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Increased Error-Related Brain Activity Distinguishes Generalized Anxiety Disorder With and Without Comorbid Major Depressive Disorder

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Abstract

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are so frequently comorbid that some have suggested that the 2 should be collapsed into a single overarching "distress" disorder. Yet there is also increasing evidence that the 2 categories are not redundant. Neurobehavioral markers that differentiate GAD and MDD would be helpful in ongoing efforts to refine classification schemes based on neurobiological measures. The error-related negativity (ERN) may be one such marker. The ERN is an event-related potential component presenting as a negative deflection approximately 50 ms following an erroneous response and reflects activity of the anterior cingulate cortex. There is evidence for an enhanced ERN in individuals with GAD, but the literature in MDD is mixed. The present study measured the ERN in 26 GAD, 23 comorbid GAD and MDD, and 36 control participants, all of whom were female and medication-free. Consistent with previous research, the GAD group was characterized by a larger ERN and an increased difference between error and correct trials than controls. No such enhancement was evident in the comorbid group, suggesting comorbid depression may moderate the relationship between the ERN and anxiety. The present study further suggests that the ERN is a potentially useful neurobiological marker for future studies that consider the pathophysiology of multiple disorders in order to construct or refine neurobiologically based diagnostic phenotypes.

Keywords

error-related negativity; generalized anxiety disorder; major depressive disorder; anterior cingulate cortex; event-related potential

Generalized anxiety disorder (GAD) and major depressive disorder (MDD) are among the most frequently comorbid Axis I disorders. Between 60% and 70% of individuals with GAD report a lifetime history of MDD (R. Carter, Wittchen, Pfister, & Kessler, 2001; Kessler, DuPont, Berglund, & Wittchen, 1999), and as many as 63% of individuals with MDD report lifetime experience with GAD (Fava et al., 2000). Some portion of this overlap may derive from shared diagnostic criteria (e.g., fatigue, poor concentration, sleep disturbance; Mennin, Heimberg, Fresco, & Ritter, 2008; Mineka, Watson, & Clark, 1998), but there is also substantial evidence for a shared genetic diathesis (Hettema, Neale, Myers, Prescott, & Kendler, 2006; Kendler, Neale, Kessler, Heath, & Eaves, 1992), shared childhood risk factors (Moffitt et al., 2007), and similarities in response to pharmacological treatment between the two disorders (Kuzma & Black, 2004; Watson, 2005). Combined, this body of evidence has led some to suggest that the two disorders might be better conceptualized as

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nondistinct expressions of a single, underlying disease process (Watson, 2005), and that simultaneous occurrence of GAD and MDD might simply signal greater severity (Merikangas et al., 2003; Mineka et al., 1998).

Despite both phenotypic and genotypic overlap, there is also evidence that GAD and MDD have distinct courses, predictors, and correlates (Aldao, Mennin, Linardatos, & Fresco, 2010; Beesdo, Pine, Lieb, & Wittchen, 2010; Moffitt et al., 2007; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000). There is also evidence that the two disorders demonstrate separable associations with impairment (Mennin et al., 2008; Stein & Heimberg, 2004), suggesting that these may be distinct, albeit related, phenomena.

Differences in motivational orientation may be helpful in clarifying the boundaries between GAD and MDD. Theoretical models of the overlap of the two disorders posit that high trait negative affect (NA) is common to both phenomena (Tellegen, 1985; Watson, Clark, & Carey, 1988), but that anhedonia and broad deficits in approach motivation may be unique to depression and may indeed constitute a core deficit of the disorder (Davey, Yucel, & Allen, 2008; Eshel & Roiser, 2010; Joiner, Catanzaro, & Laurent, 1996; Martin-Soelch, 2009; Snaith, 1993; Watson et al., 1988; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995). There is also accumulating evidence that MDD is characterized by physiological hypoarousal characteristic of motivational disengagement (Klinger, 1975; Lang, McTeague, & Cuthbert, 2007; Nesse, 2000; Rottenberg, Gross, & Gotlib, 2005; Shankman, Klein, Tenke, & Bruder, 2007).

Although there is evidence for autonomic suppression and inflexibility associated with worry and GAD (e.g., Borkovec, Lyonfields, Wiser, & Deihl, 1993; Lyonfields, Borkovec, & Thayer, 1995; Thayer, Friedman, & Borkovec, 1996), the disorder is also frequently characterized by hyperactive defensive mobilization (Lang, Bradley, & Cuthbert, 1998; Mogg & Bradley, 2005; Nitschke et al., 2009; Weinberg & Hajcak, 2011a; Weinberg, Olvet, & Hajcak, 2010) that underlies physiological hyperarousal and hypervigilance for threats (MacNamara & Hajcak, 2010; Ray et al., 2009; Weinberg & Hajcak, 2011a; Weinberg et al., 2010). These data suggest that comorbid MDD may mask or even alter the relationship between GAD and measures of motivational engagement and mobilization of defensive resources (Lang et al., 2007; McTeague & Lang, in press). However, relatively little work to date has explicitly examined GAD with and without MDD despite models of, and high rates of, comorbidity.

Combining biological evidence with traditional diagnostic tools may be helpful in clarifying sources of homogeneity and heterogeneity across the disorders (Cuthbert & Insel, 2010; Sanislow et al., 2010). For example, there is evidence that, although individuals with MDD and comorbid MDD and GAD express lower basal cortisol levels than healthy controls, individuals with GAD alone do not (Phillips et al., 2011). Furthermore, comorbid depression can attenuate the degree of fear-potentiated startle seen in multiple anxious groups, including GAD (Lang & McTeague, 2009; McTeague & Lang, in press). These data collectively suggest that GAD and MDD do not exert identical effects on neurobiological and psychophysiological markers; moreover, comorbid depression in GAD may result in decreased mobilization of defensive resources in the face of threat. Given these data, it seems that improved identification of common and distinct elements of the neurobiological underpinnings of the two disorders also may be helpful in improving diagnostic classification schemes as they move forward (Cuthbert & Insel, 2010; Sanislow et al., 2010).

In this context, the present study evaluated the neural response to errors among individuals with GAD and individuals with comorbid GAD/MDD. Errors are motivationally salient events that can threaten an individual’s safety and demand both attention and corrective

action (Olvet & Hajcak, 2008; Vaidyanathan, Nelson, & Patrick, 2012; Weinberg, Riesel, & Hajcak, 2012). Errors prompt a cascade of physiological changes that suggest defensive motivational response in preparation for action, including skin conductance response, heart rate deceleration (Hajcak, McDonald, & Simons, 2003b, 2004), potentiated defensive startle reflex (Hajcak & Foti, 2008; Riesel, Weinberg, Moran, & Hajcak, in press), and pupil dilation (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005).

Moreover, neural markers of error processing are well characterized. The error-related negativity (ERN) is a response-locked negative deflection in the event-related potential (ERP) resulting from the commission of an error. The ERN has a central–frontal scalp distribution and is maximal approximately 50 ms following erroneous responses. Variation in the ERN relates to individual differences in sustained defensive reactivity (for a review, see, e.g., Weinberg et al., 2012). In addition, the ERN has excellent test–retest reliability (Olvet & Hajcak, 2009b; Segalowitz et al., 2010; Weinberg & Hajcak, 2011b), suggesting it is trait-like (Riesel et al., in press; Weinberg et al., 2012). Indeed, some have proposed that the ERN represents a neural indicator of a *neurobehavioral trait* (Patrick & Bernat, 2010): a stable individual difference with direct referents in both neurobiology and behavior (Vaidyanathan et al., 2012; Weinberg et al., 2012). More specifically, the ERN is a trait-like neural response to errors, and its amplitude is determined by both heritable and environmental influences (Weinberg et al., 2012). The ERN may thus provide a basis for better understanding broad individual differences in cognition, personality, and psychopathology.

Electroencephalographic (EEG) source localization (Holroyd, Dien, & Coles, 1998; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006), magnetoencephalography (Miltner et al., 2003), and intracerebral recording (Brázdil, Roman, Daniel, & Rektor, 2005; Pourtois et al., 2010) indicate that the ERN is generated in the anterior cingulate cortex (ACC), and these results are consistent with functional MRI studies (C. Carter et al., 1998; Cohen, Botvinick, & Carter, 2000; van Veen & Carter, 2002). The ACC is part of the medial–prefrontal cortex (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004) and responds to both cognitive conflict and aversive affective information (Bush, Luu, & Posner, 2000).

Abnormal activity in the ACC has been linked to anxiety disorders in general (Davidson, Abercrombie, Nitschke, & Putnam, 1999; Paulus, Feinstein, Simmons, & Stein, 2004; Phan et al., 2005) and GAD in particular (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; McClure et al., 2007; Whalen et al., 2008). Consistent with these data, there is a well-established relationship between anxiety and the magnitude of the ERN. An increased ERN was first reported in patients with obsessive–compulsive disorder (Gehring, Himle, & Nisenson, 2000), a result that has since been replicated in several labs (Endrass, Klawohn, Schuster, & Kathmann, 2008; Hajcak, Franklin, Foa, & Simons, 2008; Johannes et al., 2001). More recently, evidence has emerged for an enhanced ERN in individuals with GAD (Weinberg et al., 2012; Xiao et al., 2011). Studies also have reported increased error-related brain activity in participants who report high trait levels of worry (Hajcak, McDonald, & Simons, 2003a), punishment sensitivity (Boksem, Tops, Wester, Meijman, & Lorist, 2006), and NA (Hajcak et al., 2004; Luu, Collins, & Tucker, 2000).

Although the ERN is related to ACC activity and high trait NA—and both GAD and MDD are characterized by high NA and abnormal ACC activity (Pizzagalli et al., 2006)—evidence for modulation of the magnitude of the ERN in MDD has been mixed. Some studies have found increased amplitude of the ERN in depressed populations (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008, 2010), whereas other studies have demonstrated either no difference from controls or a decreased amplitude of the ERN among depressed individuals (Olvet, Klein, & Hajcak, 2010; Ruchsow, Herrnberger, et al., 2006; Ruchsow et al., 2004;

Schrijvers et al., 2008, 2009). Recently, we proposed that these discrepant findings may relate to the relative balance of anxiety and depressive symptoms (Olvet et al., 2010). However, most studies examining the ERN in depression have not systematically considered the role of comorbid anxiety.

It may be the case that the increased ERN associated with anxiety is moderated by concurrent depression because of diminished motivational engagement. Thus, whereas GAD alone may be associated with an enhanced ERN, comorbid MDD might attenuate the ERN. The present study examined the potentially opposing effects of anxiety and depression on the ERN by determining how the relation of GAD/anxiety to the ERN is impacted by comorbid MDD/depression. It was hypothesized that the magnitude of the ERN would be enhanced in individuals with "pure" GAD (that is, without comorbid MDD) compared with healthy controls (Weinberg et al., 2012; Xiao et al., 2011). However, it was further anticipated that the ERN would be reduced in individuals who meet criteria for both GAD and MDD compared with those with GAD alone. Finally, no difference in the magnitude of the ERN between individuals with comorbid GAD/MDD and healthy controls was predicted.

Method

Participant Recruitment and Screening

Because prevalence rates of both GAD and MDD are higher in females (Carter et al., 2001; Hyde, Mezulis, & Abramson, 2008) and to increase the homogeneity of the sample, only female participants were recruited for the present study. Subsequent to approval by the institutional review board at Stony Brook University, participants were recruited from the community via electronic and print advertisements. All potential participants were phone-screened prior to their arrival to rule out current psychotropic medication usage and history of traumatic brain injury or systemic or neurological illness. In addition, the phone screen consisted of a modified version of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), a brief semistructured diagnostic interview designed to screen for 17 Axis I disorders. Two-hundred and thirty-six potential participants underwent the full screening. Based on responses to the phone screening, 90 participants (38%) who were either (a) likely to meet criteria for current GAD and no other current Axis I diagnoses, or (b) likely to meet criteria for current GAD and current MDD but no other current Axis I diagnoses, or (c) unlikely to meet criteria for any Axis I diagnoses, past or present, were invited to come to the lab.

Once in the lab, all participants were administered the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (4th ed.; *DSM–IV*; SCID-I; Spitzer, Williams, Gibbon, & First, 1992) prior to EEG recording. The SCID-I is a well-validated semistructured interview that provides a framework on which to make *DSM–IV* Axis I diagnoses. The SCID-I was administered by one of three master's-level clinicians. Each of the three clinicians was trained via SCID-I videos and supervision and feedback from two of the senior authors (GH, DNK). In addition, although interrater reliability is not available for the current study, kappas were calculated for a separate anxiety/depression study conducted in an outpatient psychiatric sample based on eight interviews for each interviewer. For the same three interviewers, kappas in assessment of anxiety and mood disorders tended to be quite high (e.g., .88 to .92 range).

In the current study, the *DSM–IV* hierarchy rule for GAD and unipolar mood disorders was followed such that those individuals who met full criteria for MDD and (a) also met full criteria for GAD, but whose GAD symptoms did not predate their current MDD episode or

(b) also presented with subthreshold symptoms of GAD were classified as MDD-only and were excluded from the current sample.

Self-Report

In addition to the SCID-I, a short form of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson & Clark, 1991) was administered to obtain a measure of symptom severity. The MASQ is a 62-item self-report measure of mood and anxiety symptoms. Participants were asked to rate each item based on how much they had experienced it in the past week, using a scale from 1 = *not at all* to 5 = *extremely*. The MASQ has four subscales: General Distress Depressive Symptoms (GDD; 12 items), General Distress Anxious Symptoms (GDA; 11 items), Anhedonic Depression (AD; 22 items), and Anxious Arousal (AA; 17 items). MASQ subscales have good internal consistency and convergent and discriminant validity (Watson, Weber, et al., 1995).

Participants

A total of 28 participants who met diagnostic criteria for GAD participated in the study, along with 25 participants who met diagnostic criteria for both GAD and MDD, and 37 healthy control (HC) participants who did not meet criteria for any Axis I disorder. One HC, two GAD, and two comorbid participants were excluded because they committed fewer than six errors (per Olvet & Hajcak, 2009c). The final sample therefore consisted of 26 GAD participants, 23 comorbid participants, and 36 HC participants. In addition, a combination of human and computer error resulted in the loss of self-report (i.e., MASQ) data from five GAD, three comorbid, and seven HC participants. Therefore, results involving the MASQ are based on 21 GAD, 20 comorbid, and 29 HC participants. All participants were paid $20/hr for their participation in the study.

Means and standard deviations for demographic and clinical variables are presented in Table 1. The mean age of the sample was 24.09 years (SD = 7.31); 50.7% of the sample was Caucasian, 15.9% was African American, 20.3% was Asian or Asian American, 15.7% was Latino/Hispanic, 5.8% endorsed multiple racial identities, and 7.2% self-identified as “other.” Education levels of the participants were as follows: 65.9% of the sample were either currently in college or had completed part of their college education, 7.1% had completed a 2-year college, 3.5% had completed a 4-year college, 21.2% were either currently working on or had completed graduate degrees, and 2.4% had completed high school only. There were no significant differences between the GAD, comorbid, and HC groups on any demographic variables.

Means, standard deviations, and omnibus analysis of variance (ANOVA) values for the MASQ subscales, number of past depressive episodes, and clinician-rated GAF ratings from the SCID-I are also presented in Table 1. As noted, each of the four subscales of the MASQ differentiated the three groups such that the HC group had lower scores on each of the four subscales than either of the two clinical groups. MASQ GDD, $t(36) = 3.04$, $p < .05$, and AD, $t(36) = 4.44$, $p < .001$, differentiated the GAD and comorbid groups such that the comorbid group was higher on each scale. GAD did not differ from comorbid GAD and MDD on GDA, $t(36) = 0.60$, $p = .55$, or on AA, $t(36) = 0.32$, $p = .75$. In addition, HC participants had higher GAF scores than either clinical group, and the GAD group was rated as higher functioning than the comorbid group, $t(47) = 2.51$, $p < .05$. Similarly, the groups differed on the number of past depressive episodes, with comorbid participants experiencing more past episodes, $t(47) = 3.45$, $p < .001$, than GAD participants.

Task and Materials

An arrow version of the flanker task (Eriksen & Eriksen, 1974) was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) to control the presentation and timing of all stimuli. Each stimulus was displayed on a 19-in. (48.3-cm) monitor. On each trial, five horizontally aligned arrowheads were presented. Half of all trials were compatible ("<<<<<" or ">>>>>") and half were incompatible ("< < > < <" or "> > < > >"). The order of compatible and incompatible trials was random. Each set of arrowheads occupied approximately 1.3° of visual angle vertically and 9.2° horizontally. All stimuli were presented for 200 ms followed by an intertribal interval that varied randomly from 2,300 to 2,800 ms.

Procedure

After a brief description of the experiment, EEG electrodes were attached and the subject was given detailed task instructions. All participants performed multiple tasks during the experiment. The order of the tasks was counterbalanced across participants, and the results of other tasks are reported elsewhere. Participants were seated at a viewing distance of approximately 24 in. (61 cm) and were instructed to press the *right* mouse button if the center arrow was facing to the right and to press the *left* mouse button if the center arrow was facing to the left. Information about each response (e.g., reaction time [RT], accuracy) was recorded. Participants performed a practice block containing 30 trials during which they were instructed to be both as accurate and fast as possible. The actual task consisted of 11 blocks of 30 trials (330 trials total) with each block initiated by the participant. To ensure that participants would maintain an optimal accuracy level throughout the experiment, participants received feedback based on their performance at the end of each block. Participants who respond too rapidly to stimuli may make multiple errors without attending to them sufficiently. Therefore, if performance was 75% correct or lower, the message "Please try to be more accurate" was displayed. On the other hand, some participants may adopt a cautious response style to limit the number of errors they make. Because commission of at least six errors is necessary for analysis of the ERN (Olvet & Hajcak, 2009c), performance above 90% correct was followed by "Please try to respond faster." If performance was between 75% and 90% correct, the message "You're doing a great job" was displayed.

Psychophysiological Recording, Data Reduction, and Analysis

Continuous EEG recordings were collected using an elastic cap and the BioSemi ActiveTwo system (BioSemi, Amsterdam, Netherlands). Thirty-four electrode sites were used, based on the 10/20 system, as well as two electrodes on the right and left mastoids. Electro-oculogram generated from eye movements and eyeblinks was recorded using four facial electrodes: horizontal eye movements (HEM) were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Vertical eye movements (VEM) and blinks were measured via two electrodes placed approximately 1 cm above and below the right eye. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 1× by a BioSemi ActiveTwo system. The data were digitized at 24-bit resolution with a least significant bit value of 31.25 nV and a sampling rate of 1,024 Hz, using a low-pass fifth order sinc filter with −3-dB cutoff point at 208 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode, located between PO3 and POz, producing a monopolar (nondifferential) channel. CMS forms a feedback loop with a paired driven right leg electrode, located between POz and PO4, reducing the potential of the participants and increasing the common mode rejection ratio. Offline, all data were referenced to the average of the left and right mastoids and bandpass filtered with low and high cutoffs of 0.1 and 30 Hz, respectively.

Eyeblink and ocular corrections were conducted using both VEM and HEM channels per a modification of the original algorithm published in Gratton, Coles, and Donchin (1983).

A semiautomatic procedure was employed to detect and reject artifacts. Data from individual channels were rejected if a voltage step of more than 50.0 μV between sample points or a voltage difference of 300.0 μV within a trial existed. In addition, data were identified as artifacts if a voltage difference of less than 0.50 μV within 100-ms intervals was present. Visual inspection of the data was then conducted to detect and reject any remaining artifacts.

Response onset was defined as the initiation of the behavioral response (i.e., the click of the mouse button) by the subject. The EEG was segmented for each trial beginning 500 ms before each response onset and continuing for 1,500 ms (i.e., for 1,000 ms following the response), and a 200-ms window from −500 to −300 ms prior to response onset served as the baseline. The ERN was evaluated as the average area of activity on error trials from response onset to 100 ms (i.e., 0 to 100 ms) at a pooling of Cz and FCz (where error-related brain activity was maximal). In addition, the correct response negativity (CRN) was evaluated in the same time window and sites on correct trials. An average of each component was then created for each subject.

Because the CRN appears to measure generic response monitoring (e.g., Simons, 2010), and a negative deflection is typically present on both error and correct trials (e.g., Burle, Roger, Allain, Vidal, & Hasbroucq, 2008; Suchan, Jokisch, Skotara, & Daum, 2007), it is often critical to examine not just the ERN and CRN themselves but also the difference between them (ERN minus CRN) to separate activity unique to error processing from activity more broadly related to response monitoring. For example, both the ERN and CRN appear to be enhanced following trials characterized by greater conflict (e.g., Bartholow et al., 2005; Yeung, Botvinick, & Cohen, 2004), but the ERN is additionally enhanced by the commission of an error. Difference scores for error minus correct trials were therefore calculated for each subject in the time window of the ERN/CRN—this is referred to as the ΔERN. This difference score typically demonstrates superior convergent validity to the ERN or CRN alone (Riesel et al., in prep), as well as reliability comparable to the ERN or CRN alone, in sessions separated by 2 weeks (Olvet & Hajcak, 2009b) or 2 years (Weinberg & Hajcak, 2011b). This suggests that it is not only neural responses to correct and error responses themselves that are stable across time, but also the degree to which these responses are differentiated.

Behavioral measures included both the number of error trials for each subject and accuracy expressed as a percentage of trials with correct responses. Average RTs on error and correct trials were also calculated separately. Number of errors, accuracy on trials following errors (i.e., double errors), and posterror RT were also evaluated to determine whether there were group differences in posterror behavior. Trials were removed from analysis if RTs were faster than 200 ms or slower than 1,000 ms (1.05% of all trials).

All statistical analyses were conducted using SPSS (Version 17.0) General Linear Model software, with Greenhouse–Geisser correction applied to p values associated with multiple-df, repeated measures comparisons when necessitated by violation of the assumption of sphericity. Group scores on each subscale of the MASQ as well as number of past depressive episodes and the clinician-rated GAF scores were compared using one-way ANOVAs, followed by post hoc independent-samples t tests. Pearson's chi-square tests were used to compare the groups on demographic variables, as well as to compare the two clinical groups on history of psychopathology. To evaluate differences in RT, posterror slowing, and activity in the time window of the ERN/CRN, we conducted three 2 (response type: correct

or error) × 3 (group: GAD, comorbid, and HC) mixed-model ANOVAs. One-way ANOVAs were then used to compare the groups on number of errors, accuracy, number of double errors, and accuracy following errors. In the time window of the ERN, three one-way ANOVAs were also run to compare the groups on the magnitude of the ERN alone, the CRN alone, and ΔERN. Following this, three Fisher's least significant difference (LSD) *t* tests were conducted for planned interaction contrasts comparing the magnitude of ΔERN between groups. One 2 (response type: correct or error) × 2 (group: GAD with and without a history of depression) mixed-model ANOVA was conducted to compare individuals with GAD with and without a past history of MDD. Finally, the Pearson correlation coefficient (*r*) was used to examine the relationship between self-reported and clinician-reported symptom measures and error-related brain activity.

Results

Behavioral Data

Accuracy and RT data are presented in Table 2. RT varied as a function of accuracy, $F(1, 82) = 192.32$, $p < .001$, $\eta_p^2 = .70$, such that participants were faster on error ($M = 342.95$, $SD = 50.39$) than correct trials ($M = 438.33$, $SD = 72.81$). However, the groups did not differ in RT, $F(2, 82) < 1$, $\eta_p^2 = .003$, nor did the effect of trial type vary as a function of group, $F(2, 82) < 1.00$, $\eta_p^2 = .01$. In addition, the GAD, comorbid, and HC groups made comparable numbers of errors, $F(2, 82) = 1.57$, $p > .20$, and had comparable accuracy, $F(2, 82) = 1.80$, $p > .15$.

Posterror accuracy and RT data are also presented in Table 2. There was a main effect of trial type, $F(1, 82) = 30.71$, $p < .001$, $\eta_p^2 = .28$, such that participants were slower on trials that occurred after an error ($M = 427.07$, $SD = 93.53$) than on trials occurring after a correct response ($M = 393.92$, $SD = 63.28$). However, the groups did not differ in posterror RT, $F(2, 82) < 1$, $\eta_p^2 = .01$, nor did the effect of trial type vary as a function of group, $F(2, 82) < 1$, $\eta_p^2 = .02$. Finally, the three groups did not differ in the number of errors committed following error trials, $F(2, 82) < 1$, or in their accuracy after error trials, $F(2, 82) < 1$.

Error-Related Brain Activity

Figure 1 presents topographic maps for the GAD (left), HC (center), and comorbid (right) groups, depicting voltage differences (in μV) across the scalp for error minus correct responses in the time window of the ERN. Grand average response-locked ERPs at a pooling of Cz and FCz, where the error minus correct difference was maximal, are also presented in Figure 1. Average ERN values are presented in Table 2.

Confirming the impression from Figure 1, the ERN ($M = 3.31$, $SD = 6.84$) was more negative than the CRN ($M = 9.89$, $SD = 6.64$) across all groups, $F(1, 82) = 156.79$, $p < .001$, $\eta_p^2 = .66$. There was no difference between the three groups in the magnitude of the overall electrocortical response (i.e., collapsing across the ERN and CRN), $F(2, 82) < 1$, $\eta_p^2 = .001$. However, the difference between the ERN and CRN varied according to group, reflected in a significant group by response interaction, $F(2, 82) = 3.72$, $p < .05$, $\eta_p^2 = .08$. One-way ANOVAs suggested that neither the magnitude of the ERN alone, $F(2, 82) < 1$, nor the CRN alone, $F(2, 82) < 1$, differentiated the three groups, although ΔERN did, $F(2, 82) = 4.00$, $p < .05$. Post hoc LSD tests confirmed that ΔERN was larger in the GAD than in the control group ($D = 3.51$, $SE = 1.28$, $p < .01$), as well as in the GAD compared with the comorbid

group (D = 2.89, SE = 1.42, p < .05). The control and comorbid groups did not differ from one another in terms of ΔERN (D = 0.62, SE = 1.32, p > .60).[1]

There is some evidence that the magnitude of the ERN is enhanced in individuals with remitted major depression (Georgiadi, Liotti, Nixon, & Liddle, 2011). To examine the possibility that the enhancement of the ERN evident in the GAD participants was related to the remission of MDD, we compared the electrocortical response in the 13 GAD participants with a past history of MDD with the 13 participants with no history of MDD. These two groups did not differ on any demographic variables or in their self-reported current symptom severity (Fs <1). As above, there was a main effect of response type (error vs. correct), F(1, 24) = 122.17, p < .001, η_p^2=.84, such that errors (M = 0.68, SD = 6.50) elicited a larger electrocortical response than correct responses (M = 10.42, SD = 7.24). There was no main effect of history of depression, F(1, 24) < 1, η_p^2=.001, nor did history of depression interact with trial type to determine response, F(1, 23) < 1, η_p^2=.02.

Relationship With Symptom Severity

Associations between error-related brain activity and the four MASQ subscales were examined, as well as with clinician-rated GAF and number of past depressive episodes, first in the whole sample and next in the two clinical groups. No electrocortical measure was significantly correlated with any clinical index in either the whole group or the clinical subsample (data available on request).

Discussion

Consistent with hypotheses, the present study replicated evidence for an enhanced ERN in individuals with GAD (Weinberg et al., 2012; Xiao et al., 2011). Furthermore, the present study demonstrated the novel finding that the relationship between GAD and the ERN is impacted by the presence of comorbid depression. Specifically, in a group of individuals who were all diagnosed with comorbid GAD and MDD, the magnitude of the ERN was decreased relative to individuals with GAD alone. Thus, the present study provides initial evidence for a neural marker that is enhanced as a function of anxiety but not anxiety with comorbid depression. If MDD alters the relationship between GAD and a neural marker, it suggests that the two constructs are not redundant. It further suggests that neurobiological markers are sensitive to differences between the two constructs that are not detected in statistical modeling of symptom data alone (e.g., Sanislow et al., 2010). The present results highlight the possible moderating effects of comorbid disorders in GAD and emphasize the need to examine or control for comorbidity in future studies.

The difference in the magnitude of the ERN was evident despite the fact that the two clinical groups reported equivalent levels of anxiety, which suggests that the diminished ERN in the comorbid group is not merely a reflection of greater anxiety, but rather that there is

[1]The error positivity (Pe) was also evaluated on error trials as the average activity at Pz from 200 to 600 ms following response onset. The same time window and site were used to evaluate activity following correct responses. In the time window of the Pe, there was a main effect of response type (error vs. correct), F(1,82) = 165.10, p < .001, η_p^2=.68, such that incorrect responses (M = 10.77, SD = 7.91) were more positive than correct responses (M = 1.68, SD = 4.35). However, there was no effect of group, F(2, 82) < 1, η_p^2=.02, nor did the effect of response type vary by group, F(2, 82) < 1, η_p^2=.01. As with the time window of the ERN, individuals with GAD with and without a history of MDD did not differ in their electrocortical response in the time window of the Pe, F(1, 23) < 1, η_p^2=.03, nor did the effect of response type vary by group, F(1, 23) < 1, η_p^2=.004. However, as above, there was a main effect of response type (error vs. correct), F(1, 23) = 54.13, p < .001, η_p^2=.70.

something specific to the presence of comorbid depression that acts to attenuate neural responses to errors. However, although the average participant in this group was only moderately depressed, the comorbid group also had lower mean GAF scores and a higher number of episodes of past depression than the GAD group, suggesting that consideration of severity and chronicity will also be important in ongoing research. Future studies exploring the relationship between depression and the ERN might therefore carefully consider the impact of anxiety, as well as the relative contributions of symptoms of anxiety and depression in the depressed sample.

The findings in the comorbid group are also apparently some-what at odds with studies that have demonstrated an enhanced ERN in clinically depressed groups (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008, 2010). As noted, in some of these studies the role of anxiety was not thoroughly examined. However, the discrepancies between studies may also be partly attributed to task differences. For example, studies that have failed to find an enhancement of the ERN in MDD have often used a simple flanker task devoid of trial-by-trial feedback (e.g., the present study; Olvet et al., 2010). In contrast, in two of the studies above, participants' responses were followed by immediate performance feedback (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008). Related to this issue, there is evidence that the presentation of evaluative feedback following responses may alter or eliminate the relationship between the ERN and anxiety (Gründler, Cavanagh, Figueroa, Frank, & Allen, 2009; Olvet & Hajcak, 2009a). Likewise, manipulations of incentive salience (e.g., associating errors with monetary gains or losses) appear to impact the magnitude of the ERN (e.g., Hajcak, Moser, Yeung, & Simons, 2005) as well as the relationship of the ERN with depression (e.g., Chiu & Deldin, 2007; Holmes & Pizzagalli, 2010). Combined, this suggests that future studies should explore the differential relationships between GAD and comorbid MDD in a variety of tasks designed to elicit errors (e.g., manipulations of incentive salience and/or feedback; per Chiu & Deldin, 2007; Holmes & Pizzagalli, 2010; Ruchsow, Beschoner, et al., 2004, 2006; Schrijvers et al., 2008, 2009).

Cognitive theories and models of error monitoring suggest that the ERN indexes an action monitoring system that functions to shape behaviors in pursuit of more favorable outcomes —both immediately and over the longer term (Holroyd & Coles, 2002; Holroyd, Yeung, Coles, & Cohen, 2005). According to these models, variation in the size of the ERN should relate to variation in behavior (Holroyd & Coles, 2002; Holroyd et al., 2005). In particular, exaggerated processing of errors should be related to increased behavioral regulation; that is, groups of individuals with larger ERNs should be characterized by fewer errors and enhanced posterror slowing or accuracy. Yet, a substantial body of clinical literature suggests at least a partial dissociation between ERN magnitude and behavioral measures (Weinberg et al., 2012). This is also true of the present study: Despite evidence for an enhanced ERN in the GAD group, no behavioral differences were observed among the three groups, although the comorbid group appeared to be characterized by a nonsignificantly increased error rate compared with both controls and individuals with GAD, along with a higher degree of variability in RTs. It is possible, therefore, that behavioral differences among the groups might become evident with greater statistical power. However, only the GAD group in the current study was characterized by an increased ERN; moreover, it is likely that the magnitude of the ERN does not simply reflect performance-related variables (Riesel et al., in press; Weinberg et al., 2012).

In addition to accumulating data to suggest that much of the variability in the ERN is trait-like (e.g., Anokhin, Golosheykin, & Heath, 2008; Olvet & Hajcak, 2009b; Riesel, Endrass, Kaufmann, & Kathmann, 2011; Segalowitz et al., 2010; Weinberg & Hajcak, 2011b), there is also evidence that these trait-like influences on the ERN may interact with state manipulations to determine the magnitude of the ERN. For example, a recent study

demonstrated that the application of an immediate punishment (i.e., an aversive noise) following errors in one condition enhanced the magnitude of the ERN in a learning and extinction period (Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012). Moreover, highly trait anxious individuals were characterized by larger punishment-related modulations of the ERN (Riesel et al., 2012). Thus, both stable individual differences and state-linked variation in motivational factors seem to modulate the ERN (Olvet & Hajcak, 2011; Endrass et al., 2010). Similarly, the present results comparing individuals with GAD with and without a history of depression suggest that, whereas the enhancement of the ERN in GAD is trait-like, the ERN is also sensitive to state-related changes in motivational disengagement that characterize depression. Thus, attenuation of the ERN related to current (but not past) depression may moderate the relation between anxiety and the ERN. Future studies following never-depressed individuals with GAD over time might further clarify the impact of changing depressive symptoms on the relation between anxiety and the ERN.

The present study also establishes the ERN as a potentially useful neurobiological referent for future research that considers the pathophysiology of multiple disorders to construct or refine neurobiologically informed phenotypes relevant for diagnoses (Insel & Cuthbert, 2009; Sanislow et al., 2010; Vaidyanathan et al., 2012; Weinberg et al., 2012;). Traditional experimental approaches with a focus on a single diagnosis have already revealed that the ERN is frequently attenuated in individuals exhibiting disinhibitory disorders and traits (e.g., Hall, Bernat, & Patrick, 2007; Herrmann et al., 2010; Mathalon, Jorgensen, Roach, & Ford, 2009; Ruchsow, Walter, et al., 2006)—perhaps related to decreased conscientiousness and motivational salience of errors (Weinberg et al., 2012). In addition, there is some evidence that, within the anxiety spectrum, “fear” disorders are unrelated to the magnitude of the ERN (Hajcak et al., 2003a; Moser, Hajcak, & Simons, 2005; Moser, Moran, & Jendrusina, 2012). These data suggest that the ERN will be useful not only in making distinctions across diagnostic categories (i.e., anxiety from depression, internalizing from externalizing) but also within diagnostic categories (i.e., anxious misery vs. fear within the anxiety disorder spectrum). Future research examining the ERN—along with other psychophysiological measures—across multiple disorders may be beneficial in ongoing efforts to establish biologically based phenotypes.

Finally, the sample in the present study may not be perfectly representative of individuals with GAD as a whole. For example, only females were recruited for the present study. There is compelling evidence that rates and expression of comorbidity of depression and anxiety differ between males and females (e.g., Breslau, Schultz, & Peterson, 1995; Fava et al., 1996; Ochoa, Beck, & Steer, 1992; Vesga-López et al., 2008). Future studies might therefore include both male and female participants to explore whether depression exerts a similar effect on the relation between anxiety and the ERN in males. In addition, this study did not include individuals with a unitary diagnosis of MDD. The inclusion of an MDD-only group in future studies might serve to further clarify how depression and anxiety interact to determine the magnitude of the ERN. For example, it is possible that an MDD-only group might exhibit a smaller ERN than the control group—especially if an MDD-only group were low on anxiety symptoms. That is, increasing disengagement with the environment in this group might be reflected in a reduced ERN (e.g., Olvet et al., 2010; Schrijvers et al., 2008).

In addition, absence of comorbidity seems to be the exception rather than the rule when it comes to GAD (Brawman-Mintzer et al., 1993), and a majority of individuals with GAD do take some form of psychotropic medications (Wittchen, Zhao, Kessler, & Eaton, 1994). Examination of the ERN in a larger and more representative sample might help clarify the relationship between anxiety, depression, and neural markers of error monitoring. Nonetheless, the results of the present study suggest that GAD and MDD are not redundant constructs, and that neurobiological evidence should be considered as new classification

schemes move forward (Cuthbert & Insel, 2010; Insel & Cuthbert, 2009; Sanislow et al., 2010).

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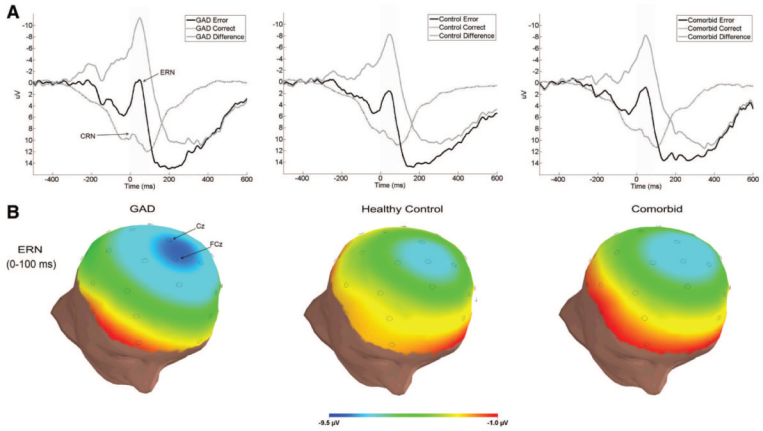

Figure 1.

(A) Response-locked event-related potential (ERP) waveforms (top) at an average of Cz and FCz for generalized anxiety disorder (GAD; left), healthy controls (HC; center), and comorbid (right) groups. For each panel, response onset occurred at 0 ms. The error-related negativity (ERN) and correct response negativity (CRN) were scored between 0 and 100 ms following response onset (area highlighted in gray). In addition to raw waveforms for correct and error responses, each panel depicts the error-correct difference (solid gray line). Per ERP convention, negative voltages are plotted up. (B) Scalp topographies (bottom) representing the ERN are also shown. These maps are derived from the average difference (error minus correct response) and represent the ΔERN for GAD (left), HC (center), and comorbid (right) groups.

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Table 1

Demographic and Clinical Characteristics of Healthy Comparison Participants and Participants With Generalized Anxiety Disorder (GAD) With and Without Major Depressive Disorder (MDD)

	GAD (n = 26)		Comorbid GAD and MDD (n = 23)		Healthy controls (n = 36)			
Characteristic	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***	***F*(2, 82)**	***p***
Age (years)	23.88	6.17	25.48	9.22	23.36	6.77	< 1	*ns*
Mood and Anxiety Symptom Questionnaire	(n = 21)		(n = 20)		(n = 29)		F(1, 64)	p
General distress (Anxiety)	24.95	8.76	26.06	4.72	15.76	4.29	20.75	<.001
General distress (Depression)	27.55 *	12.53	36.04 *	8.22	18.72	6.10	20.04	<.001
Anxious Arousal subscale	28.65	9.59	27.96	6.34	20.79	4.68	9.15	<.001
Anhedonic Depression subscale	63.50 *	16.26	78.64 *	8.64	52.72	10.36	29.05	<.001
	n	%	n	%	n	%	$\chi 2(1, 47)$	p
Past disorders								
MDD	13 *	52	17 *	74	0	0	7.45	.01
Social phobia	3	12	6	26	0	0	1.72	.27
Obsessive–compulsive disorder	2	8	1	4	0	0	0.24	1.00
Posttraumatic stress disorder	2	8	0	0	0	0	1.85	.49
Eating disorder	5	20	1	4	0	0	2.52	.19
Multiple past disorders	4	15	1	4	0	0	3.37	.07
No past disorders	9	34	14	61	36	100	1.62	.20
	Mean	*SD*	Mean	*SD*	Mean	*SD*	F(2, 82)	p
Past episodes of MDD	1.02 *	1.83	4.70 *	4.80	0	—	43.85	<.001
Clinician-rated GAF	61.08 *	5.38	57.57 *	4.26	84.65	4.24	312.22	<.001

Note. GAF = global assessment of functioning.

* The two clinical groups significantly (p < .05) differed on these items.

Table 2

Mean (Standard Deviations) Performance and Event-Related Potential (ERP) Area Measures

Variable	GAD (*n* = 26)	Comorbid (*n* = 23)	Healthy controls (*n* = 36)
Reaction time (ms)			
Error trials	334.79 (34.71)	346.45 (45.74)	345.88 (61.47)
Correct trials	439.81 (63.67)	437.14 (89.29)	436.07 (69.93)
Accuracy			
No. of errors	32.88 (22.28)	41.38 (34.38)	31.06 (18.46)
No. of correct trials	293.20 (24.61)	280.43 (39.02)	296.46 (17.74)
% correct	89.89 (6.89)	87.10 (10.77)	90.53 (5.62)
Posttrial reaction time (ms)			
Posterror trials	428.47 (79.30)	443.26 (100.25)	416.83 (100.03)
Postcorrect trials	386.18 (42.81)	405.28 (84.27)	392.96 (62.62)
Posterror accuracy			
No. of errors	6.88 (16.80)	7.25 (16.36)	3.26 (3.59)
% correct	90.15 (15.15)	90.50 (12.57)	91.67 (7.13)
ERPs (μV)			
ERN	2.11 (6.48)	3.32 (5.72)	4.18 (7.74)
CRN	10.80 (7.15)	9.37 (5.45)	9.56 (7.05)
ΔERN	−8.70 (4.20)*	−6.05 (5.40)*	−5.38 (5.19)*

Note. GAD = generalized anxiety disorder; ERN = error-related negativity; CRN = correct response negativity; ΔERN = error minus correct trials in the time window of the ERN.

*$p < .05$ for between-groups comparison.