Published in final edited form as:

Drug Alcohol Depend. 2020 January 01; 206: 107727. doi:10.1016/j.drugalcdep.2019.107727.

Interpersonal Trauma Exposure and Startle Reactivity to Uncertain Threat in Individuals with Alcohol Use Disorder

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Abstract

Background: Exposure to interpersonal trauma is highly prevalent within individuals with alcohol use disorder (AUD); however, the mechanisms underlying the pathway between trauma exposure and AUD are unclear. Preliminary evidence suggests that heightened reactivity to threats that are uncertain (U-threat) may characterize individuals with AUD and interpersonal trauma exposure and contribute to alcohol abuse within this subgroup of individuals; however, this hypothesis has yet to be tested.

Method: The aim of the study was to examine whether heightened reactivity to U-threat characterizes individuals with AUD and a history of interpersonal trauma. Specifically, the study compared defensive reactivity to U-threat (and predictable threat [P-threat]) in those with: 1) AUD and a history of interpersonal trauma (AUD+Trauma); 2) AUD and no history of interpersonal trauma (AUD-Trauma); and 3) matched controls. Participants (N=77) completed a well-validated threat-of-shock task and startle eyeblink potentiation was collected as an index of aversive responding.

Results: Results revealed a group by threat condition interaction ($F(4, 142)=3.17, p=.03; \eta^2_G = .08$) such that individuals with AUD+Trauma exhibited greater startle reactivity to U-threat, but not P-threat, compared with individuals with AUD-Trauma and controls (who did not differ from each other). The findings were significant even when controlling for current anxiety and depression symptoms.

Conclusions: Within individuals with AUD, those with a history of interpersonal trauma exposure may be a neurobiologically unique subtype characterized by exaggerated U-threat

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Contributors

Stephanie Gorka was the principal investigator of the study, conducted and interpreted the analyses, and prepared all aspects of the manuscript.

Conflict of Interest

The author declares that she has no conflicts of interest.

reactivity and high levels of anticipatory anxiety. Reactivity to U-threat may be a promising alcohol use prevention and intervention target for trauma-exposed individuals.

Keywords

alcohol use disorder; interpersonal trauma; uncertain threat; startle potentiation

1. Introduction

Exposure to trauma is a risk factor for alcohol use disorder (AUD) and highly prevalent within AUD populations. Retrospective and longitudinal studies show that individuals exposed to interpersonal trauma (e.g., physical/sexual assault) are 2–3 times more likely to develop alcohol problems than non-traumatized individuals (Harrison et al., 1997; Berenz et al., 2016; Kilpatrick et al., 1997). Within treatment settings, individuals with AUD are 6 to 12 times more likely to report physical abuse, and 18 to 21 times more likely to report sexual abuse, compared with controls (Clark et al., 1997). Even when interpersonal trauma exposure does not result in a diagnosis of post-traumatic stress disorder (PTSD), it connotes risk for alcohol abuse and a host of other mental and physical disorders (Cisler et al., 2012; McLaughlin and Lambert, 2017). To date, several empirically supported theories have been proposed to explain high rates of trauma and AUD co-occurrence (Brady et al., 2004; Suh and Ressler, 2018); however, the mechanisms underlying the pathway between interpersonal trauma exposure and subsequent alcohol use are unclear. There is a critical need to elucidate these mechanisms and identify core neurobiological features which characterize individuals with co-occurring interpersonal trauma and AUD to develop more effective mechanistic prevention and intervention approaches.

Heightened psychophysiological reactivity to uncertain stressors or threats (U-threat) may be one factor that characterizes individuals with AUD and a history of interpersonal trauma exposure. Broadly, U-threat is defined as a stressor that is temporally unpredictable and/or uncertain in intensity or duration. U-threat is universally aversive as it diminishes ability to prepare for future events, resulting in heightened anticipatory anxiety and sustained hypervigilance (Grupe and Nitschke, 2013). Our group and others have shown that there are some individuals, however, who are particularly sensitive to U-threat and display a host of maladaptive cognitive and behavioral responses in the face of uncertain negative events (Gorka et al., 2018a; Gorka et al., 2014; Carleton, 2016), including excessive alcohol use. Using startle eyeblink potentiation as an index of aversive responding, we have demonstrated that magnitude of startle reactivity to U-threat is positively associated with frequency of binge drinking and severity of coping with negative affect motives for alcohol use in young adults (Gorka et al., in press; Gorka et al., 2016). Exaggerated startle reactivity to U-threat has also been found in individuals with current and remitted AUD relative to controls (Gorka and Shankman, 2017; Gorka et al., 2013). These data coincide with several studies showing that alcohol intoxication effectively and preferentially dampens startle reactivity to U-threat, and does not impact reactivity to predictable threats (P-threat) (Bradford et al., 2013; Hefner and Curtin, 2012; Moberg and Curtin, 2009). As threat uncertainty increases, so does the magnitude of alcohol's stress-dampening effects and this association is generalizable across different forms of threat uncertainty (Hefner et al., 2013).

Based on this literature, an emerging theory is that individuals hyper-reactive to U-threat experience chronic anticipatory anxiety and are motivated to consume alcohol to dampen their distress, setting the stage for negative reinforcement processes to drive AUD.

Direct exposure to interpersonal trauma is a real-world, potent U-threat as it is unexpected, involves ambiguous contexts, and can unpredictably re-occur. Therefore, for some individuals, exposure to interpersonal trauma likely elicits heightened, sustained anxiety and can engender or reinforce beliefs that uncertainty is dangerous and intolerable. The increased distress resulting from exposure to real-world U-threats (i.e., trauma) could in-turn enhance motivation for coping-related alcohol use and facilitate and maintain AUD symptoms. We therefore hypothesize that exaggerated reactivity to U-threat is a specific AUD phenotype that may distinguish individuals with and without a history of interpersonal trauma exposure. Exaggerated reactivity to U-threat may therefore reflect a unique neurobiological pathway to problem alcohol use among trauma-exposed individuals.

Although no prior study has directly tested this hypothesis, converging lines of research broadly suggest that trauma exposure is linked to abnormalities in threat responding which facilitate excessive alcohol use. For instance, individuals exposed to trauma are more likely than controls to report depressive and anxiety symptoms (Chapman et al., 2007; Huh et al., 2017), and using alcohol as a means to cope with distress (Dixon et al., 2009). Coping-oriented motives for alcohol use also mediate the link between trauma exposure and problem drinking (Grayson and Nolen-Hoeksema, 2005). Meanwhile, laboratory studies suggest that individuals with a history of trauma display increased psychophysiological stress reactivity in response to negative stimuli. Norrholm et al. (2011) and McTeague et al. (2010) found that individuals with PTSD displayed increased startle eyeblink potentiation to conditioned fear stimuli and aversive imagery, respectively, whereas Heim et al. (2002) showed that women with a history of trauma had increased autonomic and pituitary-adrenal responses to psychosocial stress relative to controls. There is further evidence that threat reactivity is particularly enhanced in individuals with trauma exposure and comorbid AUD (Gilpin and Weiner, 2017), including a study by our lab showing greater neural response to the commission of errors in individuals with PTSD and AUD compared with PTSD alone (Gorka et al., 2016b). However, blunted stress reactivity in trauma-exposed individuals with and without AUD has also been observed (e.g., Ströhle et al., 2008). These mixed findings likely reflect differences in laboratory stress paradigms, as well as trauma and drinking-related sample characteristics. Given that no prior study has investigated group differences in reactivity to U-threat (and P-threat) specifically, it is currently unknown whether this unique form of threat reactivity characterizes individuals with AUD and a history of interpersonal trauma, as hypothesized.

The aim of the study was to examine differences in psychophysiological threat reactivity across three groups of adult volunteers: 1) controls with no history of AUD or interpersonal trauma; 2) individuals with AUD and no history of interpersonal trauma (AUD-Trauma); and 3) individuals with AUD and history of interpersonal trauma (AUD+Trauma) defined as DSM-5 Criterion A physical or sexual abuse/assault or witnessing immediate family violence. This definition of interpersonal trauma is notably consistent with several prior studies (Berenz et al., 2016; Jenness et al., 2019), and has been shown to be more closely

related to alcohol abuse than other forms of trauma (e.g., accidental traumas, emotional neglect) (Cisler et al., 2012). All individuals completed a well-validated threat-of-shock task to probe reactivity to U-threat and P-threat. Startle eyeblink potentiation was collected during the task as an index of defensive reactivity. In this cohort of individuals, we recently demonstrated that individuals with AUD display increased startle reactivity to U-threat, but not P-threat, compared with controls (Gorka et al., in press). History of trauma exposure was not examined and thus, of primary interest were differences between the AUD-Trauma and AUD+Trauma groups. In order to fully characterize the sample, we also explored group differences in drinking behaviors, coping motives for alcohol use, and current depression and anxiety symptoms. Based on the extant literature, we hypothesized that individuals with AUD+Trauma would display increased reactivity to U-threat, but not P-threat, compared with individuals with AUD-Trauma and controls. We also speculated that individuals with AUD+Trauma would report greater coping motives for alcohol use and increased depressive and anxiety symptoms relative to the other two groups.

2. Methods

2.1 Participants

Individuals were recruited via advertisements posted through social media and in the local Chicago community (e.g., parks, local medical clinics, college campuses). To be included in the study individuals were required to: 1) have no personal lifetime history of AUD (i.e., controls) or 2) meet criteria for AUD within the past two years. AUD psychopathology was assessed via the Structured Clinical Interview for DSM-5 Disorders (SCID-5; American Psychiatric Association [APA], 2015), in-person, by trained assessors, and supervised by a clinical psychologist. All participants were required to be between 21 and 30 years old and able to provide written informed consent. Exclusion criteria included any serious medical condition, psychotropic medication use, deafness, pregnancy, lifetime moderate or severe substance use disorder (other than alcohol and nicotine), and psychosis.

There were no specific inclusion or exclusion criteria pertaining to trauma exposure, which was defined as directly experiencing a DSM-5 Criterion A traumatic stressor (e.g., physical or sexual abuse), and assessed via the SCID interview. Other traumatic stressors such as hearing about something stressful that has happened to someone else was not coded as interpersonal trauma. The protocol was approved by the university Institutional Review Board and participants provided written informed consent. Individuals were instructed to abstain from drugs and alcohol at least 24-hours prior to the lab assessments which was verified via breath alcohol and urine screens. Participants were monetarily compensated for their time.

A total of 88 individuals enrolled in the study and completed the startle task. Four individuals had unusable/poor quality startle data (i.e., excessive baseline artifact and/or 75% of blinks scored as missing or non-responses in any one condition) and were excluded. The remaining subjects comprised the following three groups: 1) controls with no lifetime history of AUD or trauma exposure ($n = 28$); 2) individuals with AUD and no lifetime trauma exposure (i.e., AUD-Trauma; $n = 26$); and 3) individuals with AUD and direct trauma exposure (AUD+Trauma; $n = 23$). Of note, there were 7 remaining controls

who endorsed prior interpersonal trauma but they were excluded from the study due to the limited sample size of this group (i.e., Trauma without AUD).

2.2 Self-Report Measures

To assess drinking motives, participants completed the Modified Drinking Motives Questionnaire-Revised (M-DMQ-R; Grant et al., 2007). The M-DMQ-R includes 28-items in which participants respond using a 5-point Likert scale ranging from 1 (*almost never/never*) to 5 (*almost always/always*). Average scores for five motives subscales are computed: social, enhancement, conformity, coping-depression, and coping-anxiety.

Symptoms of internalizing psychopathology within the past two weeks were assessed using the Inventory of Depression and Anxiety Symptoms (IDAS-II) (Watson et al., 2012) – a 99-item self-report measure. Participants responded to each item using a 5-point Likert-type scale ranging from 1 (not at all) to 5 (extremely). The IDAS-II yields 17 empirically derived and symptom-specific scales (suicidality, lassitude, insomnia, appetite loss, appetite gain, ill-temper, well-being, panic, social anxiety, traumatic intrusions, traumatic avoidance, mania, euphoria, claustrophobia, checking, ordering and cleaning) and two, higher-order scales (general depression and dysphoria). For the purposes of our study, we used the ‘general depression’ scale to evaluate depressive symptoms, and created a composite ‘anxiety’ scale by averaging the three anxiety-related scales (panic, social anxiety, claustrophobia) similar to our prior studies (e.g., Gorka et al., 2018).

2.3 Startle Threat Task

The NPU startle task and laboratory procedures have been extensively described by our group (Gorka et al., 2013, 2016, 2017), including a prior paper published using the current sample (Gorka et al., in press). In brief, shock electrodes were placed on participants’ left wrist and a shock work-up procedure was completed to identify the level of shock intensity each participant described as “highly annoying but not painful” (between 1–5 mA). Ideographic shock levels were used to ensure equality in perceived shock aversiveness. Participants then completed a 2-min startle habituation task to reduce early, exaggerated startle potentiation. The task itself was modeled after Grillon and colleagues NPU threat task and thus included three within-subjects conditions: no shock (N), predictable shock (P), and unpredictable shock (U). Text at the bottom of the computer monitor informed participants of the current condition. Each condition lasted 145-s, during which a 4-s visual countdown (CD) was presented six times. The interstimulus intervals (ISIs; i.e., time between CDs) ranged from 15 to 21-s during which only the text describing the condition was on the screen. No shocks were delivered during the N condition. A shock was delivered every time the CD reached 1 during the P condition. Shocks were delivered at random during the U condition (both during the CD and ISI). Startle probes were administered during both the CD and ISI, and there was always at least 10-s between two probes or a shock and a probe. Each condition was presented two times in a randomized order (counterbalanced). Participants received 24 total electric shocks (12 in P; 12 in U) and 60 total startle probes (20 in N; 20 in P; 20 in U).

2.4 Startle Data Collection and Processing

Startle data were acquired using BioSemi Active Two system (BioSemi, Amsterdam, The Netherlands) and stimuli were administered using Presentation (Albany, CA). Electric shocks lasted 400-ms and acoustic startle probes were 40-ms duration, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones.

Startle responses were recorded from two 4-mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the left eye. The ground electrode was located at the frontal pole (Fpz) of an electroencephalography (EEG) cap that participants were wearing as part of the larger study. One startle electrode was placed 1-cm below the pupil and the other was placed 1-cm lateral of that electrode. Data were collected using a bandpass filter of DC-500-Hz at a sampling rate of 2000-Hz.

Blinks were processed (and scored) according to published guidelines (Blumenthal et al., 2005): applied a 28 Hz high-pass filter, rectified, and then smoothed using a 40 Hz low-pass filter. Peak amplitude was defined within 20–150-ms following the probe onset relative to baseline (i.e., average activity for the 50-ms preceding probe onset). Each peak was identified by software but examined by hand to ensure acceptability. Blinks were scored as non-responses if activity during the post-stimulus time frame did not produce a peak that is visually differentiated from baseline. Blinks were scored as missing if the baseline period was contaminated with noise, movement artifact, or if a spontaneous or voluntary blink began before minimal onset latency. Blink magnitude values (i.e., condition averages include values of 0 for non-responses) were used in all analyses.

2.5 Data Analysis Plan

We first tested whether the three groups differed in important variables known to influence startle potentiation using a series of planned analyses of variance (ANOVAs) and chi-square tests. We tested group differences in age, sex, race, ethnicity, rates of comorbid psychopathology, and current depression and anxiety symptoms. The groups were found to differ in levels of depression and anxiety symptoms and accordingly, these variables were included as covariates in our subsequent model.

To test our hypotheses, we conducted a repeated measures ANOVA where task condition (3: N, P, U) was specified as a within-subjects variable and group (3: controls, AUD–Trauma, AUD+Trauma) as a between-subjects variable. Raw startle magnitude during the CD phase of each condition of the task (N, P, U) was used to capture response to the task and match the three conditions on visual stimuli (i.e., a CD was on the screen), consistent with our recent publications (e.g., Gorka et al., in press; Gorka et al., 2013). Sex was included as a covariate given well-documented sex differences in psychophysiological reactivity to stressors (Grillon, 2008; Ordaz and Luna, 2012); though notably, sex differences during the NPU-threat task have not been consistently found. Depression and anxiety symptoms, measured via the IDAS-II, were also included as separate covariates. A significant condition $\times$ group interaction was followed-up by testing the effect of group at each task condition using separate ANOVAs. Significant group effects were then further probed using post-hoc Fisher's least significant difference (LSD) tests.

3. Results

3.1 Descriptives and Clinical Comparisons

Of the individuals who had a DSM-5 Criterion A trauma: 39.1% reported physical abuse/assault, 34.8% reported sexual abuse, 26.1% witnessed immediate family member violence, and 17.4% were directly shot at or involved in gun-related violence. In addition, within this cohort, 43.5% reported that they witnessed someone dying or badly hurt and 17.4% were injured in a serious accident. Forty-three percent of individuals reported exposure to more than one trauma. Only 3 out of the 23 individuals with a history of trauma exposure met criteria for lifetime PTSD. The average age of trauma onset was 18.9 (3.6) years old. Average age of AUD onset was 19.6 (2.8) years old.

Statistical data regarding differences amongst groups is presented in Table 1. Of note, the three groups were matched on all major demographic variables including age, sex, education, ethnicity and race. The three groups were also matched on rates of internalizing psychopathology including current diagnoses of depression and anxiety; however, there were notable differences at the symptom level. Specifically, individuals with AUD+Trauma reported greater current depressive and anxiety symptoms compared with individuals with AUD–Trauma and controls (who did not differ from each other).

With regard to alcohol use, individuals in both AUD groups had more binge episodes and more drinks per week than individuals in the control group. There were no differences in frequency of alcohol use between the AUD+Trauma and AUD–Trauma groups. Individuals in both AUD groups also had higher scores on all alcohol motives subscales reflecting overall increased motivation for alcohol use compared with controls. There were no differences between the two AUD groups on alcohol motives except for the enhancement subscale, in which individuals with AUD–Trauma endorsed greater enhancement motives for alcohol use than individuals with AUD+Trauma.

3.2 Group Differences in Threat Reactivity

Results of the omnibus repeated measures ANOVA are presented in Table 2. There was a main effect of task condition such that startle during the two threat conditions was significantly greater than startle during the no-threat condition. Startle during U-threat was greater than startle during P-threat ($N < P < U$). There was also a task condition by group interaction. Follow-up analyses revealed that the groups differed in startle during U-threat ($\beta = .26$, $t = 2.08$, $p = .04$), but not during P-threat ($\beta = .18$, $t = 1.44$, $p = .15$) or no-threat ($\beta = .09$, $t = 0.68$, $p = .50$). Specifically, when controlling for anxiety and depression symptoms, individuals in the AUD+Trauma group displayed greater startle during U-threat than individuals in the AUD–Trauma and control groups (see Figure 1). There were no differences in startle during U-threat between individuals in the AUD–Trauma and control groups. There were also no other significant main effects or interactions with any of the model variables.

4. Discussion

Theory suggests that exposure to interpersonal trauma may increase psychophysiological reactivity to U-threat and drive the onset and maintenance of AUD. The aim of the current

study was to provide a preliminary test of this theory by examining whether individuals with AUD+Trauma display increased startle reactivity to U-threat compared with individuals with AUD-Trauma and controls. Results were consistent with hypotheses such that individuals with AUD+Trauma exhibited greater startle reactivity to U-threat, but not P-threat, compared with individuals with AUD-Trauma and controls, who did not differ from each other. The group difference in startle reactivity was observed above and beyond the impact of co-occurring depression and anxiety symptoms suggesting that interpersonal trauma exposure may uniquely influence U-threat responding. Together, the results provide initial evidence to suggest that individuals with a history of interpersonal trauma exposure may be a neurobiologically unique subtype of those with AUD. In addition, exaggerated U-threat reactivity may be a key dysfunction associated with problem drinking in individuals with AUD+Trauma and therefore, a novel treatment target within trauma-exposed populations.

Several studies have shown that exaggerated startle reactivity to U-threat is associated with problematic alcohol use (Gorka et al., 2016a, 2017, in press; Moberg et al., 2017). An emerging theory is that individuals who are highly reactive to U-threat are motivated to consume alcohol as a means of coping with distress (Gorka et al., in press) and coincidentally, benefit the most from alcohol's ability to acutely dampen anticipatory anxiety (Moberg and Curtin, 2009). In essence, high U-threat reactors are considered vulnerable to the negative reinforcing effects of alcohol, which sets the stage for the onset and maintenance of AUD. Findings from the current study suggest that this theory may be especially true for individuals with a history of interpersonal trauma exposure. We posit that the unpredictability of interpersonal trauma exposure, and the ongoing possibility of re-occurrence, influences sensitivity to U-threat in such a way that individuals become sensitized and hypervigilant for all potential U-threats, resulting in a chronic state of anticipatory anxiety and the drive to use alcohol as a means of avoidance-based coping. Exaggerated reactivity to U-threat may therefore reflect a neurobiological mechanism underlying the well-established co-occurrence of interpersonal trauma exposure and AUD.

The hypothesis described above suggests that interpersonal trauma exposure *causes* (or at least increases) heightened startle reactivity to U-threat. However, the current study was cross-sectional and we did not recruit a trauma-exposed sample without AUD so this hypothesis cannot be tested. A few studies in non-AUD populations have explored the independent impact of trauma exposure on startle reactivity. Most relevant to the current study, Grillon et al. (2009) demonstrated that individuals with PTSD displayed greater startle to U-threat, but not P-threat, compared with healthy controls and individuals with generalized anxiety disorder using the NPU-threat paradigm. This finding converges with early studies showing that individuals with PTSD display increased baseline (i.e., non-task related) startle reactivity compared with controls (Bulter et al., 1990; Shalev et al., 1997). Meanwhile, using trauma-related imagery, McTeague and colleagues (2010) also found that relative to controls, individuals with PTSD had increased startle reactivity. However, when the PTSD group was split into single versus multiple trauma exposure subtypes, only individuals with single traumas evidenced exaggerated startle lending the authors to conclude that chronicity of trauma exposure moderates stress reactivity. Taken together, there is some evidence from the PTSD-literature that trauma exposure does indeed increase threat reactivity but the unique impact of interpersonal trauma exposure (with or without a

PTSD diagnosis) on U-threat responding is still unclear. Moreover, the extent to which trauma severity, chronicity, and/or trauma-type influences U-threat reactivity in individuals with and without AUD remains an open question as the current study was not powered to explore moderators within the AUD+Trauma group.

A related, alternative hypothesis is that interpersonal trauma exposure and U-threat reactivity are independent factors influencing AUD that act synergistically to propel some individuals along a pathway to alcohol problems. This theory was not directly tested in the current study but it would imply that not all individuals exposed to interpersonal trauma display exaggerated U-threat reactivity. Rather, of individuals exposed to interpersonal trauma, those who had a pre-existing sensitivity to uncertainty may be most affected and the trauma may act to further enhance anxiety and reinforce already-held beliefs that U-threats are dangerous and intolerable. It is this cohort of individuals who may in-turn experience increased distress and engage in excessive alcohol use. High U-threat reactors who subsequently experience trauma may therefore reflect a group of individuals at particularly high-risk for ongoing alcohol abuse. If this hypothesis were supported then screening trauma-exposed individuals for high levels of U-threat startle reactivity may be a way to accurately identify high-risk youth for early intervention. Though first, longitudinal studies with repeat assessments of startle reactivity, trauma exposure, and alcohol use in children and adolescents are greatly needed to elucidate these alternative mechanisms.

Abnormalities in other components of the startle reflex, particularly decreased pre-pulse inhibition (PPI) of startle, have also been linked to trauma exposure (Grillon et al., 1996) and vulnerability for alcohol problems (Grillon et al., 1997; Grillon et al., 2000; Marin et al., 2012). PPI is a measure of sensorimotor gating (Braff et al., 1992) and reflects an inhibitory mechanism that regulates sensory, behavioral and cognitive functions (Swerdlow et al., 1992). Reduced PPI in individuals at-risk for alcohol problems has been posited to signify difficulty suppressing irrelevant stimuli, which could in-turn facilitate sustained stress reactivity, particularly during unpredictable contexts. It will therefore be important to examine to what extent PPI and U-threat startle reactivity are overlapping psychophysiological markers of trauma and AUD comorbidity.

Results of the current study also revealed that individuals with AUD without a history of interpersonal trauma did not differ from matched controls on reactivity to U-threat (or P-threat). This finding was unexpected given that numerous prior studies have found individuals with AUD display exaggerated startle reactivity to U-threat without accounting for individual differences in trauma exposure (Gorka et al., 2013, 2016a, 2017, in press; Moberg et al., 2017). Because trauma is highly prevalent within AUD populations, it is possible that these prior findings were somewhat influenced by the presence of interpersonal trauma exposure; though it is unlikely trauma exposure accounts for all prior associations. The results nevertheless highlight that individuals with AUD are a heterogeneous group and there may be AUD subtypes with unique treatment targets. More specifically, if individuals with AUD+Trauma are uniquely characterized by exaggerated reactivity to U-threat, psychosocial and pharmacological treatments that target defensive reactivity (e.g., prescribed exercise; Lago et al., 2018) may be particularly effectively for this population. Individuals with AUD-Trauma, who the results indicate endorse high levels of enhancement motives for

alcohol use, may be better served by treatments that target positive reinforcing effects of alcohol and relatedly, the brain's reward system. In other words, individuals with AUD +Trauma may be better candidates for treatments geared towards threat reactivity whereas individuals with AUD-Trauma may be better candidates for treatments geared towards reward reactivity.

The present study had several strengths including addressing a novel theory and the use of a well-validated objective measure of threat reactivity. The study also had several limitations. First, as noted above, we did not include a trauma-only group and thus, the independent impact of interpersonal trauma exposure on U-threat reactivity is unclear. Second, the effect size of the group difference between individuals with AUD+Trauma and AUD-Trauma was relatively small and the true clinical implications of targeted U-threat interventions may prove to be insignificant; though this requires investigation. Third, there is some prior evidence to suggest that trauma characteristics (e.g., severity, chronicity) may impact stress reactivity (e.g., McTeague et al., 2010); however, the present study was underpowered to test for within-group moderators. Fourth, individuals exposed to interpersonal trauma likely experience other forms of adversity and life stress (Finkelhor et al., 2007). It is therefore possible that additional unmeasured variables could have influenced the overall pattern of results. Fifth, AUD subjects were required to be abstinent for at least 24-hours prior to the lab assessment and it is possible that at least some individuals were in a state of protracted withdrawal, which may have increased anxious responding. Therefore, future studies are needed to confirm and extend the present findings.

Results indicate that individuals with AUD+Trauma display increased startle reactivity to U-threat, but not P-threat, compared with individuals with AUD-Trauma and controls. Within individuals with AUD, those with a history of interpersonal trauma exposure may be a neurobiologically unique subtype characterized by exaggerated U-threat reactivity and high levels of anticipatory anxiety. Treatments that target the biological, affective and/or cognitive processes engaged by threat uncertainty may prove particularly effective for this notoriously difficult-to-treat subgroup.

Role of Funding Source

This research was supported by the National Institute of Alcohol Abuse and Alcoholism of the National Institutes of Health under award numbers P50AA022538 and K23AA025111. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

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Highlights

- There is limited understanding of the neurobiology of AUD with comorbid trauma
- Heightened reactivity to uncertain threat may characterize this subgroup of AUD
- This was tested by comparing controls and those with AUD with and without trauma
- Individuals with AUD+Trauma had exaggerated reactivity to uncertain threat
- Reactivity to uncertain threat is a promising clinical target for this group

Figure 1. Mean startle magnitude during each condition of the threat task by diagnostic group. P-threat = predictable threat; U-threat = unpredictable threat. Means are adjusted for model covariates. Bars reflect standard error.

Table 1.

Participant Demographics and Clinical Characteristics

	Controls (n=28)	AUD-Trauma (n=26)	AUD+Trauma (n=23)	Comparison
Demographics				
Age	24.1 (2.8)	24.4 (3.0)	24.2 (3.3)	$p = .93$
Sex (% Male)	53.6%	50.0%	47.8%	$p = .92$
Education (Years)	15.9 (1.4)	16.2 (2.2)	15.6 (1.4)	$p = .41$
Ethnicity (% Hispanic)	17.9%	23.1%	30.4%	$p = .57$
Race				
White	46.4%	50.0%	52.2%	$p = .45$
Black	14.3%	7.7%	13.0%	$p = .60$
Asian	17.9%	19.2%	8.7%	$p = .59$
American Indian or Pacific Islander	0.0%	0.0%	8.7%	$p = .05$
Biracial or Other	21.4%	23.1%	17.4%	$p = .78$
Other Current Diagnoses				
Major Depressive Disorder	7.1%	3.8%	17.4 %	$p = .23$
Generalized Anxiety Disorder	7.1%	7.7%	13.0 %	$p = .73$
Panic Disorder	0.0%	0.0%	4.3%	$p = .31$
Social Anxiety Disorder	0.0%	7.7%	0.0%	$p = .20$
Specific Phobia	3.6%	0.0%	0.0%	$p = .51$
Posttraumatic Stress Disorder	0.0%	0.0%	13.0%	$p = .07$
Substance Use				
Positive Fam History of AUD	0.0% _a	7.7 % _a	47.8% _b	$p = .01$
No. Drinks per Week in Past Month	2.6 (2.6) _a	10.1 (8.3) _b	9.4 (7.1) _b	$p = .03$
No. Binges in Past Month	1.7 (2.2)	5.6 (3.2)	5.3 (4.0)	$p = .06$
Used Cannabis in Past Month (Yes/No)	3.8% _a	19.2% _{a,b}	21.7% _b	$p = .09$
No. Times Used Cannabis in Past Month	<0.1 (0.2)	0.3 (0.7)	0.4 (0.9)	$p = .09$
Used *Other Illicit Drugs in Past Month (Yes/No)	0.0%	7.7%	4.3%	$p = .26$
No. Times Used Other Illicit Drugs in Past Month	0.0 (0.0)	0.3 (1.0)	<0.1 (0.2)	$p = .25$
Study Variables				
IDAS Depression	32.7 (8.6) _a	34.5 (11.4) _a	41.6 (11.7) _b	$p = .01$
IDAS Anxiety	7.1 (0.9) _a	7.7 (1.8) _a	9.0 (2.5) _b	$p < .01$
DMQ-R Social Motives	2.7 (1.2) _a	3.9 (0.8) _b	3.8 (0.8) _b	$p < .01$
DMQ-R Coping with Anxiety Motives	1.6 (0.7) _a	2.1 (0.8) _b	2.2 (0.8) _b	$p < .01$
DMQ-R Coping with Depression Motives	1.1 (0.2) _a	1.4 (0.6) _b	1.5 (0.6) _b	$p = .04$
DMQ-R Enhancement Motives	2.1 (0.9) _a	3.2 (0.9) _b	2.5 (0.9) _c	$p < .01$
DMQ-R Conformity Motives	1.1 (0.3) _a	1.6 (0.8) _b	1.6 (0.8) _b	$p = .02$

Note. Means or percentages with different subscripts (i.e., a, b, c) across rows were significantly different in pairwise comparisons ($p < .05$, chi-square test for categorical variables and Tukey's honestly significant difference test for continuous variables). IDAS = Inventory of Depression and Anxiety Symptoms; DMQ-R Drinking Motives Questionnaire-Revised.

* Other illicit drugs refers to any illicit drug other than cannabis (e.g., cocaine, heroin, nonmedical prescription medications).

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Table 2.

Omnibus Repeated Measures Analysis of Variance Testing the Effect of Group on Startle Magnitude

Variable	df	F value	p value	η^2
Sex	1, 71	0.12	0.73	<.01
Anxiety Symptoms	1, 71	0.03	0.87	<.01
Depression Symptoms	1, 71	0.56	0.46	<.01
Group	2, 71	1.45	0.24	0.04
Task Condition *	2, 142	3.36	0.03	0.06
Task Condition $\times$ Sex	2, 142	0.03	0.95	<.01
Task Condition $\times$ Anxiety Symptoms	2, 142	0.15	0.82	<.01
Task Condition $\times$ Depression Symptoms	2, 142	0.07	0.89	<.01
Task Condition $\times$ Group *	4, 142	3.17	0.03	0.08

Note.

* $p < .05$. Anxiety and depressive symptoms were measured using the Inventory for Depression and Anxiety Symptoms.