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Impact of Anxiety Symptoms and Problematic Alcohol Use on Error-related Brain Activity

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Abstract

Anxiety disorders are associated with enhanced defensive reactivity to errors, measured via the error-related negativity (ERN). There is some evidence to suggest that problematic alcohol use is also associated with an enhanced ERN; although prior studies have been almost exclusively in men and have yet to examine the potential interactive effects of anxiety and alcohol abuse symptoms. The aim of the current study was to address the gaps in this literature by examining the unique and interactive effects of anxiety symptoms and problematic alcohol use on the ERN in a sample of 79 heterogeneous internalizing disorder patients. All participants completed a flanker task designed to robustly elicit the ERN and questionnaires assessing current internalizing symptoms and problematic alcohol use. As expected, results revealed that greater anxiety symptoms, but not depressive symptoms, were associated with a more enhanced ERN. There was no main effect of problematic alcohol use but there was a significant anxiety by problematic alcohol use interaction. At high anxiety symptoms, greater problematic alcohol use was associated with a more enhanced ERN; at low anxiety symptoms, alcohol use was unrelated to the ERN. There was no depression by alcohol abuse interaction. The findings suggest that within anxious individuals, heightened reactivity to errors/threat may be related to risk for alcohol abuse. The findings also converge with a broader literature suggesting that heightened reactivity to threat may be a shared vulnerability factor for anxiety and alcohol abuse and a novel prevention and intervention target for anxiety-alcohol abuse comorbidity.

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Keywords

alcohol abuse; anxiety; error-related negativity; threat sensitivity; psychophysiology

1. Introduction

Anxiety disorders and alcohol use disorder (AUD) frequently co-occur. According to several, large-scale epidemiological studies, individuals with anxiety disorders are 2-4 times more likely to have a co-occurring AUD than the general population, and close to 25% of AUD patients seeking treatment have an anxiety disorder (Grant et al., 2004; Kessler et al., 1997; Kushner, Sher & Beitman, 1990). While each disorder in isolation is associated with serious adverse consequences (Stahre, Roeber, Kanny, Brewer, & Zhang, 2014; Stein et al., 2005), individuals with co-occurring anxiety and AUD evidence a markedly worse prognosis including increased rates of impairment, high rates of service utilization, and poor treatment outcomes (Kessler et al., 1997; Kushner et al., 2005). Despite the known deleterious effects of anxiety and AUD comorbidity, relatively little is known about the mechanisms underlying the relation between these disorders. In order to develop more effective prevention and intervention efforts, there is an urgent need to increase mechanistic understanding of anxiety-AUD comorbidity.

Converging lines of research indicate that anxiety disorders are characterized by an increased sensitivity to threat. Studies have shown that relative to healthy controls, individuals with anxiety disorders display an attentional bias towards threatening information, inflated estimates of threat probability and harm, and increased defensive reactivity to aversive stimuli (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Etkin & Wager, 2007; Foa, Franklin, Perry, & Herbert, 1996; Shankman et al., 2013). Several studies have also shown that increased sensitivity to threat precedes disorder onset (Meyer et al., 2015; Woud et al., 2014) and is evident in healthy individuals at-risk for anxiety disorders (Kujawa et al., 2015; Nelson et al., 2013; Nelson, Perlman, Hajcak, Klein, & Kotov, 2015). These findings together demonstrate that threat sensitivity is a key construct related to anxiety psychopathology.

One way individual differences in threat sensitivity are measured in the laboratory is via the error-related negativity (ERN) - a fronto-centrally maximal event-related potential (ERP) component that appears as a negative-going deflection in the waveform between 0 and 100ms following the commission of an error (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Errors are inherently aversive events as they signal the potential for harm and require corrective action (Hajcak & Foti, 2008; Hajcak, Moser, Yeung, & Simons, 2005). Studies have shown that the ERN is generated by the anterior cingulate cortex (ACC), a brain region implicated in several affective and motivational processes including threat detection, conflict monitoring, pain perception, and cognitive control (Debener et al., 2005; Reinhart & Woodman, 2014; Shackman et al., 2011). Several recent theories regarding the ACC suggest a fundamental role in integrating information about threats and punishment to guide goal-directed behavior (Holroyd & McClure, 2015; Shackman et al., 2011). From this perspective, the ERN reflects not only the

detection of errors but also the signaling of the salience of errors in-order to guide behavior across contexts (Olvet & Hajcak, 2008; Weinberg et al., 2016). As would be expected, numerous studies have found that individuals with current anxiety disorders, and those with high trait anxiety, display an enhanced ERN compared with healthy controls (Hajcak, McDonald, & Simons, 2003; Weinberg, Olvet, & Hajcak, 2010; Kujawa et al., 2016; Meyer, Hajcak, Glenn, Kujawa, & Klein, 2016a). An enhanced ERN is also thought to distinguish anxiety from depression. Indeed, the majority of studies investigating the ERN and depression have found either no difference (Schrijvers et al., 2009) or a blunted ERN (Ladouceur et al., 2012; Ruchsow et al., 2004) when comparing adults with depression and controls.

There have also been a few studies suggesting that problematic alcohol use is associated with an enhanced ERN. For instance, Padilla et al. (2011) reported that males with remitted AUD, who were currently abstinent, exhibited larger ERNs compared with controls. A previous study by our lab found that veterans (primarily male) with a diagnosis of post-traumatic stress disorder (PTSD) and current AUD had larger ERNs relative to veterans with PTSD without AUD (Gorka, MacNamara et al., 2016). In addition, Schellekens et al. (2010) investigated the ERN in three groups of male volunteers: healthy controls, abstinent individuals with AUD-only, and abstinent individuals with AUD and a comorbid anxiety disorder (i.e., panic disorder [PD], social anxiety disorder [SAD], or generalized anxiety disorder [GAD]). Findings indicated that those with AUD-only had a larger ERN compared with healthy controls. Moreover, individuals with AUD plus an anxiety disorder displayed an even larger ERN relative to both the AUD-only and control participants. Together, these studies indicate that individuals with current and remitted AUD display an enhanced ERN. They also suggest that anxiety and alcohol abuse may interact such that those with AUD and an anxiety disorder are particularly sensitive to threat/errors.

The studies reviewed above provide important initial evidence to suggest that heightened sensitivity to threat could reflect a shared vulnerability factor that drives AUD and anxiety comorbidity, and perhaps contributes to patterns of problematic alcohol use in anxious populations. However, only one prior study has examined the ERN in current drinkers, and that was in a sample of combat-exposed veterans, which raises concerns about the generalizability of findings to other samples (Gorka, MacNamara et al., 2016). There has also been only one study demonstrating an anxiety and AUD interaction (Schellekens et al., 2010) and in that study, it is unclear whether an enhanced ERN in the comorbid group was due to the presence of an anxiety disorder or reflects an interaction of anxiety and alcohol abuse symptoms as there was no anxiety only group for comparison. Related, all of the prior studies reviewed above have compared DSM-defined groups and it is unknown whether the same pattern of results is observed across anxiety and alcohol abuse symptom dimensions or is specific to discrete diagnoses. The question of generalization across symptom dimensions is a key topic within the field as there has been widespread recognition that categorically defined diagnoses fail to capture the full range of psychopathology and may obscure research findings (Kozak & Cuthbert, 2016; Insel et al., 2010).

The study was designed to address these gaps by examining the impact of anxiety symptoms and current problematic alcohol use on the ERN in a heterogeneous internalizing disorder

patient sample. Adult volunteers completed a flanker task designed to robustly elicit the ERN and well-validated measures of current internalizing symptoms and levels of problematic alcohol use. We hypothesized that greater anxiety symptoms, but not depressive symptoms, would be associated with an enhanced ERN. We also hypothesized that greater problematic alcohol use would be associated with an enhanced ERN and that there would be an anxiety by alcohol use interaction such that at high anxiety symptoms, compared with low anxiety symptoms, greater problematic alcohol use would be associated with an enhanced ERN.

2. Materials and Methods

2.1 Participants

The sample was taken from a larger study focused on identifying biomarkers of treatment response across internalizing psychopathologies. The aims of the larger study therefore dictated the enrollment of a patient population with a full range of depression and anxiety who consented to treatment with pharmacotherapy (selective serotonin reuptake inhibitors/SSRIs) or cognitive behavioral therapy (CBT). Participants were required to be between 18 and 65 and have a current full-threshold or sub-threshold DSM-5 depressive or anxiety disorder, report a total score of ≥ 23 on the Depression, Anxiety, and Stress Scale (DASS-21; Lovibond & Lovibond, 1995a), and a Global Assessment of Functioning (GAF) score of ≥ 60 . Axis I diagnoses were assessed via the Structured Clinical Interview for DSM-5 Disorders (SCID-5; American Psychiatric Association, 2013) by trained research staff. Exclusionary criteria included an inability to provide consent and read and write in English; major active medical or neurological problem; lifetime history of mania or psychosis; current obsessive-compulsive disorder; intellectual disability, or pervasive developmental disorder; any contraindication to receiving SSRIs; being already engaged in psychiatric treatment; psychoactive medication use within the past four months; history of traumatic brain injury; and being pregnant. This study was approved by the UIC Institutional Review Board, and informed consent was obtained from all participants.

A total of 94 patients were enrolled in the study; however, eight were excluded due to missing or poor quality ERN data (i.e., less than six errors during the flanker task [Olvet & Hajcak, 2009] or excessive artifact) and seven were excluded due to missing self-report data. An additional two participants were found to be significant outliers on behavioral task performance (i.e., reaction time and task accuracy) and were also excluded. The final sample included 79 individuals. All data used in the current study were collected prior to treatment. All participants provided a negative breath test for alcohol and a negative urine screen for illicit drugs on the day of the evaluation. At the time of assessment no participant was taking psychoactive medication including SSRIs.

2.2 Internalizing Symptoms

Participants completed the DASS-21, which is a 21-item self-report questionnaire that includes three scales: depressive symptoms, anxiety symptoms, and non-specific stress. The depression scale captures symptoms of dysphoria, hopelessness, self-deprecation and anhedonia; the anxiety scale measures automatic arousal, physical anxiety symptoms,

situational anxiety, and subjective anxious affect; the stress scale assesses irritability, agitation, affective liability and nervous arousal (Lovibond & Lovibond, 1995b). Respondents are asked to indicate the extent to which each item applied to them within the past week using a 0 (did not apply to me at all) to 3 (applied most of the time) Likert scale. The DASS-21 has been shown to have excellent convergent validity and reliability in patient populations (Antony et al., 1998). The DASS-21 also distinguishes between depressive and anxiety symptoms better than several other commonly used measures such as the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI; see Lovibond & Lovibond, 1995b). The reliability of each of the scales was excellent in the current study ($\alpha = .82 - .93$). All DASS-21 subscales were normally distributed (skew < 1.0).

2.3 Problematic Alcohol Use

Participants completed the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1989) – a widely used self-report measure of problematic alcohol use developed by the World Health Organization (WHO). The AUDIT includes 10-items assessing alcohol consumption frequency (including binges), alcohol use problems, and dependence symptoms, and has been shown to be a sensitive measure of problematic drinking in diverse populations (Saunders et al., 1993a,b). In the current study, reliability of the measure was good ($\alpha=.74$). Total scores were normally distributed (skew < 1.0).

2.4 Error Task

Participants completed a modified version of the original flanker task (Eriksen & Eriksen, 1974) to elicit the ERN. For each trial, participants viewed five horizontally aligned arrowheads. For half of the trials, arrows were compatible (“>>>>>” or “<<<<<”) and for the other half, the arrows were incompatible (“>><>>” or “<<><<”). Participants were instructed to respond as quickly and as accurately as possible to indicate the direction of the center arrow (left or right) by pressing the appropriate mouse button. Stimuli were presented for 200ms, followed by a fixation cross. Participants were given up to 1800ms after the offset of the arrows to respond, followed by an intertrial interval (1000-2000ms) during which participants viewed a fixation cross.

The task consisted of 11 blocks of 30 trials (330 total trials), interspersed with self-timed breaks. To encourage fast and accurate responding, participants received performance-based feedback at the end of each block. If accuracy was 75%, the message “Please try to be more accurate” was presented; if accuracy was >90%, the message, “Please try to respond faster” was displayed; in all other cases, participants saw the message, “You’re doing a great job”.

2.5 Data Recording

Continuous EEG was recorded during the task using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Thirty-four standard electrode sites were used and one electrode was placed on each mastoid. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio. The data were digitized at 24-bit resolution with a Least Significant Bit (LSB) value of 31.25nV and a sampling rate of 1024Hz, using a low-pass fifth order sinc filter with a -3dB cutoff point at 204.8Hz.

Off-line analyses were performed using Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). Data were re-referenced to the average of the two mastoids and high-pass (0.1Hz) and low-pass (30Hz) filtered. Standard eyeblink and ocular corrections were performed (Miller, Gratton & Yee, 1988). Data were segmented beginning 500ms before each response onset and continuing for 1500ms. Standard artifact rejection procedures were used (see Gorka, MacNamara et al., 2016). Baseline correction for each trial was performed using the 500 to 300ms prior to response onset. Across subjects, ERN amplitude peaked at $42.3\text{ms} \pm 28.5$ after responding. Therefore, in-order to capture this peak, the ERN and CRN (i.e., correct-response negatively) were scored as the average activity on error and correct trials, respectively, from 20 to 60ms after response at electrode FCz, where amplitude was maximal (see Figure 1).

In addition to the individual ERN and CRN variables, we also calculated the $\overline{\text{ERN}}$ by subtracting the correct from error waveform and averaging activity 20-60ms post-response at FCz. The $\overline{\text{ERN}}$ is used to isolate activity unique to error processing (Simons, 2010), and has been extensively used in prior studies investigating the ERN (Jackson, Nelson, Meyer, & Hajcak, 2017; Kujawa et al., 2016). The $\overline{\text{ERN}}$ was therefore considered the primary dependent variable; however, secondary models were also run using the individual ERN and CRN variables to provide additional information regarding variations in activity to errors and correct trials.

As for task performance, accuracy data were computed as the percentage of correct trials. Reaction time was computed as the amount of time it took participants to respond from stimulus onset, separately for error and correct trials.

2.6 Data Analysis Plan

To test our hypotheses, we conducted hierarchical linear regression analyses with the $\overline{\text{ERN}}$ as the dependent variable. All continuous variables were mean centered prior to analysis. Given that the sample included both males and females, biological sex was included as a covariate and tested for interactions with all study variables. Biological sex was entered in Step 1. The main effects of DASS-anxiety and total AUDIT scores were entered in Step 2, and all two-way interactions were entered in Step 3. The DASS-anxiety by AUDIT by sex three-way interaction was entered in Step 4. A significant interaction was followed-up using a standard simple slopes approach (Aiken, West, & Reno, 1991). Specifically, the moderator was re-centered at 1 *SD* above the mean for “high symptoms” and 1 *SD* below the mean for “low symptoms.” Two new interaction terms were created and *post-hoc* additional follow-up linear regression models were run at high and low symptoms.

In order to test the specificity of the present findings to anxiety symptoms, we conducted additional hierarchical linear regression models with DASS-depression scores. The model and procedures were identical except DASS-anxiety was replaced with DASS-depression. We additionally ran all models with the ERN and CRN as separate dependent variables to better understand whether variations in the ERN, CRN, or both were contributing to significant results.

3. Results

3.1 Descriptives

Demographic and descriptive statistics of the sample are presented in Table 1. Participants were primarily female, which differs from prior studies investigating the ERN and alcohol use (e.g., Schellekens et al., 2010). All participants had at least one current internalizing Axis I diagnosis, and 92% had a current anxiety disorder. Approximately 43% of participants reported at least one alcohol binge within the past 30-days (5+ drinks for men, 4+ drinks for women, in one sitting) and 25.3% of the sample had total AUDIT scores at or above the cut-off for problematic drinking (i.e., 8; Babor et al., 1989), which is similar to, or slightly above, expected rates of problematic drinking in an internalizing disorder patient sample (Wolitzky-Taylor et al., 2015). Participants did not endorse high levels of other forms of substance use.

With regard to behavioral performance during the flanker task, participants committed an average of 56.2 ± 29.8 errors on incongruent trials and 31.0 ± 41.9 errors on congruent trials. This corresponds to 83.0% and 90.6% accuracy for incongruent and congruent trials, respectively. Reaction times were faster for errors than for correct responses, $t(78) = 17.53$, $p < 0.01$. Task accuracy and RTs were not correlated with the study variables (see Table 2).

3.2 Impact of Internalizing Symptoms and Problematic Alcohol Use

Results of all hierarchical linear regression models are presented in Table 3. With regard to the ERN, there was a main effect of DASS-anxiety such that greater anxiety symptoms were associated with a larger (more negative) ERN. There was no main effect of the AUDIT; however, there was a significant DASS-anxiety by AUDIT interaction. Follow-up analyses revealed that at high levels of anxiety symptoms, greater AUDIT scores were associated with a larger ERN, $\beta = -.47$, $t = -2.58$, $p < 0.05$ (see Figure 2). However, at low levels of anxiety symptoms, AUDIT scores were not related to the ERN, though there was a trend-level effect in the opposite direction - greater AUDIT scores associated with a more blunted ERN, $\beta = .27$, $t = 1.71$, $p = 0.09$. There were no two- or three-way interactions involving sex. There were also no main effects or interactions for the ERN depression model.

Follow-up analyses analyzing the ERN and CRN separately revealed that the main effect of DASS-anxiety was observed for the ERN but not the CRN (see Table 3). The DASS-anxiety by AUDIT interaction was trending towards significance for the ERN and was not significant for the CRN suggesting that the interaction was driven by the differentiation of activity during errors vs. correct trials. The separate ERN and CRN models did not indicate any novel findings beyond what was found for the ERN.

4. Discussion

Prior evidence indicates that both anxiety disorders and AUD are associated with increased threat sensitivity, measured via the ERN. The aim of the current study was to extend this work by examining the unique and interactive effects of anxiety and alcohol abuse symptoms, across a continuum, in an internalizing disorder patient sample. Results revealed

that greater levels of anxiety symptoms, but not depressive symptoms, were associated with a more enhanced ERN. There was no main effect of problematic alcohol use but there was an anxiety by alcohol use interaction. In the context of high anxiety symptoms, greater levels of problematic drinking were associated with a more enhanced ERN. However, in the context of low anxiety symptoms, there was no relation between problematic alcohol use and the ERN. This pattern of results was notably specific to anxiety symptoms as there was no depression by problematic alcohol use interaction. These findings together suggest that anxiety and alcohol abuse interact and that increased threat sensitivity may characterize anxious individuals with a propensity towards alcohol abuse.

It is important to highlight that the present findings indicated a main effect of anxiety symptoms on the ERN, which follow-up analyses confirmed was driven by the association between anxiety and the ERN, not the CRN. The majority of prior research investigating the ERN and anxiety has been within clearly defined DSM groups (e.g., GAD, SAD) with limited comorbidities (Weinberg et al., 2010; Ruchow et al., 2005). There have been a few studies looking at anxiety symptoms, rather than DSM disorders, that have found significant relationships with the ERN, but none with a highly comorbid, representative patient population (Weinberg et al., 2016). Thus, the present findings add to a growing literature supporting an association between anxiety and the ERN across diagnostic groups, and clinical and non-clinical samples. The results also indicate that prior ERN findings are generalizable to a highly comorbid, representative, treatment-seeking patient population. Given that the ERN has been shown to be moderately heritable (Anokhin et al., 2008), stable over time (Weinberg & Hajcak, 2011), and resistant to treatment effects (Kujawa et al., 2016), it may reflect an endophenotype for anxiety psychopathology (Olvet & Hajcak, 2008) and distinguish anxiety from depression.

Based on the few existing studies examining the ERN in individuals with a history of AUD, we expected that current levels of problematic alcohol use would also be associated with a larger ERN (e.g., Schellekens et al., 2010). This hypothesis was not supported but results did show that greater problematic alcohol use was associated with a larger ERN in the context of high anxiety symptoms, and this finding was driven by the differentiation of activity during errors vs. correct trials rather than the ERN or CRN individually. This interaction is notably consistent with the results of Schellekens et al. (2010), and our prior PTSD study (Gorka, MacNamara et al., 2016), in which anxiety and AUD comorbidity was associated with an exaggerated ERN. This finding also extends prior work by suggesting that an enhanced ERN within anxiety-AUD patients is related to an interaction between symptoms. An emerging theory is that within anxious individuals, those that are especially sensitive to threat may be motivated to consume alcohol to alleviate their distress, which is negatively reinforced promoting continued, excessive alcohol use. In support of this theory, several studies have demonstrated that acute alcohol intoxication dampens the ERN and alleviates reactivity to errors (Easdon, Izenberg, Armilio, Yu, & Alain, 2005; Ridderinkhof et al., 2002). Moreover, one study has specifically shown that alcohol dampens the ERN by reducing negative affect (Bartholow, Henry, Lust, Sauls, & Wood, 2012). Thus, within anxious individuals, an exaggerated ERN may be an objective vulnerability factor for the onset and/or maintenance of problematic alcohol use.

The ERN is considered a measure of defensive reactivity to internal threat (i.e., errors) (Weinberg et al., 2015). Interestingly, the present findings converge with a parallel literature focused on defensive reactivity to external threat (i.e., threat-of-electric shock). In a series of papers, our laboratory has shown that anxiety disorders, and anxiety symptoms, are associated with an exaggerated reactivity to uncertain threat-of-shock, measured via startle eyeblink potentiation (Gorka, Lieberman, Shankman, & Phan, 2017; Lieberman, Gorka, Shankman, & Phan, 2016; Shankman et al., 2013). We have also shown in two separate samples that greater levels of problematic alcohol use are associated with an exaggerated startle response to uncertain threat (Gorka, Lieberman, Phan, & Shankman, 2016a), and that individuals with comorbid PD and alcohol dependence display greater startle to uncertain threat than individuals with PD-only (Gorka, Nelson, & Shankman, 2013). We have posited that increased sensitivity to threat may be a shared vulnerability factor for anxiety and problematic drinking as we have shown that startle potentiation to uncertain threat is related to familial risk for both classes of disorders (Nelson et al., 2013; Gorka et al., 2016b). The present findings help extend this theory to include sensitivity to internal *and* external threats. Notably, like the ERN studies, startle to uncertain threat is dampened during acute alcohol intoxication (Moberg & Curtin, 2009; Bradford, Shapiro, & Curtin, 2013), further highlighting that individuals who are particularly sensitive to threat may turn to alcohol as a means of avoidance-based coping and that exaggerated threat sensitivity may be one phenotype for anxiety-alcohol comorbidity.

At low levels of anxiety symptoms we did not find that problematic alcohol use is related to the ERN. In fact, we found a trend for the opposite such that greater problematic alcohol use was associated with a more blunted ERN. It is worth noting that there have been several studies and a recent systematic review suggesting that illicit substance use, and difficulties with impulse control, are associated with a blunted ERN and feedback error-related negativity (fERN) (see Luijten et al., 2014 for a review; Baker et al., 2011; Hall, Bernat, & Patrick, 2007; Luijten, van Meel, & Franken, 2011). For instance, findings indicate that cocaine and opiate-dependent individuals (Marhe, van de Wetering, & Franken, 2013; Forman et al., 2004), and adolescent offspring of parents with illicit substance use disorders (Euser, Evans, Greaves, Lord, Huizink, & Franken, 2013), display a reduced ERN and blunted ACC activity across a variety of cognitive tasks (e.g., Kaufman et al., 2003; Hester & Garavan, 2004). It has been suggested that a blunted ERN may be characteristic of an ‘externalizing’ phenotype susceptible to substance abuse (Hall et al., 2007; Santesso & Segalowitz, 2009); however, the existing alcohol literature has generally not corroborated this theory though one study by Smith and colleagues did find evidence for a blunted ERN in female heavy drinkers who also demonstrated impaired inhibitory control (Smith & Mattick, 2013). Based on the current findings, it is possible that there is a subgroup of problematic drinkers who display a blunted ERN and/or decreased threat sensitivity, particularly those with low levels of anxiety. However, there is also a separate subgroup of problematic drinkers who are hypersensitive to threat. Thus, a blunted response to threat and an exaggerated response to threat may reflect separate ‘externalizing’ and ‘internalizing’ phenotypes for AUD. Given that the current study included a sample of individuals with relatively high mean levels of anxiety symptoms, it is difficult to parse these two possibilities. Future studies should therefore directly test the possibility that individual

differences in threat sensitivity could be one factor that captures risk for both internalizing and externalizing pathways to problem alcohol use.

The current study addressed several important gaps in the existing literature; however, there are limitations. Most notably, the sample was comprised of internalizing disorder patients presenting to treatment. Although this is a population for whom anxiety-alcohol comorbidity is particularly salient, it is unknown whether the present pattern of results generalizes to less severely anxious samples. Additional studies that include a wide range of anxiety and alcohol abuse symptoms are needed to ensure that these findings generalize across populations. Relatedly, given the nature of the sample, we were unable to examine differences in the ERN across DSM-defined groups *and* symptom dimensions. This was never the design of the current study but it may be useful for additional research to directly compare patterns of results across categories and dimensions.

The present findings indicate that within a heterogeneous clinical sample, greater anxiety symptoms are associated with greater threat sensitivity measured via the ERN. Finding also indicate that in the context of high anxiety symptoms, but not low anxiety symptoms, greater levels of problematic alcohol use are associated with an enhanced ERN. This suggests that within anxious individuals, heightened threat sensitivity may promote drinking behaviors as a means of dampening anxiety and distress. The findings also converge with a broader literature suggesting that heightened reactivity to threat may be a shared vulnerability factor for anxiety and AUD and perhaps, a novel prevention and intervention target for anxiety-AUD comorbidity.

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Highlights

- In patients, greater anxiety symptoms relate to greater defensive reactivity
- Problem drinking is also related to defensive reactivity at high anxiety symptoms
- Defensive reactivity may underlie anxiety and alcohol abuse comorbidity
- Heightened defensive reactivity may contribute to drinking behaviors

Figure 1.

On the left, topographic map of neural activity (error minus correct) across the entire sample. On the right, response-locked ERP waveform for correct and error trials, as well as the difference waves (error-related negativity; ERN) across the entire sample.

Figure 2.

A) Graph illustrating the effect of problematic alcohol use on the ERN at high and low levels of anxiety symptoms (± 1 standard deviation from the mean). B) Scatter plot depicting the effect of problematic alcohol use on the ERN at high and low anxiety symptoms (median split). ERN = difference between error-related negativity and correct-related negativity; DASS = Depression, Anxiety, and Stress Scale; AUDIT = Alcohol Use Disorders Identification Test.

Table 1

Demographics and clinical characteristics of the sample.

	Mean (SD; Range) or % (<i>n</i> = 79)
<u>Demographics</u>	
Age (years)	27.6 (9.6; 18 - 58)
Sex (female)	73.4%
Education (years)	16.2 (3.2; 12-26)
Race/Ethnicity	
Caucasian	50.6%
African American	10.1%
Hispanic	19.0%
Asian	12.7%
'Other'	7.6%
<u>Diagnoses</u>	
Current Major Depressive Disorder	55.7%
Current Dysthymia	3.8%
Current Generalized Anxiety Disorder	67.1%
Current Post-Traumatic Stress Disorder	12.7%
Current Social Anxiety Disorder	63.3%
Current Panic Disorder	26.6%
Current Specific Phobia	11.4%
Any Current Anxiety Disorder	92.4%
<u>Flanker Task Variables</u>	
CRN	9.43 (6.4; -4.8 – 22.9)
ERN	1.90 (8.3; -16.3 – 16.3)
ERN	-7.53 (5.9; -19.3 – 9.7)
Congruent Error RT (ms)	289.47 (64.8; 201.0 – 578.3)
Congruent Correct RT (ms)	356.70 (65.3; 276.3 – 740.2)
Incongruent Error RT (ms)	304.25 (59.2; 239.0 – 633.0)
Incongruent Correct RT (ms)	415.41 (63.6; 296.1 – 717.3)
<u>Self-Report Variables</u>	
Daily Cigarette Smoker	3.8%
Used Cannabis in Past Six Months	8.9%
Used Illicit Drugs* in Past Six Months	2.5%
Binge Drank in Past Month	43.0%
AUDIT Total Score	4.8 (3.3; 0 - 16)
DASS-Anxiety	8.5 (4.4; 1 -18)
DASS-Depression	11.2 (5.6; 0 - 30)
DASS-Stress	13.4 (3.8; 5 - 22)

Note. ERN = error-related negativity; CRN = correct response negativity; ERN = ERN minus CRN; RT = reaction time. Illicit drugs were coded as any illegal substance other than cannabis.

Table 2

Pearson's correlations for all study variables.

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. DASS-Anxiety	1.0									
2. DASS-Dep	-.21	1.0								
3. DASS-Stress	.30*	-.07	1.0							
4. AUDIT	-.07	-.13	-.01	1.0						
5. ERN	-.26*	.03	-.20	.02	1.0					
6. CRN	-.03	.03	-.11	.04	.71*	1.0				
7. ERN	-.34*	<.01	-.16	-.01	.64*	-.09	1.0			
8. Task Accuracy	-.24	.10	-.21	.05	<.01	.06	-.08	1.0		
9. Correct RT	-.19	.15	.12	-.20	-.15	-.23	.15	.41*	1.0	
10. Error RT	-.03	.09	-.01	-.21	-.06	-.24	.21	.27*	.64*	1.0

Note. ERN = error-related negativity standardized residual; CRN = correct response negativity standardized residual; ERN = ERN minus CRN; RT = reaction time; Dep = Depression. Task accuracy and reaction times are collapsed across congruent and incongruent trials.

Table 3

Hierarchical linear regression analyses examining the impact of internalizing and alcohol abuse symptoms on error-related negativity, correct-related negativity, and the difference score of the two measures.

	ERN					CRN					ERN				
	β	t	p	R^2	β	t	p	R^2	β	t	p	R^2	β	t	p
Anxiety Model															
Step 1				<.01				<.01				<.01			<.01
Sex	-.02	-.21	.84		.02	.16	.87		-.05	-.47	.64		-.05	-.47	.64
Step 2				.07				<.01							.11
DASS-Anxiety	-.27*	-2.41	.02		-.05	-.43	.67		-.33*	-2.95	<.01		-.33*	-2.95	<.01
AUDIT Total	-.01	-.10	.92		.04	.29	.77		-.05	-.48	.63		-.05	-.48	.63
Step 3				.11				.02							.18
DASS-Anxiety $\times$ AUDIT	-.24	-1.48	.14		.09	.57	.51		-.29*	-2.39	.02		-.29*	-2.39	.02
Sex $\times$ AUDIT	-.08	-.40	.69		-.11	-.53	.60		<.01	.04	.97		<.01	.04	.97
Sex $\times$ DASS-Anxiety	-.22	-1.06	.29		-.17	-.76	.45		-.13	-.65	.52		-.13	-.65	.52
Step 4				.12				.02							.21
DASS-Anxiety $\times$ AUDIT $\times$ Sex	.19	1.10	.27		.04	.20	.85		.23	1.39	.18		.23	1.39	.18
Depression Model															
Step 1				<.01				<.01				<.01			<.01
Sex	-.03	-.25	.81		.02	.14	.89		-.06	-.49	.62		-.06	-.49	.62
Step 2				<.01				<.01				<.01			<.01
DASS-Depression	.03	.26	.79		.03	.23	.82		.02	.13	.90		.02	.13	.90
AUDIT Total	.02	.16	.88		.05	.39	.70		-.02	-.20	.85		-.02	-.20	.85
Step 3				.07				.03							.05
DASS-Depression $\times$ AUDIT	.20	1.47	.15		.13	.96	.34		.14	.99	.33		.14	.99	.33
Sex $\times$ AUDIT	-.09	-.51	.61		-.01	-.03	.98		-.12	-.67	.51		-.12	-.67	.51
Sex $\times$ DASS-Depression	-.27	-1.03	.31		-.14	-.52	.60		-.23	-.86	.39		-.23	-.86	.39
Step 4				.08				.03							.05
DASS-Depression $\times$ AUDIT $\times$ Sex	-.19	-.87	.39		-.17	-.78	.44		-.08	-.36	.72		-.08	-.36	.72

Note.

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$^*p < .05$

DASS = Depression, Anxiety, and Stress Scale; AUDIT = Alcohol Use Disorders Identification Test.