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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.

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 et al., 1990). While each disorder in isolation is associated with serious adverse consequences (Stahre et al., 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 threating information, inflated estimates of threat probability and harm, and increased defensive reactivity to aversive stimuli (Bar-Haim et al., 2007; Etkin and Wager, 2007; Foa et al., 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 et al., 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

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a negative-going deflection in the waveform between 0 and 100 ms following the commission of an error (Falkenstein et al., 1991; Gehring et al., 1993). Errors are inherently aversive events as they signal the potential for harm and require corrective action (Hajcak and Foti, 2008; Hajcak et al., 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 and 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 and 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 and 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 et al., 2003; Weinberg et al., 2010; Kujawa et al., 2016; Meyer et al., 2016). 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 et al., 2016a). 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 et al., 2016a). 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 and 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 and 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 and 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 and 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