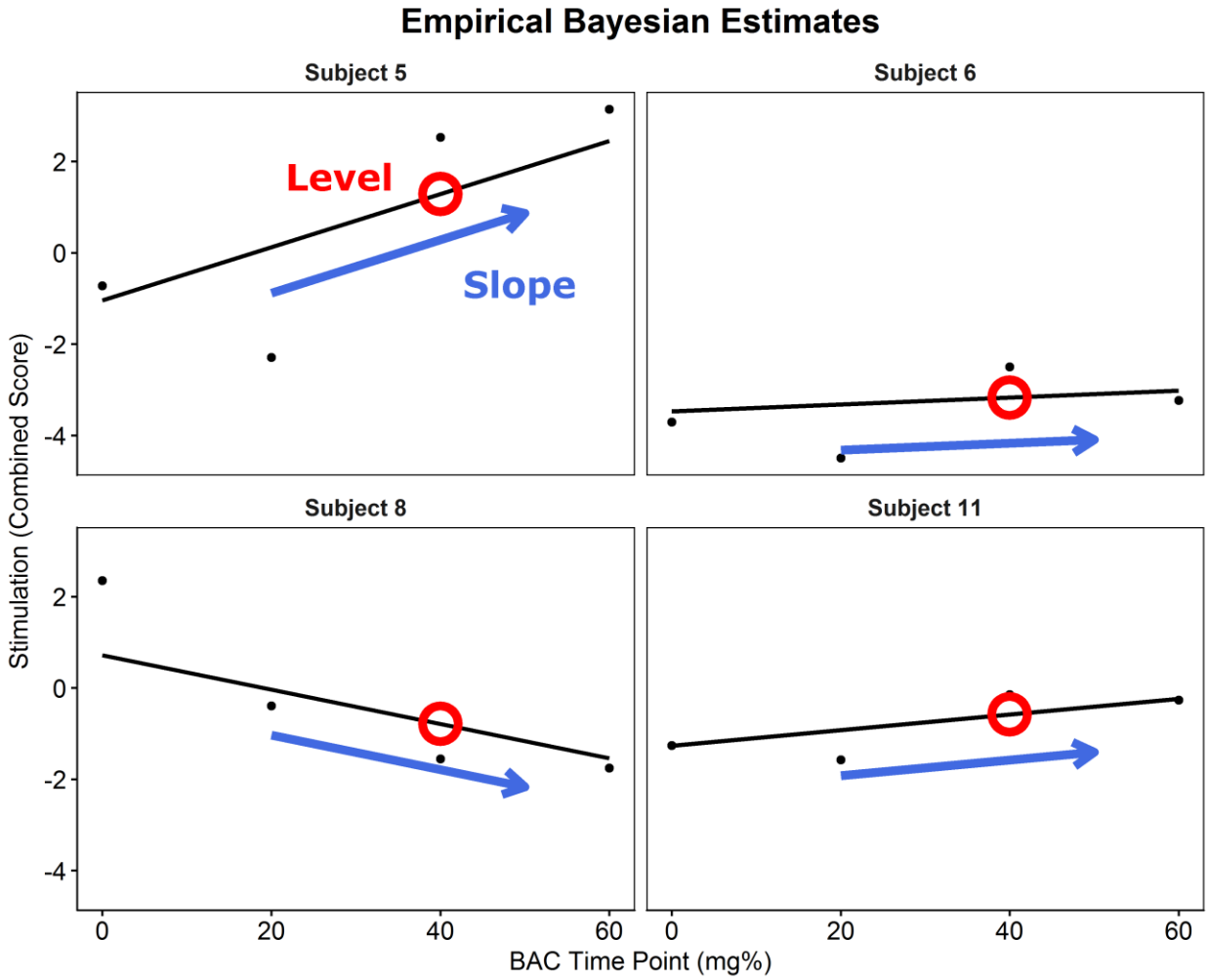
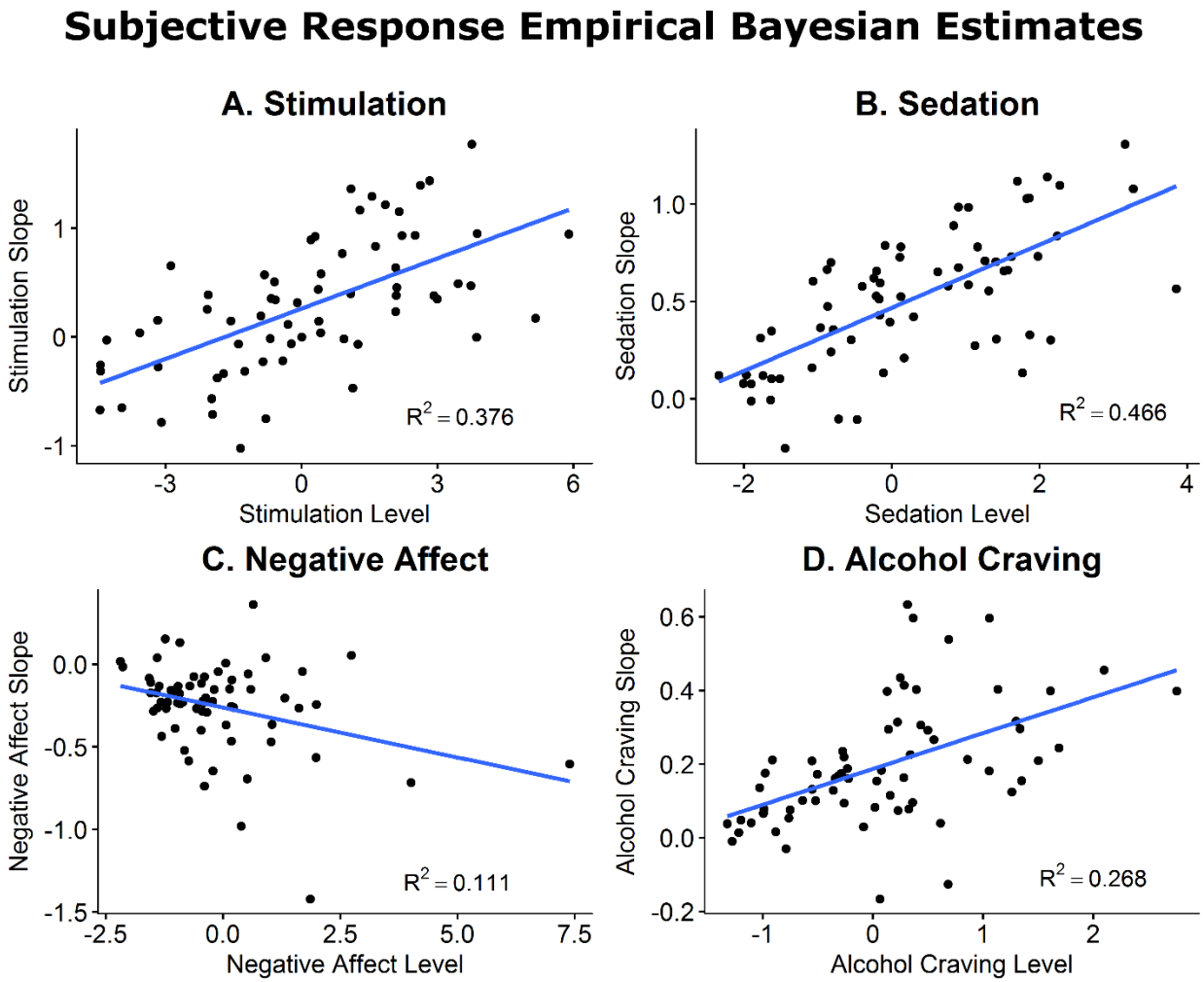


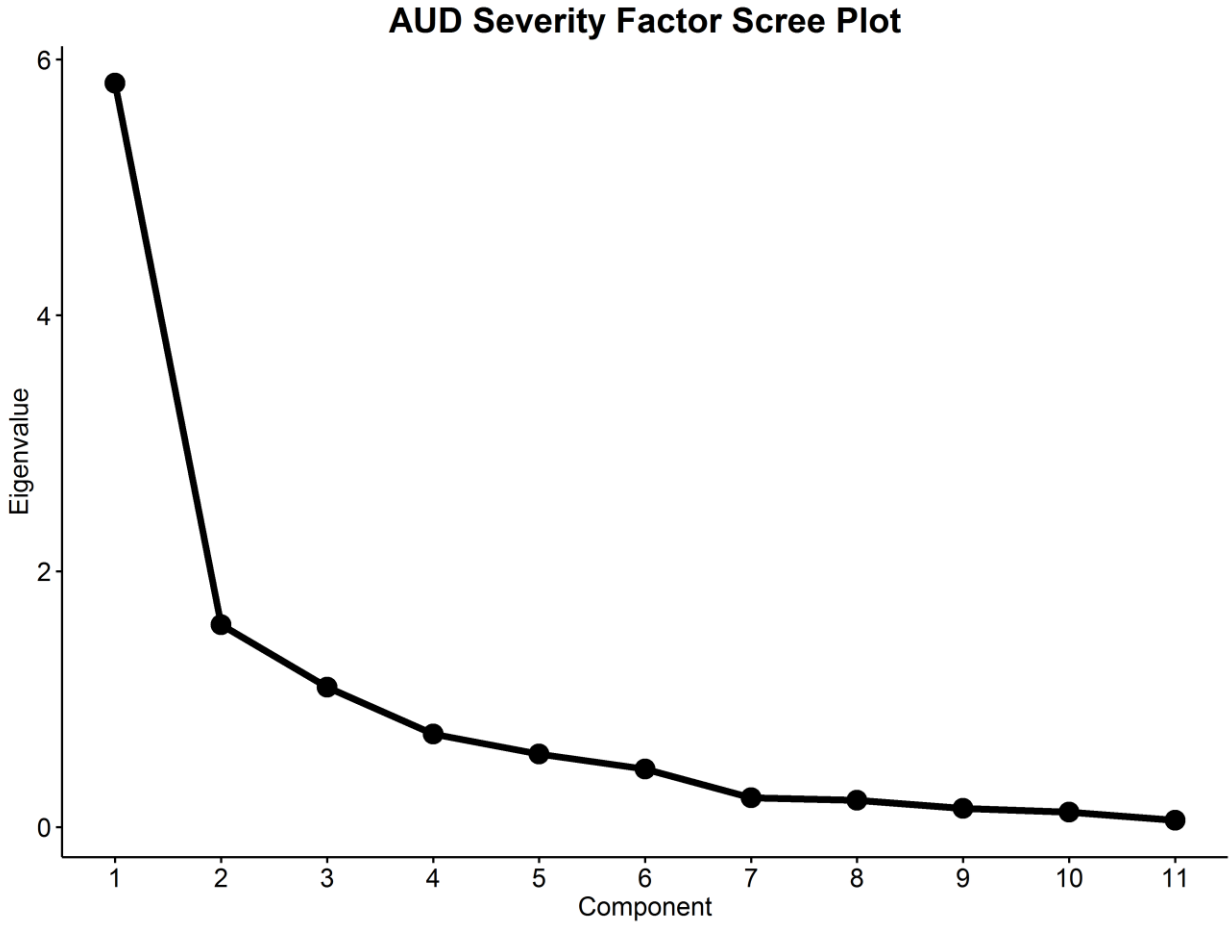
Illustration of Empirical Bayesian Estimates for subjective response (SR) variables. For each SR domain, a MLM model was run with a linear trial predictor centered at the 40mg% time point (the middle post-baseline time point). In these models, both intercept and slopes were set as random between subjects. These models thus permit via Empirical Bayesian methods the estimation of Level (model intercept, or the expected value of the SR variable at the 40mg% timepoint), and Slope (the expected change in SR from one time point to the next) for each subject. This approach has been shown to be superior to conducting an OLS regression on each subject separately in that it allows for parameter estimation with missing data and utilizes data from all participants in parameter estimation, thus reducing the influence of random measurement error (Raudenbush and Bryk, 2001).



Correlations between Empirical Bayesian estimates of SR Level and Slope across SR domains. Within each SR domain, Level and Slope were found to be correlated with each other (*p's* < 0.01), though the magnitude of these correlations varied by SR domain ranging from $R^2 = 0.111$ for Negative Affect, and $R^2 = 0.466$ for Sedation/Intoxication.



Principal component analysis scree plot of AUD Severity variables which suggested a single-factor solution accounting for 53% of the total variance. Factor loadings for the AUD Severity factor are shown below.

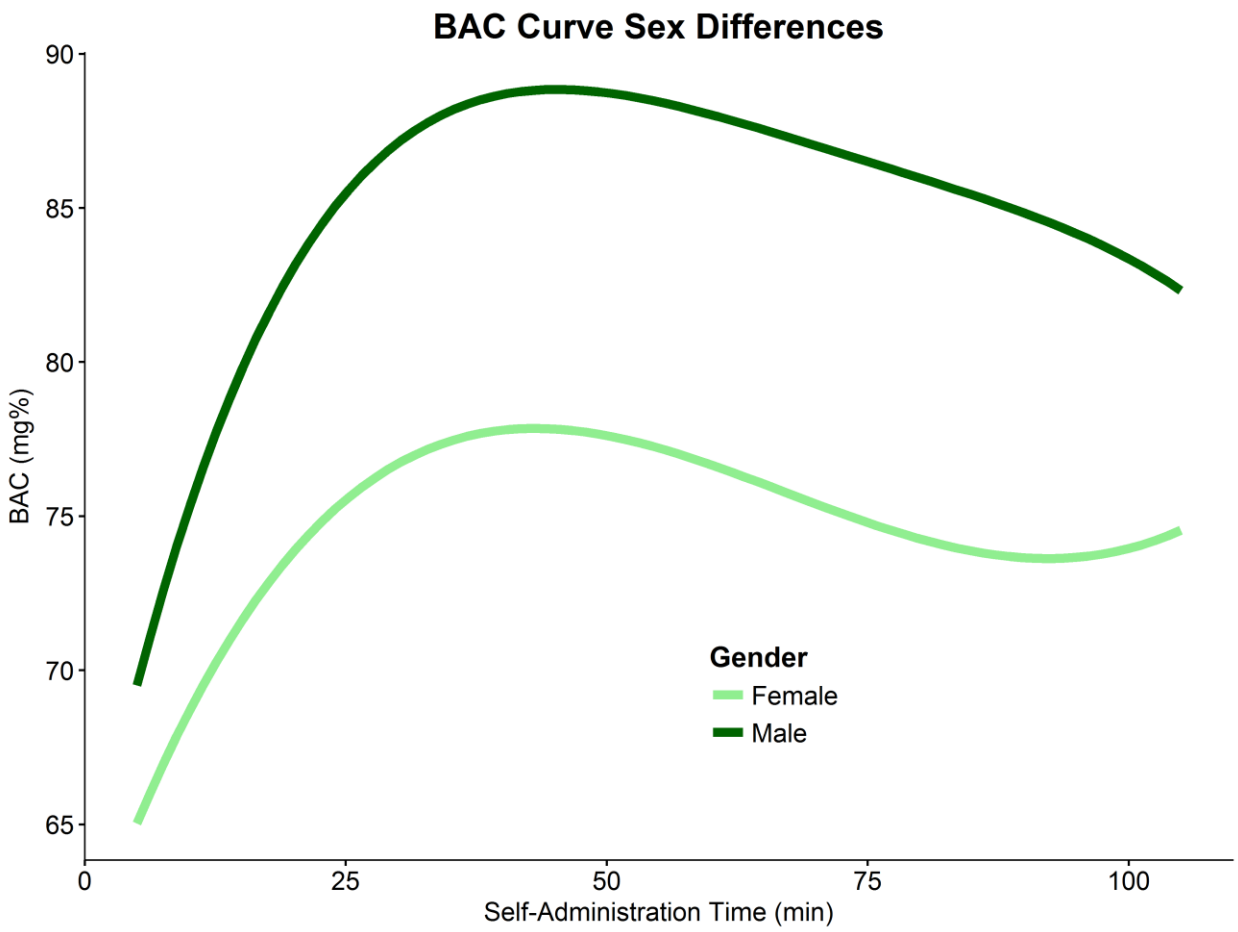


	Loadings
Drinks per Week	0.766
Drinks per Drinking Day	0.649
Drink Days per Month	0.454
% Binge Drinking Days	0.614
Alcohol Dependency Scale	0.744
Alcohol Use Disorder Identification Test	0.890
Clinical Institute of Withdrawal - Alcohol	0.495
Obsessive Compulsive Drinking Scale	0.831
Penn Alcohol Craving Scale	0.754
Lifetime AUD Symptom Count	0.812
Current AUD Symptom Count	0.859

Full results from a multilevel model testing the effect of AUD Severity as a moderator of BAC Curves as estimated by a quantic polynomial.

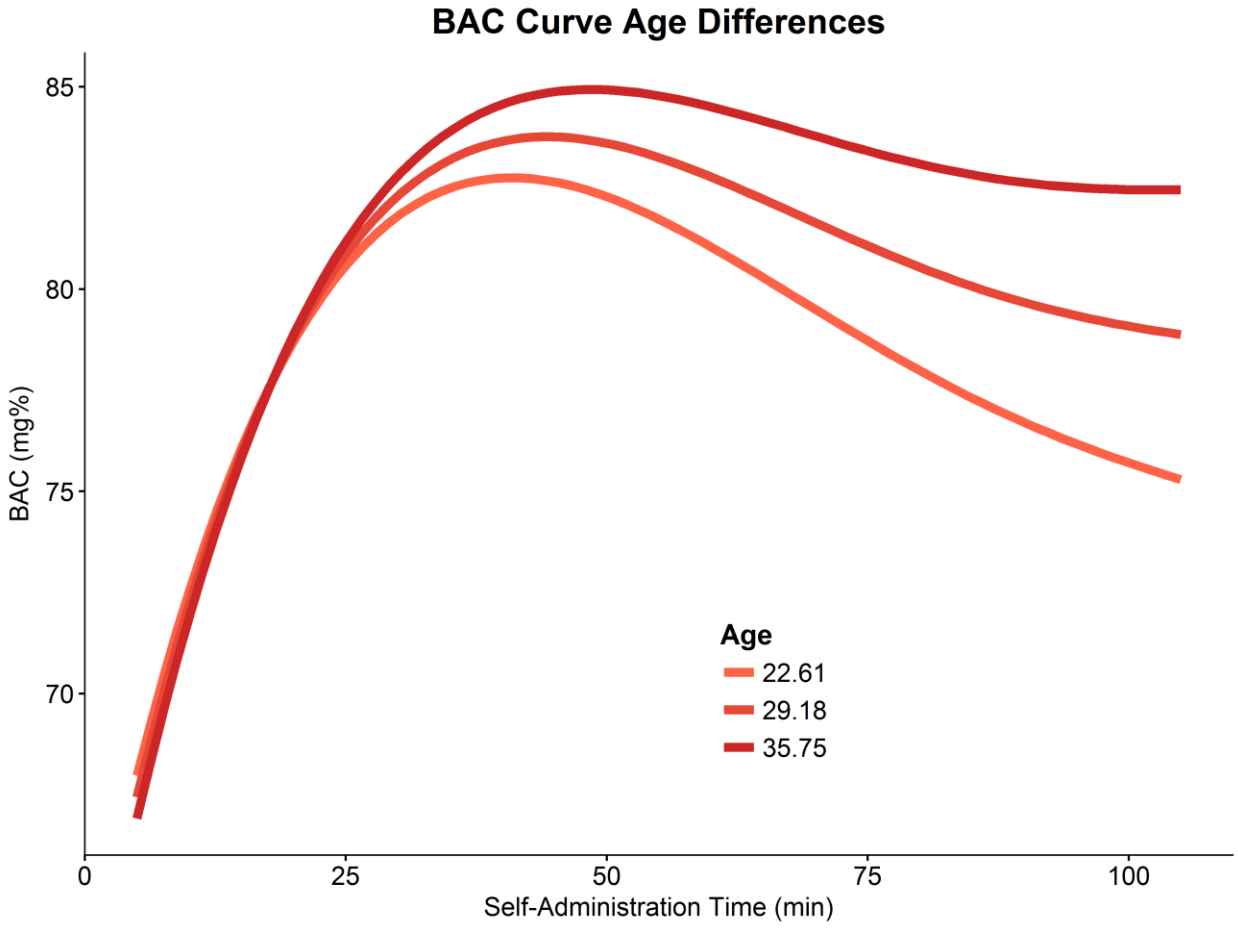
		AUD Severity		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	67.337 (0.840)	80.207 (624)	<0.001
	Trial	10.350 (1.332)	7.773 (624)	<0.001
	$Trial^2$	-2.283 (0.332)	-6.866 (624)	<0.001
	$Trial^3$	0.195 (0.049)	3.991 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.340 (624)	0.020
	AUD Severity	0.399 (0.386)	1.032 (65)	0.306
	AUD Severity × Trial	1.197 (0.603)	1.986 (624)	0.048
	AUD Severity × $Trial^2$	-0.231 (0.098)	-2.346 (624)	0.019
	AUD Severity × $Trial^3$	0.013 (0.006)	2.270 (624)	0.024
Trimmed Predictor	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.910 (623)	0.363

Sex differences in alcohol self-administration BAC curves. Male subjects administered more alcohol than female participants.



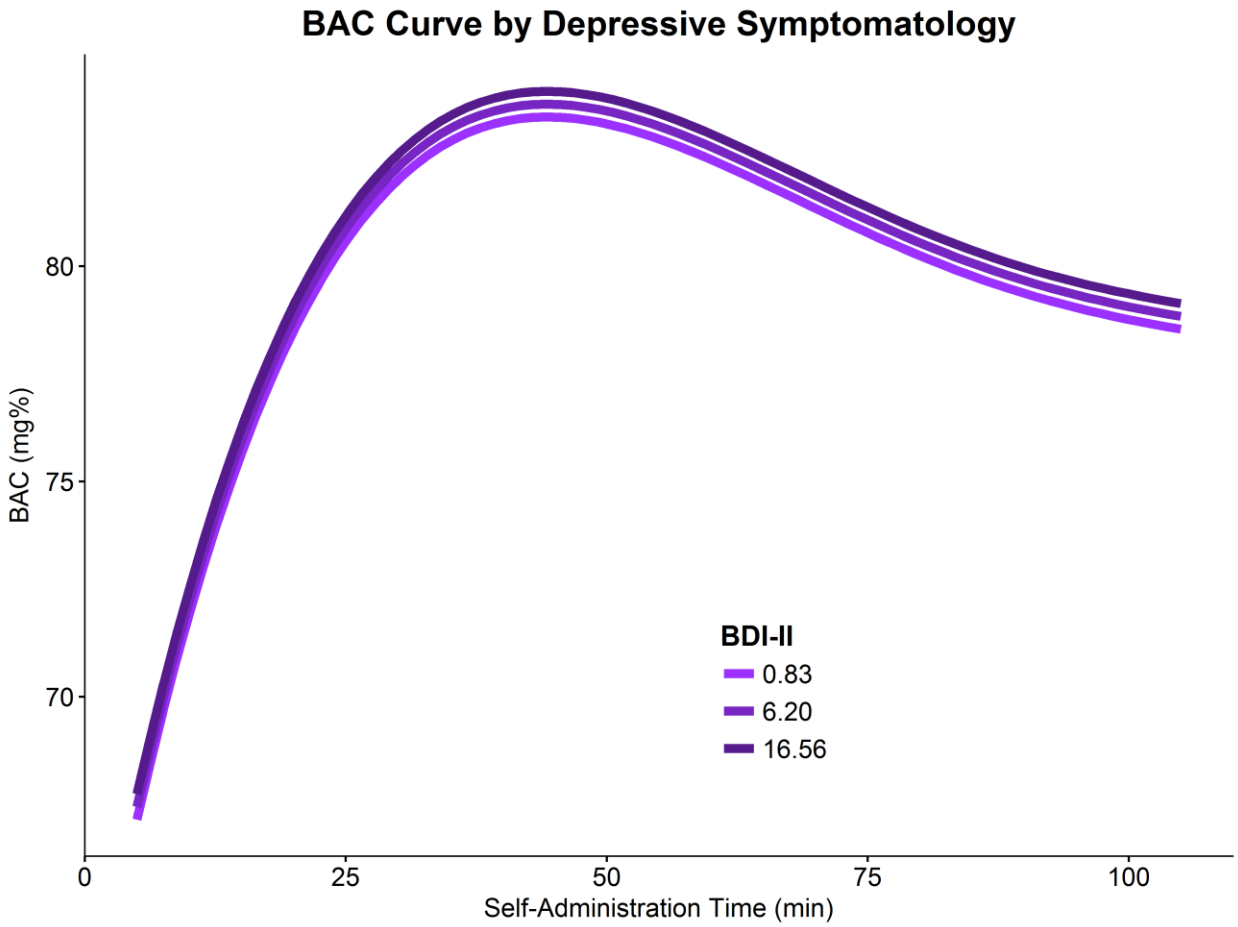
	Sex Differences		
	B (SE)	t (df)	p
Intercept	69.508 (1.095)	63.505 (623)	<0.001
Trial	12.955 (1.831)	7.075 (623)	<0.001
Trial^2	-3.027 (0.454)	-6.668 (623)	<0.001
Trial^3	0.291 (0.066)	4.387 (623)	<0.001
Trial^4	-0.011 (0.003)	-3.047 (623)	0.002
Sex	-4.477 (1.609)	-2.782 (65)	0.007
Sex × Trial	-4.921 (2.691)	-1.829 (623)	0.068
Sex × Trial^2	1.440 (0.666)	2.164 (623)	0.031
Sex × Trial^3	-0.192 (0.097)	-1.982 (623)	0.048
Sex × Trial^4	0.009 (0.005)	1.870 (623)	0.062

Age differences in alcohol self-administration BAC curves. At a trend level (p = 0.081), older subjects tended to maintain higher BAC levels. Age values displayed represent the mean ± 1 SD.



		Age Differences		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	69.787 (3.378)	20.659 (626)	<0.001
	Trial	8.824 (1.696)	5.204 (626)	<0.001
	$Trial^2$	-2.340 (0.334)	-7.014 (626)	<0.001
	$Trial^3$	0.198 (0.049)	4.052 (626)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.330 (626)	0.020
	Age	-0.081 (0.112)	-0.719 (65)	0.475
	Age × Trial	0.063 (0.036)	1.747 (626)	0.081
Trimmed Predictors	Age × $Trial^4$	0.000 (0.000)	-0.724 (623)	0.470
	Age × $Trial^3$	0.003 (0.002)	1.516 (624)	0.130
	Age × $Trial^2$	-0.010 (0.009)	-1.081 (625)	0.280

Full MLM results for the effect of depressive symptomatology as measured by the BDI-II as a moderator of BAC curves. Displayed values represent the mean ± 1 SD transformed back into the original metric from a square-root transformation.

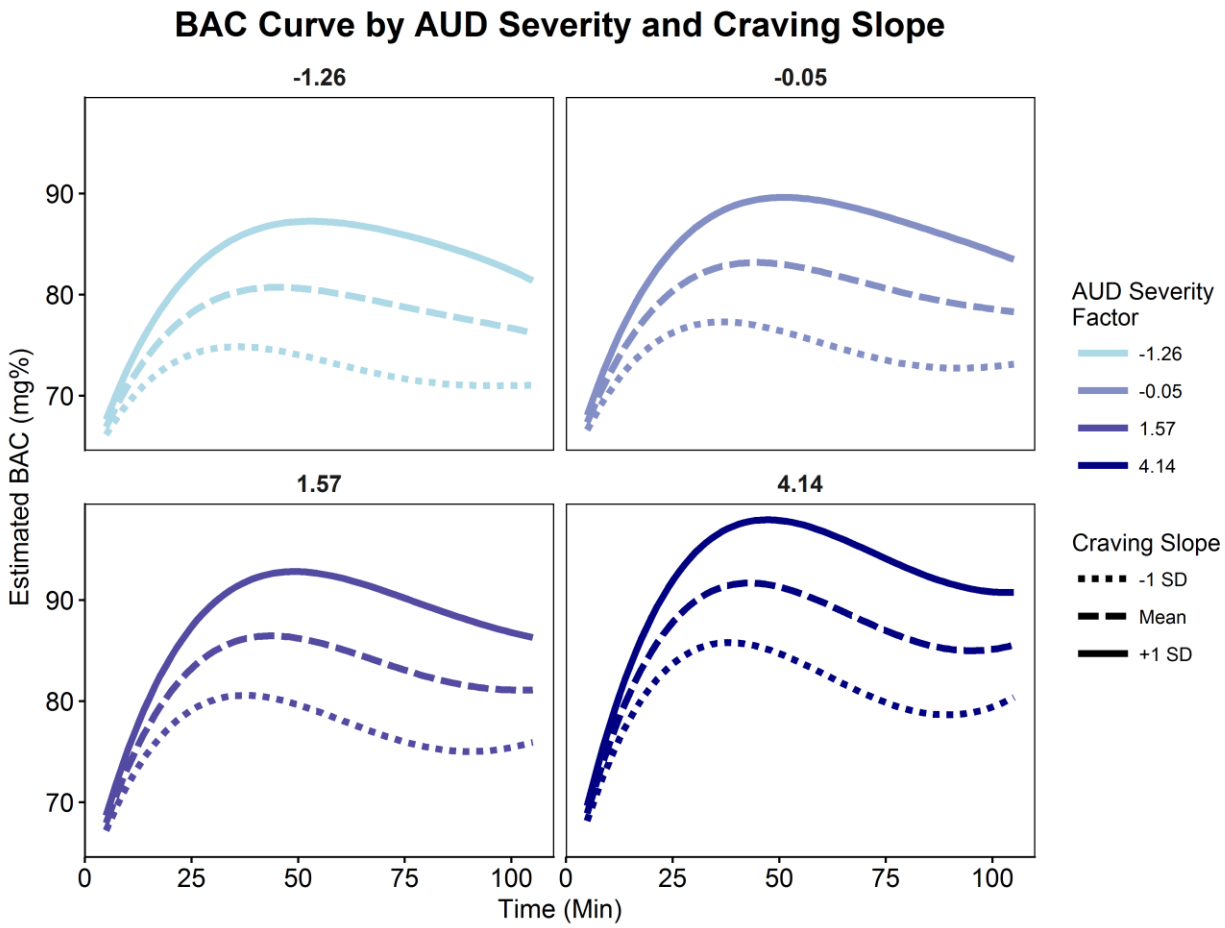


		Depressive Symptomatology		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	66.968 (1.429)	46.863 (627)	<0.001
	Trial	10.655 (1.345)	7.923 (627)	<0.001
	$Trial^2$	-2.344 (0.333)	-7.029 (627)	<0.001
	$Trial^3$	0.199 (0.049)	4.073 (627)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.355 (627)	0.019
	BDI	0.189 (0.466)	0.405 (65)	0.687
Trimmed Predictors	BDI × $Trial^4$	0.000 (0.002)	-0.196 (623)	0.845
	BDI × $Trial^3$	0.009 (0.008)	1.172 (624)	0.242
	BDI × $Trial^2$	0.010 (0.041)	0.257 (625)	0.797
	BDI × Trial	0.090 (0.156)	0.578 (626)	0.563

Full MLM model results for Alcohol Craving Level predicting self-administration BAC curves.

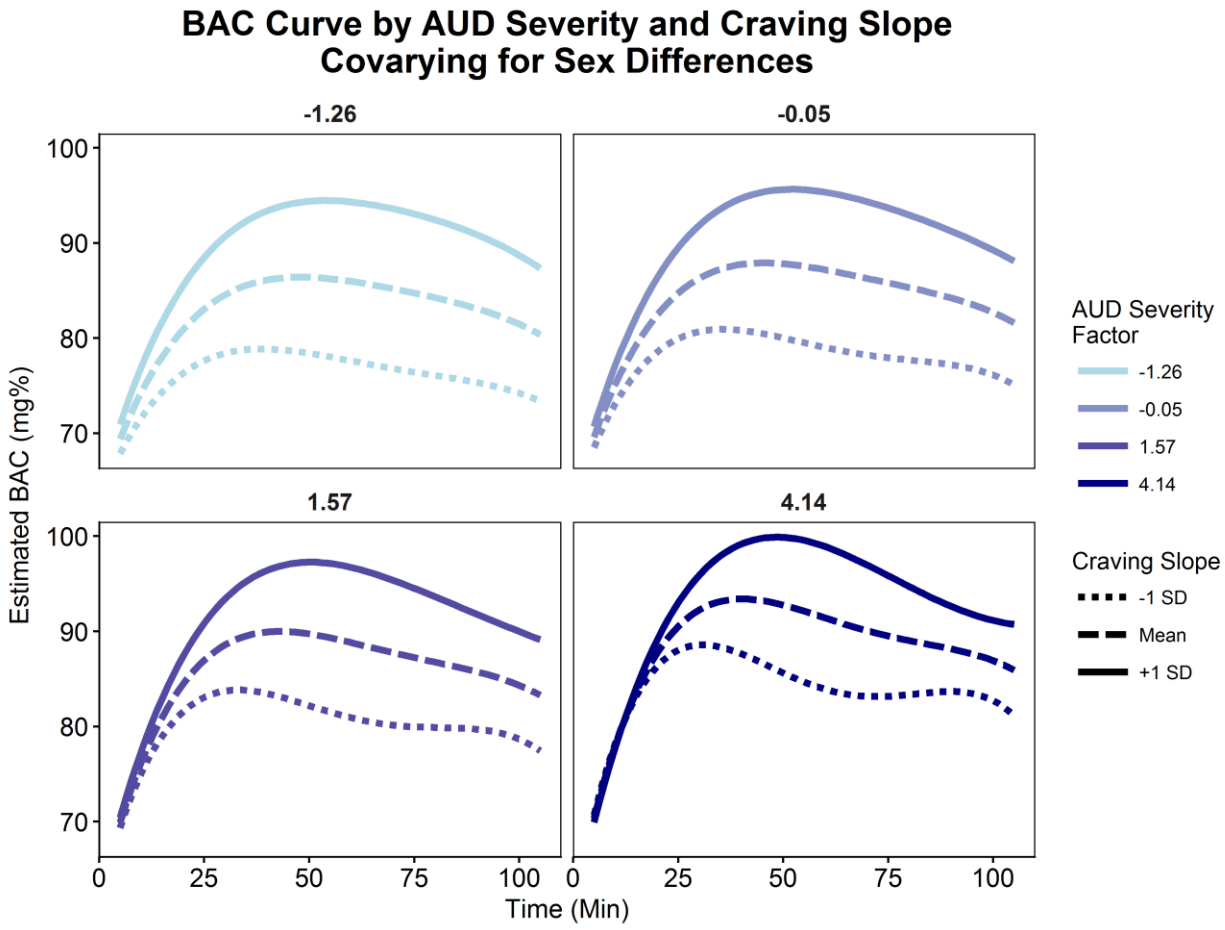
		Alcohol Craving Level		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	67.139 (0.760)	88.323 (624)	<0.001
	Trial	10.170 (1.284)	7.923 (624)	<0.001
	$Trial^2$	-2.263 (0.329)	-6.877 (624)	<0.001
	$Trial^3$	0.195 (0.049)	4.000 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.365 (624)	0.018
	AUD Severity	-0.486 (0.360)	-1.352 (64)	0.181
	Craving Level	4.279 (0.937)	4.567 (64)	<0.001
	Craving Level × Trial	4.937 (1.419)	3.478 (624)	<0.001
	Craving Level × $Trial^2$	-0.821 (0.233)	-3.518 (624)	<0.001
	Craving Level × $Trial^3$	0.042 (0.013)	3.144 (624)	0.002
Trimmed Predictors	Craving Level × AUD Severity × $Trial^4$	0.002 (0.001)	1.192 (615)	0.234
	Craving Level × AUD Severity × $Trial^3$	-0.006 (0.006)	-0.914 (616)	0.361
	Craving Level × AUD Severity × $Trial^2$	0.027 (0.033)	0.829 (617)	0.407
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.382 (618)	0.702
	AUD Severity × $Trial^3$	0.006 (0.006)	1.026 (619)	0.305
	AUD Severity × $Trial^2$	0.000 (0.033)	0.009 (620)	0.993
	Craving Level × AUD Severity × Trial	-0.177 (0.123)	-1.437 (621)	0.151
	Craving Level × AUD Severity	-0.157 (0.360)	-0.436 (63)	0.664
	AUD Severity × Trial	-0.088 (0.127)	-0.692 (622)	0.489
	Craving Level × $Trial^4$	-0.004 (0.003)	-1.506 (623)	0.133

Final model with Craving Slope and AUD Severity predicting BAC self-administration curves.



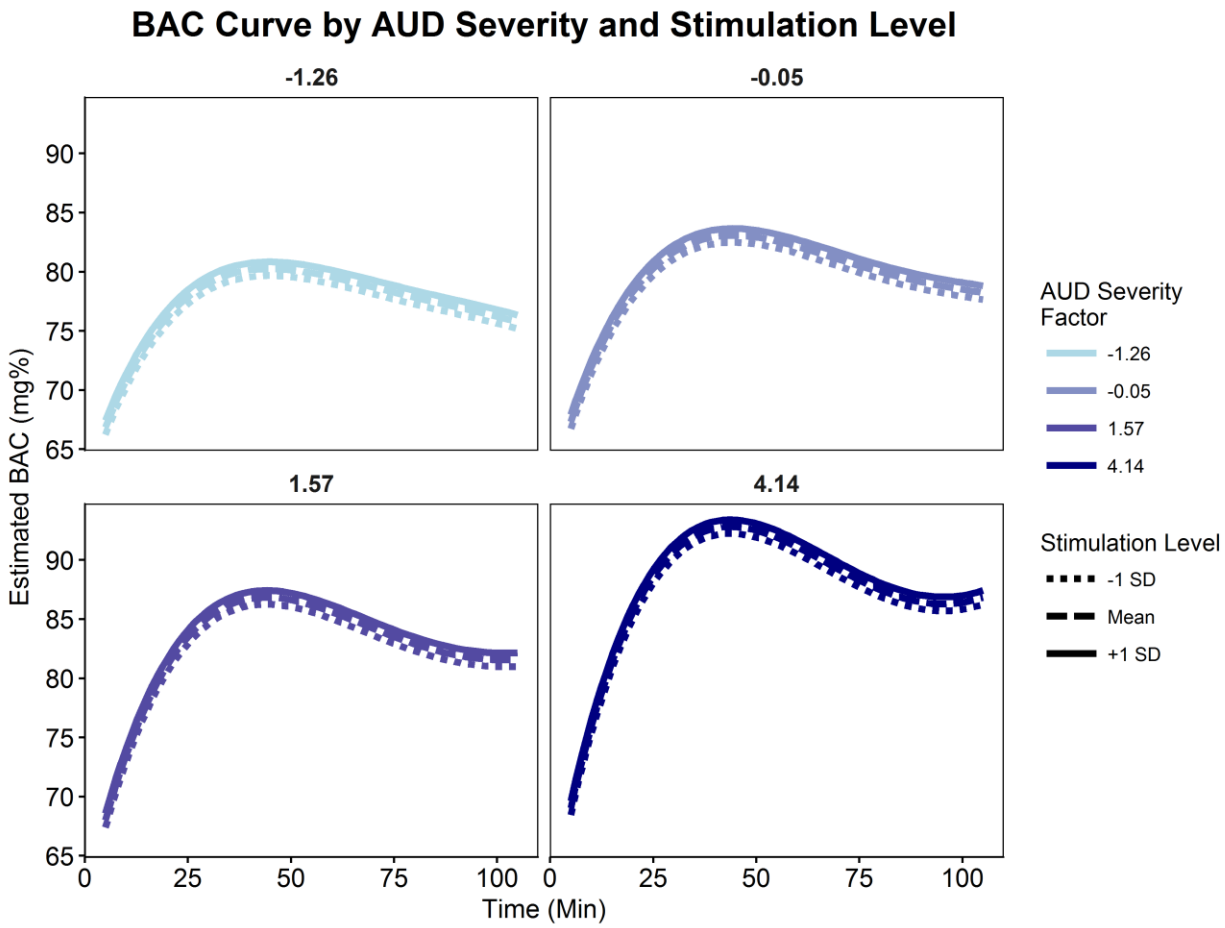
		Alcohol Craving Slope		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	66.468 (1.227)	54.173 (622)	<0.001
	Trial	7.978 (1.628)	4.901 (622)	<0.001
	$Trial^2$	-2.092 (0.341)	-6.139 (622)	<0.001
	$Trial^3$	0.194 (0.049)	3.965 (622)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.318 (622)	0.021
	AUD Severity	0.369 (0.387)	0.954 (64)	0.344
	Craving Slope	4.468 (4.611)	0.969 (64)	0.336
	AUD Severity × Trial	1.091 (0.588)	1.856 (622)	0.064
	AUD Severity × $Trial^2$	-0.219 (0.097)	-2.249 (622)	0.025
	AUD Severity × $Trial^3$	0.012 (0.006)	2.204 (622)	0.028
	Craving Slope × Trial	12.155 (5.029)	2.417 (622)	0.016
	Craving Slope × $Trial^2$	-0.946 (0.388)	-2.435 (622)	0.015
Trimmed Predictors	Craving Slope × AUD Severity × $Trial^4$	0.011 (0.008)	1.415 (615)	0.158
	Craving Slope × AUD Severity × $Trial^3$	-0.022 (0.035)	-0.623 (616)	0.533
	Craving Slope × AUD Severity × $Trial^2$	-0.102 (0.185)	-0.551 (617)	0.582
	Craving Slope × AUD Severity × Trial	-0.207 (0.719)	-0.288 (618)	0.774
	Craving Slope × AUD Severity	-1.310 (2.113)	-0.620 (63)	0.538
	AUD Severity × $Trial^4$	-0.001 (0.001)	-1.081 (619)	0.280
	Craving Slope × $Trial^4$	0.023 (0.016)	1.414 (620)	0.158
	Craving Slope × $Trial^3$	0.009 (0.073)	0.121 (621)	0.904

Final model of Craving Slope and AUD Severity predicting BAC self-administration curves after controlling for sex differences in BAC curves. Predicted values are adjusted for sex-differences through centering the binary sex predictor variable.



Alcohol Craving Slope			
	B (SE)	t (df)	p
Intercept	68.306 (1.474)	46.343 (611)	<0.001
Trial	10.263 (2.411)	4.256 (611)	<0.001
Trial^2	-3.085 (0.612)	-5.041 (611)	<0.001
Trial^3	0.357 (0.090)	3.961 (611)	<0.001
Trial^4	-0.015 (0.005)	-3.095 (611)	0.002
Sex	-4.585 (1.657)	-2.766 (62)	0.008
AUD Severity	0.588 (0.669)	0.878 (62)	0.383
Craving Slope	6.565 (4.982)	1.318 (62)	0.193
Sex × Trial	-4.161 (2.709)	-1.536 (611)	0.125
Sex × Trial^2	1.342 (0.683)	1.965 (611)	0.050
Sex × Trial^3	-0.195 (0.100)	-1.951 (611)	0.052
Sex × Trial^4	0.010 (0.005)	1.934 (611)	0.054
AUD Severity × Trial	1.768 (1.098)	1.610 (611)	0.108
AUD Severity × Trial^2	-0.697 (0.283)	-2.464 (611)	0.014
AUD Severity × Trial^3	0.095 (0.042)	2.248 (611)	0.025
AUD Severity × Trial^4	-0.004 (0.002)	-1.891 (611)	0.059
Craving Slope × Trial	10.740 (8.154)	1.317 (611)	0.188
Craving Slope × Trial^2	0.841 (2.077)	0.405 (611)	0.686
Craving Slope × Trial^3	-0.361 (0.307)	-1.175 (611)	0.241
Craving Slope × Trial^4	0.020 (0.016)	1.259 (611)	0.208
Craving Slope × AUD Severity	-2.132 (2.320)	-0.919 (62)	0.362
Craving Slope × AUD Severity × Trial	-2.919 (3.807)	-0.767 (611)	0.444
Craving Slope × AUD Severity × Trial^2	1.653 (0.987)	1.675 (611)	0.094
Craving Slope × AUD Severity × Trial^3	-0.271 (0.149)	-1.823 (611)	0.069
Craving Slope × AUD Severity × Trial^4	0.013 (0.008)	1.708 (611)	0.088

Full MLM model results for Stimulation Level predicting self-administration BAC curves.



		Stimulation Level		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	67.300 (0.837)	80.392 (624)	<0.001
	Trial	10.351 (1.333)	7.763 (624)	<0.001
	$Trial^2$	-2.283 (0.333)	-6.865 (624)	<0.001
	$Trial^3$	0.195 (0.049)	3.995 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.344 (624)	0.019
	AUD Severity	0.410 (0.385)	1.065 (64)	0.291
	Stimulation Level	0.240 (0.301)	0.796 (64)	0.429
	AUD Severity × Trial	1.197 (0.604)	1.983 (624)	0.048
	AUD Severity × $Trial^2$	-0.231 (0.099)	-2.338 (624)	0.020
	AUD Severity × $Trial^3$	0.013 (0.006)	2.260 (624)	0.024
Trimmed Predictors	Stimulation Level × AUD Severity × $Trial^4$	0.000 (0.001)	0.519 (615)	0.604
	Stimulation Level × AUD Severity × $Trial^3$	0.001 (0.003)	0.255 (616)	0.799
	Stimulation Level × AUD Severity × $Trial^2$	0.002 (0.016)	0.097 (617)	0.922
	Stimulation Level × AUD Severity × Trial	-0.021 (0.060)	-0.354 (618)	0.724
	Stimulation Level × AUD Severity	-0.082 (0.182)	-0.451 (63)	0.654
	Stimulation Level × $Trial^4$	0.001 (0.001)	0.916 (619)	0.360
	Stimulation Level × $Trial^3$	-0.001 (0.005)	-0.187 (620)	0.852
	Stimulation Level × $Trial^2$	-0.005 (0.026)	-0.195 (621)	0.846
	Stimulation Level × Trial	0.065 (0.101)	0.641 (622)	0.522
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.917 (623)	0.360

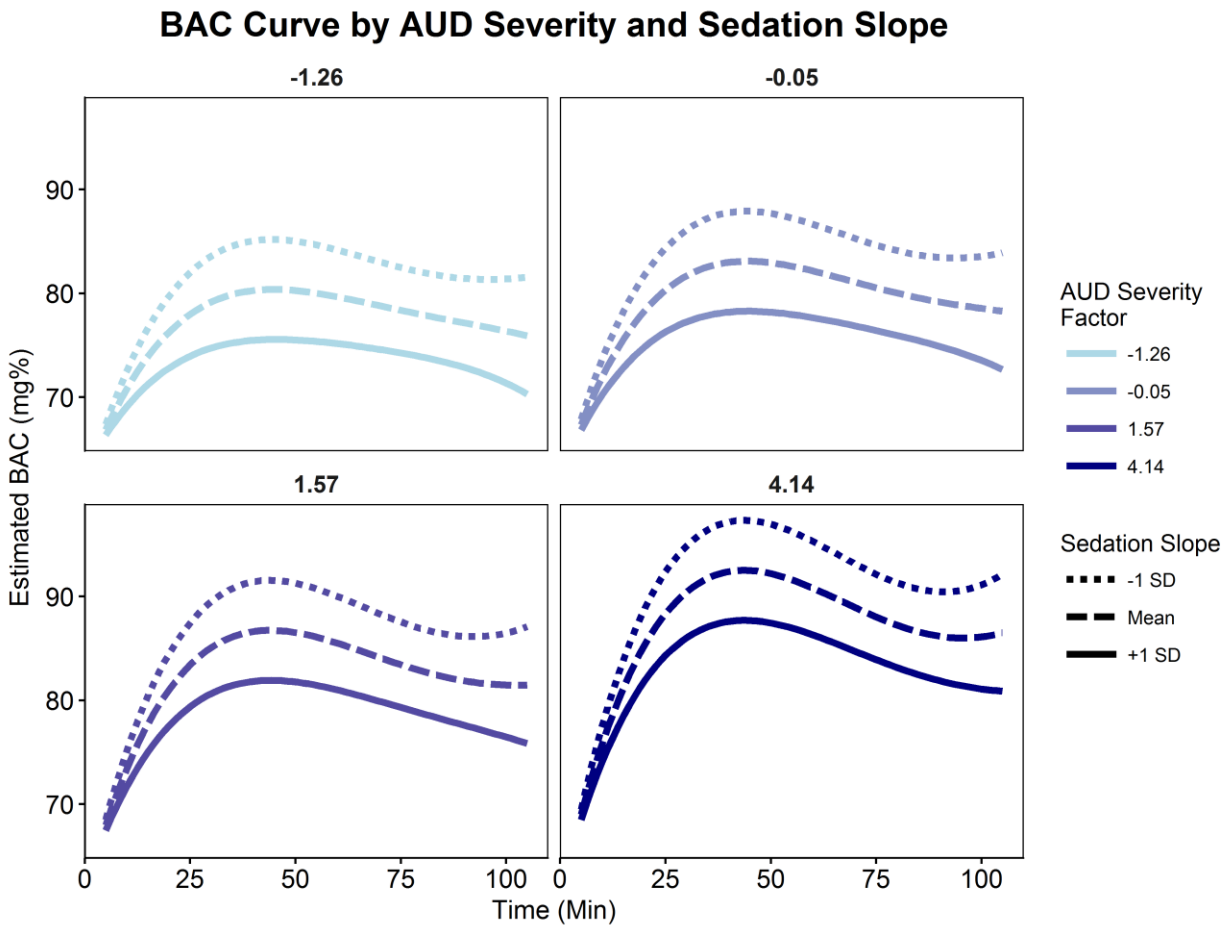
Full MLM model results for Stimulation slope predicting self-administration BAC curves.

		Stimulation Slope		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	66.750 (0.905)	73.759 (624)	<0.001
	Trial	10.354 (1.332)	7.772 (624)	<0.001
	$Trial^2$	-2.285 (0.332)	-6.884 (624)	<0.001
	$Trial^3$	0.196 (0.049)	4.013 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.360 (624)	0.019
	AUD Severity	0.405 (0.386)	1.049 (64)	0.298
	Stimulation Slope	2.079 (1.206)	1.724 (64)	0.090
	AUD Severity × Trial	1.197 (0.603)	1.984 (624)	0.048
	AUD Severity × $Trial^2$	-0.230 (0.098)	-2.340 (624)	0.020
	AUD Severity × $Trial^3$	0.013 (0.006)	2.265 (624)	0.024
Trimmed Predictors	Stimulation Slope × AUD Severity × $Trial^4$	0.000 (0.002)	-0.046 (615)	0.963
	Stimulation Slope × AUD Severity × $Trial^3$	0.010 (0.009)	1.158 (616)	0.247
	Stimulation Slope × AUD Severity × $Trial^2$	-0.021 (0.047)	-0.453 (617)	0.651
	Stimulation Slope × AUD Severity × Trial	-0.100 (0.173)	-0.580 (618)	0.562
	Stimulation Slope × AUD Severity	-0.429 (0.520)	-0.825 (63)	0.413
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.915 (619)	0.361
	Stimulation Slope × $Trial^4$	0.006 (0.004)	1.360 (620)	0.174
	Stimulation Slope × $Trial^3$	-0.022 (0.020)	-1.130 (621)	0.259
	Stimulation Slope × $Trial^2$	-0.122 (0.105)	-1.162 (622)	0.246
	Stimulation Slope × Trial	0.288 (0.400)	0.720 (623)	0.472

Full MLM model results for Sedation level predicting self-administration BAC curves.

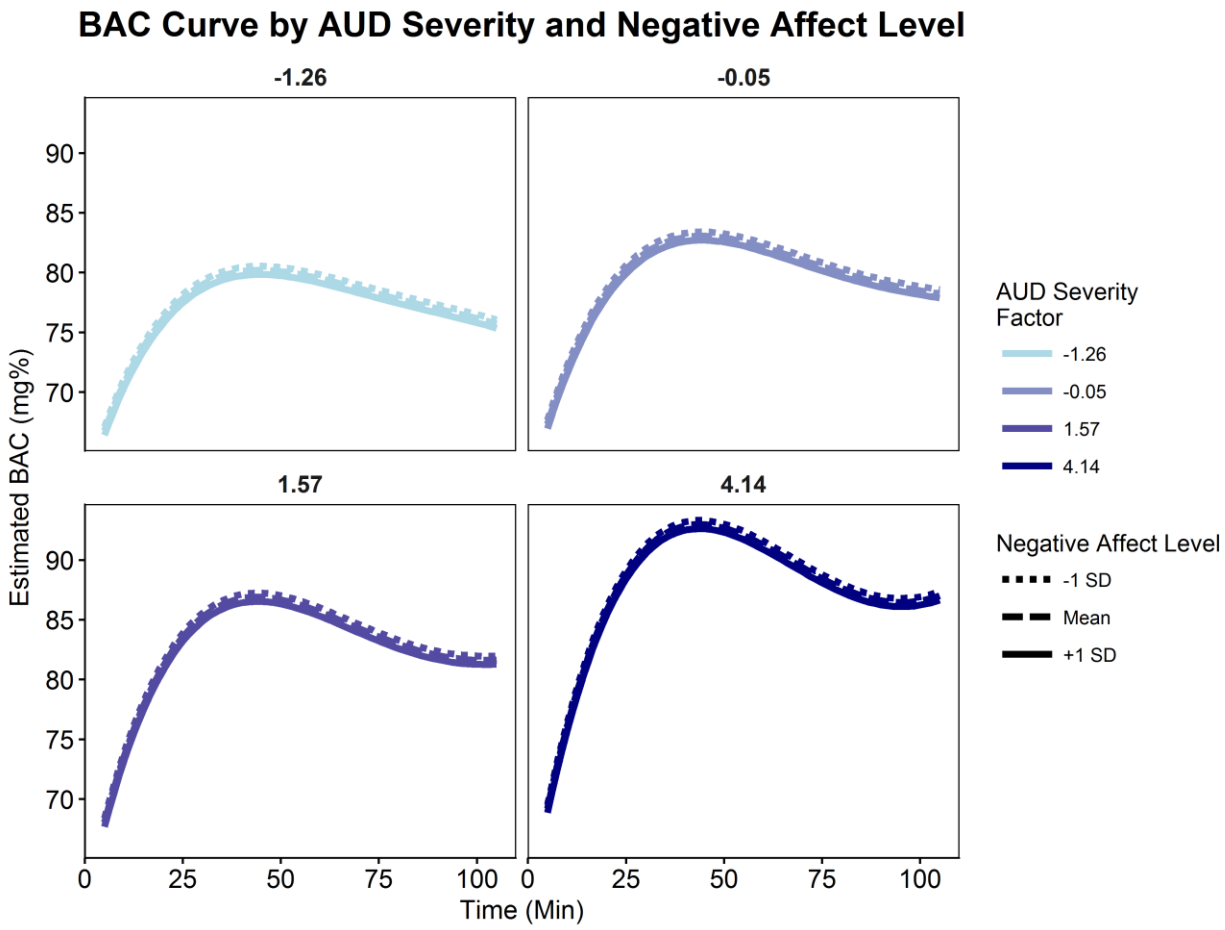
		Sedation Level		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	67.353 (0.861)	78.256 (621)	<0.001
	Trial	10.856 (1.305)	8.321 (621)	<0.001
	$Trial^2$	-2.383 (0.331)	-7.210 (621)	<0.001
	$Trial^3$	0.203 (0.049)	4.156 (621)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.422 (621)	0.016
	AUD Severity	0.411 (0.403)	1.019 (64)	0.312
	Sedation Level	-0.076 (0.592)	-0.128 (64)	0.898
	AUD Severity × Trial	1.553 (0.598)	2.598 (621)	0.010
	AUD Severity × $Trial^2$	-0.295 (0.097)	-3.039 (621)	0.003
	AUD Severity × $Trial^3$	0.016 (0.006)	2.939 (621)	0.003
	Sedation Level × Trial	-2.282 (0.879)	-2.595 (621)	0.010
	Sedation Level × $Trial^2$	0.410 (0.142)	2.898 (621)	0.004
	Sedation Level × $Trial^3$	-0.023 (0.008)	-2.867 (621)	0.004
Trimmed Predictors	Sedation Level × AUD Severity × $Trial^4$	0.001 (0.001)	1.137 (615)	0.256
	Sedation Level × AUD Severity × $Trial^3$	-0.001 (0.005)	-0.283 (616)	0.778
	Sedation Level × AUD Severity × $Trial^2$	0.010 (0.029)	0.339 (617)	0.735
	Sedation Level × AUD Severity × Trial	0.028 (0.111)	0.254 (618)	0.800
	Sedation Level × AUD Severity	0.012 (0.343)	0.036 (63)	0.972
	Sedation Level × $Trial^4$	0.001 (0.002)	0.414 (619)	0.679
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.919 (620)	0.359

Full MLM model results for Sedation slope predicting self-administration BAC curves.



		Sedation Slope		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	68.077 (1.490)	45.694 (621)	<0.001
	Trial	14.310 (2.268)	6.311 (621)	<0.001
	$Trial^2$	-3.059 (0.444)	-6.891 (621)	<0.001
	$Trial^3$	0.240 (0.052)	4.668 (621)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.350 (621)	0.019
	AUD Severity	0.393 (0.389)	1.009 (64)	0.317
	Sedation Slope	-1.452 (2.408)	-0.603 (64)	0.549
	AUD Severity × Trial	1.160 (0.588)	1.975 (621)	0.049
	AUD Severity × $Trial^2$	-0.223 (0.095)	-2.354 (621)	0.019
	AUD Severity × $Trial^3$	0.012 (0.005)	2.269 (621)	0.024
	Sedation Slope × Trial	-7.771 (3.641)	-2.134 (621)	0.033
	Sedation Slope × $Trial^2$	1.523 (0.582)	2.615 (621)	0.009
	Sedation Slope × $Trial^3$	-0.089 (0.033)	-2.746 (621)	0.006
Trimmed Predictors	Sedation Slope × AUD Severity × $Trial^4$	0.003 (0.005)	0.514 (615)	0.608
	Sedation Slope × AUD Severity × $Trial^3$	-0.017 (0.023)	-0.747 (616)	0.455
	Sedation Slope × AUD Severity × $Trial^2$	0.071 (0.130)	0.547 (617)	0.584
	Sedation Slope × AUD Severity × Trial	0.186 (0.498)	0.374 (618)	0.709
	Sedation Slope × AUD Severity	-0.359 (1.522)	-0.236 (63)	0.814
	Sedation Slope × $Trial^4$	0.005 (0.007)	0.776 (619)	0.438
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.921 (620)	0.357

Full MLM model results for Negative Affect level predicting self-administration BAC curves.



		Negative Affect Level		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	67.294 (0.844)	79.708 (624)	<0.001
	Trial	10.350 (1.333)	7.764 (624)	<0.001
	$Trial^2$	-2.283 (0.333)	-6.860 (624)	<0.001
	$Trial^3$	0.195 (0.049)	3.989 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.338 (624)	0.020
	AUD Severity	0.452 (0.404)	1.117 (64)	0.268
	Neg. Affect Level	-0.232 (0.521)	-0.445 (64)	0.658
	AUD Severity × Trial	1.197 (0.603)	1.983 (624)	0.048
	AUD Severity × $Trial^2$	-0.231 (0.099)	-2.340 (624)	0.020
	AUD Severity × $Trial^3$	0.013 (0.006)	2.262 (624)	0.024
Trimmed Predictors	Neg. Affect Level × AUD Severity × $Trial^4$	0.001 (0.001)	0.754 (615)	0.451
	Neg. Affect Level × AUD Severity × $Trial^3$	-0.003 (0.004)	-0.786 (616)	0.432
	Neg. Affect Level × AUD Severity × $Trial^2$	0.005 (0.024)	0.229 (617)	0.819
	Neg. Affect Level × AUD Severity × Trial	0.009 (0.091)	0.101 (618)	0.920
	Neg. Affect Level × $Trial^4$	0.000 (0.002)	-0.008 (619)	0.994
	Neg. Affect Level × $Trial^3$	-0.003 (0.008)	-0.371 (620)	0.711
	Neg. Affect Level × $Trial^2$	0.008 (0.045)	0.167 (621)	0.867
	Neg. Affect Level × Trial	-0.008 (0.179)	-0.043 (622)	0.966
	Neg. Affect Level × AUD Severity	-0.204 (0.262)	-0.780 (63)	0.438
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.912 (623)	0.362

Full MLM model results for Negative Affect slope predicting self-administration BAC curves.

		Negative Affect Slope		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	66.109 (1.156)	57.166 (624)	<0.001
	Trial	10.361 (1.333)	7.770 (624)	<0.001
	$Trial^2$	-2.291 (0.333)	-6.888 (624)	<0.001
	$Trial^3$	0.197 (0.049)	4.028 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.383 (624)	0.018
	AUD Severity	1.009 (0.520)	1.940 (63)	0.057
	Neg. Affect Slope	-4.623 (3.089)	-1.496 (63)	0.140
	AUD Severity × Trial	1.197 (0.604)	1.983 (624)	0.048
	AUD Severity × $Trial^2$	-0.230 (0.099)	-2.336 (624)	0.020
	AUD Severity × $Trial^3$	0.013 (0.006)	2.257 (624)	0.024
	Neg. Affect Slope × AUD Severity	3.179 (1.878)	1.693 (63)	0.095
Trimmed Predictors	Neg. Affect Slope × AUD Severity × $Trial^4$	-0.001 (0.007)	-0.106 (615)	0.915
	Neg. Affect Slope × AUD Severity × $Trial^3$	0.003 (0.031)	0.102 (616)	0.919
	Neg. Affect Slope × AUD Severity × $Trial^2$	0.034 (0.164)	0.208 (617)	0.835
	Neg. Affect Slope × AUD Severity × Trial	-0.469 (0.627)	-0.747 (618)	0.455
	Neg. Affect Slope × $Trial^4$	-0.004 (0.010)	-0.393 (619)	0.694
	Neg. Affect Slope × $Trial^3$	0.013 (0.045)	0.301 (620)	0.764
	Neg. Affect Slope × $Trial^2$	0.200 (0.240)	0.834 (621)	0.405
	Neg. Affect Slope × Trial	-0.312 (0.915)	-0.341 (622)	0.733
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.925 (623)	0.355

PAPER III – Liking, Wanting, and Incentive Salience

Testing the Incentive Salience of Alcohol Cues as a Determinant of Alcohol Reinforcement in a Clinical Sample

Abstract

Background: The Incentive Sensitization Theory (IST) suggests that drug liking and wanting are neurobiologically dissociable and that addiction is a consequence of sensitization in systems responsible for the attribution of incentive salience. To test IST in a clinical sample, this study applies a novel human laboratory paradigm designed to measure subjective liking and wanting of alcohol, alcohol self-administration, and the incentive salience of alcohol cues indexed by attentional bias towards alcohol-related images.

Methods: Sixty-seven heavy drinking participants ranging in alcohol use disorder (AUD) severity completed an intravenous alcohol administration paradigm including a standardized alcohol challenge, followed by progressive ratio self-administration. Self-reported alcohol liking and wanting were measured at 20, 40, and 60mg% timepoints during the challenge. At baseline and 60mg% timepoints participants completed an alcohol dot probe reaction time task which measures the ability of alcohol-related images to orient attention, a key component of incentive salience. Analyses tested whether AUD severity predicted subjective liking and wanting, and the correlation between liking and wanting. Analyses also tested whether incentive salience, indexed by dot probe attentional bias, mediated the relationship between AUD severity and self-administration.

Results: Overall, AUD severity predicted greater levels of self-administration. However, AUD severity did not predict self-reported liking or wanting and both remained highly correlated across the range of AUD severity. Contrary to our mediational hypotheses, AUD severity did not predict greater attentional bias and attentional bias did not predict self-administration.

Conclusions: This study represents a novel translational investigation of IST in a clinical sample. Self-reported liking and wanting remained highly correlated across AUD severity and attentional bias did not mediate the effect of AUD severity on self-administration. These results suggest that additional research is warranted to refine measures of incentive salience in human samples.

Introduction

The Insensitive Sensitization Theory (IST) suggests that addiction is due primarily to dysfunction in the neurobiological systems responsible for incentive value attribution (Robinson & Berridge, 1993, 2000, 2001). Robinson and Berridge (2001, pp. 103–104) summarize IST as consisting of four tenants: First, drugs of abuse have the capacity to produce long-lasting changes in brain organization. Second, the neurobiological systems primarily affected by chronic drug administration are those that process incentive motivation. Third, chronic drug exposure renders these incentive systems hypersensitive to drugs and drug-associated stimuli (i.e. drug cues). And fourth, these sensitized brain systems are not responsible for euphorigenic responses to drugs (i.e. drug liking), but instead subserve a related phenomenon of incentive salience or wanting (Berridge, 1996; Berridge & Robinson, 1995, 1998; Berridge & Valenstein, 1991; Berridge, Venier, & Robinson, 1989; Robinson & Berridge, 1993). IST posits that this pathological incentive salience leads to chronic drug and alcohol addiction.

IST was developed in preclinical laboratories where repeated administration of psychostimulants (e.g. cocaine and amphetamine) reliably produces sensitization to the drug's psychomotor stimulant effects (e.g. Robinson & Berridge, 1993; Segal, Geyer, & Schuckit, 1980). This psychomotor sensitization is thought to be neurobiologically related to the drugs reinforcing effect via the mesotelencephalic dopamine system (Wise & Bozarth, 1987). Furthermore, and consistent with situation-dependent relapse risk in humans, the expression of psychomotor sensitization has been shown to be context dependent (Anagnostaras & Robinson, 1996; Badiani, Anagnostaras, & Robinson, 1995; Robinson & Berridge, 1993; Robinson, Browman, Crombag, & Badiani, 1998). Of note however, psychomotor sensitization is more readily observed for stimulants than ethanol, or other drug classes (Robinson & Berridge, 2000). In numerous studies using pre-exposure paradigms, reinforcement sensitization has also been observed for drug self-administration (Horger, Shelton, & Schenk, 1990; Jentsch & Taylor, 1999; Piazza, Deminiere, le Moal, & Simon, 1990), conditioned place preference (Gaiardi et al., 1991; Lett, 1989), and progressive ratio breakpoint (Lorrain, Arnold, & Vezina, 2000).

Adaptations in dopaminergic systems are thought to subserve IST mechanisms. Increases in striatal dopamine release with repeated exposure has been observed in vitro and in vivo (Kantor, Hewlett, & Gnegy, 1999; Nestby et al., 1997; Robinson & Becker, 1982). Furthermore, dopamine D1 receptors have been shown to be sensitized following repeated stimulant administration (Henry & White, 1991). Synaptogenesis via dendritic branching has also been observed, suggesting that neuroadaptation may be occurring at the level of the receptor, the synapse, and potentially whole neuronal networks (Robinson & Kolb, 1999). Critically, it is proposed that these sensitizing adaptations are in systems supporting incentive salience of drugs and drug-associated cues rather than drug liking. This claim is supported by the observation that perturbation of dopaminergic systems drastically reduces the effects of drugs on motivated behavior (i.e. wanting) while having minimal effects on preclinical measures of hedonic reward (Berridge & Robinson, 1998; Brauer & de Wit, 1996).

Given IST's focus on biobehavioral responses to drug of abuse, alcohol researchers have sought to validate the dissociation between liking and wanting in alcohol administration paradigms (Hobbs, Remington, & Glautier, 2005). Liking and wanting of alcohol in laboratory settings have also been shown to predict future alcohol misuse and dependence (King, de Wit, McNamara, & Cao, 2011; King, McNamara, Hasin, & Cao, 2014). However, while the neurobiological and behavioral dissociation of liking and wanting is a component of IST, the central claim of IST goes beyond mere dissociation. IST claims that addiction is characterized by a state of neurobiological dysfunction wherein the incentive salience of drugs and drug-related cues come to pathologically motivate drug-seeking behavior, even in the absence of hedonic reward. Furthermore, it is not clear the degree to which self-report scales that ask participants about subjective liking and wanting in plain language (e.g. the Drug Effects Questionnaire; Morean et al., 2013) map onto the phenotypes highlighted in IST (e.g. psychomotor stimulation, prototypical affective facial responses, and instrumental reinforcement behavior).

As outlined by Robinson & Berridge (2008), stimuli that have acquired incentive salience possess three features which are observable in behavior. First, the stimulus elicits Pavlovian approach behavior, meaning that presentation of the stimulus orients attention and elicits behavioral approach. Second, the

stimulus can invigorate ongoing instrumental action (e.g. Pavlovian instrumental transfer). Third, the stimulus can serve as a positive reinforcer for novel instrumental behavior. In other words, cues that have acquired incentive salience properties are able to "[grab] attention, [become] attractive and 'wanted,' and thus [guide] behavior to the incentive" (Robinson & Berridge, 1993, p. 261). Beyond self-reported liking and wanting, measurement of these behaviorally defined features of incentive salience permits the translation of IST to clinical populations. In humans, Pavlovian approach behavior to alcohol-associated cues can be measured via the Alcohol Dot Probe Task (Duka & Townshend, 2004; Field, Mogg, Zetteler, & Bradley, 2004; Townshend & Duka, 2001). Since Pavlovian approach behavior can be subtle, this dot probe task measures the ability of alcohol cues to orient attention, which results in shorter reaction times to probes which are collocated with alcohol cues as compared to probes presented opposite to alcohol cues. Consistent with the proposed sensitization of cue incentive salience, significant differences in attentional bias have been observed between light and heavy drinkers (Townshend & Duka, 2001) and between opiate dependent and control subjects using an analogous task (Lubman, Peters, Mogg, Bradley, & Deakin, 2000).

The aim of this study is leverage a translational human laboratory paradigm to test IST in the context of alcohol reward and reinforcement. To accomplish this aim, a sample of heavy drinking participants representing a wide range of AUD severity completed a novel alcohol administration paradigm designed to capture alcohol reward, reinforcement, and incentive salience. Specifically, participants completed an IV alcohol administration session consisting of a standardized alcohol challenge (capturing subjective liking and wanting) followed by progressive ratio self-administration (capturing motivation and reinforcement). At baseline and at the final challenge BAC timepoint participants completed the alcohol dot probe task (Duka & Townshend, 2004; M. A. Miller & Fillmore, 2010; Townshend & Duka, 2001), capturing attentional bias to alcohol-related cues, our index of incentive salience. Based on IST, we hypothesized that wanting, but not liking during the Challenge will be enhanced with greater AUD severity and that the correlation between liking and wanting would diminish with greater AUD severity. Second and more critical to the translation of IST to human subjects,

we hypothesized that attentional bias to alcohol cues would mediate the effect of AUD severity on reinforcement behavior, such that AUD severity would predict greater attentional bias which in turn would predict greater self-administration.

Methods

Participants and Screening Procedures

This study was approved by the Institutional Review Board at the University of California, Los Angeles. Non-treatment seeking heavy drinkers representing a range of alcohol use/problems were recruited for an alcohol administration study from the Los Angeles community through fliers and online advertisements. Participants could receive up to $270 for participating.

Initial eligibility screening was conducted via a telephone screening interview. Eligible participants were then invited to an in-person screening session. After providing written informed consent, participants were breathalyzed to ensure no recent drinking, provided urine for toxicology screening, and completed a battery of self-report questionnaires and interviews (see Measures below). All participants tested negative on a urine drug screen (except marijuana) and all female participants tested negative for pregnancy.

Inclusion criteria for this study were: (1) age between 21 and 45, (2) Caucasian ethnicity (due to a secondary behavioral genetics aims not reported here), (3) fluency in English, (4) current heavy alcohol use of greater than 14 drinks per week for men, or 7 for women, (5) able to pass a physical exam and laboratory tests for medical eligibility, (6) if female, not pregnant or lactating; and be willing to use an reliable method of birth control (e.g., condoms) during the study, and (7) weigh less than 265 pounds so as to reduce the likelihood of exhausting the alcohol supply during the alcohol administration. Exclusion criteria included: (1) current treatment for AUD, a history of treatment in the 30 days, or seeking treatment for AUD, (2) current diagnosis of any substance use disorder other than nicotine, or alcohol, (3) lifetime diagnosis of any moderate to severe substance use disorder other than nicotine, alcohol, or cannabis, (4) current or lifetime diagnosis of schizophrenia, bipolar disorder, or a psychotic disorder, (5) current diagnosis of major depressive disorder with suicidal ideation, (6) current use of non-prescription

psychoactive drugs, other than marijuana, as determined by urine toxicology screen and/or self-report, (7) use of marijuana more than twice weekly, (8) clinically significant physical abnormalities as indicated by physical examination or clinically significant elevation on liver functioning tests as indicated on a comprehensive metabolic panel, (9) having a history of major medical conditions, such as: HIV, hepatitis, chronic liver disease, ulcer disease, seizure disorder, neurological disease, cardiac disease, obstructed bowel, hypertension, hyperthyroidism, or a circulatory disease, (10) current use of any psychoactive medications, such as antidepressants, mood stabilizers, sedatives, anxiolytics, seizure medications, pain killers, stimulants, antipsychotics, or depressants, (11) score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989), indicating clinically significant alcohol withdrawal requiring medical management, and (12) fear of, or adverse reactions to needle puncture.

Alcohol Administration Session

For the alcohol administration, participants arrived at the Clinical and Translational Research Center (CTRC) at UCLA at 10:30am. Participants' vitals, height, and weight were measured, and they were provided with a standardized high caloric breakfast. IV lines were set by registered nurses at approximately 11:30am. After participants acclimated to the IV lines, they completed the baseline assessment battery (see below). The alcohol infusion paradigm began at approximately 12:00pm and lasted a total of 180 minutes. To ensure all participants were safe to discharge, and to disincentivize low-levels of self-administration for early discharge, all participants were required to remain at the CTRC for at least four hours. Participants were discharged at approximately 7:00pm, or until their BAC fell below 40mg% if they were not driving, or zero if they were driving.

Throughout the infusion, participants were seated in a comfortable chair in a private room. Participants were not able to view the infusion pump or technician's screen. To control distractions, participants could watch a movie (BBC's Planet Earth), or listen to music. Study staff remained in the room to monitor the infusion, take breathalyzer readings, measure vital signs, administer questionnaires, and answer questions, but did not significantly engage with participants.

Infusion Parameters

To enable precise control over BAC and to dissociate biobehavioral responses to alcohol from cue-induced responses, alcohol was administered intravenously (6% v/v EtOH in saline prepared by the UCLA Research Pharmacy) using a physiologically-based pharmacokinetic model implemented in the Computerized Alcohol Infusion System (CAIS; Plawecki, Han, Doerschuk, Ramchandani, & O'Connor, 2008; Zimmermann et al., 2008, 2009; Zimmermann, O'Connor, & Ramchandani, 2013). CAIS estimates arterial BAC pseudo-continuously (every 30 seconds) based on the alcohol infusion time course and individual subject characteristics including sex, age, height, weight, as well as observed breathalyzer values and computes infusion rates accordingly. The CAIS system was modified for this study in collaboration with Drs. Ramchandani, Stangl, and O'Connor to seamlessly combine two alcohol administration paradigms. During the Challenge, participants were administered alcohol doses designed to reach target BACs of 20, 40, and 60 mg%. Each rise took 15 minutes, after which BAC's were clamped while participants completed self-report questionnaires (~5 min). This Challenge procedure closely mirrors other alcohol challenge studies by our group (e.g. Bujarski, Hutchison, Prause, & Ray, 2015; Bujarski, Hutchison, Roche, & Ray, 2015; Bujarski & Ray, 2014; Ray & Hutchison, 2004, p. 1, 2007).

Following the 60mg% timepoint, participants used the restroom, and then began the self-administration paradigm. During Self-Administration, participants were permitted to work (button press) to obtain additional alcohol "drinks" through the CAIS system according to a progressive ratio schedule. All participants were required to complete one alcohol self-administration to familiarize themselves with the procedure (participants had previously viewed a demonstration). The progressive ratio was log-linear and determined through simulations and pilot testing:

$$\text{Requirement}_i = 10 \times e^{0.3 \times Ratio_i} + 8 \times Ratio_i - 1$$

This equation resulted in a requirement schedule ranging from 20 at ratio 1, through 3139 at ratio 20. As is standard in CAIS, each "drink" was designed to increase BAC by 7.5 mg% over 2.5 minutes, followed by a decent of -1 mg%/min (Zimmermann et al., 2008, 2009, 2013). During the alcohol delivery, the

response button became inactive. For safety reasons, a maximum BAC limit was set at 120mg%. If at any point during the experiment, the next infusion would exceed this threshold, the response button was temporarily inactivated. Except for the first "drink" requirement, participants were given no instruction with respect to how much they should self-administer. After 180 minutes, the alcohol infusion ended, the IV line was removed, and participants were provided with a lunch.

Measures

Alcohol Use Disorder Severity Measures: The Structured Clinical Interview for DSM-5 (SCID; adapted from First, 2005) was administered by Master's level clinicians under the supervision of a licensed clinical psychologist (LAR). The SCID assessed for lifetime and current (i.e. past 3 months) AUD and exclusionary psychiatric diagnoses. The CIWA-Ar assessed for the severity of withdrawal symptoms (Sullivan et al., 1989). Participants also completed a 30-day timeline follow-back (TLFB) to determine drinking quantity and frequency (Sobell, Sobell, Leo, & Cancilla, 1988). Participants completed the following alcohol-related measures: the Alcohol Dependency Scale (ADS; Skinner & Allen, 1982), the Alcohol Use Disorders Identification Test (AUDIT; Allen, Litten, Fertig, & Babor, 1997), the Drinkers Inventory of Consequences (DrINC-2r; W. R. Miller, Tonigan, & Longabaugh, 1995), the Penn Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999), and the Obsessive Compulsive Drinking Scale (OCDS; Anton, 2000). As reported previously (Bujarski, Jentsch, Roche, Miotto, & Ray, in preparation), in order to control the number of statistical tests and reduce the influence of random measurement noise, AUD Severity was indexed by factor scores from a principal component analysis on the following variables: current AUD symptom count and lifetime AUD symptom count from the SCID, drinks per week, drinks per drinking day, drinking days per month, and proportion of binge drinking days from the TLFB, and the ADS, AUDIT, CIWA-Ar, OCDS, and PACS measures. A single component solution was revealed which accounted for 53% of the variance with all variables loading ≥ 0.495 (additional details in supplemental materials).

Other Baseline Measures: Naturalistic cigarette, and marijuana use were assessed using the TLFB (Sobell et al., 1988). Family history of alcohol related problems was collected via a family tree

questionnaire (Mann, Sobell, Sobell, & Pavan, 1985). The Fagerstrom Test for Nicotine Dependence assessed for smoking status and dependency (Payne, Smith, McCracken, McSherry, & Antony, 1994). Depressive symptomatology was assessed via the Beck Depression Inventory – II (Beck, Steer, & Brown, 1996).

Alcohol Liking and Wanting Measures: Subjective liking and wanting were measured with the DEQ (Morean et al., 2013). The DEQ has been well validated in alcohol challenge studies (Morean et al., 2013; Roche, Palmeri, & King, 2014) and has been shown to predict risk for AUD (King et al., 2011; King, Hasin, O'Connor, McNamara, & Cao, 2016). Liking was captured using the item "How much do you LIKE the effects you are feeling now?" with responses ranging from 0 to 10 anchored by "Dislike" and "Like Very Much" respectively. Wanting was measured with the item "How much would you like MORE of the drug right now?" measured on a 0 to 10 Likert scale anchored by "Not at All" through "Very Much." The DEQ was administered at the 20, 40, and 60 mg% time points during the Challenge.

Alcohol Dot Probe Task: The alcohol dot probe task is designed to measure attentional bias towards alcohol-related images (Duka & Townshend, 2004; M. A. Miller & Fillmore, 2010; Townshend & Duka, 2001). Analogous to Pavlovian approach behavior measured in preclinical paradigms, attentional bias in this dot probe task is defined in terms of the degree to which alcohol images orient attention (M. A. Miller & Fillmore, 2010). Attentional bias to alcohol-related images is probed through presentation of alcohol-related images and matched control images (13cm × 18cm pictures for 1000 ms), followed immediately by a visual probe (an 'X'). Participants are instructed to identify the location of the probe (left or right) as quickly as they can by pressing a computer key. Reaction time (RT) to the visual probe is measured. Mean RTs on test trials with correct responses that were greater than 100ms (to eliminate premature response) are computed resulting in two mean RTs for each subject: alcohol and neutral. The attentional bias measure is indexed by the difference between neutral and alcohol mean RTs. Greater attentional bias by this measure means quicker responses on alcohol-congruent trials as compared to incongruent trials. To reduce possible habituation, the task also contains filler trials with two control images. In total, the task consists of 80 trials, 40 of which are test trials balanced on presentation side of

the alcohol image and probe image (10 trials each combination). See supplemental materials for a schematic overview of the alcohol dot probe task. The alcohol dot probe task runs in the E-Prime software package (Schneider, Eschman, & Zuccolotto, 2012).

The alcohol dot probe task was administered at baseline and 60mg% timepoints during the Challenge (task order was randomized). Two measures of alcohol attentional bias were analyzed: attentional bias to alcohol cues at baseline, and alcohol-induced changes in attentional bias (60mg% - baseline difference scores). Thus, these two variables capture incentive salience of alcohol-related images in alcohol abstinence (baseline) and changes in incentive salience induced by a controlled alcohol administration. Baseline and 60mg% timepoint attentional bias were highly uncorrelated in these data ($r = 0.013$, $t(65) = 0.10$, $p = 0.918$).

Data Analysis

All analyses were conducted in **R** version 3.3.0 using base functions unless otherwise noted (R Development Core Team, 2008). The data analytic plan was broken into four sections.

First, the effect of AUD Severity on Liking and Wanting during the Challenge was tested via a series of multilevel models run using the **lme** function in the **multilevel** package (Bliese, 2013). Multilevel modeling was utilized due to the nested structure of the data where observations (Level 1) are nested in participants (Level 2). Predictors were Challenge timepoint (BAC; coded 0 – 2), AUD Severity factor score, and their interaction. BAC was treated as random at Level 2. Sex, Age, and BDI were tested as covariates to test robustness. Results of these models, and all subsequent models were plotted using **ggplot2** (Wickham, 2009) through computing expected values. To test whether liking and wanting were increasingly dissociated at greater AUD Severity, a series of multilevel models were conducted that tested DEQ Liking as a time-varying Level 1 predictor of Wanting, and whether this association was moderated by AUD Severity (i.e. AUD Severity × DEQ Liking interaction predicting DEQ Wanting).

Second, the total effect of AUD Severity on self-administration was analyzed. Rather than analyzing single point indicators of reinforcement (e.g. total “drinks” ordered, maximum BAC, or reinforcement breakpoint), BAC curves over the full self-administration paradigm were analyzed. This

approach capitalized on the rich self-administration data generated in CAIS and increases power to detect differences in self-administration profiles. As reported previously (Bujarski et al., in preparation), BAC estimates from CAIS were averaged over 10 minute bins in order to reduce the extreme degree of autocorrelation and non-independence in the data. This binning procedure closely tracked raw individual subject BAC curves while reducing the number of Level 1 observations from 13,323 to 698, and smoothing out short term spikes from each "drink" that was ordered (supplemental materials). A polynomial model-building approach was utilized to test BAC curves as a function of AUD Severity, with Δ-2LR tests on nested models to test for overall model fit. As models differed in their fixed effects, full information maximum likelihood estimation was used. Level-1 autocorrelation was expected to be substantial and was thus modeled in all BAC curve analyses using an AR(1) structure. To assess robustness Sex, Age, and BDI were also tested as potential predictors of BAC curves.

Third, to test the "*a*" paths in a multiple-mediational model, OLS regressions were conducted testing whether AUD Severity predicted attentional bias towards alcohol related cues using the **lm** function. Separate models were run for AUD Severity predicting baseline cue bias, and alcohol-induced change in cue bias.

Lastly, "*b*" and "*c*'" paths were examined using a series of multilevel models testing whether alcohol cue bias variables predicted reinforcement curves and whether AUD severity independently predicted self-administration after accounting for cue bias variables. Alcohol cue bias variables were entered as Level 2 predictors of BAC curves in addition to the AUD severity effects identified in step 2 above. Cue bias variables were first entered fully interactive with Trial parameters, and highest-order nonsignificant predictors were trimmed for parsimony. To visualize these results, two graphs were produced from the final model, one for each cue bias variable. In each graph, expected BAC curves are presented at ± 1SD from the mean on the cue bias variable of interest while holding the other cue bias variable constant at its mean.

Results

Sample Characteristics

140 participants completed the in-person behavioral screen, and 67 were eligible for and completed the alcohol infusion (**Figure 1**). Participants ranged in AUD diagnostic severity from no current AUD through severe. Sample characteristics for all study completers are reported in **Table 1.** As expected AUD Severity factors scores were significantly correlated with all indicator variables (*p's* < 0.001). AUD Severity also correlated with age (r = 0.365, *p* = 0.002), and sex differences were observed at a trend level (F(1,65) = 3.00, *p* = 0.088). AUD severity was also positively correlated with depressive symptomatology (r = 0.423, *p* < 0.001). Daily or occasional smokers had greater levels of AUD Severity than nonsmokers (F(2,64) = 3.21, *p* = 0.047), however within the subsample of smokers, no correlation between AUD Severity and nicotine dependence severity (i.e. FTND score) was observed (r = 0.281, *p* = 0.140). AUD Severity was not correlated with family history of alcohol-related problems (F(1,59) = 0.4, *p* = 0.627), AUD age of onset (r = -0.072, *p* = 0.609), or frequency of marijuana use (r = - 0.053, *p* = 0.671).

On average the Challenge was 70.66 ± 5.20 minutes, and the Self-Administration was 100.42 ± 5.10 minutes. BAC's during the Challenge were well controlled (20mg% timepoint: 17.34 ± 2.00; 40mg% timepoint: 38.71 ± 3.21; 60mg% timepoint: 59.10 ± 4.19). The duration of each Challenge clamp varied due to the inclusion of the alcohol dot probe task in the 60mg% timepoint (F(2,198) = 103.7, *p* < 0.001; 20mg%: 7.58 ± 2.19 min; 40mg%: 6.72 ± 1.51; 60mg%: 11.36 ± 2.17).

Liking and Wanting During Alcohol Challenge

Liking on the DEQ increased over rising BAC (B = 0.42, SE = 0.13, t = 3.21, df = 133, *p* = 0.002; **Figure 2A**). AUD Severity did not predict DEQ Liking either as a main effect (B = 0.06, SE = 0.07, t = 0.84, df = 65, *p* = 0.406), or as a moderator of BAC slopes (B = -0.04, SE = 0.06, t = -0.74, df = 132, *p* = 0.463). Males reported greater Liking (B = -1.08, SE = 0.29, t = -3.72, df = 65, *p* < 0.001), but no sex differences in BAC slopes were observed (*p* = 0.740). Controlling for sex had no effect on the null AUD Severity results. No age-related differences were observed (*p* ≥ 0.520). Similarly, no effects of BDI were observed for Liking (*p* ≥ 0.168).

Wanting on the DEQ also increased over the challenge (B = 0.58, SE = 0.15, t = 3.88, df = 133, $p < 0.001$), but no main effect of AUD Severity (B = 0.18, SE = 0.14, t = 1.27, df = 65, $p = 0.209$), or AUD Severity × BAC interactions were observed (B = -0.06, SE = 0.07, t = -0.85, df = 132, $p = 0.398$; **Figure 2B**). No sex or age effects were observed for Wanting ($p \geq 0.192$). Greater depressive symptomatology was associated with greater Wanting (B = 0.41, SE = 0.19, t = 2.21, df = 65, $p = 0.030$), though no change in BAC slope (B = 0.02, SE = 0.10, t = 0.22, df = 132, $p = 0.825$). Controlling for BDI had no effect on the null AUD Severity results.

In terms of the association between Liking and Wanting, Liking was strongly associated with Wanting overall (B = 0.64, SE = 0.08, t = 7.81, df = 131, $p < 0.001$; **Figure 2C**), and this effect was not moderated by AUD Severity (B = 0.05, SE = 0.04, t = 1.52, df = 130, p = 0.131). At a trend level, the association between Liking and Wanting decreased with rising BAC (B = -0.16, SE = 0.08, t = -1.86, df = 130, p = 0.066), but this decreasing correlation over the Challenge was also not moderated by AUD Severity (i.e. AUD Severity × BAC × Liking interaction: B = -0.01, SE = 0.05, t = -0.17, df = 128, p = 0.863). Thus, by examining DEQ Liking and Wanting, these data do not provide evidence of increasing dissociation of liking and wanting with greater AUD Severity.

AUD Severity and Alcohol Reinforcement

As reported previously in this sample (Bujarski et al., in preparation), AUD Severity was associated with greater self-administration BAC curves. AUD Severity significantly interacted with linear through cubic polynomial Trial terms (AUD Severity × Trial: B = 1.20, SE = 0.60, t = 1.99, df = 624, $p = 0.048$; AUD Severity × $Trial^2$: B = -0.23, SE = 0.10, t = -2.35, df = 624, $p = 0.019$; AUD Severity × $Trial^3$: B = 0.01, SE = 0.01, t = 2.27, df = 624, $p = 0.024$ **Figure 3A**). All quartic polynomial Trial parameters were random at the subject level (Δ-2LR ≥ 41.17, df = 5, *p's* < 0.001) and the Level 1 autoregressive AR(1) φ coefficient was 0.670. This effect of AUD severity in predicting greater progressive-ratio alcohol reinforcement represents the "total effect" in a mediational framework, which IST suggests should be mediated by incentive salience of alcohol cues.

Male participants had greater self-administration BAC curves than female participants (see supplemental materials). Due to these sex differences, all analyses of BAC curves were conducted with and without controlling for sex. The moderating role of AUD Severity on BAC curves was largely unaffected by covarying for sex differences. Age was found to moderate the linear BAC curve parameter at a trend level (see supplemental materials). The effect of AUD Severity was similarly unaffected by covarying for age differences. BDI scores did not predict self-administration (see supplemental materials).

AUD Severity and Dot Probe Incentive Salience

AUD Severity was not associated with alcohol cue bias either at baseline, or in terms of alcohol-induced change. In this sample overall, alcohol cue bias was not observed at baseline (t = 0.72, df = 66, *p* = 0.471), or at the 60 mg% time point (t = 1.22, df = 66, *p*-value = 0.228), and alcohol administration did not change mean cue bias (t = -0.37, df = 66, *p* = 0.716). Contrary to the hypothesized mediational role of alcohol cue bias *vis a vis* AUD Severity and alcohol reinforcement, AUD Severity did not predict baseline attentional bias (B = -0.52, SE = 1.22, t = -0.43, *p* = 0.668, R^2 = 0.003), or alcohol-induced change (B = 0.38, SE = 1.73, t = 0.22, *p* = 0.829, R^2 = 0.001; **Figure 3B**). Thus, attentional bias was not found to be greater among participants with more severe AUD as we would expect from IST.

Incentive Salience Mediating AUD Severity and Alcohol Motivation

The effect of AUD Severity in predicting self-administration BAC curves was unaffected by the inclusion of incentive salience variables, and neither insensitive salience variable directly predicted BAC curves (**Table 2** and **Figure 3B).** Baseline alcohol cue bias did not moderate any Trial parameters (*p's* ≥ 0.335), and was not a significant predictor of BAC averaged across the self-administration paradigm (*p* = 0.220). Similarly, alcohol-induced change in cue bias did not interact with any BAC curve parameter (*p's* ≥ 0.184), or predict BAC overall (*p* = 0.597). The direct effect of AUD Severity on BAC curves remained significant after controlling for attentional bias variables (Trial: B = 1.20, SE = 0.60, t = 1.98, df = 624, p = 0.048; $Trial^{2:}$ B = -0.23, SE = 0.10, t = -2.34, df = 624, p = 0.020; $Trial^{3}$: B = 0.01, SE = 0.01, t = 2.27, df = 624, p = 0.024). Taken together, these results are inconsistent with the proposed mediational

pathway, and suggest that AUD Severity predicted alcohol reinforcement behavior independent of attentional bias to alcohol-related cues.

Discussion

The aim of this study was to test the Incentive Salience Theory of addiction in a sample of heavy drinkers. To accomplish this aim, participants completed a novel and translational alcohol administration paradigm capturing alcohol reward via standardized alcohol challenge and reinforcement via progressive ratio self-administration paradigms. Participants also completed the alcohol dot probe task at baseline and 60mg% timepoints which captures the ability of alcohol-related images to orient attention, a key component of Pavlovian approach behavior and incentive salience (Duka & Townshend, 2004; M. A. Miller & Fillmore, 2010; Robinson & Berridge, 2008; Townshend & Duka, 2001).

In terms of subjective ratings of alcohol liking and wanting, IST suggests that AUD severity should predict greater wanting during the alcohol challenge, but not liking, and that liking and wanting would be increasingly dissociated with greater AUD severity. While wanting and liking increased over the alcohol challenge, AUD severity did not predict self-reported levels of liking or wanting. Furthermore, liking and wanting during the Challenge were highly correlated regardless of AUD severity. These results counter some findings previously reported in the literature. For example, Hobbs, Remington, and Glautier (2005) observed that liking was only weakly associated with wanting, particularly when wanting was indexed by alcohol consumption in the laboratory. Exploratory analyses with these data found that DEQ Liking during the Challenge predicted greater BAC over the self-administration paradigm (see supplemental materials). This effect however was not moderated by AUD Severity as we would expect in IST. Differences in methodology (e.g. oral versus intravenous administration), and study participants drinking levels (~ 10 weekly standard drinks US [14g EtOH] in Hobbs et al. (2005), versus ~ 22 in the present study) may explain differential results. In particular, the presence of cues in oral alcohol paradigms may elicit wanting, but not liking, leading to greater observed dissociation. Additionally, lighter drinkers may report low levels of alcohol wanting, which through a floor effect could also reduce observed correlations between liking and wanting.

Recent factor analytic work on subjective responses to alcohol in an IV challenge by our group found very high correlations between liking and wanting on the Alcohol Response Scale which is very similar to the DEQ (Bujarski, Hutchison, Roche, et al., 2015). In fact, in that study, the strongest inter-measure correlations were between liking and wanting, both of which loaded with the Alcohol Urge Questionnaire forming a Craving/Motivation factor. Lutz and Childs (2017) recently examined SR factor structure in the context of an oral alcohol challenge in a sample of moderate drinkers, and also observed high correlations between liking and wanting on the DEQ. Similarly, though the correlations between measures are not reported, King and colleagues have observed generally analogous results for liking and wanting in terms of prospectively predicting future alcohol problems and AUD symptomatology (King et al., 2011, 2014).

The high correlation between liking and wanting across these studies is possibly influenced by the measurement methods. Since both liking and wanting outcomes are assessed via single items in a short measure, these assessments are very proximal in time. Previously we suggested that responses on the liking item (which was asked first on the ARS) may contaminate the assessment of wanting as subjects may bring to mind their responses on enjoyment when responding whether they want more alcohol (Bujarski, Hutchison, Roche, et al., 2015; Podsakoff & Organ, 1986; Salancik & Pfeffer, 1977). In this study item order was randomized within measures deliberately to minimize this contamination risk. It appears that four possibilities may explain the high correlation that persisted despite random item order: (1) contamination is unidirectional from liking to wanting, but the roughly 50% of participants who answered liking first were sufficient to produce a high correlation, (2) contamination is bidirectional as participants engage in self-justification of why they want additional alcohol (Festinger, 1962; Harmon-Jones & Mills, 1999), (3) self-reported liking and wanting items are not assessing the dissociable factors highlighted in IST, and (4) liking and wanting in humans aren't as dissociable as IST suggests. Further research is needed to evaluate these competing possibilities.

To determine the role of incentive salience in motivating alcohol consumption, we tested whether attentional bias to alcohol cues, as measured by the alcohol dot probe task, mediated the effect of AUD

severity on reinforcement behavior. As expected, AUD severity predicted greater alcohol reinforcement BAC curves. This represented the "total effect" which IST hypothesizes will be mediated by enhanced incentive salience. Though we hypothesized attentional bias to mediate this total effect, none of the constituent mediational pathways were supported in these data. AUD severity did not predict attentional bias at baseline or in terms of alcohol-induced change, and neither attentional bias variable predicted self-administration.

This nonsignificant mediation may be explained by poor reliability for the alcohol dot probe task. Numerous previous studies utilizing this task (for review see Field & Cox, 2008) have demonstrated construct validity in terms of differentiating between light and heavy drinkers (Field et al., 2004; Townshend & Duka, 2001), opioid dependents and controls (Lubman et al., 2000), and responsivity to a priming dose of alcohol (Duka & Townshend, 2004). Furthermore, task development studies have suggested that the task is affected by design factors such as image complexity and duration (Field et al., 2004; M. A. Miller & Fillmore, 2010), such that simpler images displayed for between 500 and 2000ms produce more reliable attentional bias (simple images were presented for 1000ms in this study). Although this task is frequently used in the alcoholism literature, studies demonstrating its reliability are essentially lacking. In a large study of over 400 subjects, Ataya et al. (2012) showed poor internal reliability for both an alcohol and tobacco dot probe tasks (Chronbach's α between 0.00 and 0.50 across seven studies). Furthermore, across the broader psychiatric literature significant doubts have been raised regarding the reliability of dot probe tasks (Cisler, Bacon, & Williams, 2009; Schmukle, 2005). The very low pre-post alcohol challenge correlation ($r = 0.013$) observed in this study, provides additional evidence questioning the reliability of attentional bias. According to classical test theory, and inherent to the mathematics of general linear models, reliability limits validity (Carmines & Zeller, 1979; Crocker & Algina, 1986). A measure that is unable to reliably predict itself cannot reliably predict something else. Therefore, although the alcohol-dot probe benefits from strong face validity as a measure of incentive salience, more work appears necessary to develop more reliable measures of incentive salience in humans.

This study should be interpreted in light of its strengths and weaknesses. The novel, highly controlled, and translational alcohol administration paradigm capturing alcohol reward and reinforcement, and isolating alcohol-paired cues represents the study's chief strength. Study exclusion criteria which required participants to be non-treatment seeking and able to produce a zero on a breathalyzer test represent potential weaknesses. These exclusion criteria may have impeded recruitment of severe AUD patients. The subsample of participants with severe AUD (American Psychiatric Association, 2013) was considerably smaller than other groups (n = 7), and generally represented the lower range of severe AUD (6.57 ± 0.79 symptoms). Ethical standards limit the recruitment of treatment-seeking participants in alcohol administration studies (Dolinsky & Babor, 1997; Enoch et al., 2009), for concerns about exacerbating alcohol consumption. However, the available data suggests that participation in alcohol administration studies tends to decrease, not increase, naturalistic drinking, possibly by highlighting participants' patterns of maladaptive alcohol use (W. R. Miller & Rollnick, 2002; Pratt & Davidson, 2005; Sinha, Krishnan-Sarin, Farren, & O'Malley, 1999; Sommer et al., 2015). This limitation is particularly salient as many preclinical alcohol administration paradigms produce very high levels of dependence including severe withdrawal (e.g. Broadwater, Varlinskaya, & Spear, 2011; Crabbe, Harris, & Koob, 2011; Kantak & Luzzo, 2007; Macey, Schulteis, Heinrichs, & Koob, 1996). It is possible that the neuroadaptations highlighted in IST and other neurobiological theories occur only at high levels of dependence. Individuals with severe dependence may have been excluded from this study based on an indication for medically managed detoxification, or an inability to maintain short term abstinence as was required in the study. The substantial BAC curve ceiling effect, where 36% of participants were impacted by our safety threshold (120mg%), may also have affected out results. Lastly, though this study was cross-sectional, IST focuses on neuroadaptation and is thus necessarily longitudinal. Some early evidence suggests that self-reported liking and wanting are relatively stable longitudinally (King et al., 2016); however, to our knowledge no longitudinal research on the stability of AUD-dependent changes in incentive salience exists in humans. Lastly, as discussed in detail above, emergent evidence suggest that

the alcohol dot probe may not be a reliable measure, and thus may have limited experimental validity in testing incentive salience factors.

In conclusion, this study applied a novel and translational experimental paradigm to test core aspects of the Incentive Sensitization Theory in humans. While IST has garnered considerable support in preclinical and neuroscience laboratories, translational tests of IST's behavioral predictions in clinical samples are generally lacking. Those studies that do exist generally examine IST through measuring self-reported liking and wanting, and occasionally reinforcement behavior. To our knowledge this study is the first to test predictions about the proposed IST mechanism whereby alcoholism is a function of sensitization in systems that subserve incentive salience of alcohol and alcohol-paired cues. In this study, the severity of alcohol use and problems significantly predict greater levels of motivated alcohol reinforcement. However, predictions regarding increasing dissociations between alcohol liking and wanting in later stage dependence, and the role of alcohol cue incentive salience in motivating alcohol consumption, were generally not supported. Critically however, these data, and several other recent reports, call into question the reliability of dot probe tasks, our behavioral measure of incentive salience, and thus may have limited our ability to test incentive salience factors. First and foremost, research is needed to develop more reliable tasks for measuring the incentive salience of drug- and alcohol-paired cues. Additional studies are also warranted that recruit more severe AUD participants who are more similar in physiological dependence severity to preclinical models. Lastly, longitudinal research is warranted to test whether changes in liking, wanting, and incentive salience develop with AUD progression, or whether they are premorbid risk factors.

Table 1

Sample characteristics of study completers with associations between sample characteristics and AUD Severity.

	Mean (SD) N (%)	**Association with AUD Severity Factor**
Demographics		
Age	29.18 (6.57)	r = 0.365, p = 0.002
Gender (Female)	31 (46%)	F(1,65) = 3.00, p = 0.088
Beck Depression Inventory-II*	8.66 (8.35)	r = 0.423, p < 0.001
Alcohol Use Variables		
Drinks per Week	22.04 (13.19)	r = 0.650, p < 0.001
Drinks per Drinking Day	5.3 (2.56)	r = 0.424, p < 0.001
Drinking Days (past 30)	18.18 (6.45)	r = 0.395, p < 0.001
Binge Proportion	0.5 (0.31)	r = 0.428, p < 0.001
ADS	11.12 (5.47)	r = 0.741, p < 0.001
AUDIT	13.43 (5.84)	r = 0.871, p < 0.001
CIWA	1.03 (1.37)	r = 0.511, p < 0.001
OCDS	8.63 (4.85)	r = 0.866, p < 0.001
PACS	9.75 (5.81)	r = 0.779, p < 0.001
Family History Positive (n=61)	30 (49%)	F(1,59) = 0.4, p = 0.627
Alcohol Use Disorder		
AUD Symptoms Lifetime	3.96 (2.59)	r = 0.785, p < 0.001
AUD Onset (n=53)	20.72 (3.8)	r = -0.072, p = 0.609
AUD Symptoms Current	2.43 (2.09)	r = 0.839, p < 0.001
AUD Severity Factor	0.25 (2.15)	

*Beck Depression Inventory-II scores were square-root transformed to improve normality for analyses

Table 2

Alcohol cue bias (our measure of incentive salience) and AUD Severity predicting self-administration BAC curves. Attentional bias to alcohol related cues did not predict BAC curves either as a moderator of Trial parameters, or as a main effect. The effect of AUD Severity on BAC curves was unaffected by the inclusion of cue bias variables. See **Figure 2B**.

Attentional Bias to Alcohol Cues				
		B (SE)	t (df)	p
Final Model Predictors	Intercept	67.480 (0.847)	79.629 (624)	<0.001
	Trial	10.351 (1.335)	7.754 (624)	<0.001
	$Trial^2$	-2.283 (0.333)	-6.859 (624)	<0.001
	$Trial^3$	0.195 (0.049)	3.991 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.340 (624)	0.020
	AUD Severity	0.373 (0.386)	0.967 (63)	0.337
	Baseline Alcohol Cue Bias	-0.060 (0.048)	-1.240 (63)	0.220
	Alcohol-Induced Cue Bias	-0.018 (0.034)	-0.532 (63)	0.597
	AUD Severity × Trial	1.198 (0.605)	1.982 (624)	0.048
	AUD Severity × $Trial^2$	-0.231 (0.099)	-2.340 (624)	0.020
	AUD Severity × $Trial^3$	0.013 (0.006)	2.268 (624)	0.024
Trimmed Predictors	Alcohol-Induced Cue Bias × $Trial^4$	0.000 (0.000)	0.362 (616)	0.718
	Baseline Alcohol Cue Bias × $Trial^4$	0.000 (0.000)	0.523 (617)	0.601
	Baseline Alcohol Cue Bias × $Trial^3$	0.000 (0.001)	-0.075 (618)	0.940
	Baseline Alcohol Cue Bias × $Trial^2$	0.000 (0.004)	-0.022 (619)	0.982
	Alcohol-Induced Cue Bias × $Trial^3$	0.000 (0.000)	-1.041 (620)	0.298
	Alcohol-Induced Cue Bias × $Trial^2$	0.001 (0.002)	0.604 (621)	0.546
	Alcohol-Induced Cue Bias × Trial	0.015 (0.011)	1.329 (622)	0.184
	Baseline Alcohol Cue Bias × Trial	0.011 (0.012)	0.965 (623)	0.335

Figure 1

Study Recruitment Overview

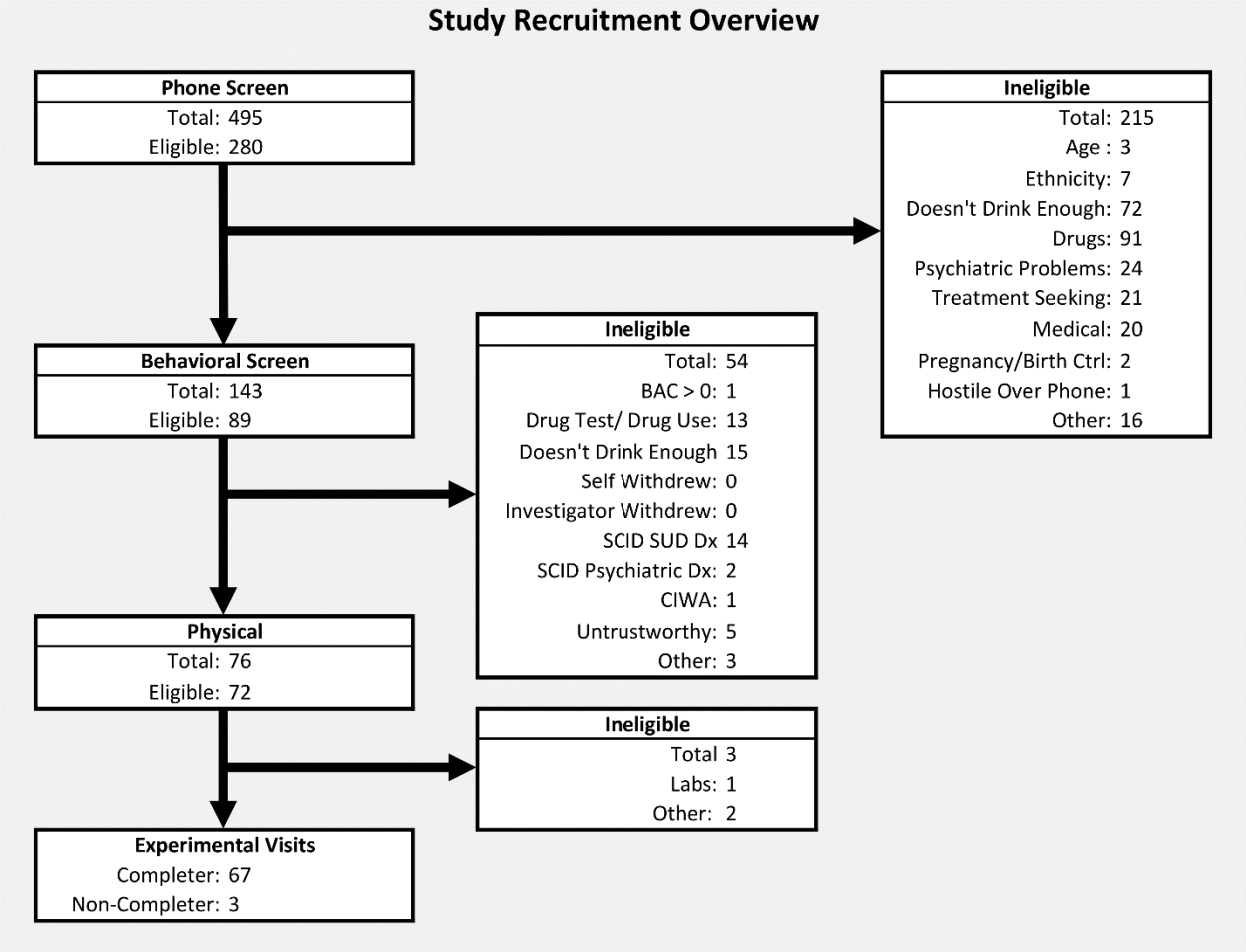


Figure 2

Liking and Wanting during the alcohol challenge. The Drug Effects Questionnaire was measured at the 20, 40, and 60 mg% time points during the challenge. Liking and Wanting increased with Rising BAC (*p's* < 0.01). AUD Severity did not predict Liking (**A**) or Wanting (**B**) either on average or as a moderator of BAC slopes. AUD Severity also did not predict correlations between Liking and Wanting (**C**). Blue colors denote level of AUD Severity factor score displayed at the mean values for none, mild, moderate, and severe AUD based on DSM-5 classification.

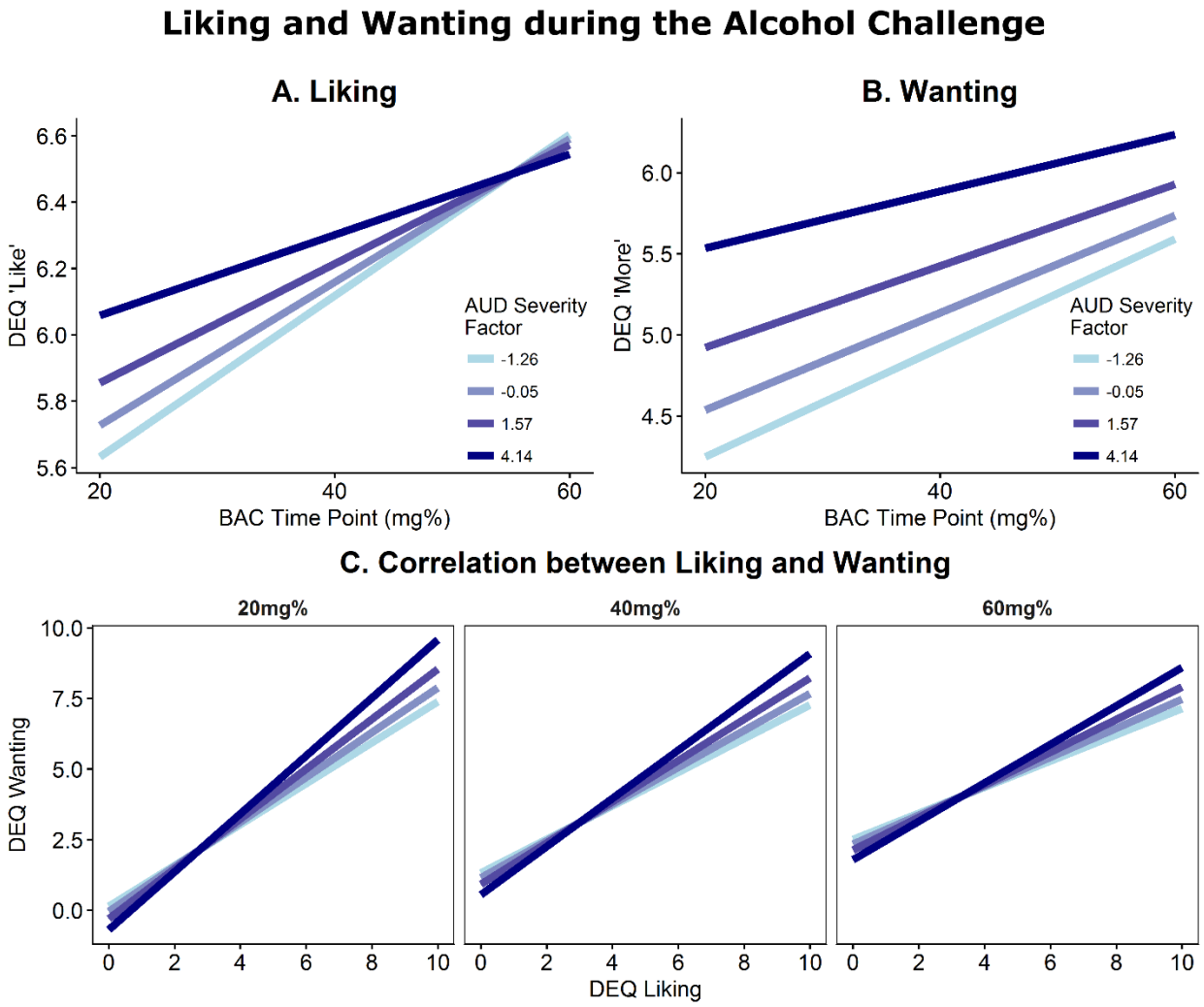
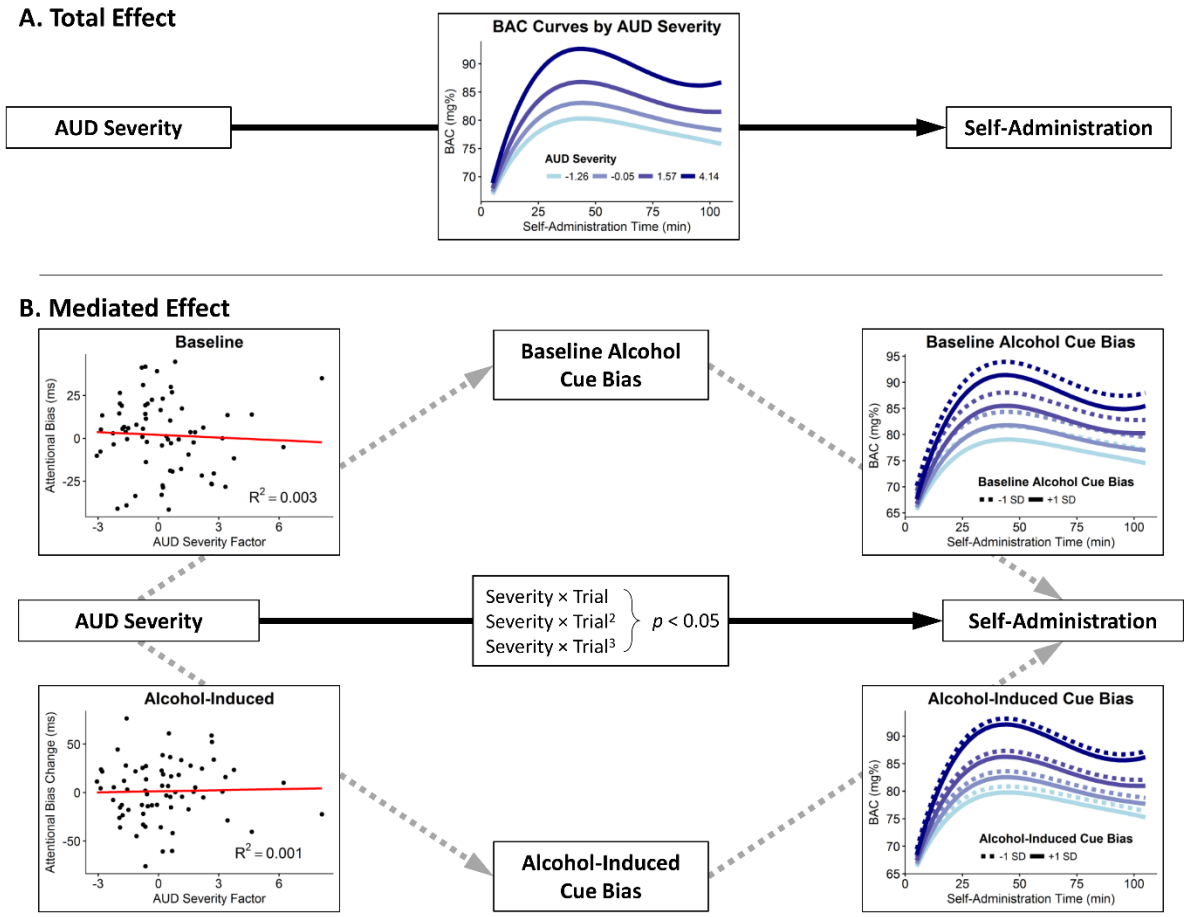


Figure 3

Mediational model as proposed by the Incentive Sensitization Theory. (**A)** AUD Severity predicted greater self-administration in a progressive ratio paradigm (i.e. the total effect). (**B)** Attentional bias to alcohol cues were hypothesized to mediate this effect. In these data, no component of the indirect mediational path was significant. AUD Severity did not predict attentional bias at baseline or alcohol-induced changes, and attentional bias did not predict self-administration. Controlling for attentional bias did not alter the significance of AUD Severity in predicting BAC curves. Statistically significant (p <0.05) and nonsignificant paths are denoted with solid black and dashed grey arrows respectively. Blue colors denote level of AUD Severity factor score displayed at the mean values for none, mild, moderate, and severe AUD. Expected BAC curves at ±1SD of attentional bias variables are displayed with dashed and solid lines respectively.



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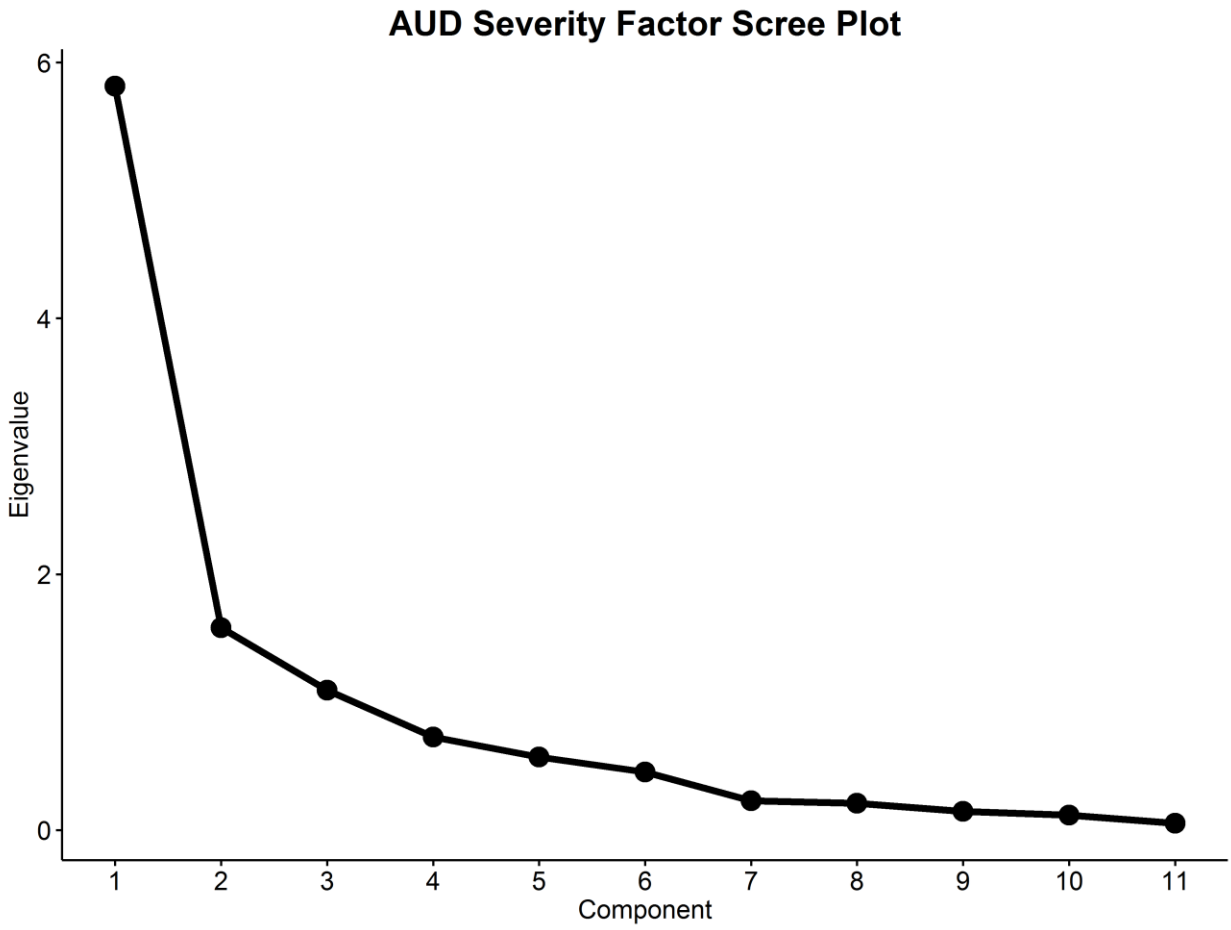
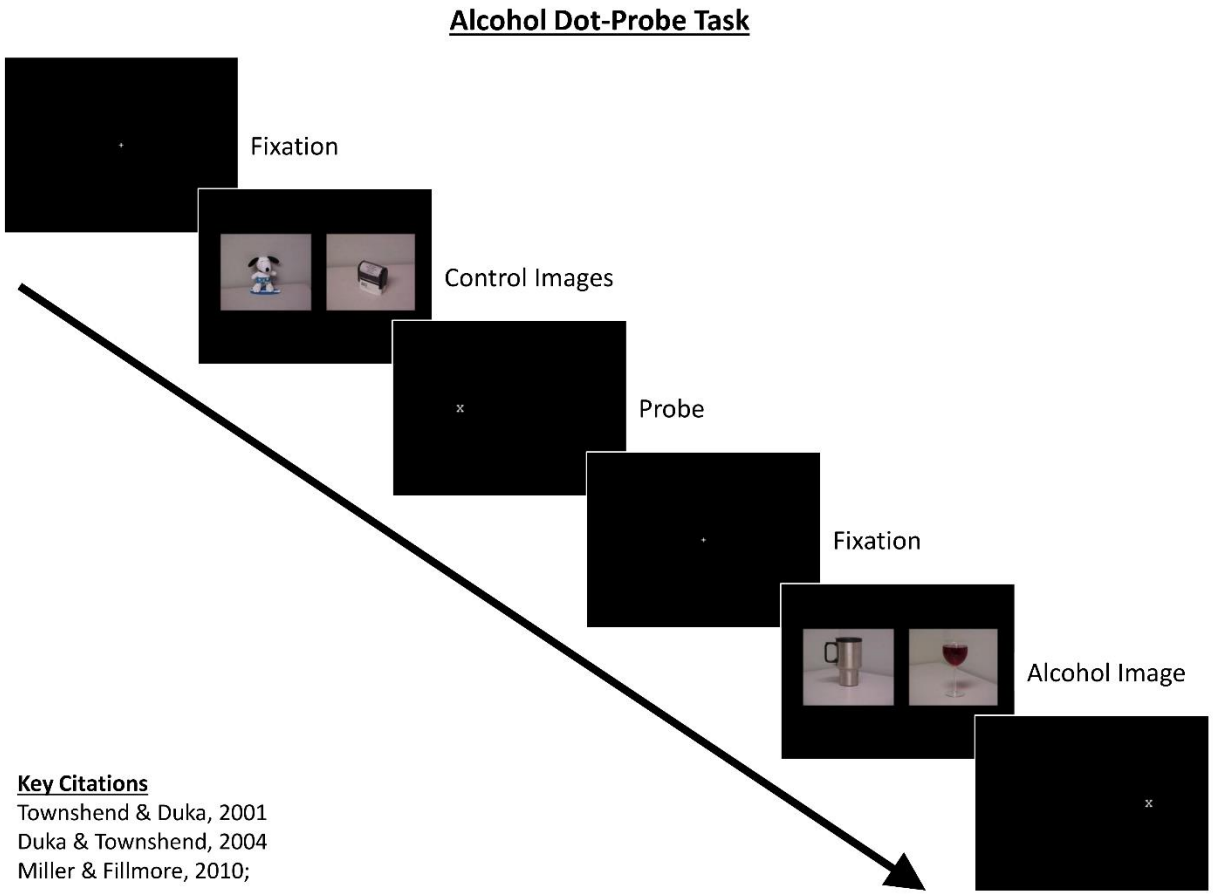
Supplemental Materials

Principal component analysis scree plot of AUD Severity variables which suggested a single-factor solution accounting for 53% of the total variance.

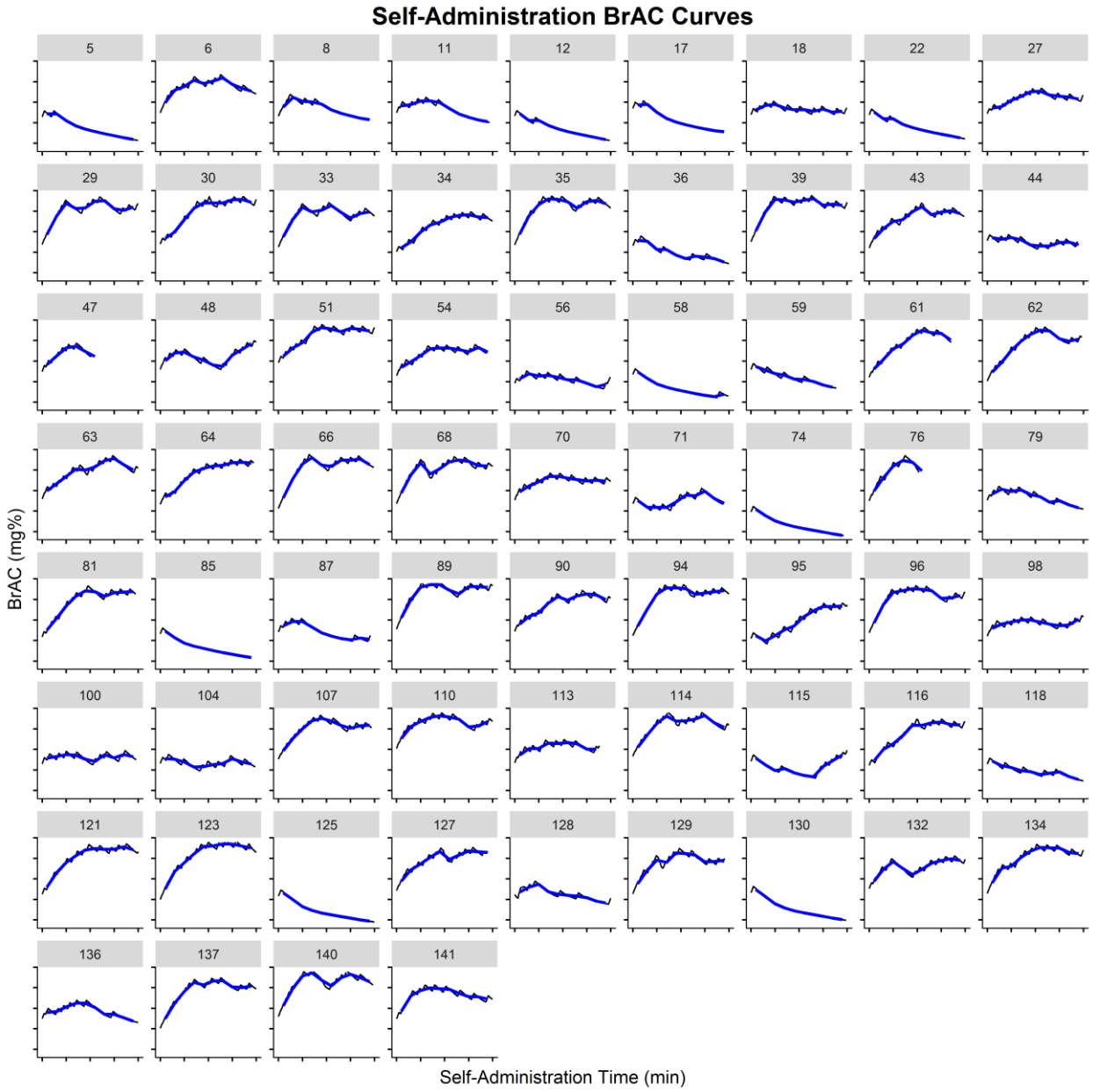


	Loadings
Drinks per Week	0.766
Drinks per Drinking Day	0.649
Drink Days per Month	0.454
% Binge Drinking Days	0.614
Alcohol Dependency Scale	0.744
Alcohol Use Disorder Identification Test	0.890
Clinical Institute of Withdrawal - Alcohol	0.495
Obsessive Compulsive Drinking Scale	0.831
Penn Alcohol Craving Scale	0.754
Lifetime AUD Symptom Count	0.812
Current AUD Symptom Count	0.859

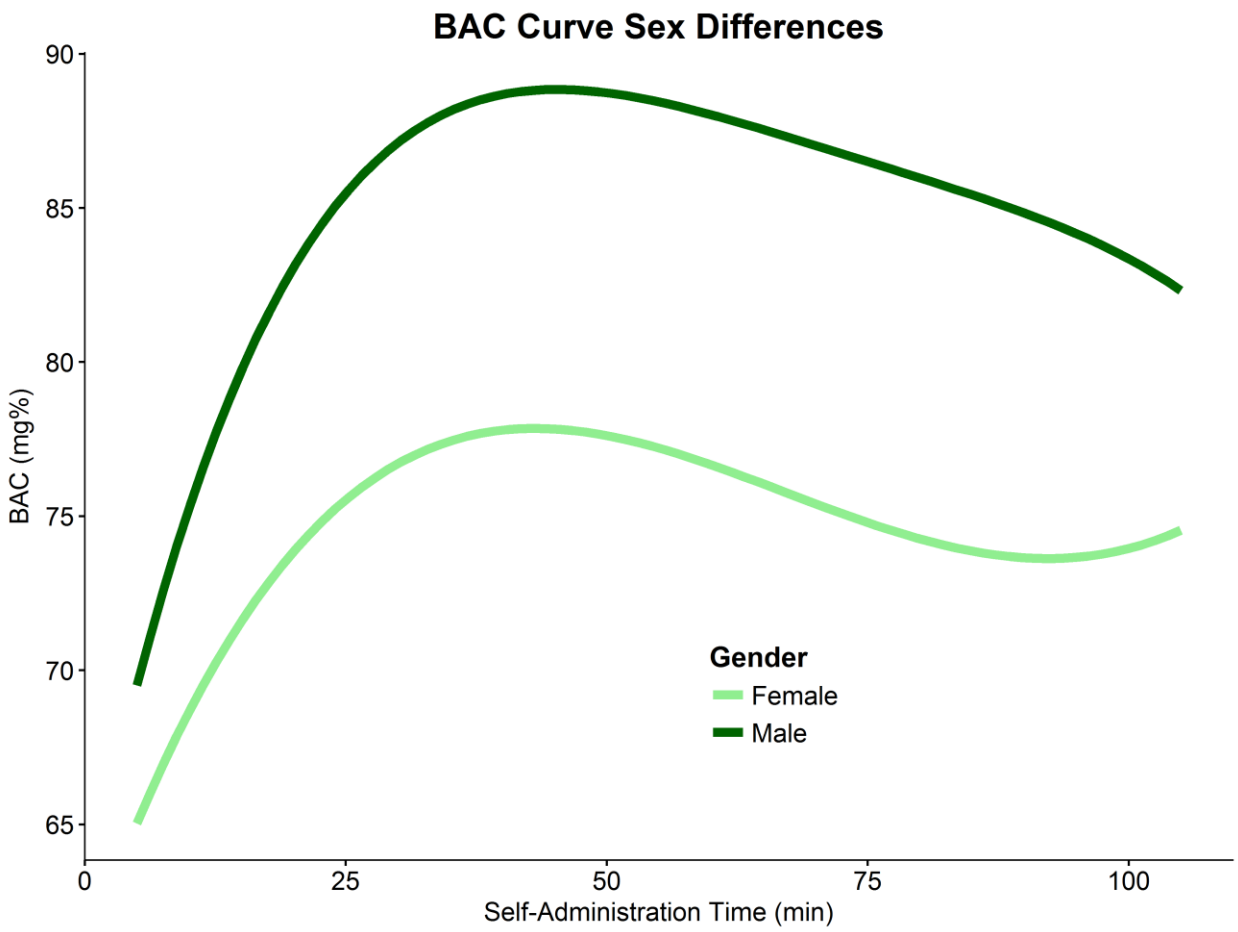
Alcohol Dot Probe Task Schematic



BAC curves computed in the CAIS software (black) with average BAC values over 10 minute bins overlaid (blue). The binned BAC means track the full BAC curves well, while reducing the degree of autocorrelation and smoothing out the short-term spikes and dips with each self-administered infusion.

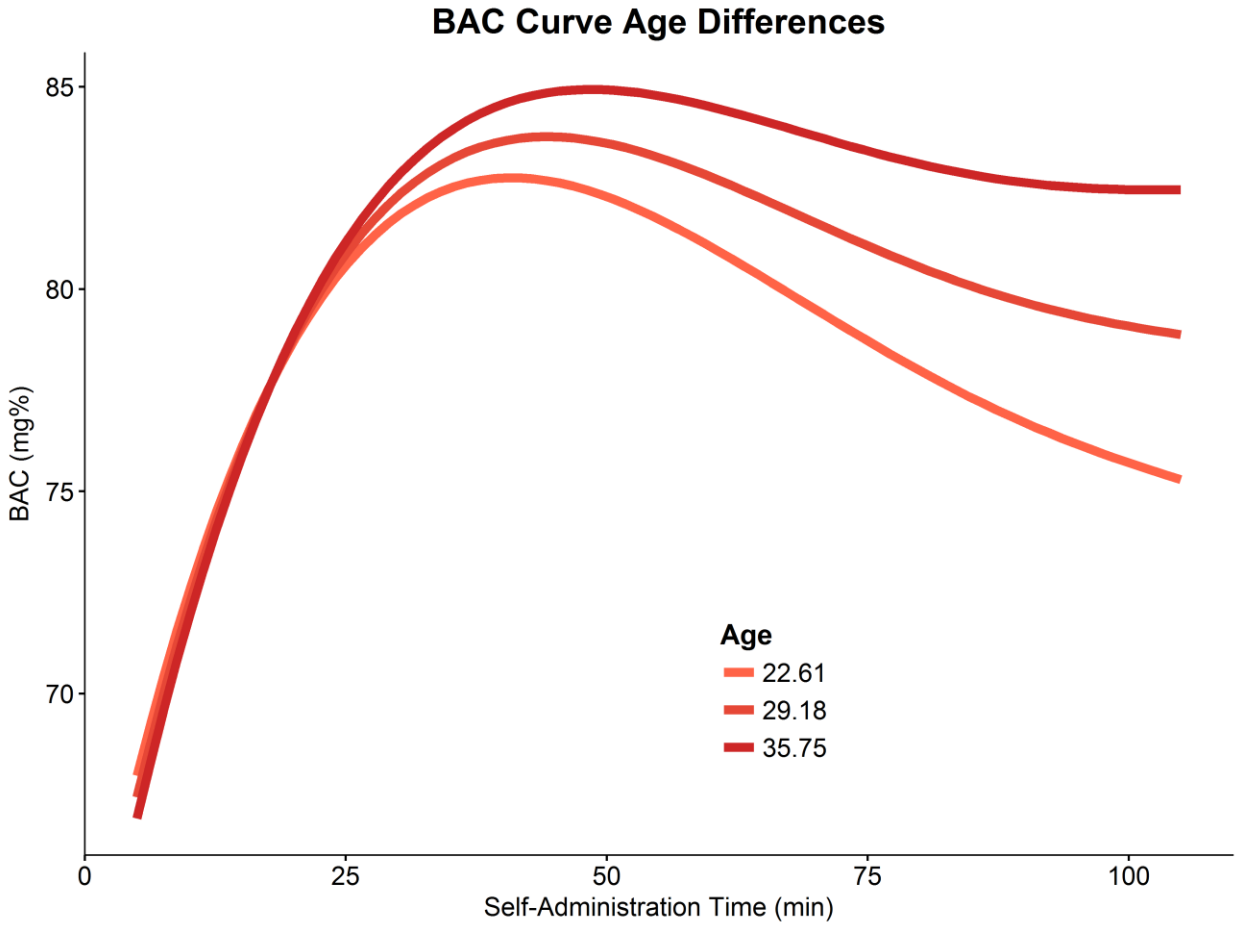


Sex differences in alcohol self-administration BAC curves. Male subjects administered more alcohol than female participants.



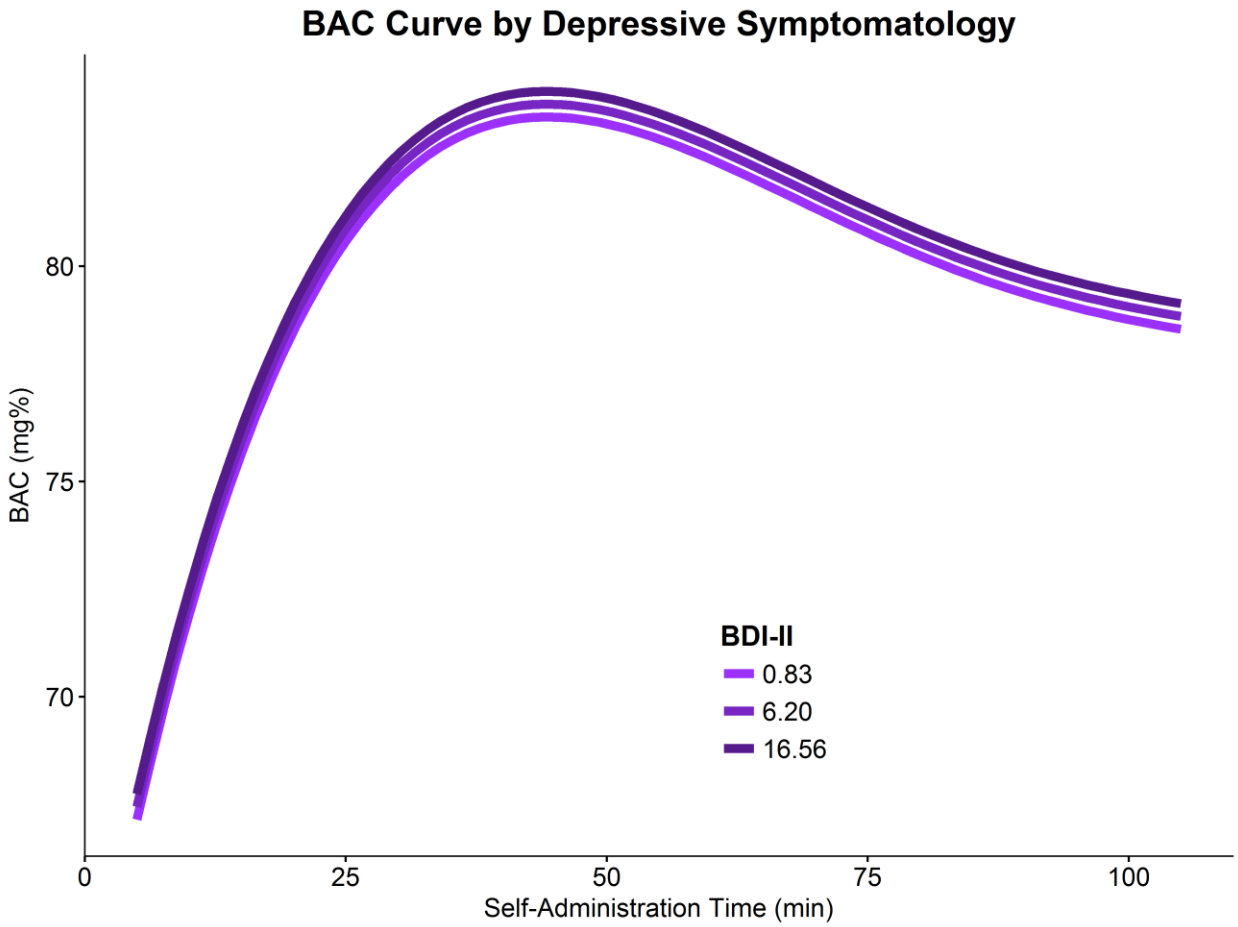
	Sex Differences		
	B (SE)	t (df)	p
Intercept	69.508 (1.095)	63.505 (623)	<0.001
Trial	12.955 (1.831)	7.075 (623)	<0.001
Trial^2	-3.027 (0.454)	-6.668 (623)	<0.001
Trial^3	0.291 (0.066)	4.387 (623)	<0.001
Trial^4	-0.011 (0.003)	-3.047 (623)	0.002
Sex	-4.477 (1.609)	-2.782 (65)	0.007
Sex × Trial	-4.921 (2.691)	-1.829 (623)	0.068
Sex × Trial^2	1.440 (0.666)	2.164 (623)	0.031
Sex × Trial^3	-0.192 (0.097)	-1.982 (623)	0.048
Sex × Trial^4	0.009 (0.005)	1.870 (623)	0.062

Age differences in alcohol self-administration BAC curves. At a trend level (p = 0.081), older subjects tended to maintain higher BAC levels. Age values displayed represent the mean ± 1 SD.



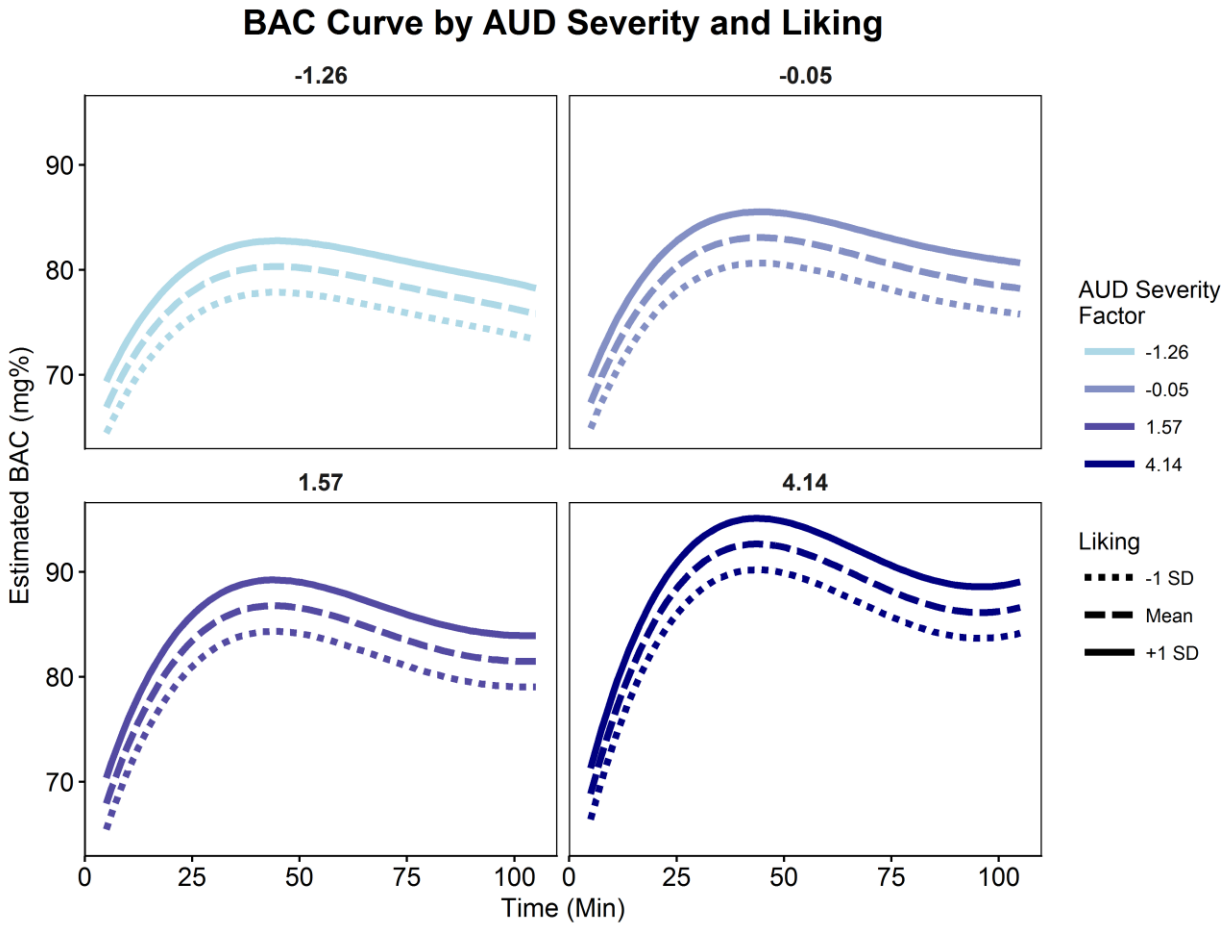
		Age Differences		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	69.787 (3.378)	20.659 (626)	<0.001
	Trial	8.824 (1.696)	5.204 (626)	<0.001
	$Trial^2$	-2.340 (0.334)	-7.014 (626)	<0.001
	$Trial^3$	0.198 (0.049)	4.052 (626)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.330 (626)	0.020
	Age	-0.081 (0.112)	-0.719 (65)	0.475
	Age × Trial	0.063 (0.036)	1.747 (626)	0.081
Trimmed Predictors	Age × $Trial^4$	0.000 (0.000)	-0.724 (623)	0.470
	Age × $Trial^3$	0.003 (0.002)	1.516 (624)	0.130
	Age × $Trial^2$	-0.010 (0.009)	-1.081 (625)	0.280

Full MLM results for the effect of depressive symptomatology as measured by the BDI-II as a moderator of BAC curves. Displayed values represent the mean ± 1 SD transformed back into the original metric from a square-root transformation to improve normality.



		Depressive Symptomatology		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	66.968 (1.429)	46.863 (627)	<0.001
	Trial	10.655 (1.345)	7.923 (627)	<0.001
	$Trial^2$	-2.344 (0.333)	-7.029 (627)	<0.001
	$Trial^3$	0.199 (0.049)	4.073 (627)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.355 (627)	0.019
	BDI	0.189 (0.466)	0.405 (65)	0.687
Trimmed Predictors	BDI × $Trial^4$	0.000 (0.002)	-0.196 (623)	0.845
	BDI × $Trial^3$	0.009 (0.008)	1.172 (624)	0.242
	BDI × $Trial^2$	0.010 (0.041)	0.257 (625)	0.797
	BDI × Trial	0.090 (0.156)	0.578 (626)	0.563

Figure depicting the final model for DEQ Liking predicting self-administration BAC curves over and above the effect of AUD Severity



DEQ Liking predicting self-administration BAC curves table of full MLM modeling results

		Liking (DEQ)		
		B (SE)	t (df)	p
Final Model Predictors	Intercept	54.794 (3.752)	14.604 (624)	<0.001
	Trial	10.363 (1.336)	7.758 (624)	<0.001
	$Trial^2$	-2.293 (0.331)	-6.928 (624)	<0.001
	$Trial^3$	0.197 (0.048)	4.069 (624)	<0.001
	$Trial^4$	-0.006 (0.003)	-2.410 (624)	0.016
	AUD Severity	0.359 (0.371)	0.968 (64)	0.337
	Liking	2.035 (0.594)	3.423 (64)	0.001
	AUD Severity × Trial	1.199 (0.606)	1.980 (624)	0.048
	AUD Severity × $Trial^2$	-0.230 (0.099)	-2.327 (624)	0.020
	AUD Severity × $Trial^3$	0.013 (0.006)	2.257 (624)	0.024
Trimmed Predictors	Liking × AUD Severity × Trial4	0.001 (0.001)	0.725 (615)	0.469
	Liking × AUD Severity × Trial3	0.003 (0.005)	0.595 (616)	0.552
	Liking × AUD Severity × Trial2	-0.005 (0.028)	-0.161 (617)	0.872
	Liking × AUD Severity × Trial	-0.116 (0.103)	-1.133 (618)	0.258
	Liking × Trial4	-0.039 (0.307)	-0.127 (63)	0.899
	Liking × Trial3	-0.001 (0.002)	-0.548 (619)	0.584
	Liking × Trial2	0.001 (0.010)	0.148 (620)	0.883
	Liking × Trial	-0.057 (0.053)	-1.073 (621)	0.284
	Liking × AUD Severity	0.284 (0.199)	1.425 (622)	0.155
	AUD Severity × $Trial^4$	-0.001 (0.001)	-0.954 (623)	0.340

DISSERTATION CONCLUSIONS

The overarching aim of this dissertation was to develop a translational framework for testing behavioral predictions from preclinical addiction theories in clinical samples. Specifically, these results tested translational predictions of the Allostatic Model and the Incentive Sensitization Theory with respect to alcohol use disorder in human subjects.

In Paper I, the factor structure of subjective responses to alcohol was examined using data from a large alcohol challenge study in light and heavy drinkers. This study successfully replicated the 3-factor structure of SR reported by Ray et al. (2009) using the BAES, SHAS, and POMS measures comprising the domains of Stimulation/Hedonia, Sedation/Motor Intoxication, and Negative Affect. These results also extend Ray et al.'s multidimensional model through incorporating alcohol craving, liking and wanting which were found to comprised a fourth Craving/Motivation factor, and demonstrating reliable factor structure across ascending and descending limbs of alcohol intoxication. Furthermore, Paper I provided early evidence that the factor structure of SR may be better defined in heavy drinkers, whereas light drinkers appeared more likely to report generally positive or generally negative responses to alcohol. Together these results suggested that alcohol challenge studies should assess these four domains of SR to ensure full coverage of alcohol's subjective effects and to capture translational phenotypes of positive reward, negative reward, punishment, and subjective motivation.

In Paper II, predictions derived from the Allostatic Model regarding a transition from positively reinforced to negatively reinforced alcohol consumption in late-stage dependence were tested (Koob & Kreek, 2007; Koob & Le Moal, 1997, 2008). Heavy drinking participants representing a range of AUD severity completed a novel alcohol administration paradigm designed to capture domains of alcohol reward and reinforcement via standardized alcohol challenge and progressive ratio self-administration paradigms respectively. As expected, severity of AUD was predictive of greater alcohol craving, and alcohol reinforcement as measured by self-administration BAC curves. Further validating the paradigm, these data demonstrated a robust relationship between self-reported alcohol craving during the challenge and subsequent reinforcement behavior. These data provided little evidence for the hypothesized

transition from positive to negative reinforcement in AUD however. Contrary to diminishing positive reinforcement in severe AUD, no differences in hedonic responses to alcohol were observed across AUD severity and AUD severity did not predict whether hedonic reward predicted reinforcement behavior. In terms of negative reinforcement, AUD severity was associated with greater basal negative affect, however alcohol-related alleviation of negative affect was not greater among more severe AUD, and negative affect did not predict self-administration regardless of AUD severity. Thus, these data provide evidence for neither a transition *from* positively reinforced alcohol consumption, nor a transition *to* negative reinforcement. Sedative response to alcohol conversely were found to predict lower levels of self-administration consistent with the Differentiator and Low-Level of Response models derived in human laboratory research (King, de Wit, McNamara, & Cao, 2011; King, McNamara, Hasin, & Cao, 2014; Newlin & Thomson, 1990; Schuckit, 1984, 1994).

In Paper III, the Incentive Sensitization Theory was tested with respect to the proposed dissociation between alcohol liking and wanting, and the role of incentive salience in motivating alcohol consumption (Robinson & Berridge, 1993, 2001, 2008). In these data, neither subjective liking nor wanting during the alcohol challenge were predicted by AUD severity, and both remained highly correlated across the range of AUD severity. In terms of incentive salience of alcohol-related cues, attentional bias on the alcohol dot probe task (Duka & Townshend, 2004; Miller & Fillmore, 2010; Townshend & Duka, 2001) was not greater among more severe AUD, and this measure of incentive salience did not predict reinforcement when measured either at baseline or in terms of alcohol-induced changes. Of note however, the low pre-post alcohol correlations for attentional bias provided additional evidence questioning the reliability of attentional bias measures (Ataya et al., 2012; Cisler, Bacon, & Williams, 2009; Schmukle, 2005). Therefore, it is possible that these null results are due to poor reliability of the incentive salience measure. Future research is thus warranted in order to develop more reliable behavioral measures of incentive salience in humans.

This dissertation should be interpreted in light of its strengths and weaknesses. Study strengths in Paper I include the large sample size, the highly-controlled alcohol administration methods, the reliance

on multiple valid measures of SR, and the analytic approach accounting for alcohol dosing, BrAC limb, and drinking pattern. Limitations include the moderate dose of alcohol (final target BAC = 60mg%), the lack of a saline or placebo control, and the lack of representation of more severe and chronic drinkers. As with all IV alcohol studies, all studies in this dissertation sacrifice external validity for greater experimental control.

Strengths of Paper II and Paper III include chiefly the novel, highly controlled, and translational alcohol administration paradigm which measures alcohol reward and reinforcement, and isolates cue-reactivity. Limitations include the fact that participants were required to be non-treatment seeking and able to produce a zero on a breathalyzer test which may have impeded our ability to recruit severe AUD patients. This difficulty enrolling severe AUD patients is particularly salient as many preclinical alcohol administration paradigms produce very high levels of dependence including severe withdrawal (e.g. Broadwater, Varlinskaya, & Spear, 2011; Crabbe, Harris, & Koob, 2011; Kantak & Luzzo, 2007; Macey, Schulteis, Heinrichs, & Koob, 1996). In terms of measuring alcohol reinforcement, the substantial ceiling effect of BAC curves may also have affected these results. Lastly, though this study was cross-sectional in terms of AUD status, both the Allostatic Model and the Incentive Sensitization Theory focus on neuroadaptation and are thus necessarily longitudinal. Future research should address this limitation via longitudinal design with high risk samples. Specific to Paper III, poor reliability of the alcohol dot probe task likely adversely impacted the study's ability to find evidence in support of a mediational role of incentive salience.

In conclusion, this dissertation advances a novel approach to translating neuroscientific theories developed in animal models to the human laboratory. Consistent with our hypotheses these data suggested a four-factor structure of alcohol's subjective effects comprising Stimulation/Hedonia, Negative Affect, Sedation/Motor Intoxication and Craving/Motivation dimensions. Additionally, AUD severity predicted greater alcohol craving and self-administration in a novel human laboratory paradigm. Insofar as sedation predicted lower levels of self-administration, these data were consistent with the Differentiator and Low-Level of Response Models, both of which were developed in human laboratory research. Conversely, few

of our hypotheses derived from preclinical theories were supported. These data provided little evidence for the allostatic processes of diminished positive reinforcement and enhanced negative reinforcement in more severe AUD. Similarly, with respect to IST, AUD severity did not predict greater dissociation between self-reported liking and wanting, and using an attentional bias measure, incentive salience was not found to be predicted by AUD severity or predict alcohol reinforcement.

Several directions for further refinement of this translational approach are warranted. First, research is needed to develop more reliable tasks for measuring the incentive salience of drug- and alcohol-paired cues. Additionally, studies utilizing the paradigm developed in Paper II and III in the context of affective manipulations would enable researchers to test the role of stress in reward and reinforcement mechanisms. Longitudinal studies would enable researchers to test whether changes in reward, reinforcement, and incentive salience are observed across AUD development, or whether they are premorbid risk factors. Additionally, given the severity of dependence induced by preclinical paradigms, recruitment of more severe AUD samples appears necessary for more robust translational tests. This dissertation also highlights the need for increased reverse translation efforts to promote consilience between preclinical and human subjects research. Ultimately, determining whether preclinical models accurately capture pathological processes in humans suffering from alcoholism is essential to both understanding alcoholism etiology and developing efficacious treatments to alleviate the sizeable human cost of alcohol addiction.

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