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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

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Conflict of Interest

The authors declare no conflicts of interest.

Contributors

All authors have participated sufficiently in the work and take responsibility for authorship and publication. NAC, SMG, KLB, and KLP made substantial contributions to the design, analysis, and writing of the manuscript. KA, CS, and AEK made substantial contributions to the data collection. KA, JEG, DMA, EP, CS, and AEK made substantial contributions to the preparation of the manuscript. All authors contributed to interpreting the results and have approved the final manuscript.

error processing may be an important therapeutic target within Alcohol Use Disorder intervention efforts.

Keywords

alcohol use; error-related negativity; veterans

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 percent 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 very chronic course and is linked to an increased risk of suicide (LeardMann et al., 2013). However, currently we do not 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 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 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. (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 using continuous measures of anxiety symptoms and alcohol-related problems and found that greater alcohol-related problems was associated with a larger ERN magnitude, but only among males and females who have high symptoms of anxiety (Gorka and Phan, 2017). Within veterans, our lab found that individuals (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 study¹.

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.

¹There were 20 participants included in the Gorka et al., 2016 paper (N=67) who were also included in the current 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 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 (CES; Keane et al., 1989) at baseline to measure

exposure to wartime stressors. CES items were rated on 5-point frequency, 5-point duration, 4-point frequency, or 4-point degree of loss scales. Total CES scores were computed by summing each weighted item (range 0–41).

2.3 Substance Use Measures

Current alcohol use was measured via the widely-used Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992), a 10-item self-report measure designed to screen for patterns of harmful and hazardous alcohol use. Participants completed the AUDIT at baseline, 3-, 6-, 9-, 12-, 15-, 18-, 21-months, and 2 years. Items were rated on a scale from 0 to 4 and a total score was computed by summing the items (range 0–40), with higher scores indicating greater levels of hazardous use. Illicit drug problems were assessed using the Drug Abuse Screening Test (DAST; Skinner, 1982), a 28-item self-report scale capturing consequences or problems related to illicit drug use at baseline, 3-, 6-, 9-, 12-, 15-, 18-, 21-months, and 2 years. Participants were asked to answer items in a binary (yes/no) format, and responses are summed to produce a total score (range 0–28). The protocol specified that if any individual was visibly intoxicated and/or reported drug or alcohol use within the past 24 hours at the laboratory session at baseline, their session would be rescheduled. If the subject felt that they were unable to abstain from substances for at least 24 hours, then their participation would be terminated. These procedures resulted in a small percentage of participants being rescheduled (i.e., < 5%) and three participants being excluded from the study.

2.4 EEG Flanker Task

Participants completed a version of the flanker task (Eriksen and Eriksen, 1974) during EEG recording. In the task participants viewed five horizontally aligned arrowheads on each trial. On half of the trials, arrows were compatible (“>>>>>” or “<<<<<”) and on the other half of trials the arrows were incompatible (“>><>>” or “<<><<”); the order of these trials was random. Participants were told to respond as quickly and as accurately as possible to indicate the direction of the center arrow by pressing the appropriate mouse button (left or right). Stimuli were presented for 200ms, followed by a white fixation cross in the center of a black background. Participants were given up to 1,800 ms to respond and trials were followed by an intertrial interval (1,000–2,000ms) during which participants again viewed a fixation cross. The task consisted of 11 blocks of 30 trials (330 trials in total) 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 EEG Data Collection and Preprocessing

Continuous EEG was recorded throughout the flanker task, using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Thirty-four electrode sites were used based on the 10/20 system and one electrode was placed on the left and right mastoids. The electrooculogram (EOG) generated from eyeblinks and eye movements was recorded from four facial electrodes: vertical eye movements and blinks were measured with

two electrodes placed approximately 1 cm above and below the right eye; horizontal eye movements were measured using two electrodes placed approximately 1 cm beyond the outer edge of each eye. The EEG signal was preamplified 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 31.25 nV and a sampling rate of 1,024 Hz using a low-pass fifth-order sinc filter with a -3-dB cutoff point at 204.8 Hz. The voltage from each active electrode was referenced online with respect to a common mode sense active electrode producing a monopolar (nondifferential) channel. Offline 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 band-pass filtered with high-pass and low-pass filters of 0.1 and 30 Hz, respectively. Data were segmented beginning 500 ms before each response onset and continuing for 1,500 ms (i.e., for 1,000 ms after the response).

Standard eyeblink and ocular corrections were performed for EEG data (Miller et al., 1988) and semiautomated artifact rejection procedures removed artifacts with the following criteria: voltage step of more than 50 μ V between sample points, a voltage difference of 300 μ V within a trial, and a maximum voltage difference of less than 0.5 μ V within 100 ms intervals. Additional artifacts were removed using visual inspection. The ERN and CRN were scored as the average activity on error and correct trials, respectively, from 0 to 100ms after response at electrode FCz where ERN amplitude was maximal (Figure 1). On average, there were 281.57 ± 46.68 clean correct trials for the CRN and 30.63 ± 27.80 clean incorrect trials for the ERN. To compute the difference between error and correct trials, we followed the Meyer et al. (Meyer et al., 2017) guidelines, calculating an ERN standardized residual score (ERN_{resid}) by saving the variance leftover in a regression where the CRN was entered predicting the ERN. The ERN_{resid} was used as the primary variable in subsequent analyses consistent with our prior studies (Gorka et al., 2017)².

Accuracy on the task was computed as the percentage of correct trials for each participant. Reaction time (RT) was computed as the amount of time it took participants to respond from stimulus onset, separately for error and correct trials. Four participants were missing reaction time measures on the task.

2.6 Statistical Procedures

Analyses were carried out using SPSS 24.0 (IBM). Data were inspected for non-normal distribution and outliers. AUDIT total score was square-root transformed. Using problematic alcohol use (AUDIT total score) as the outcome, the main effects and the interaction of time $\times$ ERN were examined, controlling for age, PTSD symptoms (CAPS total score), illicit drug use problems (DAST total score), current or past mood disorder, current or past anxiety disorder, and combat exposure (CES total score). We also examined if the interaction of ERN_{resid} and PTSD symptoms were associated with problematic alcohol use. Mixed-effects regression models using Generalized Linear Models in SPSS included both fixed effects of variables and random effects to account for the repeated measurements of participants over time. Mixed-effects regression modeling was used, as it allows for continuous modeling of

²In addition to the ERN_{resid} , we conducted all analyses with the formerly standard ERN difference score (i.e., ERN – CRN) and the pattern of results was similar across the two methods.

time, accounts for variability in between-observation durations, and handles missing data by weighting slope estimates by number of observations (Goldstein, 2011). Random effects included intercepts (capturing individual differences in problematic alcohol use at baseline) and time trends (capturing individual differences in alcohol use across the study), with an unstructured covariance structure.

Problematic alcohol use (outcome), age, PTSD symptoms, and illicit drug use problems were all time-varying, while ERN_{resid} , combat exposure, current or past mood disorder, and current or past anxiety disorder (excluding PTSD) were static and based on baseline measures. ERN_{resid} , PTSD symptoms, illicit drug use problems, and combat exposure total score were all grand mean centered. Models were run in a hierarchical order (i.e., main effects, then interactions) to obtain the correct estimates for the main effects. Follow-up analyses of the simple slopes for significant 2-way interactions used linear regression to estimate the effects of ERN_{resid} and time (Aiken et al., 1991). Specifically, the moderator (ERN_{resid}) was re-centered at 1 *SD* above the mean for “smaller ERN magnitude” and 1 *SD* below the mean for “larger ERN magnitude.” Two new interaction terms were created and *post-hoc* additional follow-up linear regression models were run. Results were deemed statistically significant when *p*-values < .05.

3. Results

3.1 Participant Characteristics

Participant characteristics are shown in Table 1. Participants completed an average of 5 study visits and the majority of participants completed at least 1 follow-up visit during 12–24 months (83% completed at least 12 months of follow-up and 54% completed at least 18 months follow-up). Eighty-nine percent of the sample was exposed to combat and overall had light-moderate exposure to combat (range: light to moderate-heavy) according to the published CES norms (Keane et al., 1989; see Table 1).

3.2 ERN and Behavioral Performance

Behavioral data means and standard deviations are displayed in Table 1. On average, participants made 32.22 ± 27.28 errors across the task and correctly responded to $89.98 \pm 8.5\%$ of trials. As expected, participants' reaction times (RTs) were faster for errors, than for correct responses (see Table 1); $t(41) = 5.17$, $p < .001$. Figure 1 displays the topographical map for all participants (in μV) across the scalp for response-locked ERP waveforms following errors, correct responses, and the error minus correct difference wave in the time window of the ERN (i.e., 0–100 ms postresponse).

3.3 Relationship between ERN and Alcohol Use Over Time

As for main effects, problematic alcohol use did not significantly change over time and in general ERN_{resid} was not significantly associated with problematic alcohol use (Table 2). Overall, more illicit drug use problems and higher symptoms of PTSD were each associated with more problematic alcohol use (Table 2). Age at baseline, current or past mood or anxiety disorder (excluding PTSD) at baseline, and combat exposure at baseline were not related to problematic alcohol use (Table 2). Results revealed a significant time $\times$ ERN_{resid}

interaction for problematic alcohol use (Table 2); however, the PTSD symptoms $\times$ ERN_{resid} interaction was not significant (Table 2).

Follow-up slopes for the time $\times$ ERN_{resid} interaction demonstrated that participants with a smaller ERN_{resid} magnitude evidenced a decline in their problematic alcohol use over time ($b=-.42$, $SE=0.18$, $t(28.56)=-2.28$, $p=.03$), whereas participants with a larger ERN_{resid} magnitude had no change in their problematic alcohol use over time, $b=.19$, $SE=0.18$, $t(32.08)=1.04$, $p=.31$ (see Figure 2 for illustration of simple slopes).

3.4 Exploratory Analysis

Given that all participants were recruited via the VA system, which provides psychiatric and health services, we explored whether treatment engagement in psychiatric services might have impacted the above time $\times$ ERN_{resid} interaction. Treatment engagement was assessed at baseline, 6-months, and 12-months and defined as 6 or more individual sessions in the past 6 months based on previous research in the VA (Myers et al., 2015), 3 or more medication management sessions in the past 6 months, and any partial/full hospitalization and was coded as binary (yes/no) nominal variable that was dummy coded. Using this variable, we performed a mixed-effects regression model, identical to above, and added 'treatment engagement' as a time-varying variable. Overall, treatment engagement was not associated with alcohol use and the interaction between treatment engagement, time, and ERN_{resid} was not significant (see Table 3).

4. Discussion

To our knowledge, this is the first study to examine the relationship between ERN and problematic alcohol use over time among U.S. military veterans returning from recent conflicts in Iraq and Afghanistan. In line with our hypothesis, we found that ERN magnitude was associated with problematic alcohol use over time, even after controlling for relevant clinical variables like PTSD symptoms, illicit drug use problems, current or past mood disorder, current or past anxiety disorder, and combat exposure. Specifically, we found that veterans with a smaller ERN magnitude decreased their problematic alcohol use over time, while veterans with a larger ERN magnitude had no change in their problematic alcohol use over time. In addition, exploratory analyses found that treatment engagement during the study did not moderate these relationships. Therefore, ERN seems to differentiate veterans who decrease their problematic alcohol use over time and veterans who continue to experience problematic alcohol use and these relationships are not significantly related to whether veterans have been engaged in treatment. It is also noteworthy that the ERN predicts problematic drinking, even when controlling for anxiety, which is also known to contribute to a larger ERN magnitude (Gorka and Phan, 2017; Weinberg et al., 2015).

Our findings build upon previous studies demonstrating larger ERN magnitudes among individuals with AUD (Gorka et al., 2016; Padilla et al., 2011; Schellekens et al., 2010), including a study with 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 (Gorka et al., 2016), and provide preliminary evidence that ERN can be used as an individual difference factor that predicts continued problematic alcohol use over time. A smaller ERN magnitude

may be a protective or resilience factor for chronic, problematic alcohol use. Thus, individuals with a smaller ERN magnitude may be at less risk of continued, problematic alcohol use. On the other hand, a larger ERN magnitude may reflect an affective disruption among individuals at risk for chronic, problematic alcohol use, as alcohol is often used to regulate negative affect, which may lead to continued alcohol use among individuals with a larger ERN magnitude.

These findings have important clinical implications. Neural response to errors, as measured by the ERN, seems to be an important, individual difference factor that can be used as therapeutic target for prevention and intervention efforts for AUD (see (Wilcox et al., 2014). In fact, recent evidence suggests that even a single session of computerized attention bias modification treatment can reduce the ERN in undergraduates (Nelson et al., 2015). This type of treatment may also be effective at dampening the enhanced neural response to errors in AUD, which may decrease individuals' need and desire to continue to drink. Additionally, evidence from our lab demonstrates that the ERN may distinguish individuals who will have better treatment outcomes with Cognitive Behavioral Therapy (CBT) compared to an antidepressant (Gorka et al., under review). Thus, the ERN may be an objective psychophysiological measure that can be used to help in guiding treatment decision-making for AUD.

The current study has several strengths, including that the sample is a racially diverse group of veterans who represent a real-world, highly vulnerable patient population receiving care at the VA and who have been followed over time; however, our findings should be considered in the context of limitations. First, the majority of participants in the study were male, and all participants were veterans, making it difficult to generalize the findings to females and civilian populations. Second, the sample size was relatively small, which may have limited our statistical power and our ability to detect other relationships. Third, we did not have detailed information about the veterans' treatment and their treatment response. We also did not have prospective treatment data. Future studies are needed to better understand the relationships between treatment, problematic alcohol use, and the ERN. Fourth, we did not collect family history of AUD, which has been shown to influence feedback ERN (Fein and Chang, 2008). Finally, many participants initiated their problematic alcohol use prior to the study, we did not collect detailed information about alcohol use history, and we were not able to measure the ERN prior to initiation of problematic alcohol use. Therefore, we were unable to examine how the ERN may be associated with the initiation of problematic alcohol use or alcohol use history. It will be important for future research to examine the longitudinal associations among problematic alcohol use, anxiety symptoms, especially fear-based anxiety, and the ERN to better understand the temporal relationships between these variables.

6. Conclusions

Our study expands upon previously reported disruptions in neural response to errors among individuals with AUD, demonstrating that veterans with a smaller ERN magnitude decrease their problematic alcohol use over time, while veterans with a larger ERN magnitude continue to engage in problematic alcohol use over time. Importantly, these findings could

not be explained by treatment engagement during the study or by the presence of other psychiatric symptoms or substance use, including PTSD symptoms, illicit drug use problems, current or past mood or anxiety disorder, and level of combat exposure. Therefore, neural response to errors could help to identify individuals at risk for continued problematic alcohol use. These findings highlight the potential importance of exploring error processing as a therapeutic target within AUD intervention efforts.

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Highlights

- We examined error-related negativity (ERN) and alcohol use in veterans over time
- ERN magnitude was associated with problematic alcohol use over time
- Veterans with a smaller ERN showed a decrease in problematic alcohol use over time
- Veterans with a larger ERN had no change in problematic alcohol use over time
- This disrupted brain error-related circuitry may be an important therapeutic target

Figure 1. Response-locked ERP waveforms following errors, correct responses, and the error minus correct difference wave for all participants. Topographic scalp maps of neural activity depict the error minus correct difference 0–100ms after the response.

Figure 2.

Graph illustrating problematic alcohol use over time at large and small magnitudes of ERN (± 1 standard deviation from the mean). ERN= difference between error-related negativity and correct-related negativity. AUDIT= Alcohol Use Disorders Identification Test.

Table 1**Participant Characteristics**

	Baseline n=46 <i>M ± SD [Range]</i>
Demographics	
Age	32.48 ± 6.44
Gender (% Male)	83%
Years of Education	14.39 ± 1.63
Race/ethnicity	
Caucasian	28%
African American	37%
Hispanic	31%
Asian	0%
Other or Unknown	4%
Clinical Variables	
Problematic Alcohol Use (AUDIT total score)	9.13 ± 9.27 [0–34]
% Current AUD	41%
Drug Use (DAST total score)	3.65 ± 5.05 [0–20]
PTSD Symptoms (CAPS total score)	40.11 ± 29.41 [0–101]
% Current PTSD	28%
Combat Exposure (CES total score)	13.85 ± 10.16 [0–34]
% Current or Past Mood Disorder	37%
% Current or Past Anxiety Disorder	7%
Engaged in Treatment	22%
Task Variables	
ERN	−0.97 ± 8.48
CRN	6.74 ± 5.96
Error RT	335.14 ± 80.37
Correct RT	424.42 ± 99.59
Accuracy (%)	89.98 ± 8.57

Note. AUD, Alcohol Use Disorder; AUDIT, Alcohol Use Disorders Identification Test; CAPS, Clinician-Administered PTSD Scale; CES, Combat Exposure Scale; CRN, correct-related negativity; DAST, Drug Abuse Screening Test; ERN, error-related negativity; RT, reaction time.

Table 2

Longitudinal Multilevel Regression Model with Problematic Alcohol Use as the Dependent Variable

Predictor	Alcohol Use (AUDIT Total)			
	Est. (SE)	df	<i>t</i>	p-value
<i>Step 1</i>				
Intercept	0.57 (1.31)	41.72	0.43	.67
Time (linear)	−0.11 (0.12)	34.49	−0.92	.36
ERN _{resid}	−0.25 (0.29)	33.98	−0.86	.40
Age at Baseline	0.04 (0.04)	41.09	1.14	.26
Current or Past Mood Disorder	0.53 (0.55)	35.47	0.95	.35
Current or Past Anxiety Disorder	0.30 (0.91)	34.21	0.33	.75
Combat Exposure (CES Total)	0.01 (0.02)	35.84	0.70	.49
<i>Time-varying predictors</i>				
Illicit Drug Use Problems (DAST Total)	0.07 (0.02)	156.3	3.67	<.001
PTSD symptoms (CAPS Total)	0.01 (0.00)	185.31	2.40	.02
<i>Step 2</i>				
<i>Interactions</i>				
Time*ERN _{resid}	−0.30 (0.14)	28.56	−2.15	.04
ERN _{resid} *PTSD Symptoms	0.00 (0.00)	182.86	−0.61	.55

Note. AUDIT, Alcohol Use Disorders Identification Test; CAPS, Clinician Administered PTSD Scale; CES, Combat Exposure Scale; DAST, Drug Abuse Screening Test; ERN_{resid}, error-related negativity residual; PTSD, Posttraumatic Stress Disorder.

Table 3

Exploratory Longitudinal Multilevel Regression Model including Treatment Engagement with Alcohol Use as the Dependent Variable

Predictor	Alcohol Use (AUDIT Total)			
	Est. (SE)	df	<i>t</i>	p-value
<i>Step 1</i>				
Intercept	0.66 (1.48)	38.43	0.45	.66
Time (linear)	−0.10 (0.23)	26.77	−0.42	.68
ERN _{resid}	−0.24 (0.31)	32.22	−0.76	.46
Age at Baseline	0.04 (0.04)	36.38	0.99	.33
Current or Past Mood Disorder	0.41 (0.61)	34.11	0.67	.51
Current or Past Anxiety Disorder	0.33 (0.95)	32.49	0.35	.73
Combat Exposure (CES Total)	0.02 (0.02)	36.43	0.69	.49
<i>Time-varying predictors</i>				
Illicit Drug Use Problems (DAST Total)	0.10 (0.03)	68.11	3.23	.002
PTSD symptoms (CAPS Total)	0.01 (0.01)	72.17	1.81	.08
Treatment Engagement	−0.09 (0.26)	44.75	−0.33	.75
<i>Interactions</i>				
<i>Step 2</i>				
Time*ERN _{resid}	−0.53 (0.29)	27.22	−1.81	.08
ERN _{resid} *PTSD Symptoms	−0.01 (0.01)	79.05	−0.9	.37
<i>Step 3</i>				
ERN _{resid} *PTSD Symptoms*Treatment Engagement	−2.22 (0.58)	35.63	−0.37	.71

Note. AUDIT, Alcohol Use Disorders Identification Test; CAPS, Clinician Administered PTSD Scale; CES, Combat Exposure Scale; DAST, Drug Abuse Screening Test; ERN_{resid}, error-related negativity residual; PTSD, Posttraumatic Stress Disorder.