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Craving and Physiological Reactivity to Trauma and Alcohol Cues in PTSD and Alcohol Dependence

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Abstract

The high comorbidity of posttraumatic stress disorder (PTSD) and alcohol dependence (AD) has been firmly established. Although laboratory studies have examined self-reported craving in response to trauma and alcohol cues, no studies have reported on alcohol-related physiological responding in response to trauma cues in PTSD-AD individuals. Using a cue reactivity paradigm, this study examined the impact of personalized trauma-image cues and *in vivo* alcohol cues on alcohol-related responding (e.g., salivation, craving) in individuals with PTSD and AD (n=40). Participants displayed reactivity to both trauma and alcohol cues when compared to neutral cues, including increased self-reported craving and distress, as well as, greater salivation. These findings suggest that through repeated pairings of trauma memories and alcohol consumption, salivation may become classically conditioned to trauma cues. Moreover, the fact that the trauma-alcohol cue combination elicited greater alcohol craving, salivary responding, distress, and arousal than either the trauma-neutral or neutral-alcohol cue combinations, suggests that effects of the trauma and alcohol cues were additive in nature. Evidence that AD individuals with PTSD report increased alcohol craving and display greater salivation in response to trauma memories, supplements prior research indicating that PTSD-related negative emotion and trauma-related alcohol craving may play an important role in the maintenance of AD.

Keywords

Alcohol abuse; posttraumatic stress disorder; comorbidity; cue reactivity; emotion; imagery

Although there is no single explanation for the high level of substance abuse and PTSD comorbidity (e.g., Reynolds et al., 2005), evidence suggests that substance use may function to regulate the negative emotion associated with PTSD symptoms (e.g., Back, Brady,

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Jaanimägi, & Jackson, 2006; Chilcoat & Breslau, 1998; Stewart, Pihl, Conrod, & Dongier, 1998; see Conrod & Stewart, 2003; and Stewart & Conrod, 2003, for reviews). Given that the most common precipitant of relapse is a situation involving negative affect/emotion (e.g., Lowman et al., 1996), trauma-related negative emotion may help explain why substance users with PTSD, compared to substance users without PTSD, improve less during treatment, relapse faster, drink more on drinking days, and have more heavy drinking days posttreatment (e.g., Brown, Stout, & Mueller, 1996, 1999; Ouimette, Finney, & Moos, 1999; Read, Brown, & Kahler, 2004).

Several drug-conditioning models (e.g., Siegel, 1983; Stewart, de Wit, & Eikelboom, 1984; Wikler, 1965) propose that negative emotional states may act as conditioned stimuli that are capable of eliciting conditioned drug responses when substance use has been reliably paired with these emotional states. Support for this view comes from a large number of laboratory-based studies demonstrating that cue-elicited negative emotion (e.g., depressed mood, anger), elicits craving for drugs of abuse (e.g., Childress, Ehrman, McLellan, MacRae, & O'Brien, 1994; Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Stasiewicz et al., 1997). Moreover, many theories of craving and addiction underscore the importance of negative emotional states in the development and maintenance of substance use and substance use disorders (e.g., Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Siegel, 1983; Solomon, 1977; Stasiewicz & Maisto, 1993; Tiffany, 1990; Wikler, 1965).

Craving has been studied in the laboratory with an experimental paradigm known as cue reactivity. Cue reactivity is a term generally used to describe a phenomenon in which individuals with a history of psychoactive substance use exhibit physiological, verbal, and behavioral responses to cues associated with their preferred psychoactive substance. Alcohol studies with cue reactivity paradigms have provided considerable evidence that both interoceptive (e.g., fear, anxiety) and exteroceptive (e.g., smell of alcohol) cues may serve as precipitating factors for increased craving in individuals with AD. Alcohol-related stimuli, such as the sight or smell of alcohol, have been shown to result in cue reactivity (e.g., self-reported craving, salivation) in numerous studies (e.g., Coffey et al., 2002; Glautier & Drummond, 1994; Rohsenow et al., 1994; Smith-Hoerter, Stasiewicz, & Bradizza, 2004). In addition, reactivity to interoceptive cues, specifically negative emotion, has been empirically demonstrated (e.g., Cooney et al., 1997; Greeley, Swift, & Heather, 1992; Rubonis et al., 1994). Evidence that individuals with AD produce alcohol-related responses to both emotional cues and alcohol cues underscores the importance of this line of investigation.

Coffey and colleagues (Coffey et al., 2002; Coffey, Stasiewicz, Hughes, & Brimo, 2006; Saladin et al., 2003) have examined the relation between trauma-related negative emotion and alcohol craving in AD individuals with PTSD. In the first of a series of studies, Coffey et al. (2002) presented imaginal trauma cues, *in vivo* alcohol cues, and neutral imaginal and *in vivo* comparison cues to AD individuals with PTSD, using a cue reactivity paradigm. In this line of research, investigators attempt to experimentally induce an intrusive memory to study the impact of the phenomenon on substance-related responding. Participants reported higher levels of alcohol craving in response to both trauma cues and alcohol cues when compared with craving elicited by neutral comparison cues. As part of a larger study, these findings were replicated by Coffey et al. (2006).

Conditioned reactivity to alcohol cues has been measured through self-reported alcohol craving, as described above, but also through physiological measures. A limitation of the cue reactivity literature examining the relation between AD and PTSD is that it has relied solely on self-reported craving and has not included physiological measures associated with alcohol craving. A physiological measure somewhat unique to the study of alcohol cue reactivity is the salivary response. Pomerleau, Fertig, Baker, and Cooney (1983) found that

alcoholics could be differentiated from nonalcoholics by the degree of salivation to a favorite alcoholic beverage (as measured by rate of swallowing). Compared to heart rate and skin conductance, salivation was found to be the measure that best differentiated alcoholics from nonalcoholics. Using a more direct measurement of salivation rate (i.e., salivation absorbed by pre-weighed dental cotton rolls), Monti et al. (1987) found that alcoholics salivated more than nonalcoholics to the sight and smell of their preferred alcoholic beverage, and alcoholics salivated more to the alcohol beverage than to a control beverage. Continuing this line of research, Monti et al. (1993) found that individuals with more severe AD salivated more to alcohol cues. In addition, Rohsenow and colleagues (Rohsenow et al., 1994) found that in alcoholics undergoing detoxification, greater salivary reactivity predicted greater frequency of drinking following treatment. Thus, among physiological measures, salivation is a robust measure of alcohol cue reactivity.

Previous published cue reactivity research examining PTSD and AD has focused on self-reported measures of craving. The current study was designed to expand the measurement domain in this area of research by including a physiological measure; specifically salivary responding in response to trauma and alcohol cues. Alcohol dependent treatment-seekers with PTSD participated in a cue reactivity study in which personalized trauma and neutral imagery cues, combined with either alcohol or water *in vivo* cues were presented to participants. Salivary responding, self-reported alcohol craving, distress, and arousal were measured in response to each cue combination. We predicted that the combined trauma image-alcohol cue would increase alcohol craving and related responses more than the cue combination containing a neutral image-alcohol cue or a trauma image-neutral cue. Moreover, we predicted all cue combinations would increase alcohol craving and related responses more than the neutral image-neutral cue combination. In addition, we predicted that salivary responding would follow a similar pattern as self-reported alcohol craving.

Methods

Study Overview

Alcohol dependent (AD) individuals with PTSD participated in a laboratory-based cue reactivity protocol that consisted of two sessions. The first session was an assessment session to determine study eligibility. During the second session, participants were administered a laboratory-based cue reactivity protocol consisting of four cue-combination trials: 1) a personalized narrative description of the participant's worst traumatic event (e.g., rape by a stranger) paired with the presentation of the participant's preferred alcoholic beverage, 2) a trauma description combined with a water cue, 3) a narrative of a neutral cue (i.e., changing a light bulb) combined with an alcohol cue, and 4) a neutral narrative combined with a water cue. Before the presentation of each trial, cotton dental rolls were placed in participants' mouths and were removed and weighed immediately following each trial. Also, following each cue combination, participants rated each cue combination with regard to alcohol craving, distress, and arousal. All laboratory sessions were conducted in a 1.8 meter by 2.4 meter sound attenuated booth (Industrial Acoustic Company, Bronx, NY).

Participants

Forty treatment-seeking individuals meeting current diagnostic criteria for PTSD and AD (DSM-IV; APA, 2000) were recruited from a community residential chemical dependency treatment facility. All participants reported alcohol use within 60 days of the laboratory session. Individuals were excluded if they met diagnostic criteria for a psychotic disorder, were currently experiencing a manic episode, or were prescribed a benzodiazapine. Participants were not excluded if they met dependence criteria for a substance other than alcohol. All participants reported intact olfactory sense. Demographic information is

provided in Table 1. The study was approved by an Institutional Review Board and all participants provided informed consent prior to study entry and were financially compensated for their participation.

Instruments

Screening measures—Following a brief description of the study, patients expressing interest in the study were administered the PTSD Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993) to assess the likelihood that the patient met criteria for PTSD. The PCL is a widely used, reliable and valid PTSD screening tool (e.g., Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). To screen for AD, the Alcohol Use Disorder Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) was used. Individuals whose scores on the PCL and AUDIT equaled or exceed 44 and 8, respectively, were scheduled for a comprehensive assessment.

Diagnostic measures—The *National Women's Study (NWS) PTSD Module* (Resnick, 1996) was used to assess participants' trauma history and establish PTSD Criterion A (APA, 2000). The NWS PTSD Module is a structured interview modified from the Diagnostic Interview Schedule used in the National Vietnam Veterans Readjustment Study (NVVRS; Kulka et al., 1990). Concurrent validity with the SCID-PTSD module was good and reliability was also acceptable (Resnick et al., 1993). The NWS PTSD Module has been used to assess PTSD Criterion A in numerous studies involving both men and women (e.g., Boscarino, Adams, & Figley, 2004; Coffey et al., 2006; Saladin et al., 2003).

The *Clinician Administered PTSD Scale* (CAPS; Blake et al., 1995), is a well established and psychometrically sound structured clinical interview designed to assess the 17 symptoms of PTSD and was used as the diagnostic tool for current PTSD (i.e., symptoms present in the past month).

The *Computerized Diagnostic Interview Schedule* (C-DIS IV; Robins et al., 2000) is a computerized version of the Diagnostic Interview Schedule, a fully structured diagnostic interview for Axis I psychiatric disorders in DSM-IV. Its psychometric properties have been extensively studied and good reliability and validity have been demonstrated for diagnoses of substance abuse and dependence (e.g., Vandiver & Sher, 1991). The current study used the C-DIS to establish substance use disorder diagnostic status.

The *Mini-International Neuropsychiatric Interview* (M.I.N.I.; Sheehan et al., 1998) is a widely used structured diagnostic interview. The M.I.N.I.'s validity has been established in multiple languages against well-validated diagnostic instruments such as the Structured Clinical Interview for DSM -Patient Version and the Composite International Diagnostic Interview for ICD-10 (Sheehan et al., 1997). The current study used the M.I.N.I to establish current Axis I psychiatric diagnostic status for all conditions except substance use disorders and PTSD (e.g., major depression, panic disorder, etc.).

Self-report ratings of trauma and alcohol dependence—To measure trauma-related symptoms, the *Impact of Event Scale-Revised* (IES-R; Weiss & Marmar, 1997) was used. Items on the IES-R represent the three DSM-IV PTSD symptom clusters of intrusion, avoidance, and arousal. The IES-R has been shown to have strong psychometric properties (e.g., Creamer, Bell, & Failla, 2003) and has demonstrated good internal reliability in a traumatized substance use disorder sample (Rash, Coffey, Baschnagel, Drobes, & Saladin, 2008).

To assess alcohol-related problems and symptoms, the *Alcohol Dependence Scale* (ADS; Skinner & Allen, 1984) was administered to participants. Numerous studies have

demonstrated the ADS to have strong psychometric properties (e.g., Drake, McHugo, & Biesanz, 1995; Ross, Gavin, & Skinner, 1990).

Cues Combinations

Four cue combinations were employed in the study: 1) a narrative description of the participant's worst traumatic event paired with the presentation of the participant's preferred alcoholic beverage (TA), 2) a trauma description combined with a neutral *in vivo* cue (TN), 3) a narrative of a neutral cue combined with an alcohol cue (NA), and 4) a neutral narrative combined with a neutral *in vivo* cue (NN). The personalized trauma cue consisted of a 60 sec audiotaped narrative presented over a speaker in a sound-attenuated chamber. Information for the trauma script, which vividly described the participants' subjectively rated worst trauma from the first person perspective, was collected during the assessment session. The type of traumas described in the trauma narrative is presented in Table 1. The neutral imagery script consisted of a 60 sec description of changing a light bulb. The alcohol cue consisted of each participant's preferred alcoholic beverage. The beverage was presented in a clear glass container directly under the participants' nose on an adjustable-height table. The container of the participant's preferred brand of alcohol also was presented with the label facing the participant. The neutral *in vivo* cue was a glass of bottled water. Similar to the alcohol cue, the water bottle also was presented with the label facing the participant.

Salivary Flow Measure

Salivary flow was measured using a method described elsewhere (i.e., Monti et al., 1987). Briefly, three pre-weighed dental cotton rolls were inserted into the participants' mouth; one placed under the tongue and the remaining two placed between the inner cheek and lower gum on both sides of the mouth. The dental rolls were weighed again following their removal from the participants' mouths. The magnitude of salivation was determined by subtracting the pre-weighed value from the value obtained after removal from the participants' mouth.

Ratings of the Imagery and In Vivo Cues

Visual analog scale ratings (VAS) were used by participants to rate their level of alcohol craving and their level of emotional discomfort in response to the cue combinations. Alcohol craving was measured with three questions: *I crave a drink right now, I have a desire for a drink right now*, and *I want a drink right now* (Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996). Each statement was rated on a 0–10 scale with zero representing the absence of the state and 10 representing the maximum presence of the state. The mean of the three statement ratings was used as the alcohol craving dependent variable. Emotional distress was measured with a common 0–100 scale known as the Subjective Units of Distress Scale (SUDS). To improve reliability of the between trial SUDS ratings (i.e., to reduce rater drift), participants created personalized anchors at, or near, "0", "25", "50", "75", and "100" on the scale (e.g., "0" = sitting by a mountain stream, "50" = getting into an argument at work, "100"= worst traumatic event). Participants responded to the question "Please rate your SUDS level while you imagined the last scene".

Procedure

Assessment session—The study design and goals were described to all participants and informed consent was obtained. To establish study eligibility, an experienced research assistant interviewed participants. The C-DIS, NWS PTSD module, CAPS, and M.I.N.I. were used to (a) establish current AD; (b) assess for exclusionary psychiatric diagnoses; (c) assess participants' victimization history and to establish the presence of the necessary

Criterion A event for PTSD; and (d) establish a current diagnosis of PTSD. Consistent with recommendations of Weathers and Keane (1999), it was not required that the diagnosis of PTSD be associated with a singular traumatic event because all participants had experienced multiple victimizations over the course of their lives. However, it was required that the participant relate PTSD symptoms to one or more traumatic events that satisfied Criterion A for PTSD. Following the interview, participants completed the IES-R and ADS. Total scores for the CAPS, IES-R, and ADS are reported in Table 1.

If participants met study inclusion and exclusion criteria following the structured interviews, they were asked to describe their worst traumatic event. Participants were told that the information they provided would be included in a 60 sec audiotaped narrative that would be presented to them during the laboratory session. Participants were encouraged to include multiple sensory dimensions in their trauma description, including physical sensations, thoughts, emotions, olfactory cues, visual details, and events that they avoided due to the trauma or elicited memories of the trauma. At the completion of the assessment session, a laboratory session was scheduled to take place within one week of the assessment session.

Participants were required to maintain abstinence from alcohol and illicit drugs for 4 days prior to the laboratory session. Participants who either reported drug or alcohol use in the 4 days preceding the laboratory session or tested positive for the metabolites of cocaine, opiates, benzodiazapines, amphetamines, methamphetamine, oxycodone, propoxyphene, barbiturates, and MDMA, were rescheduled. Due to the long half-life of THC metabolites, participants who tested positive for THC and reported marijuana use in the past 30 days, but not past 4 days, were allowed to participate in the laboratory session.

Laboratory session—All laboratory sessions were scheduled to begin between 1:00–3:00 p.m. to control for diurnal variations that could affect cue reactivity but the vast majority of cue reactivity sessions began at 1:30, approximately 1 ½ hours following lunch. Participants were asked to remove gum from their mouths when they entered the laboratory. In addition, participants' compliance with the substance use restrictions was assessed. A urine drug screen (UDS; Instant Technologies, Inc., Norfolk, VA) was conducted at the beginning of the laboratory session to test for recent drug use. To assess recent alcohol intoxication, expired air samples were analyzed (Alco-sensor IV, Intoximeters, Inc., St. Louis, MO) prior to the laboratory session. In addition, alcohol, illicit drugs, nicotine, and caffeine use was assessed by participants' self-report.

Following the substance use screen, participants were escorted to an acoustically insulated subject room where they were seated in a comfortable chair. The self-reported craving, SUDS, and arousal measures were introduced to the participant and a detailed description of the study procedure was presented.

Four image-*in vivo* cue combinations were presented to all participants in a counterbalanced fashion (i.e., trauma imagery cue followed by an alcohol cue, TA; trauma imagery cue followed by a neutral cue, TN; neutral imagery cue followed by an alcohol cue, NA; and neutral imagery cue followed by a neutral cue, NN). The presentation of the four image-*in vivo* cue combinations followed the presentation of an NN practice trial in which participants were led through the following procedure.

Participants were told that when instructed to do so they were to close their eyes and an audiotaped narrative would be played over a speaker. They were informed that following the end of the narrative they should continue to imagine the scene described in the narrative as vividly as possible. Moreover, participants were instructed to experience the emotions elicited by the scene and to imagine the physical sensations described in the scene. After

responding to the participant's questions, the experimenter removed pre-weighed dental cotton rolls from a specimen cup, placed the rolls in the participant's mouth as described above, asked the participant to close his/her eyes, and started an audiotaped narrative. Following the 60 sec script presentation, the experimenter placed an *in vivo* cue on the table in front of the participant. The participant was instructed to open his or her eyes and look at the cue while continuing to imagine the scene previously described. Participants observed the cue for 2 min. At the end of the 3 min imaginal/*in vivo* cue exposure, the dental cotton rolls were removed and placed back in the specimen cup. The *in vivo* cue was then removed from the table in front of the participant and the self-report measures (i.e., craving, SUDS, and arousal) were given to the participant to complete. While the participant completed these measures, the dental rolls were reweighed and the weight was recorded. After the participant rated the NN cue combination, participants were queried for their understanding of the task and, if needed, task clarification was provided. The TA, TN, NA, and NN cue combinations were then presented in counterbalanced fashion in the manner described above.

At the completion of the laboratory protocol, a final craving rating was obtained. The final craving rating was obtained to assure the safety of the participants upon dismissal. In the absence of elevations in alcohol craving, participants were thanked for their participation. If significant alcohol craving or distress remained after the debriefing, an experienced clinical psychologist was prepared to assist participants in reducing their craving to baseline levels, however, this safety procedure did not need to be implemented.

Statistical analyses—Repeated measures analysis of variance (ANOVA) was used to examine differences between the four cue combination trials on salivary responding, craving, distress, and arousal scores. Statistically significant omnibus *F*s were investigated with independent samples *t*-tests. Effect sizes were calculated using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007).

Results

Trial Ratings

The means and standard deviations of all ratings are presented in Table 2.

Salivary flow—On the measure of salivary flow, a significant main effect for trial was revealed, $F(3, 37)=37.00$, $p=.001$, $\eta_p^2 = .36$. Post hoc tests of the four trial types revealed that the TA trial elicited a greater salivation response than the TN, NA, or NN trials (all $p<.05$). The TN trial elicited a greater response than the NN ($p=.001$), but did not differ from the NA trial, and the NA trial elicited a greater salivation response than the NN trial ($p<.05$). Between trial effect sizes (*d*) for salivary responding ranged from small (i.e., indicating little difference between the TN and NA trials) to medium (i.e., indicating notable differences between the TA-NN and TN-NN trials). Between trial effect sizes for salivary responding are presented in Table 3.

Craving—For the VAS craving measure, a significant main effect was found for trial, $F(3, 37)=31.56$, $p<.001$, $\eta_p^2 = .72$. Post hoc analysis of the trial types revealed that the TA trial produced higher craving than the TN, NA, or the NN trials (all p's $< .001$). In addition, the TN trial produced higher craving than the NN trial ($p<.001$) but did not differ statistically from the NA trial, and the NA trial produced higher craving ratings than the NN trial ($p<.001$). Between trial effect sizes (*d*) for craving ranged from small (i.e., indicating little difference between the TN and NA trials) to quite large (i.e., indicating substantial differences between the TA-TN, TA-NN, TN-NN, and NA-NN trials). Between trial effect

sizes are presented in Table 3. See Figure 1 for a graphic presentation of salivary responding and craving.

Neither alcohol craving nor salivary responding was significantly correlated with the number of days since the participant's last drink of alcohol (all $r < \left| .16 \right|$, all $p > .32$)

Subjective Units of Distress Scale (SUDS) and arousal—Similar to the other trial ratings, for the SUDS rating, a significant main effect was found for trial, $F(3, 37)=52.43$, $p<.001$, $\eta_p^2 = .81$. Post hoc tests revealed the TA trial elicited significantly more distress than the TN ($p=.02$), NA ($p<.001$), or NN trials ($p<.001$). The TN trial elicited significantly greater distress than either the NA ($p<.001$) or NN trials ($p<.001$). Lastly, the NA trial elicited significantly more distress from participants than the NN trial ($p<.001$).

Results from the arousal rating mirrored the SUDS ratings. A significant main effect for trial was found $F(3, 37)=57.63$, $p<.001$, $\eta_p^2 = .82$. Post hoc test revealed the TA trial elicited greater arousal than the TN ($p<.05$), NA ($p<.001$), and NN trials ($p<.001$). The TN trial elicited greater arousal than the either the NA ($p=.006$) or NN trials ($p<.001$) and the NA trial elicited greater arousal than the NN trial ($p<.001$).

Between trial effect sizes (*d*) for SUDS and arousal ratings generally mirrored one another and ranged from small (i.e., difference between the TA-TN trials) to quite large (i.e., differences between the TA-NA, TA-NN, TN-NN, and NA-NN trials). Between trial effect sizes for SUDS and arousal ratings are presented in Table 3. Graphic depiction of SUDS and arousal ratings for each trial type are presented in Figure 1.

No sex differences were found on salivary responding, alcohol craving, SUDS, or distress during the cue reactivity paradigm.

Discussion

Studies have documented increased craving in substance dependent individuals with PTSD when they are presented with personalized trauma image narratives (Coffey et al., 2002; Coffey et al., 2006; McDermott, Tull, & Lejuez, 2008; Tull, McDermott, Gratz, Coffey, & Lejuez, 2009). However, previous studies have focused on self-reported craving and have not measured physiological indices associated with craving. The present study proposed to build on previous research by measuring salivary responding to cues, a robust physiological measure associated with alcohol craving (e.g., Coffey, Saladin, Libet, Drobes, & Dansky, 1999; Monti et al., 1993; Rohsenow et al., 1994). Personalized trauma and neutral imagery cues and *in vivo* alcohol and neutral cues were presented to individuals with comorbid AD and PTSD. Reactivity to the imagery-*in vivo* cue combinations were assessed on the following dimensions: salivary response, alcohol craving, distress, and arousal.

Consistent with the existing literature, participants reported increased salivation and alcohol craving when presented with alcohol-related cues compared to a neutral cue combination. Also consistent with the existing literature, participants reported increased alcohol craving in response to trauma cues. A novel finding from the current study is that a personalized trauma imagery cue also elicited an elevated salivary response when compared to a neutral cue combination. In addition, both alcohol craving and salivary responding did not differ between the trauma image-neutral cue and neutral image-alcohol cue combinations, although both cue combinations elicited greater craving and salivation than the neutral image-neutral cue combination. This is important because, although the literature is somewhat mixed as to whether salivary flow rate is insensitive to stress or decreases in response to stress, there is general consensus that salivary flow rate does not increase in

response to stress (e.g., Hugo et al., 2008; Queiroz, Hayacibara, Tabchoury, Marcondes, & Cury, 2002; Rohleder, Wolf, Maldonado, & Kirschbaum, 2006). Therefore, the greater salivary flow rate elicited by the trauma-alcohol cue combination compared to all other cue combinations and the equivalence of the trauma-neutral and neutral-alcohol cues (and both the trauma-neutral and neutral-alcohol cues being higher than the neutral image-neutral cue combination) may suggest that salivary responding in these participants has been classically conditioned by repeated pairings of trauma memories and alcohol consumption. Moreover, the fact that the trauma-alcohol cue combination elicited greater alcohol craving, salivary responding, distress, and arousal than either the trauma-neutral or neutral-alcohol cue combinations, suggests that effects of the trauma and alcohol cues were additive in nature.

Effect sizes for the between trial differences describe above ranged from small to large/very large (d=0.8–2.07). A small effect size was noted for both salivary responding and alcohol craving when the TN and NA cue combinations were compared suggesting that the absence of a statistically significance difference was less an issue of power and more an issue of less-than-meaningful differences between the dependent measures on those trials. All contrasts with a small-medium or medium effects size were also statistically significant suggesting the current study was adequately powered to reveal small-medium effect sizes. Some of the contrast produced large to very large effect sizes and, based on previous research (e.g., Coffey et al., 2002; 2006), were expected to be large to very large. For example, it was expected that all contrasts comparing cues containing a trauma image and neutral image on either SUDS or arousal ratings, and all contrasts comparing cues containing an alcohol *in vivo* cue and a neutral *in vivo* cue on alcohol craving, would be large (e.g., d=.93) to very large (e.g., d=2.07). For salivary responding, it is interesting to note that only two sets of contrasts, the TA-NN contrast and the TN-NN contrast produced a medium effect size. The medium effect size is not surprising for the TA-NN contrast since alcohol was part of the cue combination. However, the medium effect size produced by the TN-NN contrast is surprising since the difference is being driven solely by the trauma narrative. This meaningful difference between the TN-NN underscores the important role of classical conditioning in PTSD-AD (i.e., alcohol consumption paired with PTSD symptoms).

Neither cue elicited alcohol craving nor cue elicited salivary responding was correlated with number of days since last drink of alcohol. The failure to find a relation between days since last drink and both craving and salivary responding is interpreted as support for the experimental control used in this study excluding participants who had not consumed alcohol in the last 60 days. The goal of the 60-days-since-last-drink restriction was to assure that the sample would be highly responsive to the cues. More variability on days since last drink would have likely lead to greater variability on craving and salivary responding and, thus, a significant relation between these variables might have been revealed.

The current study has at least three limitations. First, the sample is a substance abuse treatment-seeking sample so it is not clear how findings may generalize to a non-treatment-seeking sample of AD individuals with PTSD. In light of this possible selection bias, interpretation of the results from this study should be limited to AD treatment-seekers. Second, the entire sample consisted of AD individuals with PTSD so it is not known if a personalized trauma narrative may elicit an increased salivary response in individuals with PTSD but without alcohol dependence. Increased salivary responding to a personalized trauma narrative is unlikely since there is no evidence that stress increases salivary responding. However, given that the current study did not include a PTSD-only comparison group, this possibility cannot be eliminated. A third limitation is that interrater reliability was not established for our diagnostic measures.

Findings from the current study add to the literature documenting the strong relation between PTSD and AD. Specifically, the current study replicates previous research demonstrating that an experimentally-induced intrusive memory of a traumatic event increases craving in AD treatment-seekers. The current study also suggests that craving elicited by trauma memories is not only experienced as a cognitive phenomenon (i.e., self-report of alcohol craving), but also physiologically in the form of presumed classically conditioned salivary responding. This is the first study to report trauma cue-elicited alcohol-related physiological responding in alcohol dependent individuals with PTSD. Given that Coffey et al. (2006) reported a decrease in trauma cue-elicited alcohol craving following a reduction in trauma-related negative emotion, future studies should test whether a reduction in trauma-related negative emotion can also decrease salivary responding that has presumably been conditioned to a trauma memory.

Perhaps the most important implication of this study is to underscore the importance of treating both substance dependence and PTSD when they co-occur. Numerous researchers have documented the poorer substance abuse treatment outcome of SUD-PTSD comorbid individuals and have recommended concurrent treatment for the two disorders (e.g., Coffey et al., 2005; Hien et al., 2010; Stewart & Conrod, 2003). The results from the current study provide experimental evidence that trauma-related memories increase self-reported alcohol craving and physiological responding associated with AD in treatment-seeking individuals suffering from both PTSD and AD. As trauma-related intrusive memories are a core diagnostic feature of PTSD, it is reasonable to assume that symptoms of PTSD may play a significant role in the maintenance of alcohol dependence in PTSD-AD comorbid treatment-seekers and, therefore, should be addressed in substance use treatment.

Future studies using a cue reactivity paradigm with PTSD-AD treatment seekers may wish to address the role of both positive and negative affect cues in craving and salivary responding. In addition, future studies should examine individual differences in craving and salivary responding. For example, cue reactivity research has reliability identified the presence of craving and salivation responders and non-responders in reaction to alcohol cues (e.g., Coffey et al., 1999; Monti et al., 1993). Using fine grained analyses to better understand those who respond or do not respond to trauma and alcohol cues may lead to more targeted treatments for this at risk population.

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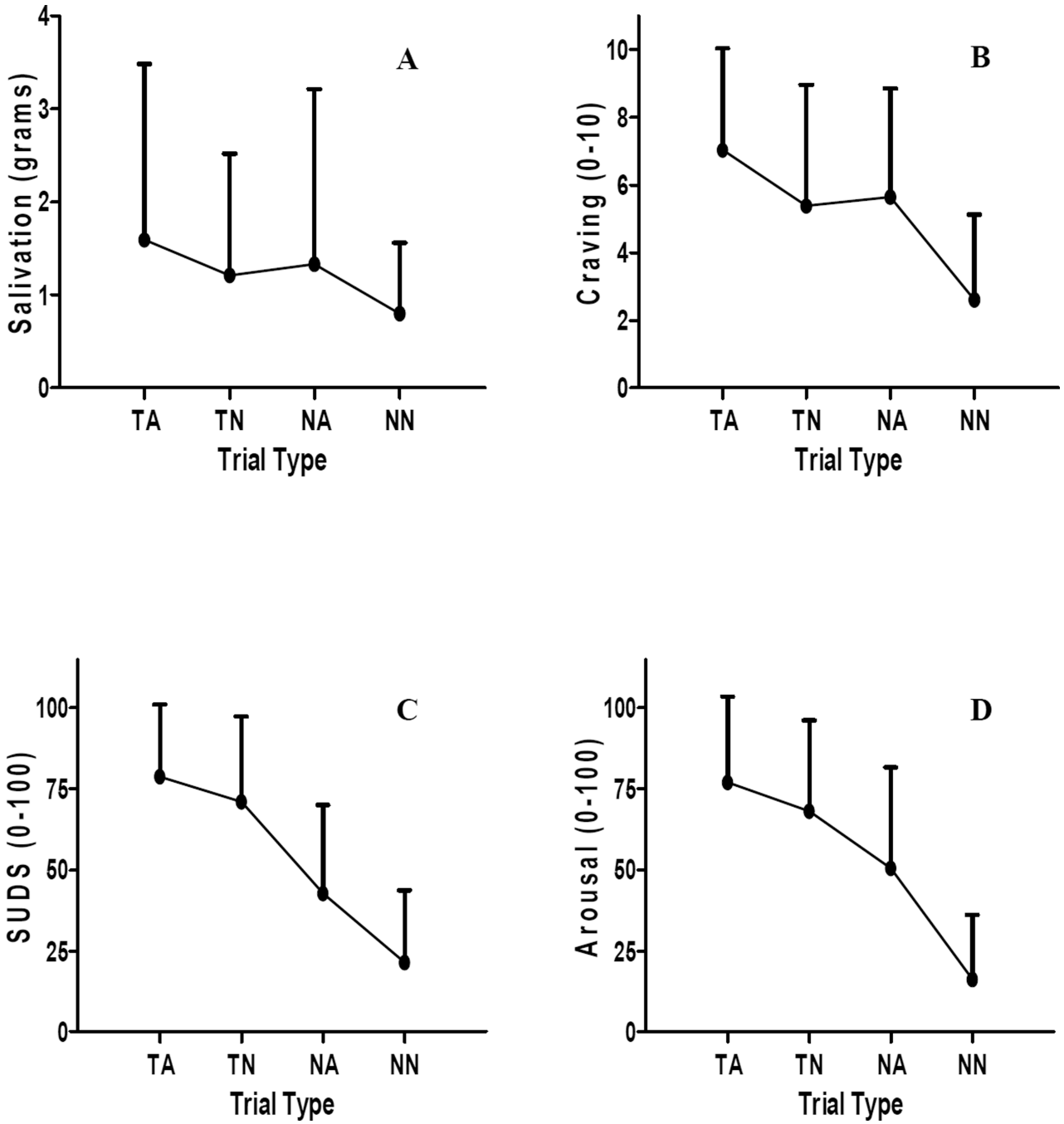

Figure 1.

Salivary response (panel A), craving ratings (panel B), Subjective Units of Distress Scale (SUDS; panel C) and arousal ratings (panel D) of the four cue combination trials. Trauma-image cue - *in vivo* alcohol cue = TA; trauma-image cue - *in vivo* neutral cue = TN; neutral-image cue - *in vivo* alcohol cue = NA; neutral-image cue - *in vivo* neutral cue = NN. The error bars represent the standard deviation.

Table 1

Mean (S.D.) participant and trauma characteristics (N=40).

Age	**34.18 (9.69)**
Gender	
Female	63%
Race	
White	77%
Black/African American	20%
Other	3%
Education	
< 12th	18%
H.S. diploma	30%
Post H.S.	42%
≥ 4 yr degree	10%
Employment[a]	
Full-Time	46%
Part-Time	13%
Unemployed	28%
Homemaker	10%
Student	3%
Current co-occurring drug use disorders	
Cocaine use disorder	48%
Amphetamine use disorder	30%
Marijuana use disorder	30%
Sedative use disorder	38%
Opiate use disorder	40%
Any co-occurring drug use disorder	75%
Current comorbid psychiatric conditions	
Major Depression	68%
Panic Disorder	20%
Social Anxiety Disorder	55%
Obsessive-Compulsive Disorder	28%
Generalized Anxiety Disorder	70%
Anorexia or Bulimia Nervosa	2.5%
Clinician Administered PTSD Scale Total Score	76.83 (16.46)
Impact of Event Scale-Revised Total Score	51.78 (15.25)
Subjectively identified worst traumatic event type[b]	
Sudden death of loved one	30%

Age	**34.18 (9.69)**
Childhood sexual abuse	20%
Childhood physical abuse	15%
Assault/shooting as adult	12.5%
Rape as adult	7.5%
Motor vehicle accident	5%
Other	10%
Alcohol Dependence Scale	28.05 (9.29)
Days since last drink of alcohol	21.10 (14.43)

[a] *Note:* Employment status prior to entering treatment.

[b] *Subjectively indentified worst traumatic event type* was the event described in the 60 sec narrative used as the trauma imagery cue.

Table 2

Mean (SD) of participants' (N=40) salivary response to, and ratings of, the cue combinations during each of the four trials. The four trials are: trauma-image – in vivo alcohol cue = TA; trauma-image – in vivo neutral cue = TN; neutral-image – in vivo alcohol cue = NA; neutral-image – in vivo neutral cue = NN.

	Trial			
	TA	**TN**	**NA**	**NN**
Salivary response (grams)	1.59 (1.89)	1.21 (1.31)	1.33 (1.88)	0.80 (0.76)
Craving (0–10)	7.03 (3.00)	5.38 (3.58)	5.64 (3.21)	2.61 (2.52)
SUDS (0–100)	78.82 (22.21)	71.10 (26.24)	42.67 (27.34)	21.38 (22.42)
Arousal (0–100)	77.03 (26.49)	68.20 (28.11)	50.60 (31.11)	16.12 (20.10)

Note: SUDS = Subjective Units of Distress Scale.

Table 3

Between trial effect sizes (d) for salivary response, alcohol craving, Subjective Units of Distress Scale (SUDS), and arousal.

Trial Differences	Salivary response	Craving	SUDS	Arousal
TA-TN	0.33	0.80	0.35	0.40
TA-NA	0.31	0.55	1.32	0.80
TA-NN	0.58	1.51	1.98	2.07
TN-NA	0.10	0.09	0.93	0.46
TN-NN	0.56	0.92	1.74	1.83
NA-NN	0.38	1.15	0.80	0.97

Note: TA = trauma-image/*in vivo* alcohol cue, TN = trauma-image/*in vivo* neutral cue, NA = neutral-image/*in vivo* alcohol cue, NN = neutral-image/*in vivo* neutral cue. Small effect size (*d*) = 0.2, medium effect size = 0.5, large effect size = 0.8.