Sex Differences in Trauma and Alcohol Cue Reactivity

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THESIS

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LIST OF ABBREVIATIONS

AD	Alcohol Dependence
AUD	Alcohol use Disorder
AUQ	Alcohol use Questionnaire
AUDIT	Alcohol use Disorder Identification Test
CAPS	Clinician Administered PTSD Scale for DSM-5
MINI	Mini-International Neuropsychiatric Interview
PTSD	Posttraumatic Stress Disorder
TLEQ	Traumatic Life Events Questionnaire
TLFB	Timeline Follow Back
SUDS	Subjective Units of Distress Scale

SUMMARY

Available research suggests that men and women may differ in their risk for and presentation of PTSD-AUD comorbidity; PTSD and AUD symptoms and diagnoses appear to be more strongly associated for women compared to men. The trauma and alcohol cue reactivity paradigm may be useful for understanding sex differences in PTSD-AUD risk, given that this paradigm has the potential to simultaneously assess markers of self-medication risk (e.g., craving and salivation to trauma cues) as well as general alcohol risk (e.g., craving and salivation to alcohol cues). The aim of this study was to evaluate sex differences in trauma and alcohol cue reactivity through a laboratory paradigm that allows for the examination of craving responses to personalized trauma narratives and alcohol cues in a sample of 200 trauma-exposed college students who use alcohol regularly. It was hypothesized that men would have a stronger craving response to the trauma narrative compared to women, consistent with stronger self-medication alcohol use. It was also hypothesized that PTSD symptoms would evidence a stronger association with trauma cue-elicited craving for women than men, given evidence that PTSD and AUD correlate more strongly for women than men. Finally, it was hypothesized that men would demonstrate a greater craving response to the alcohol cues compared to women, given evidence that men exhibit greater risk for AUD than women. Contrary to hypotheses, there was no effect of sex on narrative status or beverage cue (t = -0.843, p = .400; t = -0.237, p = .813, respectively) when predicting craving, nor was there an effect of sex on narrative status or beverage cue (t = 0.434, p = .665; t = -0.660, p = 0.510, respectively) when predicting salivation. These results suggest that sex differences in PTSD-AUD may not be due to sex differences in self-medication alcohol use or reactivity to alcohol cues.

I. INTRODUCTION

Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) co-occur at elevated rates (Kessler, 1995). Almost a third of individuals with a lifetime diagnosis of PTSD also meet lifetime criteria for AUD (Brown, Campbell, Lehman, Grisham, & Mancill, 2001), compared to 13.7% of those without a history of PTSD (Blanco et al., 2013). Approximately half of individuals seeking treatment for AUD meet current criteria for PTSD (Brown, Stout, & Mueller, 1999). The frequent co-occurrence of these disorders is problematic for a number of reasons. First, individuals with comorbid PTSD and AUD experience greater PTSD and AUD symptom severity compared to individuals with either disorder alone (Blanco et al., 2013). In addition, individuals with both of these disorders are at greater risk for additional psychiatric comorbidities, show less improvement during AUD treatment (Brown et al., 1999; Read, Brown, & Kahler, 2004), relapse more quickly than individuals without PTSD upon completion of treatment (Ouimette, Finney, & Moos, 1999) and report more intense cravings for alcohol than individuals with either disorder alone (Drapkin et al., 2011).

Available research suggests that men and women may differ in their risk for and presentation of PTSD-AUD comorbidity. First, men are exposed to a greater number of traumatic events than women (Breslau, 2002; Kessler, 1995), but women are roughly twice as likely to develop PTSD (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), and experience greater chronicity of PTSD than men (Breslau, 2002). The types of traumatic events that men and women are exposed to also differ; men are more likely to report exposure to physical assault, combat and life-threatening accidents, whereas women are more likely to report child abuse, sexual molestation or sexual assault (Kessler, 1995). With regard to differences in alcohol use, it has been found that men drink more heavily and more frequently than women

(Holmila & Raitasalo, 2005), engage in higher levels of binge drinking (Naimi et al., 2003), and experience higher rates of adverse consequences from drinking (Wilsnack et al., 2000). In addition, rates of alcohol use disorders are higher among men than women (Grant et al., 2004) with one study estimating lifetime prevalence rates of DSM-5 alcohol use disorder as 36.0% for men and 22.7% for women (Grant et al., 2015).

Fewer studies have directly evaluated sex differences in PTSD-AUD comorbidity, although there is some evidence that women may experience a stronger association between these disorders compared to men. For example, it has been found that the odds of being diagnosed with PTSD in the presence of lifetime alcohol abuse are significantly greater among women than among men (Kessler et al., 1997). In addition, trauma exposure and past-year PTSD were more strongly associated with binge and hazardous drinking for women compared to men (Kachadourian, Pilver, & Potenza, 2014). In a nationally representative sample of individuals who endorsed lifetime alcohol consumption and trauma exposure, it was found that bidirectional associations between PTSD and *DSM-IV* alcohol dependence were stronger for women compared to men (Berenz et al., 2017). Age of onset was comparable for men and women with respect to both disorders; however, having an initial onset of alcohol dependence was associated with earlier initiation of alcohol use as well as an earlier onset of heavy alcohol use for women but not for men (Berenz et al., 2017). These findings collectively suggest that women and men may experience differences in the trajectories to developing PTSD-AUD comorbidity.

Sex differences in PTSD-AUD comorbidity should be explored in the context of existing theoretical models. The primary etiological models of PTSD-AUD comorbidity include the shared liability model, susceptibility models, and the self-medication model, with gender differences being demonstrated in key aspects of the latter two models (Berenz, McNett, &

Paltell, in press).The *shared liability* model states that PTSD and AUD often co-occur due to common familial risk, including shared environmental and genetic factors (Stein et al., 2002). *Susceptibility models* on the other hand state that alcohol use and/or problems may increase the risk for subsequent trauma exposure and/or PTSD (Acierno, Resnick, Kilpatrick, Saunders, & Best, 1999). In other words, these models posit that individuals are at greater risk for PTSD due to externalizing predispositions (e.g., risk for risky alcohol use), the consequences of which result in trauma and PTSD. Greater alcohol use is associated with increased risk for severe forms of trauma (e.g., sexual assault), particularly for women (Kaysen, Neighbors, Martell, Fossos, & Larimer, 2006; Kilpatrick, Acierno, Resnick, Saunders, & Best, 1997; Testa, Livingston, Vanzile-Tamsen, & Frone, 2003). In addition, alcohol exposure may disproportionately lead to impairments in executive functioning in adolescent girls compared to boys, possibly increasing risk for PTSD and other emotional disorders (Medina et al., 2008). Further, as stated previously, a diagnosis of alcohol dependence has been shown to convey greater risk for PTSD for women compared to men, even after covarying for lifetime trauma exposure (Berenz et al., 2017). The mechanisms accounting for this pattern of association are not well studied or understood.

The *self-medication model*, the most well studied model of PTSD-AUD comorbidity, posits that individuals with a history of trauma and/or PTSD are at an increased risk for AUD due to repeated use of substances to cope with trauma-related symptoms (Khantzian, 1999).This model states that individuals experiencing high levels of negative affect engage in coping-oriented alcohol use to provide temporary relief of aversive states. As such, the use of alcohol becomes negatively reinforced, as alcohol effectively reduces levels of negative affect in the short term (Khantzian, 1999), but is associated with greater symptom distress in the long-term

(Bolton, Cox, Clara, & Sareen, 2006). In a nationally representative sample, men with PTSD were more likely to endorse using alcohol to self-medicate than women with PTSD (Leeies, Pagura, Sareen, & Bolton, 2010). In addition, men with anxiety disorders, which share some commonalities with PTSD, are significantly more likely than women to engage in self-medication behaviors, including alcohol use (Bolton et al., 2006). Another study, however, found that men and women with anxiety disorders were equally likely to self-medicate with alcohol (Robinson, Sareen, Cox, & Bolton, 2009). Other research conducted in a small treatment-seeking sample of individuals with PTSD found that greater levels of PTSD symptoms were associated with greater coping motives for alcohol use comparably for men and women (Lehavot, Stappenbeck, Luterek, Kaysen, & Simpson, 2014). Related work has found that coping motives for alcohol use mediate the relationship between interpersonal trauma (e.g., childhood sexual assault, domestic violence) and alcohol consumption, as well as PTSD symptoms and alcohol consumption (Grayson & Nolen-Hoeksema, 2005; Kaysen et al., 2006), with one study finding that coping motives for alcohol mediates the relationship between trauma exposure and problem drinking for women but not for men (Fossos, Kaysen, Neighbors, Lindgren, & Hove, 2011).

Together, the available research supports a few preliminary hypotheses: (1) women may exhibit stronger associations between PTSD and AUD compared to men; (2) men may predominately exhibit risk for PTSD-AUD by way of a self-medication pathway; and (3) women may be at risk for developing PTSD-AUD due both to self-medication risk as well as a susceptibility pathway of risk, whereby problematic alcohol use increases risk for trauma and PTSD. Laboratory paradigms of trauma and alcohol cue reactivity would be particularly useful for understanding sex differences in PTSD-AUD risk, given that this paradigm has the potential to simultaneously assess self-medication risk (i.e., reactivity to trauma cues) as well as general

alcohol risk (i.e., reactivity to alcohol cues). The trauma and alcohol cue reactivity paradigm further allows for both within- and between-subjects evaluation of craving responses to trauma (i.e., self-medication) and alcohol cues.

A. Trauma and Alcohol Cue Reactivity Paradigm

In this paradigm, trauma-exposed individuals are presented with two sets of cues, an imaginal narrative cue, followed by an *in-vivo* beverage cue. The imaginal cue is comprised of a neutral script (e.g., changing a light bulb) or a trauma script, personalized to each individual's worst traumatic event. The *in-vivo* beverage cue consists of either spring water or the individual's preferred alcoholic beverage (Coffey et al., 2002). This paradigm includes presentation of all four possible narrative and beverage cue combinations (i.e., trauma-alcohol, trauma-neutral, neutral-alcohol, and neutral-neutral) in counterbalanced order. Reactivity to these cues has typically been measured through self-report and physiological measures of craving (e.g., salivation), as well as by changes in mood and subjective units of distress (Coffey et al., 2002, 2010). Prior literature on the trauma-alcohol cue reactivity paradigm in comorbid PTSD-AUD samples has found increased craving and salivation in response to both the trauma and alcohol cues, with the highest levels being observed for the trauma-alcohol cue combination (Coffey et al., 2002; Coffey, Stasiewicz, Hughes, & Brimo, 2006; Saladin et al., 2003). However, the trauma-alcohol cue reactivity literature is limited to treatment-seeking populations with full diagnoses of PTSD and AUD, which inhibits our ability to draw conclusions about the role of self-medication alcohol use, measured by response to the trauma cue, in PTSD-AUD etiology. Ongoing work in the current sample has found that trauma cue-elicited craving and alcohol cue-elicited craving are unique processes (Berenz et al., in preparation); in other words, some participants may react to one set of cues but not the other, which provides a unique opportunity

to evaluate different mechanisms of alcohol-related risk (e.g., self-medication vs. general alcohol cue reactivity) in trauma exposed individuals.

Finally, sex differences have been evaluated in the context of alcohol cue reactivity (Nesic & Duka, 2006) but less so in trauma and alcohol cue reactivity. Sex differences in the broader alcohol cue reactivity literature appear mixed, with some studies indicating that alcohol cues elicit increases in craving (Willner, Field, Pitts, & Reeve, 1998) and electrophysiological responding (Petit, Kornreich, Verbanck, & Campanella, 2013) for men but not women, while others indicate no sex differences in reactivity to alcohol cues (Jansma, Breteler, Schippers, De Jong, & Van Der Staak, 2000). Another study found that among alcohol 'urge reactors' (i.e., individuals who demonstrate increased urge to drink alcohol in response to an alcoholic beverage cue), women demonstrated more urge reactivity in the context of negative mood induction than men (Rubonis et al., 1994). In terms of trauma and alcohol cue reactivity, Coffey and colleagues (2010) did not find support for sex differences in craving, salivation, subjective anxiety, or mood across the four cue combinations; however, the sample was small (e.g., $n = 40$) and imbalanced across sex (63% women; Coffey et al., 2010). No studies have evaluated sex differences in trauma and alcohol cue reactivity in non-treatment seeking samples. Understanding sex differences in trauma and alcohol cue reactivity in pre-clinical samples would inform the literature on potential sex differences in the etiology of PTSD-AUD (e.g., self-medication risk).

B. <u>Aims/Hypotheses</u>

The aim of the current study is to evaluate sex differences in trauma and alcohol cue reactivity through a laboratory paradigm that allows for the examination of craving responses to personalized trauma narratives and alcohol cues. This study utilizes a sample of undergraduate students who have been exposed to interpersonal trauma and drink alcohol regularly. Men and

women will be compared with respect to their self-reported and physiological (i.e., salivation) craving in response to trauma and alcohol cues. It is hypothesized that men will have a stronger craving response to the trauma narrative compared to women, consistent with stronger self-medication alcohol use. It is also hypothesized that PTSD symptoms will evidence a stronger association with trauma cue-elicited craving for women than men, given evidence that PTSD and AUD correlate more strongly for women than men. Finally, it is hypothesized that men will demonstrate a greater craving response to the alcohol cues compared to women, given evidence that men have higher rates of alcohol use disorders than women.

II. Method

A. Study Overview

This study utilized a trauma and alcohol cue reactivity paradigm (procedure modeled after Coffey et al., 2002) to evaluate sex differences in craving responses to personalized trauma narratives and alcohol cues in a sample of high-risk college students. Interested individuals contacted a member of the study team who conducted a brief telephone screen to assess participant eligibility. Individuals meeting eligibility criteria by telephone were scheduled for a Session 1 appointment, in which participants completed a battery of questionnaires and clinical interviews, as well as provided a personalized trauma narrative for use in Session 2. Session 2 consisted of a laboratory-based trauma and alcohol cue reactivity protocol.

B. Participants

Participants included 200 (50% female) college students (ages 18-25) recruited from both the University of Illinois at Chicago and the University of Virginia using recruitment materials geared toward survivors of interpersonal trauma who use alcohol regularly. Individuals were recruited via online advertisements (e.g., Craigslist, email list serves for campus organizations) and flyers placed on campus and in businesses that were likely to attract college students.

To be included in the study, participants were required to be a college student between the ages of 18 and 25 who endorsed a history of one or more traumatic events meeting *DSM-5* Criterion A for PTSD that were interpersonal in nature (e.g., sexual or physical assault, child abuse, witnessing family violence). Participants also needed to endorse weekly alcohol use (i.e., frequency of alcohol use ≥ 1 day per week) and be able to provide informed consent and complete study procedures in English. Participants were excluded for using craving-reducing medications (e.g., naltrexone) or medications that could interfere with cue-elicited craving or

salivation (e.g., tricyclic antidepressants, neuroleptic or anticholinergic medications), a history of participation in exposure-based therapy for PTSD symptoms, and past 6-month participation in alcohol or substance use disorder treatment, or current desire to quit drinking or seek alcohol or substance use treatment. Participants were also excluded for being a minor (i.e., individuals <18 years of age), or being unable to complete the study procedures in English, as both the consent process and session visits were conducted in English.

C. Measures

1. Screening Measures (Session 1)

Participants were administered the Timeline Follow Back (TLFB; Sobell & Sobell, 1992) to assess the presence and quantity of alcohol use for each day of the past 90-day period. Illicit drug use was also assessed during the past 90 days. The TLFB was used to assess the inclusion criterion of weekly alcohol use for enrollment in the study. The TLFB has evidenced good concurrent validity with other measures of alcohol consumption (Grant, Tonigan, & Miller, 1995) and good reliability (Sobell & Sobell, 1996).

Participants were also administered the Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000) which is an assessment of 22 types of potentially traumatic events. For each event, participants answer questions regarding the frequency, timeline, and severity of each event. The TLEQ was administered to assess interpersonal traumatic events to be followed up using a clinical interview. The TLEQ has evidenced good test-retest reliability and good convergent validity with interview assessments of potentially traumatic events (Gray, Litz, Hsu, & Lombardo, 2004).

2. Diagnostic Measures (Session 1)

The Clinician Administered PTSD Scale for DSM-5 (CAPS; Blake et al., 1990) is a diagnostic interview for current and lifetime PTSD symptoms using DSM-5 diagnostic criteria. The CAPS was used to assess Criterion A for PTSD for all interpersonal potentially traumatic events endorsed on the TLEQ (e.g., physical or sexual assault, witnessing family violence). The remaining DSM-5 PTSD symptoms were assessed in reference to all interpersonal traumatic events meeting Criterion A for PTSD. The CAPS administration resulted in a current (past 30 day) continuous PTSD symptom severity score (i.e., CAPS total score) and diagnosis (present/absent). The CAPS has evidenced high inter-rater, test-retest, and convergent reliability, as well as high internal consistency across a multitude of settings (Blake et al., 1995; Hovens et al., 1994; Weathers, Keane, & Davidson, 2001).

The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) is a semi-structured clinical interview used to assess DSM-5 anxiety and mood disorders, eating disorders, AUD and other substance use disorders, and possible psychotic symptoms. This interview was used to determine AUD diagnostic status and associated severity (i.e., mild, moderate, severe) for each participant based on DSM-5 criteria. The MINI has been found to have high validity and reliability (Sheehan et al., 1998).

3. **Subjective Measures (Session 2)**

The Subjective Units of Distress Scale (SUDS; Wolpe, 1958) is a commonly used 0-100-point scale (0 = "totally relaxed" and 100 = "highest distress/fear/anxiety/discomfort that you have ever felt") to assess emotional distress. The SUDS was administered following completion of each of the four laboratory trials. Participants responded to the questions "Please rate your SUDS level while you imagined the last scene" and "Please rate your arousal level while you imagined the last scene."

Alcohol craving is measured by three questions assessed on a 0-10 Likert-type scale: "I crave a drink right now," "I want a drink right now," and "I have a desire for a drink right now" (Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996). The numerical responses to each of these questions are averaged to identify a total craving score.

The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) is a reliable and valid 20-item instrument that contains a positive and negative affect sub-scale consisting of 10 items each. The PANAS was used to assess cue-related changes in affect.

4. Physiological Measure (Session 2)

Salivary response to each of the laboratory trials administered during Session 2 was assessed using a method described by Monti and colleagues (1987). Three cotton dental rolls per trial were stored in specimen cups and weighed on a digital scale with tolerances to .05 gram. The three pre-weighed dental rolls were inserted into the participant's mouth, one placed under the tongue and two placed between the inner cheek and lower gum on each side of the mouth. Following removal, the dental rolls were immediately placed in the same specimen cup and weighed again. The magnitude of salivation was determined by subtracting the pre-weighed value from the value obtained after removal from the participant's mouth. The specimen cup and dental rolls were then immediately discarded.

D. Procedure

Individuals who were interested in participating in the study contacted a member of the research team by phone or email. The research staff then conducted a brief telephone screen to assess inclusion and exclusion criteria. Individuals eligible for the study were scheduled for Session 1, in which eligibility was confirmed with regard to past 30-day alcohol use (i.e., participant endorsed at least weekly alcohol consumption) and exposure to a Criterion A

interpersonal traumatic event. Participants who were no longer eligible for participation after completing Session 1 were compensated for their participation, but not scheduled for the next session.

1. **Session 1**

Participants met a member of the research team in the lab space, where informed consent was obtained and student status was verified. Participants then completed a battery of questionnaires, including demographics and the TLEQ. The TLFB was administered by a trained research staff member, and preferred alcoholic beverage was queried in preparation for Session 2 (e.g., type of alcohol, preferred glassware, to be used as an in-vivo beverage cue during Session 2). The MINI and CAPS-5 were administered by a trained doctoral student. Following the clinical interviews, a member of the research team obtained a personalized trauma narrative of participants' self-identified worst interpersonal traumatic event. This narrative consisted of a detailed description of the traumatic event, including where it took place, as well as the participant's thoughts, feelings and emotional response at the time of the event. A member of the research team then adapted this narrative into an audio-recorded 60-second trauma script, using present tense and first-person perspective, that was used as the trauma narrative cue in Session 2. At the conclusion of Session 1, participants were scheduled to return for Session 2 within two weeks and instructed to abstain from alcohol 24 hours prior to Session 2.

2. **Session 2**

Participants' alcohol abstinence was verified via breathalyzer, and time since last use of alcohol, nicotine, and caffeine was queried. Participants then sat in a comfortable chair behind an adjustable-height table for cue presentation. The participant was monitored via a non-recording video camera from behind a room partition to ensure participant safety and protocol compliance.

At the beginning of each cue presentation, pre-weighed dental cotton rolls were placed in the participant's mouth. Participants then listened to either the 60-second pre-recorded trauma narrative or a 60-second neutral script consisting of a description of the participant changing a lightbulb. Participants were instructed to keep their eyes closed during the presentation of the audio narrative and to imagine what was being described as vividly as possible, as if the event described was actually occurring. After the presentation of the audio narrative, participants were presented with a beverage cue placed on the table directly in front of them. This in-vivo beverage cue was either the participants' preferred alcoholic beverage or a neutral water cue. Participants were instructed to continue actively imagining the scene for two minutes while viewing the beverage cue in front of them. After two minutes, a member of the research team returned the dental rolls to the original specimen cup for reweighing. The participant completed a number of self-report measures including the SUDS, AUQ, a 3-item measure of craving, and the PANAS while the experimenter weighed the specimen cup with dental rolls. These procedures were repeated for a practice trial, as well as four experimental trials: 1) trauma-alcohol, 2) trauma-water, 3) neutral-alcohol, and 4) neutral-water. The presentation of cue combinations was counter balanced between and within subjects by sex.

E. <u>Analytic Approach</u>

Prior to evaluating the main hypotheses, manipulation checks were conducted to ensure that the alcohol condition elicited greater craving than the water condition, and that the trauma narrative elicited greater distress (i.e., SUDS) compared to the neutral narrative. Linear mixed effects models were conducted to examine (a) whether sex moderates trauma and alcohol cue reactivity (i.e., craving and salivation, respectively), and (b) whether sex modifies the interaction of PTSD symptoms and trauma cue on craving and salivation. The outcome variables were

salivation (in grams) and self-reported craving for alcohol (as measured by the 3-item craving scale). Forward-fitting models with deviance testing (parsimonious random effects; Bates, Kliegl, Vasishth, & Baayen, 2015; Matuschek, Kliegl, Vasishth, Baayen, & Bates, 2017) were utilized to determine the best-fitting model for craving and salivation, respectively. Model testing assumed a base model (Model 1) for the dependent variables of craving and salivation, based on prior model fit analyses in this sample (Berenz et al., in preparation).

For craving, the base model (Model 1a) included narrative status (i.e., 0=neutral, 1=trauma), beverage cue (0=water, 1=alcohol), the covariate of cumulative trauma history (i.e., number of traumatic event categories endorsed on the TLEQ), and a PTSD*narrative status interaction term. Model 1b added an interaction of narrative status and gender. Model 1c removed the gender interaction with narrative status, and added an interaction of beverage cue and gender. Model 1d removed the interaction of gender with the beverage cue, and added an interaction of gender to the PTSD*narrative status interaction term. Each subsequent model (Model 1b, Model 1c, and Model 1d) was compared to the original base model (Model 1a).

For salivation, the base model (Model 2a) included narrative status (i.e., 0=neutral, 1=trauma), beverage cue (0=water, 1=alcohol), and a PTSD*narrative status interaction term. Model 2b added an interaction of narrative status and gender. Model 2c removed the gender interaction with narrative status, and added an interaction of beverage cue and gender. Model 2d removed the interaction of gender with beverage cue, and added an interaction of gender to the PTSD*narrative status interaction term. Each subsequent model (Model 2b, Model 2c, and Model 2d) was compared to the original base model (Model 2a).

III. RESULTS

A. Sample Characteristics and Descriptive Statistics

See Table 1 for descriptive statistics for the total sample and split by gender. The sample was racially diverse (with more than one-third identifying as nonwhite), with equal proportions of men and women. The most frequent interpersonal PTEs endorsed were witnessing family violence growing up and witnessing a physical assault by a stranger. Participants endorsed exposure to approximately 5 different types of traumatic events and the mean total symptom severity score as measured by the CAPS was moderately high, with approximately half of the sample screening positive for PTSD. Approximately three quarters of the sample indicated having at least moderate problems with alcohol, as measured by the AUDIT.

B. Manipulation Checks

The alcohol cue (TA: $M = 4.28$, $SE = 0.22$; NA: $M = 3.25$, $SE = 0.18$) elicited greater subjective craving than the water cue (TN: $M = 2.85$, $SE = 0.19$; NN: $M = 1.81$, $SE = 0.16$), and all three experimental conditions (i.e., TA, TN, and NA) elicited greater craving than the neutral-neutral cue combination ($F(1,190) = 148.928$, $p < .001$). The trauma narrative (TA: $M = 53.69$, $SE = 1.96$; TN: $M = 48.92$, $SE = 1.96$) elicited greater SUDS ratings than the neutral narrative (NA: $M = 15.55$, $SE = 1.21$; NN: $M = 15.67$, $SE = 1.23$; $F(1,190) = 684.49$, $p < .001$).

C. Subjective Craving

To build upon the base model (Model 1a), sex was interacted with narrative status in Model 1b. Contrary to the stated hypothesis, this interaction was not significantly associated with craving ($t = -0.843$, $p = .400$). In Model 1c, sex was interacted with beverage condition, which also was not significantly associated with craving ($t = -0.237$, $p = .813$). In Model 1d, sex was interacted with narrative status and PTSD symptoms (sex*narrative*PTSD); the three-way

interaction did not significantly predict craving (t = -1.386, p = .167). None of the hypothesized models improved fit beyond Model 1a, nor was there a simple effect of sex on craving in Model 1a. See Table II for model fit statistics.

D. Salivation

To build upon the base model of salivation (Model 2a), sex was interacted with narrative status in Model 2b. Contrary to hypothesis, the sex* narrative interaction did not significantly predict salivation (t = 0.434, p = .665). In Model 2c, sex was interacted with beverage condition; however, this interaction was not significantly associated with salivation (t = -0.660, p = 0.510). In Model 2d, sex was interacted with narrative status and PTSD symptoms (sex*narrative*PTSD); however, the three-way interaction was not significantly associated with salivation (t = 0.086, p = 0.932). None of the hypothesized models improved fit beyond Model 2a, nor was there a simple effect of sex on salivation in Model 2a. See Table III for model fit statistics.

IV. DISCUSSION

The primary aim of this study was to examine sex differences in a trauma and alcohol cue reactivity laboratory paradigm. Contrary to hypotheses, there were no differences between men and women in response to the trauma narrative or to the alcohol cues with regard to craving or salivation. Given that trauma cue-elicited craving and salivation are believed to approximate self-medication alcohol use outside of the laboratory, it is possible that previously observed sex differences in PTSD-AUD associations (e.g., Berenz et al., 2017; Kachadourian et al., 2014) are not due to sex differences in the tendency to use alcohol to cope with trauma-related affect and symptoms. Should the present findings be replicated, it may be the case that PTSD-AUD sex differences are better attributed to susceptibility models, which suggest that individuals are at greater risk for PTSD due to externalizing predispositions (e.g., such as the risk for risky alcohol use), for which the consequences result in trauma or PTSD (Acierno et al., 1999). Given that greater alcohol use is associated with increased risk for severe forms of trauma (e.g., sexual assault), particularly for women (Kaysen et al., 2006), and that alcohol exposure may disproportionately lead to executive functioning impairments in adolescent girls but not boys (Medina et al., 2008), it is possible that susceptibility models better explain the sex differences previously observed in PTSD-AUD associations. Future research would benefit from a greater evaluation of adolescent alcohol use and its impact on brain development, as well as how risky alcohol use relates to sexual assault victimization more often in women than men.

The current study results, however, are in contrast with emerging literature demonstrating sex differences in the strength of association between PTSD and subsequent risk for AUD (Berenz et al., 2017; Kachadourian et al., 2014; Kessler et al., 1997). Specifically, stronger associations have been found between PTSD and AD, as well as trauma exposure/PTSD and

binge/hazardous drinking for women compared to men (Berenz et al., 2017; Kachadourian et al., 2014). It is possible that differences between the current study findings and past work are due in part to sampling differences. In the Berenz et al., 2017 study, the number of traumatic event categories participants endorsed was covaried for, but participants were not matched on trauma type (e.g., interpersonal compared to accidental trauma), nor were analyses conducted in subsets of the sample on the basis of trauma type. Given that women are more likely to be exposed to interpersonal trauma (e.g., rape, sexual assault; Kilpatrick et al., 2013), and men are more likely to be exposed to accidental trauma (e.g., life threatening accident, natural disaster; Kessler et al., 1995; Creamer, Burgess, & McFarlane, 2001) observed gender differences in prior work may have been better accounted for by differences in trauma history. It is well known that interpersonal trauma is more strongly associated with PTSD and AUD compared to accidental trauma (Schwandt, Heilig, Hommer, George, & Ramchandani, 2013; Stewart, 1996) and the present study recruited individuals who experienced one or more interpersonal traumatic events (e.g., sexual or physical assault, child abuse, witnessing family violence). It is possible that recruiting individuals based on high severity trauma exposure removes sex differences that would have existed in a more heterogeneous trauma sample.

It is also possible that other demographic characteristics across samples, such as participant age, could account for discrepancies between the current study findings and other published studies. For example, the previously cited epidemiologic studies reported an average participant age in the mid-forties (Kachadourian et al., 2014; Berenz et al., 2017), whereas the sample of the present study is younger (age 18-25) and comprised of college students. These age differences represent different stages of life for the respective samples, and as a result it is possible that sex differences begin to emerge as changes in one's role begin to occur. Literature

has suggested elevated rates of binge drinking among college students, (Wechsler, Dowdall, Davenport, & Rimm, 1995), and that rates of binge drinking uptake is similar for males and females in college (Weitzman, Nelson, & Wechsler, 2003). Whereas when individuals begin to age, and enter the workforce, men have elevated rates of binge drinking compared to women (Naimi et al., 2003) and there is more social disapproval and stigmatization of alcohol abuse in women than men (For review, see van der Walde, Urgenson, Weltz, & Hanna, 2002). Perhaps leaving college, where heavy drinking is more socially acceptable for women, and entering a role where it is less accepted, leads to a change in how women with comorbid PTSD and AUD cope with symptoms.

Relatedly, perhaps the length of time that an individual has had PTSD and AUD contributes to a change in coping style and as a result leads to an emergence of sex differences as individuals age. In adults with comorbid PTSD-AUD (M_{age} = 44.75), PTSD symptoms were associated with drinking for enhancement motives for men (but not women) and symptom severity was positively associated with drinking to cope for both men and women (Lehavot et al., 2014). Some research in college-aged individuals has not found support for sex differences in the reciprocal associations between PTSD and negative coping strategies (e.g., avoidance, self-blame, venting) nor in the mediating role of negative reinforcement coping in the relationship between alcohol consequences and PTSD symptoms (Read, Griffin, Wardell, & Ouimette, 2014). However, in college students, there has been evidence to suggest that enhancement motives mediated the relationship between childhood abuse and alcohol consequences for men, but coping-depression motives mediated this relationship for women (Goldstein, Flett, & Wekerle, 2010), partially mirroring what Lehavot and colleagues (2014) found in their study (for men

only). Future research would benefit from evaluating developmental changes in coping styles among individuals with PTSD and AUD.

Finally, it is important to consider the current findings in the broader context of cue reactivity research. With respect to the cue reactivity literature, prior findings from alcohol cue reactivity studies (with no narrative cue condition) evaluating sex differences have been mixed, with some studies finding increases in craving (Willner et al., 1998) and electrophysiological responding (Petit et al., 2013) for men but not women, while others indicate no sex differences in reactivity to alcohol cues (Jansma et al., 2000). Trauma and alcohol cue reactivity studies have rarely evaluated sex differences, with the one available study finding no support for sex differences in craving or salivation; however, this study was conducted in a small sample of treatment-seeking individuals with current diagnoses of PTSD and AUD (n = 40; Coffey et al., 2010). The current study extends prior literature on sex differences in cue reactivity by recruiting men and women on comparable trauma types (e.g., interpersonal trauma) and by increasing the sample size typically used in cue reactivity studies (n = 200). The larger sample size also allowed for advanced statistical methods for evaluating interactions between sex and cue type on craving and salivation. Finally, the present study recruited a pre-clinical sample, which enhances an ability to comment on etiological processes in PTSD-AUD.

There are a few limitations that exist in this study. First, findings from this study cannot be generalized to treatment-seeking or veteran populations, in which many PTSD-AUD studies are conducted. However, the information gleaned from this pre-clinical sample is valuable, given that college represents a time when interpersonal trauma exposure, PTSD, and AUD often onset. Second, the results from this study cannot be generalized beyond individuals exposed to trauma that it not interpersonal in nature, such as those with combat or accidental trauma (e.g., natural

disaster) exposure. Future studies replicating this work in diverse samples would be useful. Lastly, it is possible that the power for detecting a three-way interaction between sex, trauma narrative, and PTSD symptoms was too low. Although the current study represents the largest trauma and alcohol cue reactivity study to date, larger samples may be needed to investigate complex interactions.

In conclusion, our findings suggest that men and women with a history of interpersonal trauma may exhibit equal risk for PTSD-AUD by way of self-medication alcohol use. Future studies investigating sex differences in self-medication alcohol use at alternate points in the lifespan (e.g., middle age) or in alternate pathways of PTSD-AUD risk may be more fruitful.

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TABLE I

Descriptive Statistics

Variable	Total M(*SD*) or %	Gender	
		Men M (*SD*)	Women M(*SD*)
Gender	(51% Female)	---	---
Race			
African American	13.2%	13.3%	13.5%
Asian	16.9%	18.9%	14.6%
Caucasian/White	55.0%	54.4%	56.3%
Multi-Racial	9.0%	8.9%	8.3%
Other	5.8%	4.4%	7.3%
Interpersonal Trauma Types			
Armed robbery	21.5%	29.7%	14.4%
Physical assault by stranger	24.6%	39.6%	10.3%
Witnessed physical assault by stranger	42.9%	56.0%	30.9%
Threatened death or serious injury	37.2%	45.1%	28.9%
Physical abuse growing up	27.2%	27.5%	25.8%
Witnessed family violence growing up	44.2%	42.9%	44.8%
Physical assault by intimate partner	24.6%	20.9%	27.8%
Childhood sexual assault before age 13	17.8%	11.0%	24.7%
Childhood sexual assault ages 13-17	19.9%	7.7%	32.0%
Sexual assault as adult (18 or older)	40.8%	19.8%	60.8%

Accidental Trauma Types			
Natural disaster	50%	43.3%	56.7%
Motor vehicle accident	26%	27.5%	26.8%
Other accident	21.2%	24.4%	17.7%
Unexpected death of a loved one	67.9%	75.6%	61.9%
Loved one survived life-threatening illness/accident	50%	46.2%	55.2%
Life-threatening illness (self)	6.8%	7.7%	6.2%
No. of lifetime trauma types	5.67 (*2.85*)	6.03 (*2.95*)	5.47(*2.81*)
Total PTSD Symptom Severity	15.19 (*11.21*)	11.55(*9.4*)	18.55(*11.76*)
Past-Month PTSD Diagnosis	48.9%	31.9%	64.6%
AUDIT Total Score	11.98 (*5.80*)	11.95(*5.85*)	12.10 (*5.8*)
Positive Screen for Moderate Alcohol Problems	75.7%	73.3%	78.3%

Note. Number of lifetime trauma types assessed via TLEQ (Traumatic Life Events Questionnaire). Total PTSD Symptom Severity assessed via CAPS-5 (Clinician Administered PTSD Scale for DSM-5) Total Score. Total Score Past-Month PTSD Diagnosis assessed via CAPS-5. AUDIT= Alcohol Use Disorders Identification Test; Positive Screen for Moderate Alcohol Problems = AUDIT ≥ 8.

TABLE II

Estimates, Standard Error, and Model Fits for Craving

	Model 1a	Model 1b	Model 1c	Model 1d
Intercept	1.750*** (0.155)	2.352*** (0.477)	2.426*** (0.469)	2.335*** (0.489)
Narrative Status: Trauma	1.130*** (0.130)	1.462*** (0.396)	1.136*** (0.130)	1.592*** (0.405)
Beverage Cue: Alcohol	1.536*** (0.127)	1.542*** (0.128)	1.640*** (0.368)	1.542 (0.128)
Trauma History	0.382* (0.172)	0.338 . (0.173)	0.338 . (0.173)	0.339 . (0.173)
PTSD	0.558** (0.181)	0.652*** (0.193)	0.663*** (0.193)	0.567 (0.603)
PTSD*Narrative Status	0.410** (0.131)	0.443** (0.139)	0.401** (0.132)	1.108* (0.500)
Gender		-0.381 (0.286)	-0.428 (0.281)	-0.376 (0.288)
Narrative Status*Gender		-0.207 (0.238)		-0.242 (0.238)
Beverage Cue*Gender			-0.063 (0.221)	
PTSD*Gender				0.051 (0.347)
PTSD*Narrative Status*Gender				-0.402 (0.290)
AIC	2845.644	2832.856	2833.530	2834.915
BIC	2904.432	2900.599	2901.273	2911.690

Log Likelihood	-1409.822	-1401.428	-1401.765	-1400.457
Observations	680	676	676	676
N	170	169	169	169
Var: ID (Intercept)	2.889	2.870	2.871	2.869
Var: ID Narrative Status:Trauma	1.266	1.253	1.267	1.222
Var: ID Beverage Cue: Alcohol	1.162	1.164	1.161	1.163
Cov: ID (Intercept) Narrative Status: Trauma	-0.008	-0.031	-0.036	-0.028
Cov: ID (Intercept) Beverage Cue: Alcohol	0.306	0.291	0.290	0.290
Cov: ID Narrative Status: Trauma Beverage Cue: Alcohol	0.375	0.365	0.367	0.366
Var: Residual	1.594	1.602	1.602	1.602

Note. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, . $p < 0.1$. PTSD = PTSD symptoms as measured by the CAPS (Clinician Administered PTSD Scale for DSM-5).

TABLE III

Estimates, Standard Error and Model Fits for Salivation

	Model 2a	Model 2b	Model 2c	Model 2d
Intercept	1.187*** (0.065)	1.461*** (0.198)	1.438*** (0.193)	1.463*** (0.201)
Narrative Status: Trauma	0.029 (0.036)	-0.011 (0.108)	0.033 (0.036)	-0.012 (0.110)
Beverage Cue: Alcohol	0.115 *** (0.030)	0.113 *** (0.030)	0.167 . (0.087)	0.113 *** (0.030)
PTSD	-0.044 (0.066)	-0.012 0.069)	-0.015 (0.069)	0.003 (0.238)
PTSD*Narrative Status	0.089 * (0.036)	0.078 * (0.038)	0.084 * (0.036)	0.067 (0.130)
Gender		-0.178 (0.120)	-0.163 (0.117)	-0.178 (0.120)
Narrative Status*Gender		0.028 (0.066)		0.029 (0.066)
Beverage Cue*Gender			-0.035 (0.053)	
PTSD*Gender				-0.010 (0.141)
PTSD*Narrative Status*Gender				0.007 (0.077)
AIC	1400.934	1394.660	1394.411	1398.650
BIC	1456.343	1459.228	1458.980	1472.443
Log Likelihood	-688.467	-683.330	-683.206	-683.325
Observations	748	744	744	744

N	187	186	186	186
Var: ID (Intercept)	0.686	0.680	0.680	0.680
Var: ID Narrative Status:Trauma	0.095	0.090	0.090	0.090
Var: ID Beverage Cue: Alcohol	0.018	0.017	0.017	0.017
Cov: ID (Intercept) Narrative Status: Trauma	-0.034	-0.030	-0.031	-0.030
Cov: ID (Intercept) Beverage Cue: Alcohol	0.083	0.080	0.080	0.080
Cov: ID Narrative Status: Trauma, Beverage Cue: Alcohol	-0.032	-0.029	-0.029	-0.029
Var: Residual	0.151	0.152	0.152	0.152

Note. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, . $p < 0.1$. PTSD = PTSD symptoms as measured by the CAPS (Clinician Administered PTSD Scale for DSM-5).

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Faulkner, P., Ghahremani, D. G., Tyndale, R. F., Paterson, N. E., **Cox, C.**, Ginder, N., Hellemann, G., & London, E. D. (2018). Neural basis of smoking-induced relief of craving and negative affect: Contribution of nicotine. *Addiction biology*.

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POSTER PRESENTATIONS:

Cox, C.M., Demos, A.P., & Berenz, E.C. (2019). Sex differences in trauma and alcohol cue reactivity. Abstract submitted for poster presentation at the 2019 Center for Alcohol Research in Epidgenetics Fourth Annual Retreat, Chicago, IL.

Paltell, K., **Cox, C.,** Edalatian Zakeri, S., Berenz, E. (2019). Gender differences in the association between posttraumatic stress disorder symptoms and alcohol use problems and PTSD alcohol expectancies in college students with interpersonal trauma exposure. Poster presented at the 2019 Anxiety and Depression Conference, Chicago, IL.

Cox, C.M., Cho, S.B., Edalatian Zakeri, S., Bing-Canar, H., Paltell, K.C., Langdon, K.J., Dick, D.M., Berenz, E.C. (2019). Interpersonal Trauma and Smoking Trajectories in an Undergraduate Sample. Poster presented at the 2019 Society for Research on Nicotine and Tobacco, San Francisco, CA.

C.M. Cox, P. Faulkner, D.G. Ghahremani, M. Palmeri, J.D. Kassel, and E.D London (2017). The effect of reduced-nicotine cigarettes on self-reported positive and negative affect in a sample of emergent adults. Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Florence, Italy.

C.M. Cox, P. Faulkner, D.G. Ghahremani, M. Palmeri, J.D. Kassel, and E.D London (2017). Reduced-nicotine cigarettes reduce some, but not all, withdrawal symptoms in emergent adults. Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Florence, Italy.

N Petersen, P Faulkner, D Ghahremani, **C Cox**, ED London (2017). Sex differences in subjective evaluations of reduced nicotine cigarettes. Coll. Problems Drug Depend. June 17-22, Montreal, Canada.

N Petersen, P Faulkner, DG Ghahremani, **CM Cox**, ED London (2016). Reduced nicotine cigarettes alleviate craving and withdrawal more effectively in women than in men. Org. Study Sex Differences. May 23-26, Phila., PA

P Faulkner, DG Ghahremani, N Petersen, **CM Cox**, G Hellemann, ED London (2016). Reduced nicotine cigarettes alleviate craving and withdrawal, but do not alter attention or coupling between functional networks in young smokers. Tobacco Regulatory Sci. Conf. May16-18, Bethesda, MD.

DG Ghahremani, P Faulkner, CM Cox, **ED London** (2016). Effects of reduced nicotine cigarettes on behavioral and neural markers of craving regulation in young adult smokers. Tobacco Regulatory Sci. Conf. May 16-18, Bethesda, MD.

C.M. Cox, D.G. Ghahremani, P. Faulkner, E.D. London (2015). Behavioral and neural effects of cigarette craving regulation using a proximal/distal reappraisal strategy in young-adult smokers. Poster presented at the annual meeting of the Society for Neuroscience, Chicago, IL.

Faulkner, P, Ghahremani, D.G, **Cox**, **C.M**., Hellemann, G. and London, E.D. (2015). Effects of smoking reduced nicotine cigarettes on coupling between functional networks in brain, craving and withdrawal in young smokers. Poster presented at the annual meeting of the Society for Neuroscience, Chicago, IL.

C. M. Cox, P. Faulkner, D.G. Ghahremani, E.D. London (2015). The behavioral effects of smoking reduced nicotine cigarettes in young smokers. Poster presented at the Translational Nicotine Research Group Symposium, University of California, Los Angeles.

P. Faulkner, D.G. Ghahremani, G. Hellemann, **C.M. Cox**, E.D. London (2015). Craving-related behavioural response to reduced nicotine cigarettes: preliminary findings. Poster presented at the annual meeting of the Society for Research on Nicotine and Tobacco, Philadelphia, PA.

K. Lunny, S. Bujarski, T. Rohrbaugh, J. Jun, **C. Cox**, S. Manukian, Y. Quezada, B. Skagen, R. Green, J. Nguyen, K. Radstrom, L. Ray (2014). The relationship between alcohol use and methamphetamine use in a community sample of regular methamphetamine users. Poster presented at the annual meeting of the Research Society on Alcoholism, Bellevue, *WA. Alcoholism: Clinical and Experimental Research, 38*, S1

TEACHING EXPERIENCE:

Graduate Teaching Assistant (Jan 2019-May 2019)
Psychology 343: Statistical Methods in Behavioral Science
Psychology 321: Laboratory in Developmental Psychology

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