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Neural response to errors is associated with problematic alcohol use over time in combat-exposed returning veterans: An event-related potential study

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ABSTRACT

Background: Currently, we do not have biomarkers to help identify individuals at-risk for chronic, problematic alcohol use, especially among veteran populations, who have notoriously high rates of alcohol use. One biomarker that may predict individuals at risk for chronic, problematic alcohol use is error-related brain activity. We examined longitudinal associations between the error-related negativity (ERN), an event-related potential observed following the commission of errors, and problematic alcohol use among U.S. military veterans returning from recent conflicts in Iraq and Afghanistan.

Methods: Forty-six military veterans, aged 18–55 years, completed a well-validated flanker task known to elicit the ERN at baseline. Problematic alcohol use and other clinically relevant variables were assessed at baseline, 3-, 6-, 9-, 12-, 15-, 18-, 21-months, and 2 years.

Results: Results indicated that the ERN magnitude was associated with problematic alcohol use over time, even after controlling for relevant clinical variables. Specifically, veterans with a smaller ERN magnitude evidenced a decline in problematic alcohol use over time, while veterans with a larger ERN magnitude had no change in their problematic alcohol use across the follow-up. In addition, exploratory analyses found that treatment engagement during the study did not moderate these relationships.

Conclusions: Our findings provide preliminary evidence that ERN can be used as a predictor of problematic alcohol use over time. Therefore, neural response to errors could help to identify individuals at risk for continued problematic alcohol use for intervention efforts and suggests that error processing may be an important therapeutic target within Alcohol Use Disorder intervention efforts.

1. Introduction

Excessive alcohol use is associated with increased risk of death, adverse physical and mental health outcomes, poorer functional outcomes (e.g., less educational attainment, lost productivity), and great economic burden (CDC, 2016). In 2010 alone, excessive alcohol use cost the United States almost $250 billion (Sacks et al., 2015). Rates of excessive alcohol use are especially high among veterans; around 12–24% of veterans returning from recent conflicts in Iraq and Afghanistan endorsed problematic alcohol use following their return from combat (Hoge et al., 2004; Jacobson et al., 2008; Milliken et al., 2007). High rates of alcohol use among veterans are particularly problematic, as alcohol use among veterans often has a highly chronic course and is linked to an increased risk of suicide (LeardMann et al., 2013). However, we do not currently have biomarkers to help identify individuals at risk for chronic, problematic alcohol use, especially among veterans, many of whom may be vulnerable to chronic alcohol use and adverse outcomes. Therefore, it is critical to identify potential biomarkers that can help to identify which individuals are at greatest risk for continued, chronic problematic drinking in order to develop targeted interventions.

One biomarker that may predict individuals at risk for chronic, problematic alcohol use is error-related brain activity. Error processing is a core component of cognitive control and involves the monitoring of errors and ongoing behavioral performance in order to prevent future errors (Ridderinkhof et al., 2004). Notably, converging evidence

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indicates that individuals with Alcohol Use Disorder (AUD) display abnormal error monitoring and neural reactivity to commission errors (see Luijten et al., 2014). Preliminary data suggests that neural response during error processing can be used to predict relapse to cocaine use in treatment-seeking individuals (Marhe et al., 2013; Luo et al., 2013). Error processing involves monitoring ongoing behavior and adjusting behavior based on changing contextual information, and impaired error processing can result in maladaptive behavior, including impulsivity and failure to use past mistakes to inform present decisions (Botvinick et al., 2004). Thus, targeting error processing to enhance individuals' ability to monitor and modify their behavior based on contextual information may prevent future relapses, serving as an intervention target for AUD (see Wilcox et al., 2014). To our knowledge, only a few studies have examined whether neural activation during error processing predicts problematic alcohol use over time and these studies were in adolescents (Heitzeg et al., 2014; Whelan et al., 2014). Therefore, it is important to study neural activation during error processing in other samples to better understand if it is a biomarker that could help inform treatment decision-making and intervention efforts for AUD across development.

One measure that has reliably been used in the laboratory to measure neural activation during error processing is error-related negativity (ERN) – a fronto-centrally maximal event-related potential (ERP) component that appears as a negative deflection in the waveform between 0 and 100 ms following an error (Falkenstein et al., 1991; Gehring et al., 1993). The ERN is often examined by looking at the difference between neural activation to errors (ERN) and neural activation to correct response (correct response negativity (CRN); see Meyer et al., 2017). The ERN is thought to reflect initial and automatic error detection and is sensitive to the motivational significance of errors, as well as affective factors, in order to guide behavior across contexts (Hajcak et al., 2005; Olvet and Hajcak, 2009; Weinberg et al., 2015). Further, several studies demonstrate that the ERN is generated by the anterior cingulate cortex (ACC), a brain region involved in cognitive control, conflict monitoring, threat detection, and pain perception (Debener et al., 2005; Reinhart and Woodman, 2014; Shackman et al., 2011). Although there is a debate about the functional significance of the ERN, several have suggested that it is a trait-like index of threat sensitivity (Weinberg et al., 2015).

Despite some mixed findings (Franken et al., 2017; Smith et al., 2016; Smith et al., 2017), several studies have now shown that individuals with AUD exhibit a larger ERN magnitude. For instance, Padilla et al. (2011) found that males with remitted AUD demonstrated larger ERN magnitudes compared to controls. Moreover, recently detoxified males with AUD-only displayed a larger ERN magnitude relative to controls, and individuals with AUD and a comorbid anxiety disorder evidenced a larger ERN magnitude relative to the other two groups, suggesting that AUD and anxiety may interact to potentiate error reactivity (Schellekens et al., 2010). Recently, our lab expanded upon this study; we employed continuous measures of anxiety symptoms and alcohol-related problems and found that more severe alcohol-related problems were associated with a larger ERN magnitude, but only among males and females who have high symptoms of anxiety (Gorka and Phan, 2017). Our lab found that veterans (primarily male) with comorbid PTSD and AUD had larger ERN magnitudes compared to veterans with PTSD alone (Gorka et al., 2016), using a sample drawn from the same project as the current study and also drawn from a separate, cross-sectional project not included in the current study.[1]

Individuals with AUD may display exaggerated threat sensitivity, which could motivate their drinking behaviors. Indeed, several lines of research indicate that many individuals, particularly those with psychiatric symptoms or disorders, use alcohol to regulate negative affect and dampen defensive reactivity, leading to continued alcohol use and onset of AUD (see Baker et al., 2004; Koob and Volkow, 2010). Additionally, repeated alcohol use is known to impact neural circuits involved in affective and motivational systems, which, in turn, contribute to the need and desire to continue drinking (Koob and Le Moal, 2008). Thus, heightened threat sensitivity among problematic drinkers may play a role in not only the onset of AUD, but also the maintenance of AUD, making threat sensitivity, as measured by the ERN, an important biomarker for future study.

To our knowledge, no studies have examined the ERN as a potential biomarker to predict continued, problematic alcohol use over time. Further, only one other study (Gorka et al., 2016) has studied the association between alcohol use and the ERN among veterans, despite evidence suggesting a relationship between AUD and exaggerated error-related brain activity. As such, the goal of the current study was to examine if the ERN predicts problematic alcohol use over time among U.S. military veterans returning from recent conflicts in Iraq and Afghanistan, many of whom have AUD as well as other psychiatric disorders like PTSD. These veterans completed a well-validated flanker task, a measure of attention and error processing (see Kramer et al., 2001) that requires participants to make behavioral responses both quickly and accurately, thereby inherently facilitating errors as well as correct responses. The flanker task is known to robustly elicit the ERN (Riesel et al., 2013). The veterans also completed a two year multi-wave follow-up. We hypothesized that a larger ERN magnitude at baseline would predict more problematic alcohol use over the two-year period, even after controlling for relevant psychiatric symptoms.

2. Material and methods

2.1. Participants

Forty-six participants, aged 18–55 years, were selected from a larger sample of U.S. military veterans returning from recent conflicts in Iraq and Afghanistan and recruited at the Jesse Brown Veterans Administration (VA) Medical Center via advertisements placed in public spaces within the hospital, through clinic referrals, and through outreach to veteran communities. Exclusionary criteria for all participants included presence of a clinically significant medical or neurological condition, presence of an organic mental syndrome, mental retardation or pervasive developmental disorder, lifetime psychosis, and current substance abuse or suicidal ideation at a level that would interfere with the study protocol. Participants completed diagnostic and questionnaire-based screening and the electroencephalography (EEG) session at the first laboratory visit. Following the baseline appointment, participants completed several follow-up visits at 3-, 6-, 9-, 12-, 15-, 18-, 21-months, and 2 years. For the present study, participants were included if they completed three or more assessments to ensure adequate follow-up data for prediction. The Institutional Review Boards at the University of Illinois at Chicago and the Jesse Brown VA Medical Center approved the study and written informed consent was obtained.

2.2. Demographics and clinical measures

Demographic information including age, gender, race/ethnicity, and years of education was obtained through self-report questionnaires at baseline. Participants were assessed for current and lifetime mood and anxiety disorders using the Mini International Neuropsychiatric Interview 6.0 (M.I.N.I; Sheehan et al., 1998). All participants completed the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) at baseline, 3-, 6-, 9-, 12-, 15-, 18-, 21-months, and 2 years. The CAPS is an interview-based measure, designed to capture DSM–IV criteria for PTSD, that includes 17 PTSD symptom dimensions that are rated on frequency and intensity using a 5-point (0–4) scale. A composite PTSD severity score was computed by summing the ratings (range 0–136). Participants also completed a 7-item self-report Combat Exposure Scale

[1] There were 20 participants included in the Gorka et al., 2016 paper (N = 67) who were also included in the current study.