Increased error-related brain activity in generalized anxiety disorder

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Abstract

The error-related negativity (ERN) is a negative deflection approximately 50 ms following an erroneous response, and is thought to reflect activity of the anterior cingulate cortex (ACC), a region of the medial prefrontal cortex implicated in the pathophysiology of a number of affective disorders, including generalized anxiety disorder (GAD). Pathological worry, the hallmark of GAD, has been linked to increased error-related brain activity, although no studies to date have examined the ERN among a clinical GAD sample. The present study measured electrocortical indices of error monitoring in a well-characterized, medication-free GAD sample. Brain activity was recorded in 17 GAD and 24 control subjects. The GAD group was characterized by a larger ERN and an increased difference between error and correct trials; a larger ERN was associated with increased self-reported anxiety and depression symptoms. Individuals with GAD have exaggerated early neural responses to errors, consistent with fMRI work implicating ACC abnormalities in GAD.

Keywords:
ERN
Generalized anxiety disorder
Anterior cingulate cortex
Worry
EEG
ERP

Generalized anxiety disorder (GAD), the most commonly diagnosed anxiety disorder in primary care (Ormel et al., 1994; Wittchen, 2002), is characterized by excessive, uncontrollable worry about everyday concerns (APA, 1994). In addition, deficits in executive processes related to regulatory abilities, increased doubts about actions, perfectionistic tendencies, and excessive concern over mistakes and errors are typical among individuals with GAD (Brown et al., 1993; Etkin et al., 2010; Kendall et al., 2004; Ladouceur et al., 1998; Stöber and Joormann, 2001). Research examining the neural correlates of the disorder has been limited relative to its public health impact (Etkin, 2009); however, emerging neuroimaging evidence suggests that the anterior cingulate cortex (ACC), a region of the medial prefrontal cortex associated with the integration of affective and cognitive information (Bush et al., 2000), may be critically implicated in the pathophysiology of GAD (Etkin et al., 2010; McClure et al., 2007; Nitschke et al., 2009; Paulus et al., 2010; Whalen et al., 2008).

Functionally, abnormal ACC activity in GAD has been interpreted in terms of deficits in the recruitment of executive processes such as regulating emotional responses and arresting worried thoughts (e.g., Etkin et al., 2010; McClure et al., 2007; Nitschke et al., 2009; Paulus et al., 2010; Whalen et al., 2008). A growing body of evidence indicates that the ACC is also activated during response monitoring and the commission of errors (Carter et al., 1998; Fitzgerald et al., 2005; Mathalon et al., 2003b; Ursu et al., 2003), suggesting that investigations of error monitoring may further enhance our understanding of ACC activity in anxiety disorders. Indeed, increased error-related ACC activity has been observed in both clinical obsessive–compulsive disorder (Fitzgerald et al., 2005; Ursu et al., 2003) as well non-clinical populations high in trait anxiety (Paulus et al., 2004).

In addition to ACC measures derived from the hemodynamic response, error-related brain activity is increasingly studied using the error-related negativity (ERN), a component of the event-related potential (ERP) observed following the commission of an error. The ERN is a frontocentrally maximal response-locked negative deflection in the ERP that peaks approximately 50 ms following errors, and has been observed across tasks that employ a variety of stimulus and response modalities (Bernstein et al., 1995; Holroyd et al., 1998; Van’t Ent and Apkarian, 1999) and levels of difficulty (Band and Kok, 2000; Mathalon et al., 2003a; Mathewson et al., 2005; Moser et al., 2005; Themanson et al., 2006). Source localization (Holroyd et al., 1998; Pizzagalli et al., 2006), magnetoencephalography (Miltner et al., 2003) and intracerebral recording (Bradzil et al., 2005) indicate that the ERN is generated in the ACC. Likewise, single-unit recording studies show increased error-related potentials in the ACC in monkeys (Gembai et al., 1986; Ito et al., 2003), and evidence from human lesion studies indicates that patients with ACC lesions have diminished ERNs (Stemmer et al., 2004).

Because the ACC is reliably activated by response conflict, negative feedback, pain, and errors, some suggest that the ERN may...
reflect the integration of cognitive and affective processing of errors (Hajcak and Foti, 2008; Luu et al., 2000; Luu et al., 2003; Olvet and Hajcak, 2008; Tucker et al., 2003). Consistent with this possibility, there is increasing evidence that the ERN reflects the motivational significance of errors: the magnitude of the ERN is larger when errors are more costly or significant (Chiu and Deldini, 2007; Hajcak et al., 2005; Kim et al., 2005), and when accuracy is emphasized over speed (Gehring et al., 1993).

The magnitude of the ERN also is sensitive to individual differences: an enhanced ERN has been demonstrated in a number of populations characterized by exaggerated concern over errors (e.g., Gehring et al., 2000; Hajcak et al., 2008; Hajcak et al., 2003a,b; Pizzagalli et al., 2006). An increased ERN was first reported in patients with obsessive–compulsive disorder (Gehring et al., 2000), a result which has since been replicated in several labs (Endrass et al., 2005; Hajcak et al., 2008; Hajcak and Simons, 2002; Johannes et al., 2001). Recent studies further suggest that the ERN is specifically related to trait–rather than state-anxiety, as an enhanced ERN has been shown to be insensitive to successful therapeutic treatment (Hajcak et al., 2008) and state-related changes in anxiety among phobic participants (Moser et al., 2005).

Furthermore, there is evidence for increased error-related brain activity among individuals reporting high levels of negative affect (Hajcak et al., 2004; Ladouceur et al., 2010), behavioral inhibition (Amadio et al., 2008; Boksem et al., 2006; McDermott et al., 2009) and punishment sensitivity (Boksem et al., 2006)—all personality traits elevated in multiple anxiety disorders, including GAD (Weinstock and Whisman, 2006). Although an increased ERN has been demonstrated in an analogue GAD sample of college students reporting extreme levels of worry (Hajcak et al., 2003a,b), and in a mixed pediatric anxiety sample which included GAD participants (Ladouceur et al., 2006), no studies to date have examined error-related brain activity in a clinical GAD group.

In addition to the ERN, other ERP components associated with error-responsing may be useful in understanding neural correlates of response monitoring in GAD. For example, correct responses elicit a small ERN-like component (Falkenstein et al., 2000; Ford, 1999; Gehring and Knight, 2000; Scheffers and Coles, 2000; Vidal et al., 2000) called the correct response negativity (CRN). The CRN is morphologically and topographically similar to the ERN (Luu and Tucker, 2001; Luu et al., 2004; Vidal et al., 2003; Vidal et al., 2008), and may reflect a general response monitoring process that is enhanced on error trials. In other words, it is possible that the ERN reflects a summation of neural response monitoring activity (i.e., CRN) and neural activity specifically related to error processing (e.g., Luu and Tucker, 2001). In this way, enhanced vigilance for errors, specifically, would be reflected in the magnitude of the difference between the ERN and CRN, whereas abnormal response monitoring in general might be evident as an increase in both components. Evidence from clinical samples has thus far been mixed: while several studies have found an enhanced ERN but no relationship between anxiety and the magnitude of the CRN (Gehring et al., 2000; Hajcak et al., 2008; Ruchso et al., 2005; Stern et al., 2010) others have demonstrated an enhancement of both the ERN and CRN in individuals with OCD (Endrass et al., 2008, 2010; Hajcak and Simons, 2002), anxious individuals (Hajcak et al., 2003a,b), and individuals with high trait levels of NA (Hajcak et al., 2004). Because of these mixed findings, the current study examined the relationship between GAD and the ERN, as well as the differentiation between the ERN and CRN.

In addition, following the ERN is a positive-going deflection in the waveform, the error positivity (Pe; Falkenstein et al., 2003; Nieuwenhuis et al., 2001; Overbeek et al., 2005). The Pe has a posterior midline scalp distribution, similar to a P300 orienting response (Arbel and Donchin, 2009), and is uniquely sensitive to and may reflect error awareness (Endrass et al., 2005; Leuthold and Sommer, 1999; Nieuwenhuis et al., 2001). The Pe may also be related to individual differences in the motivational salience of errors (Ridderinkhof et al., 2009); it is also sensitive to the frequency of error commission, such that individuals who commit fewer errors display a larger Pe (Falkenstein et al., 2000). Relative to the ERN, however, the Pe is less well understood (Overbeek et al., 2005) and has not yet been examined in relation to pathological worry. Evidence thus far for its relationship to individual differences has been mixed (Overbeek et al., 2005; Ridderinkhof et al., 2009). For example, though an enhanced ERN has repeatedly been demonstrated in anxious groups, significant differences in Pe amplitude have frequently not been found (Endrass et al., 2008; Hajcak et al., 2008; Ladouceur et al., 2006; McDermott et al., 2009; Ruchso et al., 2005).

Overall, the current study sought to extend prior work in non-clinical populations to examine error-related brain activity in a well-characterized community GAD sample. Because there is evidence that multiple cases of psychiatric medications differentially impact the magnitude of the ERN (e.g., de Bruijn et al., 2006; Schrijvers et al., 2008), all participants recruited for the study were also medication-free at the time of their participation. Further, only GAD participants without comorbid diagnoses were recruited to reduce potential confounds from other disorders, particularly because abnormal response to errors has also been demonstrated in depressed samples (Holmes and Pizzagalli, 2008; Olvet et al., 2010; Schrijvers et al., 2008; Schrijvers et al., 2009).

By measuring electrocortical response to correct and incorrect responses during a simple motor response task, the current study aims to examine abnormalities in neural processing of errors in an unmedicated clinical GAD sample. Based on previous research, we hypothesized that, compared to healthy controls, error-processing would be enhanced in individuals with GAD. In order to examine both differences in generic response monitoring processes and differences specific to error-processing, both the ERN and a difference score (error minus correct) were examined. Further, if the enhanced ERN represents exaggerated activity of an error-monitoring system in GAD, its magnitude might correlate with symptom severity (e.g., Gehring et al., 2000). Based on previous work in worried undergraduates (Hajcak et al., 2003a), as well as other clinical groups (e.g., Endrass et al., 2010; Gehring et al., 2000; Hajcak and Simons, 2002; Hajcak et al., 2004; Moser et al., 2005; Olvet et al., 2010; Ruchso et al., 2005; Stern et al., 2010), we hypothesized that the GAD and control groups would be comparable in terms of behavioral measures (e.g., reaction time, number of errors committed, etc.).

1. Method

1.1. Participant recruitment and screening

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, in order to rule out current anti-depressant 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 (MINI; Sheehan et al., 1998), a brief semi-structured diagnostic interview designed to screen for 17 Axis I disorders. Based on responses to the phone screen, participants who were either (a) likely to meet criteria for current GAD and no other current Axis I diagnoses or (b) 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 (DSM)-IV fourth edition (SCID-I; Spitzer et al., 1992) prior to electroencephalographic recording. The SCID-I is a well-validated semi-structured interview that provides a framework upon which to reflect DSM-IV Axis I diagnoses. The SCID was administered by four master’s-level clinicians. For each group, 5 diagnostic interviews were recorded for inter-rater reliability assessment; all 10 diagnoses were confirmed by a clinical psychologist (GH).
were presented for 200 ms followed by an ITI that varied randomly from 2300 to 4740 ms.

The Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995) 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 have 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 (12 items), General Distress Anxious Symptoms (11 items), Anhedonic Depression (22 items), and Anxious Arousal (17 items). MASQ subscales have good internal consistency, and convergent and discriminant validity (Watson et al., 1995).

A total of 20 participants (17 female) who met diagnostic criteria for GAD participated in the study along with 26 healthy control (HC) participants (16 female) who did not meet criteria for any Axis I disorder. Fifteen (2 male) GAD participants and 15 (2 male) HC participants also participated in MacNamara and Hajcak (2010); 17 (2 male) GAD and 21 (8 male) HC participants also participated in Weinberg and Hajcak (in press). Participants who committed fewer than six errors (per Overt and Hajcak, 2009) were excluded from analysis; three GAD (2 female) and two HC participants (1 female) were excluded from analysis on this basis. The final sample therefore consisted of 17 GAD participants (15 female) and 24 HC participants (15 female). In addition, a combination of human and computer error resulted in the loss of self-report data for five participants (2 GAD). Therefore, results involving the MASQ are based on 15 GAD (13 female) and 21 HC participants (13 female). All participants were paid $80.00 for their participation in the study.

Means and standard deviations for demographic variables are presented in Table 1. The mean age of the sample was 30.98 (SD = 11.67); 63% of the sample was Caucasian, 10% was African-American, 15% was Asian, and 12% was Latino/Hispanic. 48.8% of the sample were either currently in college or had completed part of their college education. 17.1% had completed a 4-year college, and 24.4% had graduate degrees. 9.8% had completed high school only. There were no significant differences between the GAD and HC groups on any demographic variables.

Among the 17 GAD participants, 9 met criteria for past major depressive episodes (MDE); at the time of their participation, none met criteria for current MDE. Three individuals in the GAD group met criteria for past panic disorder, one for past anorexia, one met criteria for past social phobia, and one met criteria for past substance abuse. Four GAD participants met criteria for multiple past disorders. Seven of the GAD participants did not meet criteria for any past disorder. None of the healthy control participants met criteria for any Axis I disorder, past or current.

1.4. Task and materials

An arrow version of the flanker task (Eriksen and Eriksen, 1974) was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, California, USA) 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 ITI that varied randomly from 2300 to 2800 ms.

After a brief description of the experiment, EEG electrodes were attached and the subject was given detailed task instructions. All GAD and HC participants performed multiple tasks during the experiment. The order of the tasks was counterbalanced across subjects and the results of other tasks were reported elsewhere (see MacNamara and Hajcak, 2010; Weinberg and Hajcak, in press). 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. 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 encourage both fast and accurate responding, participants received feedback based on their performance at the end of each block. If performance was 75% correct or lower, the message “Please try to be more accurate” was displayed; performance above 90% correct was followed by “Please try to respond faster”; otherwise, the message “You’re doing a great job!” was displayed.

1.5. Procedure

Continuous EEG recordings were collected using an elastic cap and the ActiveTwo BioSemi 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. Electrooculogram (EOG); generated from eye movements and eyeblinks was recorded using four facial electrodes: horizontal eye movements were measured via two electrodes placed approximately 1 cm above and below the right eye. The EEG signal was pre-amplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 16 x by a BioSemi ActiveTwo system (BioSemi, Amsterdam). The data were digitized at 24 bit resolution with a sampling rate of 1024 Hz using a low-pass fifth order sine filter with a half-power cutoff of 204.8 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode producing a monopolar (non-differential) channel. Offline, all data were referenced to the average of the left and right mastoids, and band-pass filtered with low and high cutoffs of 0.1 and 30 Hz, respectively; eye-blink and ocular corrections were conducted per Gratton et al. (1983).

A semi-automatic procedure was employed to detect and reject artifacts. The criteria applied were a voltage difference of more than 500 μV within a trial, and a maximum voltage difference of less than 50 μV within 100 ms intervals. These intervals were rejected from individual channels in each trial. Visual inspection of the data was then conducted to detect and reject any remaining artifacts. No trials or subjects were excluded from analyses by the experimenter with knowledge of their group membership. There was no significant difference in the number of error trials (t(39) = .98, p = .33) retained for the GAD (M = 25.35, SD = 10.11) or HC groups (M = 30.00, SD = 17.50), nor in the number of correct trials (t(39) = .80, p = .45) retained for the GAD (M = 286.94, SD = 31.36) or HC groups (M = 292.04, SD = 27.77).

The EEG was segmented for each trial beginning 400 ms before each response onset and continuing for 1400 ms (i.e., for 1000 ms following the response), and a 200 ms window from –400 to +200 ms prior to response onset served as the baseline. Because peak measures may be more sensitive to noise, or low trial numbers, (Luck, 2005), the ERP was evaluated as the average area of activity on error trials from response onset to 100 ms (i.e., –100 to 0 ms) at FCz (where error-related brain activity was maximal). In addition, the correct response negativity (CRN) was evalu-
correlation coefficient (Gender: Male and Female) mixed-model ANOVAs were conducted. The Pearson reported symptom measures and error-related brain activity. ERN and Pe, four 2 (response type: correct or error) of the assumption of sphericity. In order to evaluate differences in reaction time, with multiple-df, repeated-measures comparisons when necessitated by violation Model software, with Greenhouse-Geisser correction applied to
not differ between groups (800 ms (1.3% of all trials). The number of trials excluded based on this criterion did
to determine if there were group differences in post-error behavior. Trials were
Mean performance and ERP area measures (standard deviations).

<table>
<thead>
<tr>
<th></th>
<th>GAD (N = 17)</th>
<th>Healthy Controls (N = 24)</th>
</tr>
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<tbody>
<tr>
<td>Reaction time (ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error trials</td>
<td>344.64 (46.89)</td>
<td>345.10 (61.88)</td>
</tr>
<tr>
<td>Correct trials</td>
<td>426.61 (52.33)</td>
<td>424.81 (54.47)</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of errors</td>
<td>28.29 (11.67)</td>
<td>30.91 (17.31)</td>
</tr>
<tr>
<td>No. of correct trials</td>
<td>296.23 (15.45)</td>
<td>293.29 (24.03)</td>
</tr>
<tr>
<td>% correct</td>
<td>91.25 (3.63)</td>
<td>90.39 (5.60)</td>
</tr>
<tr>
<td>Post-trial reaction time (ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-error trials</td>
<td>438.47 (50.14)</td>
<td>414.35 (44.75)</td>
</tr>
<tr>
<td>Post-correct trials</td>
<td>356.83 (65.77)</td>
<td>347.52 (52.46)</td>
</tr>
<tr>
<td>Post-error accuracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of errors</td>
<td>5.64 (4.31)</td>
<td>6.45 (5.32)</td>
</tr>
<tr>
<td>% correct</td>
<td>76.82 (13.42)</td>
<td>74.54 (19.37)</td>
</tr>
<tr>
<td>ERPs (μV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERN</td>
<td>–2.72 (5.66)*</td>
<td>.42 (4.01)*</td>
</tr>
<tr>
<td>CRN</td>
<td>6.52 (6.35)</td>
<td>5.62 (4.14)</td>
</tr>
<tr>
<td>ΔERN</td>
<td>–9.24 (6.12)*</td>
<td>–5.20 (4.54)*</td>
</tr>
<tr>
<td>Pe on error trials</td>
<td>14.61 (13.09)</td>
<td>11.30 (11.42)</td>
</tr>
<tr>
<td>Pe on correct trials</td>
<td>4.42 (5.69)</td>
<td>2.61 (4.08)</td>
</tr>
<tr>
<td>ΔPe</td>
<td>10.19 (10.04)</td>
<td>8.69 (9.57)</td>
</tr>
</tbody>
</table>

Note: *Indicates p < .05 for between-groups comparison; ΔERN refers to error minus correct trials in the time window of the ERN; ΔPe refers to error minus correct correct trials in the time window of the Pe.

ated in the same time window and site on correct trials. Finally, the Pe was evaluated on error trials as the average activity from 200 to 400 ms at Pe following response onset. 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 the negative deflection may be present on both error and correct trials (e.g., Burle et al., 2008; Meckler et al., in press; Suchan et al., 2007), it is often critical to examine not just the ERN and CRN themselves, but also the difference between them (ERN minus CRN), in order to separate activity related to error-processing from activity related to response-monitoring. Difference scores for error minus correct trials were therefore calculated in the time windows of the ERN/CRN and the Pe – we refer to these as the ΔERN and ΔPe, respectively.

Behavioral measures included both the number of error trials for each subject, as well as accuracy expressed as a percentage of correct trials. Average reaction time of all trials (RTs) on error and correct trials were also calculated separately. Number of errors, RT and accuracy on trials following errors (i.e., double errors) were also evaluated to determine if there were group differences in post-error behavior. Trials were removed from the analysis if reaction times were faster than 200 ms or slower than 800 ms (1.3% of all trials). The number of trials excluded based on this criterion did not differ between groups (F(40) = 12, p > .50).

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. In order to evaluate differences in reaction time, ERN and Pe, four 2 (response type: correct or error) × 2 (group: GAD and HC) × 2 (Gender: Male and Female) mixed-model ANOVAs were conducted. The Pearson correlation coefficient (r) was also used to examine the relationship between self-reported symptom measures and error-related brain activity.

2. Results

2.1. Behavioral data

Accuracy and RT data are presented in Table 2. Reaction time varied significantly as a function of accuracy (F(1, 37) = 86.40, p < .001; \( \eta_p^2 = .70 \); observed power = 1.00), such that participants were faster on error (M = 340.76, SD = 55.76) than correct trials (M = 425.56, SD = 52.90). Males and females did not differ in RT (F(1,37) = 1; \( \eta_p^2 = .000 \); observed power = .05), nor did the effect of gender vary by Trial Type (F(1,37) = 3.39, p = .08; \( \eta_p^2 = .08 \); observed power = .43), or group type (F(1,37) = 1.43, p = .24; \( \eta_p^2 = .04 \); observed power = .21). However the groups did not differ in RT (F(1,37) < 1; \( \eta_p^2 = .02 \); observed power = .13), nor did the effect of group vary as a function of Trial Type (F(1,37) < 1; \( \eta_p^2 = .03 \); observed power = .16). Likewise, the groups did not differ in post-error RT (F(1,37) < 1; \( \eta_p^2 = .01 \); observed power = .06), nor did the effect of groups vary as a function of Trial Type (F(1,37) < 1; \( \eta_p^2 = .01 \); observed power = .08). Finally, the GAD and HC groups did not significantly differ in the number of errors committed following error trials (t(1,39) = 52, p > .60), or in their accuracy after error trials (t(1,39) = .39, p > .70).

Fig. 1 presents topographic maps for the GAD (left) and HC (right) groups. The two maps are derived from the average difference waveforms (error minus correct response) and represent the ERN effect for GAD (left) and HC (right) groups. (B) Scalp topographies representing the error-positivity (Pe). As with the ERN, the two maps are derived from the average difference waveforms, and represent the Pe effect for GAD (left) and HC (right) groups.

Post-error accuracy and RT data are also presented in Table 2. There was a main effect of Trial Type, such that participants were slower on trials that occurred after an error than after a correct response (F(1,37) = 22.16, p < .001; \( \eta_p^2 = .38 \); observed power = 1.00). Males and females did not significantly differ in their post-error RT (F(1,37) = 3.69, p = .09; \( \eta_p^2 = .08 \); observed power = .40), nor did the effect of gender vary as a function of Trial Type (F(1,37) < 1; \( \eta_p^2 = .03 \); observed power = .16). Likewise, the groups did not differ in post-error RT (F(1,37) < 1; \( \eta_p^2 = .01 \); observed power = .06), nor did the effect of groups vary as a function of Trial Type (F(1,37) < 1; \( \eta_p^2 = .01 \); observed power = .08). Finally, the GAD and HC groups did not significantly differ in the number of errors committed following error trials (t(1,39) = 52, p > .60), or in their accuracy after error trials (t(1,39) = .39, p > .70).

2.2. Error-related brain activity

Fig. 1 presents topographic maps for the GAD (left) and HC (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 FCz, where the error minus correct difference was maximal, are presented in Fig. 2. Average ERN values are presented in Table 2. Confirming the impression from Figs. 1 and 2, the ERN (M = –1.15, SD = .75) was significantly more negative than the CRN (M = 6.07, SD = .82) in both the GAD and HC groups (error vs. correct; F(1,37) = 53.65, p < .001; \( \eta_p^2 = .59 \); observed power = 1). There was no difference between the GAD and control groups in the magnitude of the overall electrocorti-
Fig. 2. Response-locked ERP waveforms at FCz (top) and Pz (bottom) comparing correct and error trial waveforms for GAD (left) and HC groups (middle). The right panels compare error and correct trials for the two groups. For each panel, response onset occurred at 0 ms and negative is plotted up.  

Such that incorrect responses ($M = 12.96$, $SD = 12.09$) were significantly more positive than correct responses ($M = 3.52$, $SD = 4.83$). There was a significant main effect of group ($F(1,37) = 6.02$, $p < 0.05$; $n^2_p = .14$; observed power $= 67$), such that the overall electrocortical response in this time window was larger in the GAD ($M = 14.88$, $SD = 13.09$) compared to the control group ($M = 7.02$, $SD = 11.42$), but this did not vary by response type ($F(1,37) = 3.09$, $p = .09$; $n^2_p = .08$; observed power $= .40$). In addition, there was a main effect of gender ($F(1,37) = 5.15$, $p < 0.05$; $n^2_p = .12$; observed power $= .60$), such that males had a larger overall electrocortical response in this time window ($M = 14.59$, $SD = 20.27$) than females ($M = 7.32$, $SD = 7.58$); this effect varied by group ($F(1,37) = 4.44$, $p < 0.05$; $n^2_p = .11$; observed power $= .54$), such that males in the GAD group ($M = 21.90$, $SD = 30.72$), had a larger overall electrocortical response than males in the HC group ($M = 7.28$, $SD = 17.13$). However, the effect of gender did not vary by response type ($F(1,37) = 1.99$, $p = .17$; $n^2_p = .05$; observed power $= .28$), nor did the interaction between gender and group vary by response type ($F(1,37) = 4.12$, $p = .06$; $n^2_p = .10$; observed power $= .51$).

2.3. Correlations with symptom severity

Means and standard deviations for the MASQ subscales are presented in Table 1. The GAD group had significantly higher scores on the MASQ Distress Depression ($t(33) = 3.91$, $p < 0.001$), Distress Anxiety ($t(33) = 7.20$, $p < 0.001$), Anhedonic Depression ($t(33) = 4.01$, $p < 0.001$), and Anxious Arousal ($t(33) = 5.15$, $p < 0.001$) subscales compared to the HC group. Table 3 presents Pearson correlation coefficients for error-related brain activity with these four subscales. Across the whole sample, the ERN was significantly and negatively correlated with three of the four subscales: General Distress Depression, General Distress Anxiety, and Anhedonic Depression, such that larger (more negative) ERNs were associated with greater self-reported symptoms of depression and anxiety. The negative correlation suggests that, as self-reported measures of anxiety and depression increased, the ERN was larger (i.e., more negative). However, the CRN and Pe
were not significantly related to any of the four subscales of the MASQ.

Following this, a simultaneous multiple regression was conducted, in which the ERN was the dependent variable, and each of the four subscales of the MASQ were simultaneous predictors. The overall model significantly predicted the ERN ($R^2 = .39; F(4, 33) = 4.59$, $p < .01$), but only the unique association with General Distress Anxiety remained significant ($\beta = -.55, t(33) = 2.20, p < .05$). General Distress Depression ($\beta = -.11, t(80) = .46, p = .65$), Anhedonic Depression ($\beta = -.32, t(80) = 1.47, p = .15$), and Anxious Arousal ($\beta = .44, t(80) = 1.88, p = .07$) were not significantly associated with the ERN when controlling for General Distress Anxiety.

### 3. Discussion

Consistent with work in other anxiety disorders (Endrass et al., 2008, 2010; Gehring et al., 2000; Hajcak et al., 2008; Johannes et al., 2001; Stern et al., 2010), individuals with GAD were characterized by increased error-related brain activity. More specifically, both an enhanced ERN and a greater difference between the ERN and the CRN distinguished the GAD from the HC group. Across both groups, greater continuous measures of anxious distress were associated with a larger ERN. This effect was specific to the ERN; neither the CRN nor the Pe related to self-reported distress across participants. Finally, though error-related brain activity was enhanced in the GAD compared to the HC group, there were no observed behavioral differences, suggesting that exaggerated processing of errors in the groups emerged in both the magnitude of the ERN and the difference between the ERN and the CRN. Conversely, only the ERN was significantly related to clinical variables, suggesting that GAD may differ from controls not in generic response monitoring processes evident on correct trials, but specifically in the evaluation of errors. This is consistent with several other studies in adult and pediatric OCD which have demonstrated similarly unique effects for the ERN in both OCD (Gehring et al., 2000; Hajcak et al., 2008; Ruchsow et al., 2005; Stern et al., 2010). However, other studies have found evidence for both larger ERNs and CRNs in anxious groups (e.g., Hajcak et al., 2003a,b; Hajcak et al., 2004; Endrass et al., 2008, 2010), which has been interpreted in terms of hyperactive response monitoring on both correct and error trials. Future work in clinical GAD populations will be necessary to better delineate whether the disorder is best characterized by hyperactive response monitoring in general, or excessive neural response to errors in particular.

Because the ACC is a likely neural generator of the ERN (Brázdil et al., 2005; Carter et al., 1998; Gemba et al., 1986; Holroyd et al., 1998; Itô et al., 2003; Millner et al., 2003; Pizzagalli et al., 2006; van Veen and Carter, 2002), the results of the present study are consistent with emerging evidence that abnormal activation of the ACC may be critically implicated in the pathophysiology of GAD (Etkin et al., 2010; McClure et al., 2007; Whalen et al., 2008). Studies combining ERP and fMRI methodologies, as well as source-localization techniques (e.g., Pizzagalli et al., 2006) may further illuminate the relationship between ACC activation and specific component processes of error monitoring.

In addition, because there is evidence that multiple classes of psychopharmacological medications can impact the magnitude and latency of ERPs (de Bruin et al., 2006; Schrijvers et al., 2008), individuals who were currently taking psychotropic medications were excluded from the present study. However, a substantial percentage of individuals with GAD are on some form of psychotropic medications (Vasile et al., 2005). Therefore, the subjects in the present study may not be entirely representative of GAD as a whole. Importantly, recent research in OCD demonstrates an increased ERN in both chronically medicated and unmedicated patient samples (Endrass et al., 2010; Stern et al., 2010); it will be important for future work to similarly examine the ERN among medicated and unmedicated individuals with GAD. Additionally, the HC and GAD groups were not identically matched on gender, though they did not significantly differ in this regard. However, our analyses demonstrated that, consistent with previous studies, gender did
Recently, it has been suggested that the ERN might be a useful endophenotype for internalizing disorders (Hajcak et al., 2008; Olvet and Hajcak, 2008; Riesel et al., in press), reflecting information-processing abnormalities that mediate the pathway between genetic predisposition and disease states (Cottman et al., 2003).

In addition, it has been demonstrated that increased error-related brain activity characterizes anxiety disorders in both child and adult populations (Endrass et al., 2010; Gehring et al., 2000; Hajcak et al., 2008; Hajcak et al., 2003a;b; Hajcak and Simons, 2002; Ladouceur et al., 2006; Ruchsova et al., 2005). Further, enhanced error-processing appears to be heritable (Anokhin et al., 2008) and state-independent, in that it is insensitive to successful treatment (Hajcak et al., 2008) and symptom provocation (Moser et al., 2005). Finally, there is emerging evidence that enhanced error-related brain activity is more evident in unaffected first-degree relatives of OCD patients (Riesel et al., in press). Although this question is far from settled, the potential role of the ERN as an endophenotype is an exciting avenue for future work.

An enhanced ERN has been demonstrated in clinical samples of both OCD and GAD; however, it may not be evident in all anxiety disorders. Based on the available data, we believe that an increased ERN should be evident among disorders more characterized by anxious apprehension/distress (e.g., OCD, GAD) than anxious arousal/fear (e.g., phobias, panic; Simons, 2010; Watson, 2005). In fact, worried but not phobic individuals had an increased CRN/ERN in one study (Hajcak et al., 2003a). In the present study, the magnitude of the ERN was significantly correlated with each clinical variable except anxious arousal, which captures symptoms of panic and acute fear responding. Further, when controlling for other clinical variables, only General Distress Anxiety, which is closely related to indices of worry and rumination (Fresco et al., 2002), characteristic of GAD and the distress disorders (Watson, 2005) remained significantly associated with the magnitude of the ERN. Replication of this work in larger, mixed clinical anxiety samples will be imperative. In particular, it would be interesting to examine whether individuals with panic disorder, characterized by anxious arousal and fear (Watson, 2005), demonstrate exaggerated error-related brain activity.

In addition, if the ERN can indeed be considered an endophenotype for disorders characterized by anxious apprehension and distress, further work exploring its role in mood disorders will be important. Though none of the individuals in the present GAD group met criteria for a current diagnosis of depression at the time of their participation, GAD and MDD have lifetime rates of comorbidity between 40% and 75% (Clark, 1989), and indeed, slightly more than half of the present GAD group had a history of depression. Though evidence for a relationship between the ERN and anxiety is robust, existing studies have not adequately addressed the role of depression (Gehring et al., 2000; Hajcak et al., 2003a; Hajcak and Simons, 2002; Johannes et al., 2001; Ruchsova et al., 2005), and evidence thus far for modulation of the magnitude of the ERN in MDD has been mixed at best. Although some studies have found increased amplitude of the ERN in clinically depressed populations (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008; Tucker et al., 2003) others have demonstrated decreased amplitude of the ERN among depressed individuals (Ruchsova et al., 2006; Ruchsova et al., 2004). These discrepant findings may relate to the level of depressive symptoms: individuals with moderate levels of depressive symptoms have often displayed enhanced ERN amplitudes (Chiu and Deldin, 2007; Compton et al., 2008; Ruchsova et al., 2004) whereas individuals with more severe depressive symptoms have displayed attenuated ERN amplitudes (Olvet et al., 2010; Schrijvers et al., 2008; Schrijvers et al., 2009). Further work examining error processing in depression is necessary; in addition, studies seeking to clarify the nature of this relationship should consider comorbid diagnoses of anxiety and depression and evaluating the potential additive and interacting effects of anxiety and depressive symptom severity.

References


