

Gender Specific Effects of Mood on Alcohol Seeking Behaviors: Preliminary Findings using
Intravenous Alcohol Self-Administration

Melissa A. Cyders, Ph.D.¹

J. Davis VanderVeen, B. A.¹

Martin Plawecki, M.D., Ph.D.²

James B. Millward, B.S.²

James Hays, B.S.²

David A. Kareken, Ph.D.^{2,3}

Sean O'Connor, M.D.^{2,4}

¹Indiana University – Purdue University Indianapolis, Department of Psychology

²Indiana University School of Medicine, Department of Psychiatry

³Indiana University School of Medicine, Department of Neurology

⁴R.L. Roudebush VAMC, Indianapolis

Author Note: Corresponding author – Melissa A. Cyders, Department of Psychology, LD 124, 402 N. Blackford St., Indianapolis, IN 46202. Email: mcyders@iupui.edu. Supported by the National Institute of Alcohol Abuse and Alcoholism K01AA020102 (MAC), the Indiana Alcohol Research Center (P60AA07611), and an Indiana University – Purdue University, Indianapolis University Fellowship (JDV). We also want to express our gratitude to the Indiana (CTSI) Clinical Research Center (UL1TR001108) and Nicholas Grahame, Sage Bates, and Eva Agriyou for their continued effort in making this project possible.

This is the author's manuscript of the article published in final edited form as:

Cyders, M. A., VanderVeen, J. D., Plawecki, M., Millward, J. B., Hays, J., Kareken, D. A., & O'Connor, S. (2016). Gender-Specific Effects of Mood on Alcohol-Seeking Behaviors: Preliminary Findings Using Intravenous Alcohol Self-Administration. *Alcoholism: Clinical and Experimental Research*, 40(2), 393–400. <http://doi.org/10.1111/acer.12955>

ABSTRACT

Background: Although negative mood has long been implicated in differences in alcohol seeking by men and women, little research has used precise, well-controlled laboratory experiments to examine how negative mood affects alcohol seeking behaviors.

Methods: A total of 34 (19 Women) community-dwelling, alcohol using adults aged 21-32 (mean age=24.86, SD=3.40, 74.3% Caucasian; Alcohol Use Disorder Identification Test [AUDIT]= 10.1, SD= 3.4) completed two counter-balanced intravenous alcohol self-administration sessions: one under negative mood and one under neutral mood. Fourteen individuals (9 women; mean age=25.00, SD=2.77) participated in an alcohol “liking” experiment (i.e., free access drinking) and 20 individuals (10 women; mean age=24.77, SD =3.73) participated in an alcohol “wanting” experiment, in which gaining access to alcohol required progressively effortful work. There was no significant difference between men and women on the AUDIT ($t(34)=-0.38, p=.71$).

Results: Priming with negative mood induction caused a significant decrease in self-reported mood (*mean change*=-1.90, $t(39)=-6.81, p<.001$), as intended. In free access, negative mood was associated with a significantly increased peak breath alcohol concentration (BrAC; $F=9.41, p=.01$), with a trend toward a greater effect in men than in women ($F=2.67, p=.13$). Negative mood also had a significant effect on peak BrAC achieved in the progressive work paradigm ($F=5.28, p=.04$), with a significantly stronger effect in men ($F=5.35, p=.03$) than women; men also trended toward more consistent work for alcohol across both neutral and negative sessions.

Conclusions: These preliminary findings demonstrate a gender-specific response on how mood affects alcohol seeking and suggest gender-specific interventions to prevent mood-based alcohol consumption.

Keywords: alcohol, intravenous infusion, gender

INTRODUCTION

Research has long supported the association between negative mood and increased alcohol use. Specifically, negative affectivity (i.e., neuroticism) is associated with problematic alcohol consumption (e.g., Tice et al., 2001) and familial alcoholism risk (e.g., Martin and Sher, 1994). Additionally, individuals report higher alcohol craving and consumption on days when experiencing negative events or emotions (e.g., Steptoe and Wardle, 1999; Carney et al., 2000), and a commonly reported motive for drinking is to regulate a negative mood (e.g., Cooper et al., 1995). Negative mood is, in turn, a strong and consistent provocation of alcohol craving (e.g., Litt and Cooney, 1999).

There are strong gender differences in alcohol use patterns: in general, men consume more alcohol and have greater alcohol-related problems than women, but women who engage in heavy drinking tend to experience greater negative consequences (see Nolen-Hoeksema, 2004). The mechanisms explaining these differences are not yet well understood and could be driven by gender differences in liking or wanting of alcohol (Hobbs et al., 2005). However, most of the foregoing studies have focused on self-reported mood and alcohol use, which are limited by accuracy and subject to social desirability biases (e.g., Babor et al., 1987; Del Boca and Darkes, 2003). Additionally, men and women differ in self-report patterns (e.g., Hebert et al., 1997), which could further bias conclusions about gender-specific relationships between negative mood and alcohol seeking.

Finally, studies have yet to examine mood effects on separate aspects of alcohol reinforcement, such as the consumption patterns of freely available alcohol and how motivated one is to work to gain access to an alcohol reward (Hobbs et al., 2005)—systems which are dissociable in both humans and animals. Research suggests that mood

differentially affects behaviors attributed to these different alcohol seeking patterns (Hobbs et al., 2005; Zimmermann et al., 2013). For instance, although weakly positively correlated, alcohol priming appears to affect motivation to work for alcohol, but not in administration of freely available alcohol (Hobbs et al., 2005). Understanding how negative mood differentially affects these behaviors is important in understanding how to mitigate negative-mood-based increases in alcohol consumption.

Most previous studies examining alcohol self-administration in the laboratory have used oral alcohol administration. One difficulty with ingestion is that high variability in the time courses of consequent breath alcohol concentrations (BrACs) across subjects is inevitable, even when gender is used in the calculation of the dose ingested (Ramchandani et al., 1999). To directly compare men's and women's alcohol seeking behaviors, a method that provides identical incremental brain exposures to alcohol, independent of gender, age, body weight and drinking history is required. The Computer-assisted Alcohol Infusion System (CAIS) (Plawecki et al., 2013; Zimmermann et al., 2008; 2009), using direct control of the rate profile of intravenous alcohol administration, based on predictions of a physiologically-based pharmacokinetic model with parameters tailored to the individual subject, provides such a method (Plawecki et al., 2007). CAIS adjusts the individual's dose to achieve identical exposures across participants.

The current pair of preliminary studies sought to examine how negative mood induction affects alcohol self-administration in a within-subjects design using men and women who are matched on drinking level. We hypothesized that negative mood would cause gender-divergent patterns of alcohol self-administration in paradigms that quantitatively measure different alcohol seeking behaviors. How the relationship between

negative affect and alcohol consumption differs across women and men has varied across studies (Nolen-Hoeksema, 2004; Nolen-Hoeksema & Hilt, 2006)– with some finding a stronger relationship in men (e.g., Aneshensel & Huba, 1983; Hussong, Hicks, Levy & Curran, 2001), others finding a stronger relationship in women (e.g., Hartka et al., 1991), and still others suggesting no moderation by gender (e.g., Conner et al., 2009). Due to these mixed findings, we did not have a specific hypothesis concerning how gender might moderate the association between negative mood and alcohol self-administration patterns. We conducted a pair of preliminary studies using moderate to high social drinking, non-dependent, healthy young adults on two separate paradigms addressing alcohol seeking behavior: Free Access (FA), which is the self-administration of alcohol when it is available without cost or work) and Progressive Work (PW), which is the self-administration of alcohol with progressively tedious work needed to gain access to the next increment in exposure.

MATERIALS AND METHODS

Participants

Participants were community dwelling, alcohol using men and women. Inclusion/exclusion criteria for both samples included: age 21-35, current alcohol users, good medical and mental health, able to understand and complete procedures in English, no past/present alcohol dependence, not currently pregnant or intending to become pregnant, or breastfeeding. The FA sample population was recruited for social drinking (at least 4 standard drinks per week and at least two binge episodes per month – defined as 4 or more drinks at a time for women and 5 or more drinks at a time for men; NIH, 2014). The PW sample was recruited for heavy social drinking (consumed at least 7 drinks per

week and at least one binge episode per week). This difference in recent drinking history reflects the reality that PW requires more motivation (i.e., more effort, reflected in more recent use of alcohol) to gain access to alcohol than does FA. The difference also reflects our experience that heavier drinkers performing the FA paradigm often achieve a ceiling effect (CAIS limited BrAC to 120 mg/dl in our FA paradigm, 150mg/dl in the PW paradigm). Given the group differences in drinking, no direct comparisons were made between the two samples (only within-subjects effects within each sample).

Measures

Life Events Narratives (Abele, 1990) were used to induce either a negative or neutral mood. The negative life events narrative asks respondents to write about an event that made them particularly sad or upset in their lives. The neutral life events narrative asks respondents to write about their activities on a typical day for approximately twenty minutes. Writing procedures are effective at inducing negative mood states (mean $r = 0.52$; e.g., Westermann et al., 1996).

Musical Mood Induction Procedure (MMIP; Västfjäll, 2002) was used to maintain the negative or neutral mood. Initial song lists were taken from Västfjäll (2002). All songs were then rated by four trained raters, and songs that were not correctly categorized as negative or neutral were removed from the list. Negative songs are associated with a more negative subjective mood rating compared to neutral songs ($p < 0.05$; Västfjäll, 2002), and neutral songs are associated with a more positive subjective mood rating than negative songs, but a less positive mood rating than positive songs ($p < 0.05$; Västfjäll, 2002). Music was played continuously during the writing, priming, and working sessions (songs and order of presentation are shown in Supplemental Table 1).

The Affect Grid (Russell et al., 1989) is a single-item, 2-dimensional scale designed to assess current mood along orthogonal axes of pleasure-displeasure and arousal-sleepiness. It has adequate correlations with other, longer measures of current mood states such as the Mehrabian and Russell (1974) scale ($r= 0.77$), making it a more practical measure of current emotional ambience. In the present study, the affect grid was used as a check for the effectiveness of the mood manipulation.

The Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) is a ten-item scale that assesses hazardous alcohol consumption, abnormal alcohol consumption behavior, and alcohol related problems. Data obtained by the AUDIT allows for discriminating between hazardous and non-hazardous drinkers (Saunders et al., 1993) and responses show concurrent validity with other measures of alcohol use (Saunders et al., 1993).

Procedures

Participants were recruited through the use of advertisements posted in public areas (e.g. bars, liquor stores, etc.), on local college campuses, and on the Internet. Participants were first administered a phone screen to assess eligibility for inclusion and exclusion criteria. If qualified after the phone screen, participants were invited to provide informed consent and complete a more in-depth screening where they completed a series of questionnaires, interviews, and computer tasks, including study measures listed above, to assess subject eligibility and to examine study hypotheses. Mental health and alcohol dependence were assessed at this session using the Semi-structured Assessment of the Genetics of Alcoholism (SSAGA, Bucholz et al., 1994). Participants also completed a urine drug screen and (for women only) a urine pregnancy screen.

Participants then completed two counterbalanced IV alcohol administration sessions, scheduled approximately one week apart: one in which they engaged in a negative mood induction and one in which they engaged in a neutral mood induction. Participants arrived at the Indiana General Clinical Research Center at approximately 8 a.m. on study days (see Figure 1). They had their height and weight measured (for calibration of the IV alcohol administration software) as well as their blood pressure, temperature, and heart rate. Participants then provided a BrAC and a urine sample for drug and pregnancy screen. Participants testing positive for marijuana were interviewed to ensure they were no longer under the effects of the drug. Thus, $n=7$ participants that tested positive for marijuana completed the study; others whose responses indicated they may still be experiencing effects were dismissed ($n=4$). One participant was excluded for testing positive with a drug other than marijuana.

Then, participants put on headphones, mood congruent music was turned on, and they completed the life event narrative (either negative or neutral) for 20 minutes, which is comparable to the duration of previous mood induction studies (Gadea et al., 2005). Following the narrative, participants were given a standardized light breakfast (500 kcal), monitored by the hospital staff. Thirty minutes after breakfast, a member of the nursing staff inserted a 22 ga. indwelling catheter in the participants' non-dominant arm and the infusion hardware setup was completed. Participants were infused with a solution prepared by the Indiana University Research Pharmacy by mixing half-normal saline with 95% ethanol to create a 6.0% (v/v) solution. The CAIS software, as described by Zimmerman et al. (2008; 2009) and Plawecki et al. (2013) and developed at Indiana University, was used to control the infusion rate profile. Prior to infusion, the subject's age,

height, weight, and gender were entered into the CAIS software, which transformed those measurements into the parameters of the physiologically-based pharmacokinetic (PBPK) model, tailoring the model's estimation of future BrAC to the individual (Ramchandani et al., 1999; Plawecki, 2007). By eliminating sensitivity to alcohol absorption kinetics and controlling for variation in distribution and elimination kinetics, CAIS provided an identical incremental reward for alcohol in every subject for every reward. The CAIS reward chosen for this study increased arterial blood concentration from its current value by 7.5mg/dl in 2.5 min (a linear ascending limb slope of +3mg/dl/min), followed by a linear descent at -1.0 mg/dl/min until the next reward delivery began.

A priming interval began with two prompted alcohol rewards (the priming "dose"), which yielded a BrAC consistent with ingesting one standard alcoholic drink. The prime was employed to familiarize participants with the task and the experience of IV administered alcohol and produced a 15mg/dl BrAC after 10 min. Participants were then informed by video-screen that no more drinks could be requested for the next 10 min; CAIS tracked the prescribed descending BrAC slope of -1.0 mg/dl/min, resulting in a BrAC of approximately 5 mg/dl at 20 minutes in all participants. During this break, participants listened to mood music and then read their life narrative aloud before beginning their 2-hour voluntary alcohol self-administration interval using either the FA or PW paradigm. Participants were told that they could self-administer either alcohol or water, as much or as little as they like, but that the session would still last 2 hours and they would be required to stay in the hospital until 7pm regardless of their intoxication level achieved. The participant saw the message "the bar is temporarily closed" for the 2.5 min ascending limb of the rewards, and whenever more alcohol would raise the BrAC above the 150 mg/dl

safety limit (for the free access session) or the 120 mg/dl safety limit (for the progressive work session). Bathroom breaks occurred *ad lib* without disconnection from the CAIS apparatus, and the CAIS technician remained screened from the subject throughout the session.

Fourteen participants (FA sample) self-administered alcohol or water by simply pressing a button labeled either “A” for alcohol or “W” for water, and received the corresponding reward immediately. Twenty participants (PW sample) completed the Constant Attention Task (CAT), an attentionally effortful task in which they completed a predefined series of successful CAT trials to earn alcohol (or water; Plawecki, 2013). The CAT task was organized into work sets. At the beginning of each work set, the participant chose to work for either alcohol or water, defining the reward that was delivered immediately upon completion of the work set. The CAT task adapted the response window duration to result in approximately 50% response error, independent of practice, intoxication or fatigue. The number of successful trials required to obtain a reward increased exponentially throughout the session and progress on the schedules for alcohol and water rewards was independent.

At the end of the session, the IV catheter was removed and the subject was required to remain on the unit until his/her BrAC was below 20mg/dl, usually around 7pm, and the nursing staff could no longer identify behavioral signs of intoxication. Participants were provided lunch and dinner during their stay and were paid in cash upon discharge from the Clinical Research Center.

Statistical Analysis Plan

First, we used a repeated measures analysis of covariance (ANCOVA) with follow up t-test contrasts to examine the effectiveness of our mood manipulation, across women and men. Second, we conducted a series of repeated measures ANCOVAs with Mood (neutral session, negative session) as the within-subjects variable, participant gender as a between-subjects factor, and age and ordering of the negative and neutral sessions entered as covariates. We examined these effects on a series of dependent variables, including peak BrAC (*mg/dl*) and area under the BrAC curve (*AUC; min*mg/dl*) in the voluntary FA and PW self-administration intervals and *break point* (the number of attempted CAT trials required in the last completed reward work set) and *cumulative work* (the total number of CAT trials performed during the session while seeking a reward) in the PW session only. Because of the small sample sizes, we examined effect sizes (partial η^2) in addition to statistical tests to inform future work, using standard values to denote small (0.01), medium (0.06), and large (0.14).

RESULTS

Sample Characteristics and Paradigm Manipulation Check

A total of 34 (19 women) community-dwelling alcohol-using adults aged 21-32 (mean age=24.86, SD=3.40) completed the study. The sample was mostly Caucasian (74.3%), with 17.1% African American, 5.7% Asian, and 2.9% Latino. Fourteen individuals (9 women; mean age=25.00, SD=2.77) comprised the FA sample; 20 individuals (10 women; mean age=24.77, SD =3.73) the PW sample. The overall sample's mean AUDIT score was 10.1 (SD=3.35), with no significant difference between men and women ($t(32)=-0.38, p=.71$; Table 1). Repeated measures ANCOVA found a significant large effect on affect grid scores prior to and after negative mood induction ($F=43.80, p<.001, \text{partial } \eta^2=0.53$),

but no significant interaction with gender ($F=1.95, p=.17, \text{partial } \eta^2=0.05$). As expected, there was neither a significant gender effect (Mood $F=0.32, p=.58, \text{partial } \eta^2=0.01$), nor a mood by gender interaction ($F=0.56, p=.46, \text{partial } \eta^2=0.01$) in the neutral mood condition. Negative mood induction was associated with a significant decrease in self-reported mood ($\text{mean change}=-1.85 (SD=1.72), t(32)=-6.81, p<.001$), whereas the neutral mood induction was not ($\text{mean change}=-0.10 (SD=1.42), t(32)=-0.44, p=.58$). The change following negative mood induction was also significantly larger than the change after neutral mood induction ($t(32)=-4.96, p<.01$). Self-reported mood changes were not significantly associated with alcohol seeking behaviors in either the PW or FA session.

Mood Effects on Free Access to Alcohol

For peak BrAC, the main effect of mood alone was significant and large in size ($F=9.41, p=.01, \text{partial } \eta^2=0.16$), and there was a trend toward a small mood by gender interaction ($F=2.67, p=.13$): Men showed greater peak BrAC in the negative session (mean peak BrAC=149 mg/dl, $SD=10$) than in the neutral session (mean peak BrAC=113 mg/dl, $SD=20$); women showed the opposite (mean peak BrAC in neutral session=128 mg/dl, $SD=10$ and mean peak BrAC in negative session=121 mg/dl, $SD=10$; see Figure 2, left panel). Follow up contrasts indicated that men and women did not significantly differ on peak BrAC in either the neutral session ($t(13)=0.25, p=.80$) or the negative session ($t(13)=-0.49, p=.63$). For AUC, the main effect of mood was significant ($F=7.16, p=.02$) as was a mood by gender interaction ($F=4.89, p=.05$): again, men had a greater AUC in the negative (mean AUC=12800, $SD=1670$) compared to the neutral session (mean AUC=8600, $SD=2140$), but women showed a slight decrease (mean AUC in neutral session=11000, $SD=1540$ and mean AUC in negative session=9940, $SD=1210$; see Figure 2, right panel). Follow up contrasts

indicated that men and women did not significantly differ on AUC in either the neutral session ($t(13)=-0.79, p=.44$) or the negative session ($t(13)=-0.22, p=.83$).

Mood Effects on Motivation to Work for Alcohol

Mood had a significant effect on both peak BrAC and AUC, and mood by gender interactions were apparent in both BrAC-related outcome measures in the PW paradigm. For peak BrAC, the main effect for mood was significant and large in size ($F=5.28, p=.04$, partial $\eta^2=0.25$), with a significant mood by gender interaction that was also large in size ($F=5.35, p=.03$, partial $\eta^2=0.25$): men achieved a smaller peak BrAC in the neutral (mean peak BrAC=82 mg/dl, $SD=10$) compared to the negative session (mean BrAC=100 mg/dl, $SD=10$); women showed the opposite pattern (neutral session mean BrAC=82 mg/dl, $SD=10$ and negative session mean BrAC=67 mg/dl, $SD=10$, see Figure 3, left top panel). Follow up contrasts indicated that men and women had significantly different peak BrAC values in the negative session ($t(18)=2.69, p=.02$) but not in the neutral session ($t(18)=0.02, p=.98$). For AUC, the main effect for mood was significant and large in size ($F=4.87, p=.04$, partial $\eta^2=0.23$), with a trend mood by gender interaction that was large in size ($F=3.31, p=.09$, partial $\eta^2=0.17$): again, men had an increase in AUC between the neutral (mean AUC=7120, $SD=1001$) and negative (mean AUC=8480, $SD=831$) sessions, and women showed a decrease (neutral mean AUC=6750, $SD=1001$ and negative (mean AUC=5480, $SD=831$; see Figure 3, left bottom panel). Follow up contrasts indicated that men and women had significantly different AUC in the negative session ($t(18)=2.24, p=.04$), but not in the neutral session ($t(18)=0.27, p=.79$).

Mood had a significant and large main effect on cumulative work for alcohol ($F=5.45, p=.03$; partial $\eta^2=0.24$; see Figure 3, right bottom panel) and a trend toward a large effect

on break point ($F = 3.54, p = .08, \text{partial } \eta^2=0.18$; see Figure 3, right top panel), indicating less work in the negative as compared to the neutral session. Although there were no significant mood by gender interactions on the work variables ($p's > .20$), the patterns suggest that a trend toward this effect being stronger in women but small in size (partial $\eta^2=0.03$ for cumulative work and partial $\eta^2=0.02$ for break point; men showed a pattern of being more consistent in their work across neutral and negative sessions, while women showed a pattern towards more work in the neutral than in the negative session (see Figure 3, right panel). Follow up contrasts indicated that men and women had significantly different cumulative work in the negative session ($t(18)=2.47, p=.02$), but not in the neutral session ($t(18)=1.47, p=.15$). Follow up contrasts indicated no gender differences in break point in either the negative ($t(18)=1.67, p=.13$) or neutral ($t(18)=0.99, p=.33$) sessions. There were no main mood or interactive effects on cumulative work for water (the total number of CAT trials performed during the session while seeking a water reward) (all $F's > .17$) or on break point for water (the number of attempted CAT trials required in the last completed water reward work set) (all $F's > .20$). Mean cumulative work and breakpoint for alcohol was larger than for water across each session (e.g., neutral session alcohol cumulative work $M=384.7, SD = 292.9$ vs. neutral session water cumulative work $M = 228.7, SD = 299.7$; negative session alcohol cumulative work $M = 341.3, SD = 232.7$ vs. negative session water cumulative work $M = 265.5, SD = 277.3$), although they were not significantly different.

DISCUSSION

Findings from these preliminary studies suggest that negative mood affects alcohol seeking behaviors differently across men and women. Specifically, mood had large effects

on working for alcohol that interacted with gender. However, there was a small differential effect of mood on free access of alcohol across men and women: men showed a pattern of increased free access administration of alcohol in negative as compared to neutral mood states, reaching higher peak BrAC and AUC in the negative session, whereas women show no change in free access of alcohol as demonstrated by peak BrAC and AUC across negative and neutral conditions. Interestingly, differential mood effects across men and women were large when examining working for alcohol: Men showed significantly higher BrAC, break point, and AUC in the negative mood condition, as compared to women; however, men and women did not differ in work in the neutral mood condition. Importantly, in each session the primary reward was alcohol and these mood effects were specific to alcohol. These observations suggest that men and women use alcohol differently in response to negative mood states: 1) mood has a larger effect on working for alcohol rather than on the free access administration of alcohol, 2) men show a pattern of increased alcohol free access of and work for alcohol in a negative mood as compared to a neutral mood, 3) although women freely administered alcohol similarly across negative and neutral mood, they show a pattern of decreased working of alcohol in a negative mood as compared to a neutral mood, and 4) men demonstrate significantly more work for alcohol in negative mood states as compared to women, but men and women do not differ on free access or work for alcohol in neutral mood states.

In the PW session, changes in the distribution of a similar amount of work for alcohol produces highly variable alcohol exposure properties, including peak BrAC. From this perspective, in the PW paradigm portion of this study, under negative versus neutral mood conditions, men appear to change self-administration patterns to produce an

increase in peak BrAC despite their relative consistent total effort expenditure – a change in consumption pattern. In contrast, women worked less for alcohol but a similar amount for water which produced a lower peak BrAC, again indicative of sex-related differences in alcohol self-administration. Although a similar pattern was observed in the FA sessions, the results did not reach significance, likely related to reduced magnitude of effect sizes of how mood and gender influence FA as compared to PW alcohol seeking behaviors.

These findings suggest a gender-specific response on how mood moderates alcohol seeking in a laboratory setting. Though previous work largely suggests that negative mood increases alcohol consumption (e.g., Carney et al., 2000; Steptoe & Wardle, 1999; Tice, et al, 2001), these findings may have largely been driven by research traditionally done primarily in men. Additionally, self-report of these experiences may lead to inaccurate conclusions about gender differences in these behaviors. The present data suggest that gender differences are important, as determinants of alcohol use (e.g. negative mood state, cue-reactivity, etc.) could have differential effects across men and women. For instance, previous work suggests that women are less likely to drink to reduce distress (see Nolen-Hoeksma, 2004) and the present study supports that observation, showing that women, although similarly reactive to the mood induction, were less likely to seek alcohol in response to the negative mood induction.

The underlying mechanisms explaining these gender divergent patterns are not yet well documented; however, we offer some potential mechanisms for future analysis. First, gender divergent patterns in alcohol seeking have not been consistent across previous work (e.g., Aneshensel & Huba, 1983; Conner et al., 2009; Hartka et al., 1991; Hussong, Hicks, Levy & Curran, 2001), potentially driven by lack of power to detect gender

differences (Nolen-Hoekma & Hilt, 2006). Similar inconsistencies in gender divergent patterns are found in other drug seeking behaviors. However, a somewhat recent review of the literature on gender differences in alcohol use (Nolen-Hoeksma & Hilt, 2006) suggests that men are more likely to drink to alleviate negative affect and that women expect alcohol to interfere with their ability to cope, although we did not examine this mechanism here. Second, it is possible that the mood experience of the negative life events narratives differed systematically between men and women, which resulted in these differences in alcohol seeking. For example, if men experienced more changes in one type of negative emotion that is associated with increased alcohol, whereas women experienced more changes in another type of negative emotion that is associated with decreased alcohol seeking, these differences in specific mood experiences could explain the results in the current study. However, since we asked only about negative affect and not about more specific types of negative emotions, we were not able to examine this in the current study. Third, the single person design of the study might have differentially impacted men and women's alcohol seeking behaviors in response to negative mood manipulation; examination of mood effects on alcohol seeking in a social interaction paradigm might differ from the current findings.

Interestingly, although alcohol seeking behaviors differed across neutral and negative sessions, alcohol seeking behaviors were unassociated with self-reported mood changes in response to the mood manipulation. Therefore, it appears that alcohol seeking did not relate linearly with how much a person (man or woman) responded to the mood manipulation, thus making self-reported mood ratings likely not a good indicator of alcohol seeking behavior in negative mood experiences. This lack of relationship could mean that

mood change does not affect alcohol seeking in a similar way across all individuals (i.e., some individuals might be more highly affected by a mood change than another individual) or could be driven by biases in mood reporting (i.e., some individuals use a small portion of the self-report scale, while others might use a different portion of the scale).

Results from these preliminary studies, although in need of replication, could suggest gender-specific interventions to prevent mood-based alcohol consumption. For instance, training or psychoeducational materials focusing on reducing distress-based drinking may be less effective for women. For men, encouraging reflection before action could help reduce the initial increases in alcohol seeking in immediate response to negative moods. Behavioral strategies such as not having alcohol readily available or imposing some sort of work requirement on alcohol consumption could help to slow and reduce the increase in alcohol consumption in response to negative emotional states, particularly for women and for those attempting to reduce their problematic alcohol consumption. Though this would likely not influence alcohol consumption that occurs outside of negative mood experiences.

Further work capturing the richness of the alcohol exposure trajectories produced by subjects employing the CAIS system for alcohol self-administration is planned. While peak BrAC and AUC are highly correlated, precise control over incremental BrAC exposures by the CAIS system provides the opportunity to partially disentangle these drinking aspect through consideration of the temporal pattern of alcohol self-administration (a phenomenon reminiscent of drinking style).

The current study implications should be viewed in context of study limitations: First, individuals do not typically consume alcohol through an IV infusion, so the ecological

validity of the IV alcohol infusion paradigm is limited. On the other hand, this methodology allows for a more precise and controlled examination of alcohol seeking behaviors across men and women when brain exposure to alcohol occurs absent other factors, such as alcohol's taste. We can also be more confident that any gender differences in alcohol seeking are not due to gender-specific differences in metabolism. Second, the current sample was a young, healthy, and homogenous sample of alcohol drinkers, so the generalizability of the findings should be replicated in more diverse samples, particularly those with or at risk for alcohol use disorders. Third, there was no examination of positive mood so it is unclear if positive mood would also show gender specific effects on alcohol seeking behaviors. Fourth, alcohol seeking was limited by BrAC safety limits, particularly men in the FA sample, many of whom reached the limit of 150 mg/dl in the negative session; thus, ceiling effects could have limited range and power to detect gender interaction effects. Finally, the findings are from a small sample, and require replication. However, these preliminary findings do suggest viability of examining gender specificity in the relationship between negative mood and alcohol consumption using larger samples.

In conclusion, findings from this pair of preliminary studies suggest viability of the theory the mood differentially affects alcohol seeking behaviors and does so differently across men and women. The current findings provide effect size estimates for future work in this area and suggest that 1) these mood effects are larger in working for alcohol as compared to administration of freely available alcohol and 2) interactions with gender are larger in working for alcohol as compared to freely available alcohol. Future work should replicate these findings and should consider the current findings' effect sizes in designing

future studies powered to detect these effects. Should these result replicate, it would suggest gender-specific interventions to prevent mood-based alcohol consumption.

REFERENCES

- Abele A 1990. Recall of Positive and Negative Life Events. Studies of Mood-Inducing Effect and Production of Texts. *Z Exp Angew Psychol*, 37, 181-207.
- Aneshensel RA, Huba GJ 1983. Depression, Alcohol Use, and Smoking Over One Year: A Four-Wave Longitudinal Causal Model. *J Ab Psychol*, 92, 134-150.
- Babor TF, Stephens RS & Marlatt GA 1987. Verbal Report Methods in Clinical Research on Alcoholism: Response Bias and Its Minimization. *J Stud Alcohol*, 48, 410-24.
- Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, Reich T, Schmidt I, Schuckit MA 1994. A New Semi-Structured Psychiatric Interview for Use in Genetic Linkage Studies: A Report on the Reliability of the SSAGA. *J of Stud Alcohol*, 55, 149-158.
- Carney MA, Armeli S, Tennen H, Affleck G & O'neil TP 2000. Positive and Negative Daily Events, Perceived Stress, and Alcohol Use: A Diary Study. *Journal of Consulting and Clinical Psychology*, 68, 788.
- Conner KR, Pinquart M, Gamble SA 2009. Meta-Analysis of Depression and Substance Use among Individuals with Alcohol Use Disorders. *J Sub Abuse Treatment*, 37, 127-137.
- Cooper ML, Frone MR, Russell M & Mudar P 1995. Drinking to Regulate Positive and Negative Emotions: A Motivational Model of Alcohol Use. *J Pers Soc Psychol*, 69, 990-1005.
- Del Boca FK & Darkes J 2003. The Validity of Self-Reports of Alcohol Consumption: State of the Science and Challenges for Research. *Addiction*, 98 Suppl 2, 1-12.

- Gadea M, Gomez C, Gonzalez-Bono E, Espert R & Salvador A 2005. Increased Cortisol and Decreased Right Ear Advantage (Rea) in Dichotic Listening Following a Negative Mood Induction. *Psychoneuroendocrinology*, 30, 129-38.
- Hartka E, Johnstone BM, Leino EV, Motoyoshi MM, Temple MT, Fillmore KM 1991. A Meta-Analysis of Depressive Symptomatology and Alcohol Consumption over Time. *Brit J Addict*, 86, 1283-1298.
- Hebert JR, Ma Y, Clemow L, Ockene IS, Saperia G, Stanek EJ, Merriam PA & Ockene JK 1997. Gender Differences in Social Desirability and Social Approval Bias in Dietary Self-Report. *American Journal of Epidemiology*, 146, 1046-1055.
- Hobbs M, Remington B & Glautier S 2005. Dissociation of Wanting and Liking for Alcohol in Humans: A Test of the Incentive-Sensitisation Theory. *Psychopharmacology (Berl)*, 178, 493-9.
- Hussong AM, Hicks RE, Levy SA, Curran PJ 2001. Specifying the Relations between Affect and Heavy Alcohol Use among Young Adults. *J Ab Psychol*, 110, 449-461.
- Koob G. Niaaa Update. 38th Annual RSA Scientific Meeting, 2015 San Antonio, TX.
- Litt MD & Cooney NL 1999. Inducing Craving for Alcohol in the Laboratory. *Alcohol Res Health*, 23, 174-8.
- Martin ED & Sher KJ 1994. Family History of Alcoholism, Alcohol Use Disorders and the Five-Factor Model of Personality. *J Stud Alcohol*, 55, 81-90.
- Mehrabian A & Russell JA 1974. *An Approach to Environmental Psychology*, the MIT Press.
- Nolen-Hoeksema S 2004. Gender Differences in Risk Factors and Consequences for Alcohol Use and Problems. *Clin Psychol Rev*, 24, 981-1010.

- Nolen-Hoeksma S, Hilt L 2006. Possible Contributors to the Gender Differences in Alcohol Use and Problems. *J of Gen Psychol*, 133, 357-374.
- Plawecki MH, Decarlo R, Ramchandani VA & O'connor S 2007. Improved Transformation of Morphometric Measurements for a Priori Parameter Estimation in a Physiologically-Based Pharmacokinetic Model of Ethanol. *Biomed Signal Process Control*, 2, 97-110.
- Plawecki MH, Wetherill L, Vitvitskiy V, Kosobud A, Zimmermann US, Edenberg HJ & O'connor S 2013. Voluntary Intravenous Self-Administration of Alcohol Detects an Interaction between Gabaergic Manipulation and Gabrg1 Polymorphism Genotype: A Pilot Study. *Alcohol Clin Exp Res*, 37 Suppl 1, E152-60.
- Ramchandani VA, Bolane J, Li TK & O'connor S 1999. A Physiologically-Based Pharmacokinetic (Pbpk) Model for Alcohol Facilitates Rapid Brac Clamping. *Alcohol Clin Exp Res*, 23, 617-23.
- Russell JA, Weiss A & Mendelsohn GA 1989. Affect Grid: A Single-Item Scale of Pleasure and Arousal. *Journal of personality and social psychology*, 57, 493.
- Saunders JB, Aasland OG, Babor TF, De La Fuente JR & Grant M 1993. Development of the Alcohol Use Disorders Identification Test (Audit): Who Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--Ii. *Addiction*, 88, 791-804.
- Steptoe A & Wardle J 1999. Mood and Drinking: A Naturalistic Diary Study of Alcohol, Coffee and Tea. *Psychopharmacology (Berl)*, 141, 315-21.
- Tice DM, Bratslavsky E & Baumeister RF 2001. Emotional Distress Regulation Takes Precedence over Impulse Control: If You Feel Bad, Do It! *J Pers Soc Psychol*, 80, 53-67.

U.S. Department of Health and Human Services NIOHN, National Institute on Alcohol Abuse and Alcoholism 2014. Moderate and Binge Drinking.

Västfjäll D 2002. Emotion Induction through Music: A Review of the Musical Mood Induction Procedure. *Musicae Scientiae*, 5, 173-211.

Westermann R, Spies K, Stahl G & Hesse FW 1996. Relative Effectiveness and Validity of Mood Induction Procedures: A Meta-Analysis. *European Journal of Social Psychology*, 26, 557-580.

Zimmermann U, O'connor S & Ramchandani V 2013. Modeling Alcohol Self-Administration in the Human Laboratory. In: SOMMER, WH & SPANAGEL, R (eds.) *Behavioral Neurobiology of Alcohol Addiction*. Springer Berlin Heidelberg.

Zimmermann US, Mick I, Laucht M, Vitvitskiy V, Plawecki MH, Mann KF & O'connor S 2009. Offspring of Parents with an Alcohol Use Disorder Prefer Higher Levels of Brain Alcohol Exposure in Experiments Involving Computer-Assisted Self-Infusion of Ethanol (Case). *Psychopharmacology*, 202, 689-697.

Zimmermann US, Mick I, Vitvitskiy V, Plawecki MH, Mann KF & O'connor S 2008. Development and Pilot Validation of Computer-Assisted Self-Infusion of Ethanol (Case): A New Method to Study Alcohol Self-Administration in Humans. *Alcoholism: Clinical and Experimental Research*, 32, 1321-1328.

Table 2. Sample Characteristics by Gender

	Age	Race	AUDIT
Total Sample	Mean=24.81 (SD=3.36)	72.2% Caucasian 16.7% African American 5.6% Asian American 5.6% Latino/Hispanic	Mean=10.05 (SD=3.35)
Men (n=15)	Mean=26.53 (SD=3.23)	66.7% Caucasian 26.7% African American 6.7% Latino/Hispanic	Mean=9.8 (SD=2.78)
Women (n=19)	Mean=23.57 (SD=2.94)	76.2% Caucasian 9.5% African American 9.5% Asian American 4.8% Latino/Hispanic	Mean=10.2 (SD=3.77)

Figure 1. Mood and gender effects of free access alcohol infusion. Left panel effects on peak BrAC (mg/dl) and Right panel effects on area under the curve (AUC) of the BrAC (min*mg/dl).

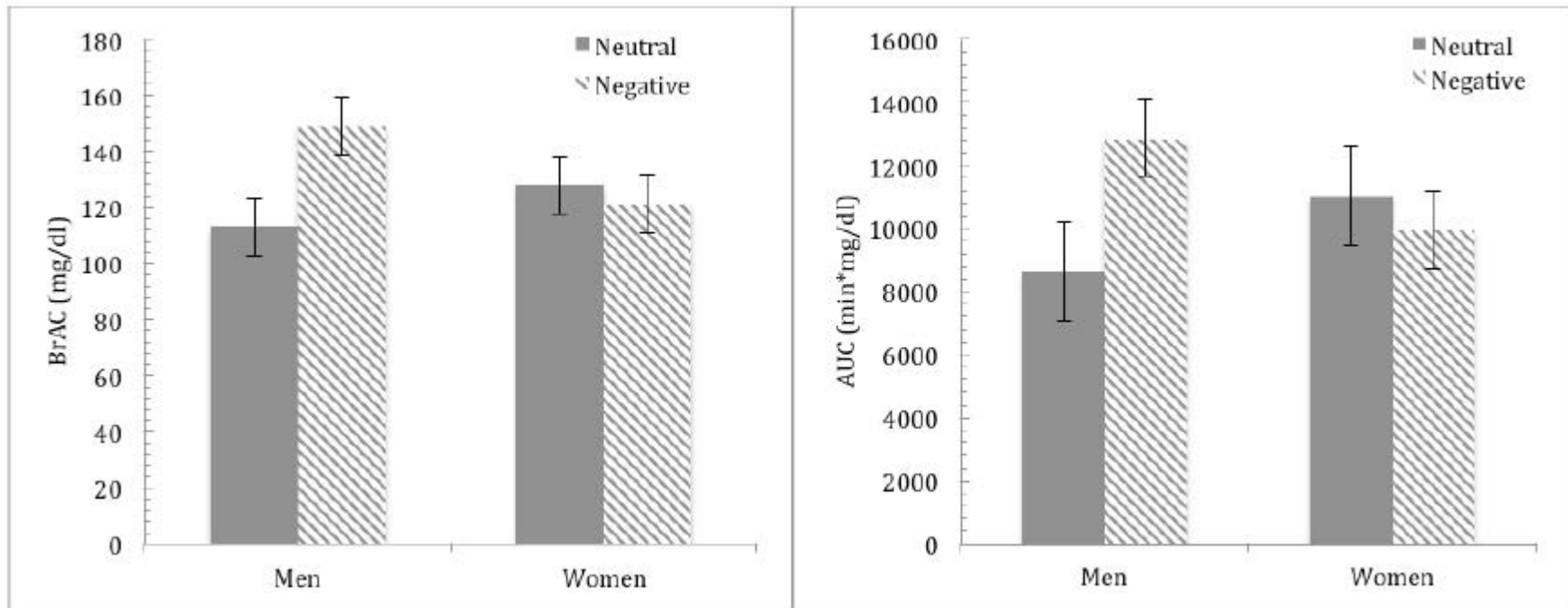
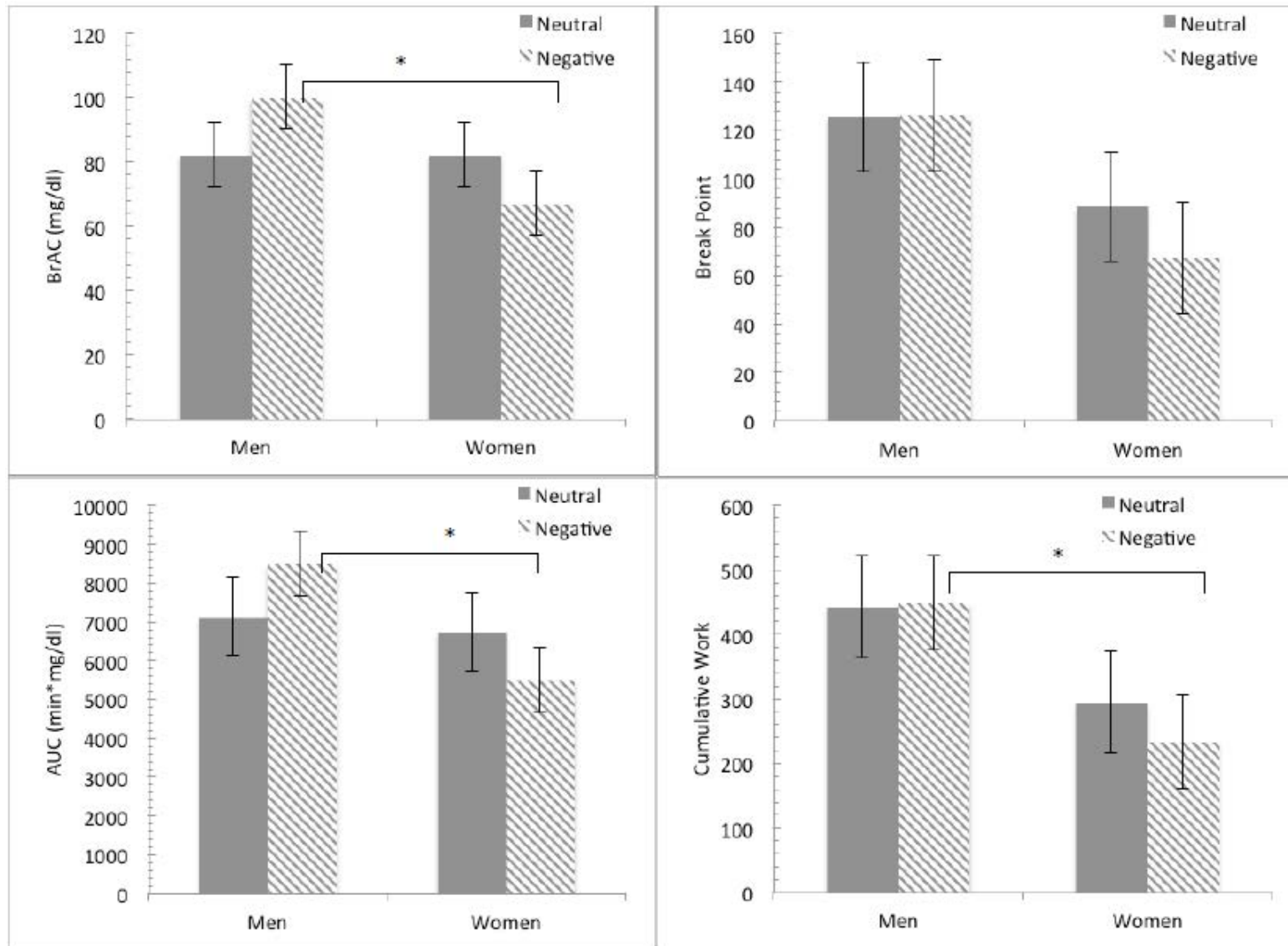


Figure 2. Mood and gender effects on progressive work alcohol infusion. Left top panel effects on peak BrAC (mg/dl) and Left bottom panel effects on area under the curve (AUC) of the BrAC (min*mg/dl). Right top panel effects on break point and right bottom panel effects on cumulative work.



Note. *denotes followup t-test contrast significant at $p < .05$

Figure 1. Session Timeline

