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Error-related Brain Activity as a Treatment Moderator and Index of Symptom Change during Cognitive-Behavioral Therapy or Selective Serotonin Reuptake Inhibitors

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Increased neural error monitoring, as measured by the error-related negativity (ERN), is a transdiagnostic neurobiological marker of anxiety. To date, little is known about whether the ERN can inform the choice between first-line anxiety disorder treatments and whether the ERN changes following treatment completion. The aim of the study was to therefore assess whether the ERN is a treatment moderator and index of symptom change during cognitive-behavioral therapy (CBT) or selective serotonin reuptake inhibitors (SSRIs). Participants included adult volunteers (*M* age = 25.8 ± 8.5; 67% female) with principal anxiety disorders ($n = 60$) or no lifetime history of Axis I psychopathology (ie, healthy controls; $n = 26$). A flanker task was used to elicit the ERN at baseline and 12 weeks later, following either CBT or SSRIs in the patient sample. Results indicated that baseline ERN was a significant treatment moderator such that a more enhanced baseline ERN was associated with greater reduction in anxiety symptoms within individuals who received CBT but not SSRIs. Results also revealed that the ERN increased pre- to post-treatment among patients randomized to SSRIs, but remained stable among patients randomized to CBT and healthy controls. Together, these novel findings highlight that ERN may help guide treatment decisions regarding engagement in CBT or SSRIs, especially among individuals with an enhanced ERN. The findings also suggest that SSRIs have the capacity to alter individual differences in the ERN, providing evidence that the ERN is not entirely static in patients with anxiety disorders.
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INTRODUCTION

Increased neural reactivity to errors is a transdiagnostic indicator of anxiety (see Weinberg *et al*, 2015 for a review). Accordingly, the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) Initiative has identified neural error monitoring as a key biologically based dimension of psychological dysfunction that may explain core features of psychopathology, particularly anxiety (Hanna and Gehring, 2016; Weinberg *et al*, 2015). Neural reactivity to errors is often measured using the error-related negativity (ERN), an event-related potential that appears as a negative-going deflection in the electroencephalogram (EEG) waveform following the commission of an error (Falkenstein *et al*, 1991; Gehring *et al*, 1993). The ERN is a well-validated neural response that is observed across various levels of task difficulty, response modalities, age ranges, and species (Endrass *et al*, 2012; Riesel *et al*, 2013), and therefore reflects activity of a fundamental neural error detection system. In humans, one of the primary sources of the ERN has been localized to the anterior cingulate cortex (Miltner *et al*, 2003), a neural region known to mediate conflict monitoring and error processing (Botvinick *et al*, 2004).

To date, an enhanced ERN has been repeatedly observed in individuals with obsessive compulsive disorder (OCD; Ruchsow *et al*, 2005), generalized anxiety disorder (GAD; Weinberg *et al*, 2010), and social anxiety disorder (SAD; Endrass *et al*, 2014). Beyond discrete diagnostic categories, individuals with high trait anxiety (Olvet and Hajcak, 2009), high negative affect (Hajcak *et al*, 2004), and increased behavioral inhibition (Boksem *et al*, 2006) are also characterized by an increased ERN. Contributing to this literature, we recently found that greater ERN amplitude was associated with greater levels of fear-based anxiety symptoms (eg, panic, social anxiety), but was unrelated to distress/misery symptoms (eg, depression), in a heterogeneous comorbid patient population (Gorka *et al*, 2017) and

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concluded that the ERN may be an objective, psychophysiological marker that tracks the severity of anxiety psychopathology. Of note, however, is that the functional significance of the ERN is still a topic of debate and there are several existing theories that shed light on the mechanisms that may contribute to an enhanced ERN in anxious populations. Researchers have specifically posited that the ERN reflects conflict between two activated response tendencies (Botvinick *et al*, 2004), a negative reinforcement learning signal generated by phasic activity of the neural dopamine system (Holroyd and Coles, 2002), and a defensive response to the threatening nature of errors (Hajcak and Foti, 2008). Regardless of theoretical differences, most agree that the ERN indexes the functioning of a performance monitoring system designed to flexibly control and modify behavior, and this system tends to be over-active in anxious individuals (Weinberg *et al*, 2016).

The ERN has been extensively studied with regard to anxiety psychopathology; however, very few studies have addressed the potential role of the ERN in the psychiatry clinic. For instance, a major question within the ERN literature is the degree to which individual differences in ERN predict treatment outcomes and can therefore inform clinical decision-making. Evidence to date is limited to two cognitive-behavioral therapy (CBT) studies with OCD patients, where baseline ERN did not predict symptomatic outcomes (Hajcak *et al*, 2008) nor differentiate treatment responders from non-responders (Riesel *et al*, 2015). There have been no studies of treatment prediction with other internalizing disorders or with pharmacological interventions such as selective serotonin reuptake inhibitors (SSRIs). This is noteworthy given that SSRIs are considered a first-line pharmacological treatment for anxiety (Baldwin *et al*, 2014). Moreover, although both CBT and SSRIs are both effective at reducing internalizing symptoms, treatment response is heterogeneous and the two modalities have some distinct mechanisms that could differentially impact outcomes and treatment prediction (eg, Kennedy *et al*, 2007). Broadly, CBT is an amalgam of strategies directed at altering maladaptive ways of thinking and coping with negative mood and events (Arch and Craske, 2009), whereas increased serotonin neurotransmission is considered the mechanism of action of SSRIs (Schloss and Williams, 1998). A primary goal of RDoC is to develop objective dimensional assays that can quantify disease status and guide clinical decision-making, especially between first-line treatment options (Kozak and Cuthbert, 2016). Thus, given the potential for positive predictive findings with respect to disorders other than OCD and with respect to pharmacological treatment, we elected to evaluate ERN as a treatment predictor within anxiety disorder patients in order to advance the mission of precision treatment.

In addition to questions regarding treatment moderation, it is necessary to understand whether the ERN is a static marker of anxiety risk or fluctuates with time and symptom change and could therefore be used as an objective treatment target. As for time, there is some evidence that the ERN is stable over two years in unselected samples (Weinberg and Hajcak, 2011). As for change in symptoms, there have been two studies showing that patients with OCD display an enhanced ERN before and after cognitive CBT (Hajcak *et al*, 2008; Riesel *et al*, 2015). Similarly, we found that youth and young adults with SAD had an enhanced ERN relative to healthy controls and individuals with GAD prior to and following treatment with either CBT or SSRIs (Kujawa *et al*, 2016). Based on existing data, the ERN appears to be a stable anxiety marker that is resistant to internalizing disorder treatments. However, research that extends beyond OCD and SAD diagnostic categories to transdiagnostic symptom change is critically needed to determine whether the ERN has utility as a treatment target.

The current study examined: (1) whether baseline ERN is associated with change in anxiety symptom severity from pre- to post-treatment in a transdiagnostic, anxiety disorder patient population and (2) if the ERN is malleable to change after 12 weeks of either CBT or SSRI treatment. We notably included two separate measures of anxiety symptoms, one capturing broad, non-specific anxiety and the other capturing symptoms specific to fear-based anxiety disorders (ie, panic disorder, SAD, phobias, and post-traumatic stress; Watson, 2005). Based on the existing literature, we hypothesized that the ERN would be relatively stable across time in both healthy controls and individuals with anxiety disorders. We did not have specific hypotheses regarding the association between baseline ERN and change in symptoms with CBT compared to SSRIs given the lack of research in this area.

MATERIALS AND METHODS

Participants

The current study was designed to be consistent with, and funded by, the NIMH RDoC Initiative (RFA-MH-13-080). A community sample of individuals with a range of internalizing psychopathologies and symptoms were enrolled if they met criteria for full-threshold or sub-threshold DSM-5 depressive or anxiety disorder and reported a total score of $\geqslant 23$ on the Depression, Anxiety, and Stress Scale (DASS-21; Lovibond and Lovibond, 1995), and a Global Assessment of Functioning score of $\leqslant 60$. Controls had no lifetime Axis I disorders. Exclusionary criteria for all participants included an inability to provide consent and read and write in English; major active medical or neurological problem; lifetime history of mania, psychosis, intellectual disability, or pervasive developmental disorder; current substance dependence; contraindications to receiving SSRIs; engaged in psychiatric treatment including the use of psychiatric medications within the past 4-weeks; traumatic brain injury; and pregnancy. This study was approved by the UIC Institutional Review Board, and informed consent was obtained from all participants.

Given the aims of the current study, only patients with a full-threshold DSM-5 principal anxiety disorder were included in the study (ie, no patient had principal depression). Comorbidities including additional current anxiety disorders and/or major depressive disorder were permitted. A total of 46 healthy controls and 165 patients initially enrolled in the study. For the healthy controls, 10 were deemed ineligible and withdrawn from the study, seven dropped out prior to the baseline assessment, two were lost to follow-up, and one had poor quality ERN data (ie, excessive artifact), resulting in a final sample of 26 controls. For the patients, 47 were deemed ineligible, 36 dropped out

prior to baseline, 13 were lost to follow-up, and 9 had poor quality ERN data (ie, one made less than six errors (Olvet and Hajcak, 2009); eight had excessive artifact), resulting in a final sample of 60 patients. Of these remaining subjects, 23 received SSRIs and 37 received CBT.

Assessment of Psychopathology

Lifetime Axis I diagnoses were assessed via the Structured Clinical Interview for DSM-5 Disorders (SCID-5) by a master's degree or PhD/MD assessor. A consensus panel of at least three study staff/trained clinicians determined subjects' eligibility and if there were co-occurring disorders, which was the principal disorder warranting treatment. Individuals were not excluded for comorbid disorders but instead classified by their clinician-determined principal diagnosis, as determined by the most severe and impairing symptoms from clinical interviews and self-reports. In the present study, specification of the principal disorder was also used to identify patients with a primary anxiety disorder. Principal anxiety disorders included in the present sample were as follows: SAD = 20, GAD = 32, panic disorder (PD) = 3, and post-traumatic stress disorder (PTSD) = 5.

At pre- and post-treatment, the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) was administered by research assessors to measure broad anxiety symptoms (T1 HAMA-A $\alpha = 0.89$) given that the sample was comprised of individuals with principal anxiety disorders. To capture more specific symptoms, participants also completed the Inventory for Depression and Anxiety Symptoms-II (IDAS-II; Watson *et al*, 2012), which includes distinct, factor analytically derived symptom scales that map onto DSM-IV anxiety disorders. Within the current sample, we have previously demonstrated that baseline ERN amplitude is specifically associated with fear-based anxiety symptoms, and not broad anxiety/general distress (Gorka *et al*, 2017). In our prior paper, fear-based anxiety symptoms were captured using the IDAS-II by Z-scoring and averaging the panic, social anxiety, claustrophobia, traumatic intrusions and avoidance subscales. These scales were chosen, in particular, as they reflect the symptoms of the 'fear disorders' (ie, PD, SAD, phobia, and PTSD), identified in numerous large-scale, factor analytic studies (Slade and Watson, 2006). Given the findings from Gorka *et al* (2017), and the potentially unique relation between the ERN and fear-based anxiety, we calculated an identical IDAS-II fear dimension in the current study (T1 α for IDAS fear dimension $= 0.90$).

At the final treatment session, treating clinicians rated participant clinical improvement using the Clinical Global Impressions Scale (CGI; Guy, 1976). Patients with CGI global improvement ratings of 1 or 2 (ie, very much or much improved) were classified as 'treatment responders'.

Treatment Procedures

Participants were randomized to either 12 weeks of CBT or SSRI treatment. For SSRIs, the dosing schedule was flexible depending on tolerability and aimed to reach target dose by week 8 (eg, 100–200 mg/day for sertraline). The flexibility of the SSRI protocol was designed to match real-world psychiatric practice. Of the 23 patients randomized to SSRIs, 12 were provided sertraline, 8 were provided escitalopram, and 3 were provided paroxetine. SSRI patients attended 20–30 min medication management sessions with their study psychiatrist at 0, 2, 4, 8, and 12 weeks. For CBT, treatment was delivered through 12, once-weekly 60-min sessions led by a PhD-level clinical psychologist using evidence-based manuals for the patient's principal diagnosis and predominant symptoms (eg, Barlow and Craske, 2006; Craske *et al*, 1992). As per the manualized protocols, sessions began with psychoeducation and CBT orientation and then expanded to include strategies such as cognitive restructuring and behavioral change (eg, exposure exercises, behavioral activation) around the treatment mid-point (ie, week 6). Sessions ended with a focus on relapse prevention.

Flanker Task to Elicit ERN

At T1 and T2 participants completed a modified version of the original flanker task (Eriksen and Eriksen, 1974) to measure neural activity to error and correct responses (ie, the ERN and correct response negativity (CRN), respectively). 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 accurately as possible to indicate the direction of the center arrow (left or right) by pressing the appropriate mouse button. Arrows were presented for 200 ms and participants were given up to 1800 ms to respond. Trials were followed by an intertrial interval (1000–2000 ms) during which a fixation cross appeared. The task consisted of 11 blocks of 30 trials (330 total trials). To encourage fast and accurate responding, participants received performance-based feedback at the end of each block. If accuracy was 75% correct or lower, the message 'Please try to be more accurate' was presented; if accuracy was greater than 90%, the message, 'Please try to respond faster' was displayed; in all other cases, participants saw the message, 'You're doing a great job'.

Electroencephalogram Data Collection and Processing

Detailed descriptions of our EEG recording and processing procedures have been published elsewhere (eg, Gorka *et al*, 2017; Gorka *et al*, 2016). In brief, EEG was recorded during the task using the ActiveTwo BioSemi system (BioSemi, Amsterdam, the Netherlands). Thirty-four standard electrode sites were used and one electrode was placed on each mastoid. 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 (0.1 Hz) and low-pass (30 Hz) filtered. Data were segmented beginning 500 ms before each response onset and continuing for 1500 ms. Standard artifact rejection procedures were used (see Gorka *et al*, 2017; Gorka *et al*, 2016). Baseline correction for each trial was performed using the 500 to 300 ms prior to response onset.

ERN data were considered unusable if the EEG data were contaminated by excessive artifact and/or the participant made less than six errors during the flanker task (Olvet and Hajcak, 2009). The ERN and CRN were scored as the average activity on error and correct trials, respectively, from 0 to 100 ms after response at electrode Cz, consistent with prior

studies (eg, Meyer *et al*, 2013) and where ERN amplitude was maximal. The ERN and CRN were highly correlated ($r = 0.70$, $p < 0.01$), as expected. Therefore, to quantify the difference between error and correct trials, we followed guidelines by Meyer *et al* (2017) and calculated 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 pre-treatment study (Gorka *et al*, 2017). (In addition to the ERN_{resid}, we conducted all analyses with the formerly standard ΔERN difference score (ie, ERN − CRN). The

Table 1 Demographics and Clinical Characteristics of Healthy Controls and Anxiety Disorder Patients

	Healthy controls ($n = 26$)	CBT patients ($n = 37$)	SSRI patients ($n = 23$)
Demographics			
Age (years)	23.5 (8.2)$_a$	27.3 (8.8)$_a$	26.0 (8.0)$_a$
Sex (% female)	53.8%$_a$	67.6%$_a$	73.9%$_a$
Hispanic ethnicity	7.7%$_a$	18.9%$_a$	17.4%$_a$
Race			
Caucasian	53.8%$_a$	64.9%$_a$	73.9%$_a$
African American	15.4%$_a$	16.2%$_a$	8.7%$_a$
Asian	30.8%$_a$	10.8%$_b$	8.7%$_b$
American Indian or Alaskan Native	0.0%$_a$	0.0%$_a$	4.3%$_a$
Other/Biracial	0.0%$_a$	8.1%$_a$	4.3%$_a$
Comorbid diagnoses			
No. of current internalizing disorders	0.0$_a$	2.7 (1.3)$_b$	2.6 (1.1)$_b$
Principal anxiety disorder	0.0$_a$	100.0%$_b$	100.0%$_b$
Comorbid current anxiety disorder	0.0%$_a$	70.3%$_b$	78.3%$_b$
Comorbid current major depressive disorder	0.0%$_a$	41.7%$_b$	43.5%$_b$
Past anxiety disorder	0.0%$_a$	40.5%$_b$	26.1%$_b$
Past major depressive disorder	0.0%$_a$	40.5%$_b$	21.7%$_b$
Current mild substance use disorder	0.0%$_a$	5.4%$_a$	4.3%$_a$
Past substance use disorder	0.0%$_a$	13.5%$_a$	8.7%$_a$
Clinical characteristics			
HAM-A symptoms at T1	1.3 (1.7)$_a$	16.7 (6.4)$_b$	18.6 (7.2)$_b$
IDAS fear symptoms at T1 (Z-score)	−1.1 (0.2)$_a$	0.4 (0.9)$_b$	0.6 (0.8)$_b$
HAM-A symptoms at T2	N/A	6.0 (3.7)$_a$	6.4 (6.0)$_a$
IDAS fear symptoms at T2 (Z-score)	N/A	−.07 (1.1)$_a$	.11 (0.9)$_a$
Flanker task variables			
ERN_{resid} at T1	−0.10 (0.9)$_a$	.08 (0.8)$_a$	−.16 (0.9)$_a$
ERN_{resid} at T2	0.17 (0.8)$_a$	−.31 (0.9)$_a$	−.03 (1.1)$_a$
Accuracy at T1	90.3% (5.2)$_a$	88.4% (8.4)$_a$	90.9% (8.0)$_a$
Accuracy at T2	89.4% (6.1)	91.3% (6.6)	92.2% (5.5)
Range of no. errors made at T1	6–66	6–151	6–143
Range of no. errors made at T2	7–76	6–78	6–67
Error congruent trial reaction time at T1	303.3 (88.3)$_a$	292.3 (89.4)$_a$	263.7 (86.7)$_a$
Error congruent trial reaction time at T2	219.6 (42.5)$_a$	286.7 (53.6)$_a$	364.0 (146.1)$_b$
Error incongruent trial reaction time at T1	314.7 (101.2)$_a$	315.2 (80.9)$_a$	305.0 (51.1)$_a$
Error incongruent trial reaction time at T2	290.7 (51.1)$_a$	325.0 (95.8)$_a$	320.3 (82.9)$_a$
Correct congruent trial reaction time at T1	321.4 (34.1)$_a$	363.6 (83.4)$_a$	353.5 (44.7)$_a$
Correct congruent trial reaction time at T2	344.8 (56.7)$_a$	361.6 (73.6)$_a$	358.5 (59.5)$_a$
Correct incongruent trial reaction time at T1	375.5 (49.6)$_a$	413.1 (69.5)$_{a,b}$	425.8 (88.7)$_b$
Correct incongruent trial reaction time at T2	394.2 (66.9)$_a$	411.3 (69.1)$_a$	418.3 (58.2)$_a$

Note: Means (and standard deviations) or percentages with different subscripts (a, b) across rows were significantly different in pairwise comparisons ($p < 0.05$, chi-square test for categorical variables and Tukey's honestly significant difference test for continuous variables). Some participants met criteria for more than one disorder. HAM-A, Hamilton Anxiety Rating Scale; IDAS, Inventory of Depression and Anxiety Symptoms—II.

pattern of results was identical across the two methods of quantifying the ERN.)

Data Analysis Plan

We initially conducted a series of planned within-subjects and between-subjects analyses of variance (ANOVAs) to confirm that patients and controls differed at baseline on symptoms and that treatment was successful in reducing self-reported anxiety.

We then assessed whether the ERN_{resid} at T1 moderated change in anxiety symptom severity during CBT and/or SSRIs within patients (only). To do so, we conducted two hierarchical linear regressions with percent change (pre- to post-treatment) of HAM-A or IDAS fear symptoms as the dependent variable. For both models, the ERN_{resid} at T1 and Treatment (2; CBT, SSRI) were entered in Step 1. The ERN_{resid} at T1 × Treatment interaction term was entered in Step 2. Significant interactions were followed using standard simple effects approaches.

We next assessed whether the ERN_{resid} changed from T1 to T2 and correlated with anxiety symptom reduction. First, we conducted a Time (2; T1 and T2) × Treatment (3; no treatment, CBT, SSRI) omnibus ANOVA. Significant interactions were followed using paired-samples *t*-tests within subjects in each treatment arm. Second, to examine correlations with symptom change, we conducted Pearson's correlations between change in the ERN_{resid} and change in HAM-A and IDAS fear symptoms from T1 to T2.

RESULTS

Demographics and Clinical Characteristics

As expected, patients reported higher levels of HAM-A, $F(1, 85) = 136.23$, $p < 0.01$, and IDAS fear symptoms, $F(1, 85) = 71.15$, $p < 0.01$, relative to controls at pre-treatment. Within patients, HAM-A, $t(59) = 12.42$, $p < 0.01$, and IDAS fear symptoms, $t(59) = 9.35$, $p < 0.01$, decreased pre- to post-treatment (average reduction in HAM-A: 63.8% ± 26.5; average reduction in IDAS fear: 26.5% ± 17.8). There were no differences in pre-treatment symptom severity between the CBT and SSRI groups and the extent of symptom reduction on either measure did not differ based on treatment modality, sex, or race ($ps > 0.16$). Based on CGI ratings, 70% of participants responded to treatment.

During the flanker task, participants achieved 89.6% and 90.9% accuracy, and committed 34.1 ± 24.7 and 29.8 ± 20.5 errors at T1 and T2, respectively. Group differences in task accuracy and reaction times for congruent and incongruent trials are presented in Table 1. Neither task accuracy nor reaction times correlated with $ERN_{resid,}$ T1 anxiety symptoms, or change in either anxiety symptom measure (all $ps > 0.24$). Change in ERN_{resid} from T1 to T2 also did not correlate with change in task accuracy, correct trial reaction time, or incorrect trial reaction time (all $ps > 0.16$).

ERN at T1 as a Treatment Moderator

Results of the hierarchical linear regressions are displayed in Table 2. For change in IDAS fear symptoms, findings revealed no main effects of treatment arm or T1 ERN_{resid} but there was a significant treatment arm × T1 ERN_{resid} interaction. Follow-up analyses indicated that within patients randomized to CBT, a more enhanced T1 ERN_{resid} was associated with greater reduction in fear symptoms ($\beta = -0.34$, $t = -2.22$, $p = 0.03$; Figure 1). Meanwhile, within patients randomized to SSRIs, there was no association between T1 ERN_{resid} and change in fear symptoms ($\beta = 0.37$, $t = 1.58$, $p = 0.12$). (Given the significant symptom overlap and high rates of comorbidity between anxiety and depression (Kessler *et al*, 2005), we ran an analogous model testing whether baseline ERN amplitude moderated change in depressive symptoms during CBT and/or SSRI treatment using the IDAS depression symptom subscale. Our results did not converge with the anxiety findings as there was no significant baseline ERN × treatment arm interaction ($\beta = -.054$, $t = -0.74$, $p = 0.46$).)

Table 2 Hierarchical Linear Regression Analyses Examining Whether Baseline ERN_{resid} Predicts Change in Anxiety Symptoms Pre- to Post-Treatment

	Change in HAM-A				Change in IDAS Fear			
	β	*t*	*p*-value	R^2	β	*t*	*p*-value	R^2
Step 1				0.05				0.03
T1 ERN_{resid}	−0.22	−1.66	0.10		−0.13	−0.96	0.34	
Arm	−0.11	−0.81	0.42		−0.12	−0.86	0.39	
Step 2				0.06				0.13
T1 ERN_{resid} × Arm	0.65	0.82	0.41		−1.95*	−2.53	0.01	

Abbreviations: Arm, medication or cognitive behavioral therapy; T1, baseline assessment.
*$p < 0.05$.

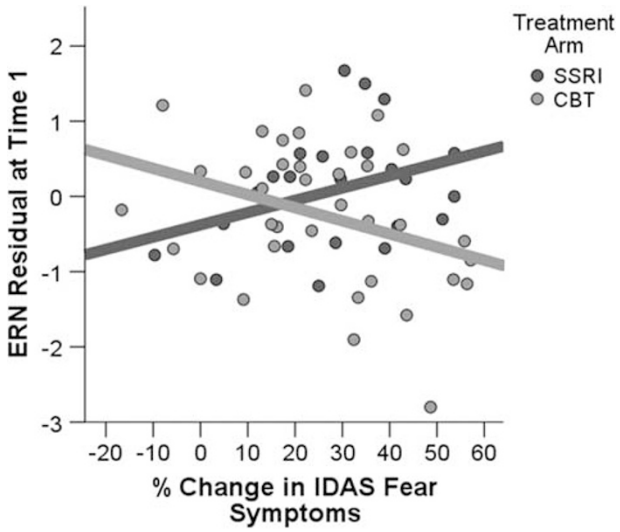

Figure 1 Scatter plots reflecting the association between pre-treatment ERN and change in IDAS fear symptoms during CBT and SSRIs (separate colors). IDAS, Inventory of Depressive and Anxiety Symptoms; ERN, error-related negativity; CBT, cognitive-behavioral therapy; SSRIs, selective serotonin reuptake inhibitors.

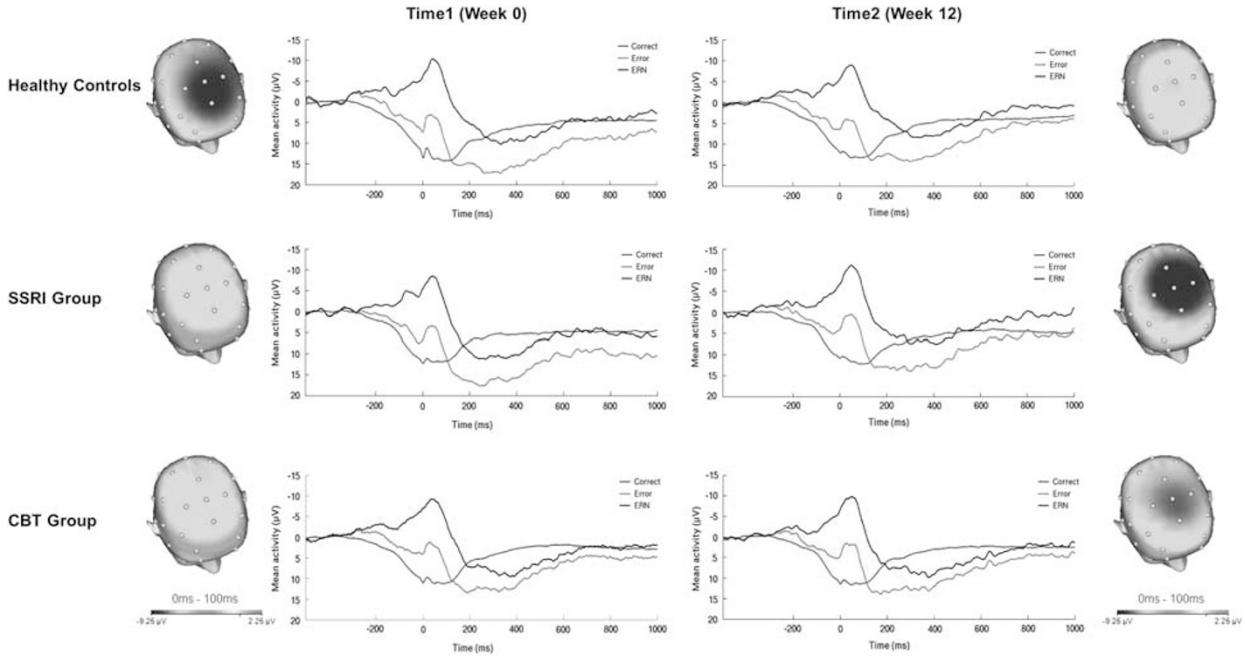

Figure 2 Response-locked ERP waveforms for healthy controls ($n = 26$), individuals randomized to SSRIs ($n = 23$), and individuals randomized to CBT ($n = 37$) at Time 1 (pre-treatment) and Time 2 (post-treatment). Green lines correspond to correct responses, red lines to errors, and black lines to the ΔERN or the error minus correct difference waveform. Topographic scale maps of neural activity depict the error minus correct difference 0–100 ms after the response. CBT, cognitive-behavioral therapy; SSRIs, selective serotonin reuptake inhibitors. A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

For change in HAM-A symptoms, there were no main effects of treatment arm or T1 ERN_{resid}. There was also no significant treatment arm × T1 ERN_{resid} interaction.

Change in the ERN Pre- to Post-Treatment

Results of the omnibus ANOVA indicated that there was no significant main effect of time on the ERN_{resid} ($F[1, 83] = 0.03$, $p = 0.86$, $np^2 < 0.01$). There was also no main effect of treatment ($F[1, 83] = 0.99$, $p = 0.32$, $np^2 < 0.01$); however, there was a time × treatment interaction ($F[2, 83] = 3.91$, $p = 0.02$, $np^2 = 0.09$). Within the healthy controls and patients randomized to CBT, there was no effect of time on the ERN_{resid} (controls: $t[25] = -1.73$, $p = 0.10$; CBT patients: $t[36] = -0.83$, $p = 0.41$). In contrast, for individuals randomized to SSRIs, ERN_{resid} amplitude significantly increased from pre-to-post treatment ($t[23] = 1.96$, $p = 0.04$) (Figure 2).

With regard to symptom change, across all patients, the extent of change in the ERN_{resid} from T1 to T2 did not correlate with change in HAM-A ($r = -0.03$, $p = 0.85$) or IDAS fear symptoms ($r = 0.09$, $p = 0.48$). Within the SSRI group specifically, there was also no association between change in ERN_{resid} and change in HAM-A ($r = -0.04$, $p = 0.88$) or IDAS fear symptoms ($r = 0.28$, $p = 0.24$).

DISCUSSION

Results of the current study indicated that within a comorbid anxiety disorder patient population, baseline ERN was a significant treatment moderator such that a more enhanced baseline ERN was associated with greater reduction in fear-based anxiety symptoms within individuals who received CBT but not SSRIs. Results of the study also indicated that the ERN is modulated by SSRI but not CBT treatment. Among patients randomized to SSRIs, the ERN increased pre- to post-treatment, whereas among patients randomized to CBT and healthy controls, the ERN remained relatively stable. Together, these novel findings highlight that baseline ERN can help guide treatment decisions regarding engagement in CBT or SSRIs. Findings also suggest that SSRIs have the capacity to alter individual differences in the ERN.

The present findings provide important information regarding the utility of the ERN for guiding treatment decision-making. Within individuals randomized to CBT, but not SSRIs, an enhanced ERN was associated with *greater* reduction in anxiety symptoms, specifically fear-based anxiety and not broad, non-specific anxiety. This treatment moderation finding suggests that individuals with an enhanced pre-treatment ERN who report ongoing fear symptoms such as panic, social anxiety, phobias, and/or traumatic intrusions or avoidance achieve greater levels of symptom relief with CBT than individuals with a more blunted ERN. Patients with an enhanced ERN could therefore be screened and guided towards CBT during treatment decision-making or the ERN could one day be used in a larger objective algorithm for guiding patients to the most appropriate treatment based on their personalized neural and behavioral profile.

The results revealed that an enhanced ERN was associated with preferential CBT outcomes and it is interesting to consider the mechanisms that may underlie this specific finding. Theory and data suggest that cognitive-behavioral therapies achieve fear reduction via inhibitory learning or the development of new inhibitory memories that compete with original excitatory memories to reduce fear expression

(Craske *et al*, 2008). Although SSRIs also reduce fear, the mechanisms involve less direct learning and more pharmacological regulation of neural circuitry (Phan *et al*, 2013). It is possible that individuals with an enhanced ERN achieve better outcomes in the context of structured, new learning and worse outcomes in the absence of such direct manipulations. If conceptualizing the ERN as an indicator of threat sensitivity (Hajcak and Foti, 2008), it is possible that individuals who are highly sensitive to threat display increased CBT engagement and attention towards threat stimuli during CBT exercises which in turn facilitates new learning and reduces fear symptoms (Price *et al*, 2011). Considering other cognitive theories of the ERN, it is also possible that an increased ERN at baseline reflects an enhanced learning signal and greater working memory and executive capacity (Larson and Clayson, 2011), which sets the stage for increased cognitive gains and improved outcomes within the CBT framework. More specifically, individuals with an enhanced ERN may have better pre-treatment cognitive capabilities and consequently, achieve better CBT outcomes given that CBT requires memory retention and the ongoing use of cognitive and attentional resources (Mohlman and Gorman, 2005; Wild and Gur, 2008).

We did not originally hypothesize that an enhanced ERN would be associated with change in fear symptoms, only. However, within this sample, we have previously shown that the ERN is more related to current fear-based anxiety than distress/misery symptoms (Gorka *et al*, 2017), and our broad anxiety measure (ie, HAM-A) notably taps into aspects of depression and distress/misery. It is therefore possible that the ERN is a better predictor of change in fear symptoms because it is a more robust and reliable indicator of the fear-based dimension of psychopathology. Thus, although our findings were observed across individual anxiety disorder diagnoses, pre-treatment ERN screening may be particularly useful for patients presenting to treatment with a fear-based anxiety disorder (eg, PD, SAD) and less useful for distress/misery anxiety disorders such as GAD. Interestingly, the two prior studies testing whether the ERN is a treatment moderator failed to find significant effects (Hajcak *et al*, 2008; Riesel *et al*, 2015) and neither included fear patients or measured fear-based anxiety symptoms suggesting that there may be some specificity to ERN treatment moderation within the anxiety disorder spectrum.

In addition to treatment moderation, the current study also investigated the extent to which individual differences in the ERN change pre- to post-treatment. The ERN is often conceptualized as a stable, trait-like individual difference factor (Olvet and Hajcak, 2008) and indeed, studies have shown that the ERN is stable over 2 years in healthy individuals, is moderately heritable, and related to specific genotypes (Anokhin *et al*, 2008; Weinberg and Hajcak, 2011). The handful of existing treatment studies have also indicated that the ERN is relatively stable pre- to post-treatment (Hajcak *et al*, 2008; Riesel *et al*, 2015) and no differences in ERN amplitude have been observed between medicated (including the use of SSRIs) and unmedicated OCD patients (Stern *et al*, 2010). However, none of these prior studies have examined the impact of CBT and SSRIs separately and none have included a transdiagnostic anxiety disorder patient sample. The present findings contribute to this literature by corroborating that the ERN is relatively unchanged post-CBT but suggest that SSRIs can increase ERN amplitude in a non-OCD anxiety disorder sample. The ERN is therefore not entirely trait-like and can be manipulated pharmacologically, which is supported by non-treatment studies demonstrating that the ERN is attenuated by alcohol (Ridderinkhof *et al*, 2002) and enhanced by stimulants (Riba *et al*, 2005). Notably, the ERN is posited to be mediated by dopamine neurotransmission in the ACC (Holroyd and Coles, 2002), which is why the ERN is sensitive to acute administration of substances such as stimulants. Although SSRIs are not directly linked to the dopaminergic system, dopamine and serotonin are known to interact and SSRIs modulate several dopamine receptor subtypes (Ainsworth *et al*, 1998; Renard *et al*, 2001), including D2 receptors in the ACC (Klimke *et al*, 1999; Larisch *et al*, 1997). Thus, SSRI's indirect effects on dopamine may have contributed to the present change in ERN pre- to post-SSRIs but not CBT.

We found that SSRIs increased the ERN, not decreased as one may expect. At the same time, within individuals randomized to SSRIs, there was no corresponding increase in anxiety symptoms and treatment outcomes were equivalent in the CBT and SSRI groups. Change in ERN amplitude also did not correlate with change in anxiety symptoms. This pattern of results suggests that there is a disassociation between SSRI-related increases in ERN amplitude and current levels of anxiety symptomatology in patients. It also raises the possibility that the increase in the ERN observed post-SSRIs is a transient phenomenon that reflects dynamic shifts and changes in ACC circuit functioning that are eventually consolidated along with successful symptom reduction. Given that ERN amplitude has been shown to map onto levels of anxiety symptoms (Moser *et al*, 2013; Gorka *et al*, in press), it is possible that an exaggerated ERN immediately following SSRI treatment would, over time, decrease to match the level of post-treatment anxiety symptoms and/or anxiety risk. At the same time, if SSRIs do increase ERN amplitude, especially if they do so more chronically, they may serve as a targeted (adjunct) therapy for certain populations that are known to have blunted ERN and poor error processing such as individuals with illicit substance use disorders (Franken *et al*, 2007) and high levels of externalizing traits (Hall *et al*, 2007). Given that the present study only included two assessments (pre- and post-treatment), it will be important for future studies to better map the time course of ERN changes following SSRI treatment and assess their clinical utility in samples with known ERN deficits (eg, substance users).

There were several limitations of the current study. First, due to the RDoC strategy of open enrollment of any anxiety disorder there was an unequal number of individual diagnoses which prevents us from examining diagnostic groupings individually. Though this was never the intention of the RDoC approach, future studies may benefit from examining whether these effects are specific for certain diagnostic groups, especially fear-based anxiety disorders. Second, the naturalistic patient sample had high levels of comorbidity. This enhances the external validity of the present findings but also highlights a potential impact of co-occurring psychopathology on the pattern of results. Third, there are several additional factors that are known to influence the ERN (eg, attention-deficit hyperactivity

disorder (ADHD)) and not all variables were measured and accounted for in the present analyses. Fourth, the present study addressed several aims and therefore included numerous statistical models. Taking this into account, the primary findings would not survive correction for multiple comparisons (eg, Bonferroni correction) and therefore require replication. Lastly, the current study only included two assessment points and in order to accurately model state and trait ERN influences and course of symptoms over time, additional assessment points are needed.

The current study indicates that within anxiety disorder patients, the ERN increases after 12 weeks of SSRIs but not 12 weeks of CBT. The ERN is therefore sensitive to pharmacological manipulation within anxious individuals and it may be possible to target the ERN with novel compounds or drugs to ultimately reduce anxiety symptoms and/or anxiety risk. The findings also indicate that the ERN holds promise as an objective psychophysiological tool for the precision medicine approach as patients with an enhanced, pre-treatment ERN were found to achieve better fear symptom reduction during CBT than individuals with a less enhanced ERN. Given that the ERN is a cost-effective, reliable neural measure, research should continue to explore and validate its use in the clinic.

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