Depression symptom severity and error-related brain activity

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ABSTRACT

The present study examined the relationship between depression and neural correlates of response monitoring using event-related potentials (ERPs). The error-related negativity (ERN) and correct response negativity (CRN) are ERPs that present as a negative deflection approximately 50 ms following an erroneous and correct response, respectively; the error positivity (Pe) is a positive deflection approximately 200 ms following an erroneous response. Some studies have reported an increased ERN in individuals with major depressive disorder (MDD), but others have failed to find such differences. Results on the Pe in MDD have also been mixed. In the current study, unmedicated individuals with MDD (N=22) and healthy controls (N=22) performed an arrow version of the flanker task. Although these groups did not differ on the ERN or CRN overall, depression severity related to the CRN and the differentiation between the ERN and CRN (ΔERN) in the MDD group: more severe depression was associated with an increased CRN and a reduced ΔERN. Additionally, the difference between the Pe on error and correct trials (ΔPe) was reduced among individuals with MDD compared to healthy controls. These data suggest that individuals with severe depression have a reduced differentiation between error and correct trials on ERPs that index error monitoring and awareness.

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1. Introduction

Making a mistake is aversive, and is accompanied by a host of physiological responses (Hajcak et al., 2003; Hajcak et al., 2004; Hajcak and Foti, 2008). For individuals with major depressive disorder (MDD), who are characterized by excessive concern over mistakes (Enns and Cox, 1999; Shafrian and Mansell, 2001), errors may be experienced in an amplified manner. After receiving feedback about their mistakes, individuals with high levels of depressive symptoms report increased depressed mood (Abela and D’Alessandro, 2002; Henriques and Leitenberg, 2002) and difficulty suppressing failure-related thoughts (Conway et al., 1991). Behaviorally, depressed individuals are characterized by decreased accuracy after errors (Pizzagalli et al., 2006; Holmes and Pizzagalli, 2007; Holmes and Pizzagalli, 2008b), further suggesting impaired performance monitoring in depression.

In order to elucidate abnormal neural responses to errors in depressed individuals, recent studies have focused on an event-related potential (ERP) known as the error-related negativity (ERN). The ERN presents as a negative deflection approximately 50 ms following an erroneous response at frontal-central midline recording sites (Falkenstein et al., 1991; Gehring et al., 1993) and the neural source of the ERN appears to be the anterior cingulate cortex (ACC; Dehaene et al., 1994; Holroyd et al., 1998; van Veen and Carter, 2002). An ERN-like component is sometimes evident on correct response trials, and has been called the correct response negativity (CRN; Ford, 1999; Falkenstein et al., 2000; Vidal et al., 2000). It is likely that the CRN represents response monitoring activity in the ACC on correct trials (Falkenstein et al., 2000; Vidal et al., 2000).

Following the ERN, the ERP on error trials is characterized by a positive deflection referred to as the error positivity (Pe). The Pe is maximal 200–400 ms after the commission of an error (Nieuwenhuis et al., 2001; Falkenstein et al., 2003; Overbeek et al., 2005) and has a posterior midline scalp distribution (Falkenstein et al., 2000). The Pe may reflect error awareness (Leuthold and Sommer, 1999; Nieuwenhuis et al., 2001), similar to a P300-like orienting response following error commission (Davies et al., 2001; Hajcak et al., 2003; Ridderinkhof et al., 2009), or the affective appraisal of an error (Falkenstein et al., 2000).

Some studies have identified an increased ERN among individuals with MDD (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Holmes and Pizzagalli, 2010). Individuals who report high levels on the broader construct of negative affect also have an increased ERN (Luu et al., 2000; Hajcak et al., 2004). However, Compton et al. (2008) found that although college students endorsing high depression scores had a somewhat higher ERN amplitude than students with low depression scores, this difference was not statistically significant. Moreover, Schrijvers et al. (2008, 2009) recently reported that the...
ERN was non-significantly smaller in magnitude for individuals with severe MDD compared to healthy controls. Although there is some evidence to suggest that individuals with MDD have increased error-related brain activity, not all studies have confirmed these findings. It is possible that depression symptom severity may be the key to understanding the discrepancies in the ERN literature. Specifically, in samples with mild to moderate depression, depression was associated with a numerically larger ERN compared to healthy controls (Chiu and Deldin, 2007; Compton et al., 2008; Holmes and Pizzagalli, 2008b; Holmes and Pizzagalli, 2010), whereas in samples with severe depression, depression was associated with a numerically smaller ERN compared to healthy controls (Schrijvers et al., 2008; Schrijvers et al., 2009). Therefore, there may be a non-linear relationship between symptom severity and the ERN. This is consistent with a study by Tucker et al. (2003), who found that individuals reporting moderate depression symptoms had larger negative feedback-related brain activity than both individuals reporting no depression and severe depression symptoms—whereas the latter two groups did not differ from one another. Thus, there is a need to further investigate the relationship between the ERN and MDD with a focus on depressive symptom severity.

Although the Pe has not typically been the focus of ERP investigations of response monitoring in MDD, some studies have found that the Pe is smaller among individuals with MDD than healthy controls (Schrijvers et al., 2008; Schrijvers et al., 2009), but not all studies have confirmed this (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b) and task incentives may moderate the relationship between the Pe and MDD (Holmes and Pizzagalli, 2010). Again, the main factor differentiating these findings could be depression symptom severity: only studies with more severely depressed participants have reported a diminished Pe in MDD.

In the current study, we examined the relationship between depression symptom severity and ERP components associated with response monitoring: the ERN, CRN and Pe. Individuals with MDD and healthy controls performed an arrow version of the flanker task (Eriksen and Eriksen, 1974). Based on the literature, we hypothesized that the ERN would be larger in individuals with MDD compared to healthy controls. However, within the MDD group, we hypothesized that the ERN would be increased among individuals with mild-to-moderate MDD, but decreased in individuals with severe MDD. We also hypothesized that individuals with MDD would have a decreased Pe compared to healthy controls, which would be smaller with more severe depression symptoms.

2. Methods

2.1. Subjects

All participants were recruited from the Stony Brook community and university by posting flyers, placing advertisements on the internet, and contacting patients who participated in past studies conducted in the Department of Psychology. Additionally, participants were recruited through the Survey Research Center by randomly calling individuals in the community in order to screen them for eligibility. Individuals who were interested in participating in the study were given a brief phone screen, which included the administration of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), to assess inclusion/exclusion criteria. Individuals who were eligible based on the phone screen were invited for the lab session.

All participants were between the ages of 18 and 65, had the capacity to provide informed consent, and did not have any systemic or neurological illness, head injury or gross cognitive impairments. DSM-IV criteria were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders – Non-Patient Edition, Version 2 (SCID I/NP; Spitzer et al., 1992). Individuals in the major depressive disorder (MDD) group (N = 22) met DSM-IV criteria for a current major depressive episode (MDE) and scored greater than 14 (corresponding to an HRS, score of ≥8) on the Inventory of Depressive Symptomatology, Self-Report (Rush et al., 1996). Participants were excluded if they were currently on antidepressant medications or met DSM-IV criteria for another current Axis I disorder (with the exception of specific phobia: N = 1). All participants had stopped antidepressant medication at least one month prior to participating in the study. Individuals in the healthy control (HC) group (N = 25) were excluded if they met criteria for any current or past DSM-IV Axis I diagnosis. For each group, 5 diagnostic interviews were recorded for inter-rater reliability assessment; all 10 diagnoses were confirmed by a clinical psychologist. This research was formally approved by the Stony Brook University Institutional Review Board. No participants discontinued their participation in the experiment once procedures had begun, and all participants received $80 for their participation.

2.2. 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 occupied the entirety of a 19 inch 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. All stimuli were presented for 200 ms followed by an ITI that varied randomly from 2300 to 2800 ms.

2.3. Procedures

After a brief description of the experiment, EEG electrodes were attached and the participants were given detailed task instructions. Participants were seated at a viewing distance of approximately 24 in. 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 and 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.

2.4. Psychophysiological recording, data reduction and analysis

The continuous EEG was recorded using the ActiveTwo head cap and the ActiveTwo BioSemi system (Biosemi, Amsterdam, Netherlands). Recordings were taken from 34 scalp electrodes based on the 10/20 system (i.e., 32 channel montage plus sensors at FCz and Iz), as well as two electrodes placed on the left and right mastoids. The electrooculogram (EOG) generated from blinks and eye movements were recorded from four facial electrodes: two approximately 1 cm above and below the subject’s left eye, one approximately 1 cm to the left of the left eye, and one approximately 1 cm to the right of the right eye. As per BioSemi’s design, the ground electrode during acquisition was formed by the Common Mode Sense active electrode and the Driven Right Leg passive electrode. The EEG was sampled at 1024 Hz. All bioelectric signals were digitized on a laboratory microcomputer using ActiView software (BioSemi, Amsterdam, Netherlands).

Offline analysis was performed using Brain Vision Analyzer software (Brain Products, Gilching, Germany). EEG data were re-referenced to the numeric mean of the mastoids. The data was band-pass filtered in two ways: first, the data was filtered in the theta range with cutoffs of 4 and 7 Hz in order to isolate the ERN; and second, the data was filtered with cutoffs of 0.1 and 30 Hz in order to score the Pe. This was done because data supports the notion that the ERN represents theta activity (Luu and Tucker, 2001; Makeig, 2002; Makeig et al., 2002; Luu et al., 2003; Luu et al., 2004). Additionally, theta activity is thought to arise from either the ACC (Gevins et al., 1997; Asada et al., 1999; Ishii et al., 1999) or the DLPFC (Sasaki et al., 1996), similar to the ERN (Dehaene et al., 1994; Holroyd et al., 1998; van Veen and Carter, 2002). Filtering in the theta range also removes slow-wave activity that occurs in response to the presentation of the stimuli, which may affect response-locked ERPs. On the other hand, the Pe is a slow-wave ERP that is filtered-out using theta-range cutoffs, therefore it was necessary to filter the data using a wider frequency range to score the Pe.

The EEG was segmented for each trial beginning 400 ms before each response onset and continuing for 1000 ms; thus, the 600 ms after response onset was represented in the ERP averages. The EEG was corrected for blinks and eye movements using the method developed by Gratton et al. (1983). Specific intervals for individual channels were rejected in each trial using a semi-automated procedure, with physiological artifacts identified by the following criteria: a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals; all segments were also visually inspected for additional artifacts. Based on the literature (Olvet and Hajcak, 2008b), participants who made fewer than 6 errors were excluded from the analysis (HC: N = 3).

Response-locked ERPs were averaged separately for error and correct trials, collapsing across compatible and incompatible trials. The number of errors on compatible (mean [S.D.], MDD: 7.65 [8.45], HC: 6.50 [7.05]) and incompatible trials (mean [S.D.], MDD: 24.23 [12.20], HC: 23.82 [11.07]) were similar in the MDD and HC groups (compatible trials: t(42) = −0.48, P = 0.63; incompatible trials: t(42) = −0.12, P = 0.91). The ERN was evaluated as the average activity on error trials from response onset to 100 ms (i.e., 0–100 ms) at FCz and the CRN was evaluated in the same time window and electrode on correct trials. The Pe was evaluated on error trials as the average activity from 200–300 ms at Fz following response onset. A 200 ms window from −400 to −200 ms prior to
response onset served as the baseline. An area measure of the ERPs was chosen because peak measures might be especially sensitive to noise, or low trial numbers (Luck, 2005). 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 times (RTs) on error and correct trials were also calculated separately. Finally, number of errors, RT and accuracy on trials following errors (i.e. double errors) were evaluated to determine if there were group differences in post-error behavior. To reduce the influence of outliers, trials were removed from the analysis if reaction times were faster than 200 ms (0% of all trials) or slower than 800 ms (1.80% of all trials). The number of trials removed did not differ between the MDD (mean [S.D.], 8.18 [13.35]) and HC (mean [S.D.], 3.64 [7.74]) groups (t (42) = −1.138, P = 0.17).

2.5. Clinical measures

The Inventory for Depressive Symptomatology, Self-Rated (IDS-SR; Rush et al., 1996) was used to assess depressive symptom severity. The IDS-SR is a 30-item scale on which participants were asked to rate their response from 0 to 3 based on how the item best described them for the past seven days. The IDS-SR has good internal consistency and concurrent validity (Rush et al., 1996; Biggs et al., 2000; Trivedi et al., 2004), and it is highly related to scores on the Hamilton Rating Scale for Depression (Rush et al., 1996).

The Mood and Anxiety Symptom Questionnaire (MASQ; Watson and Clark, 1991) is a 90-item self-report measure of mood and anxiety symptoms. Participants were asked to rate the items based on how much they have experienced in the past week, using a scale from 1 = “not at all” to 5 = “extremely.” The MASQ has five subscales: General Distress Mixed Symptoms (15 items), 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). Although the IDS-SR was included as an inclusion criteria, we used the MASQ to examine correlations between the ERPs and symptom severity because it is a finer grained measure that takes into account the multidimensionality of depressive symptoms.

2.6. Statistical analyses

All data was checked for normality prior to analysis. Any measure that had a skewness or kurtosis value greater than 2 was log transformed in order to create a normal distribution. The following measures were log transformed: reaction time, number of double errors, post-error accuracy, and MASQ scores. Averages for these data are presented using the raw data.

In all cases, behavioral and ERP data were statistically evaluated using SPSS General Linear Model software (Version 16.0; SPSS Inc., Chicago, Illinois, USA). Group differences on demographic, clinical characteristics, and behavioral measures of accuracy and number of errors were assessed using an independent samples t-test comparing healthy controls (HC) and individuals with MDD (MDD). Group differences on reaction time and ERPs were assessed using a mixed ANOVA with Trial Type (Error vs. Correct) as the within-subjects factor and Group (HC vs. MDD) as the between-subjects factor. The Pearson correlation coefficient (r) was used to examine the relationship between the ERPs and clinical measures. In addition to examining correlations between depression measures and the ERN, CRN, and Pe on both error and correct trials, these clinical measures were also evaluated in relation to difference-score measures (i.e., ERN-CRN, or ∆ERN, and the Pe on error trials minus Pe on correct trials, or the ∆Pe) that capture the differentiation between error and correct trials. We performed 60 correlations, therefore in order to correct for multiple comparisons, the familywise error rate was set at P = 0.05, therefore any correlation with a P-value <0.016 was considered significant.

3. Results

3.1. Sample characteristics

The final sample consisted of 22 healthy controls (HC group) and 22 individuals with MDD (MDD group). Demographic and clinical information are presented in Table 1. The MDD group had a mean IDS-SR score of 44 (range = 27–69), which corresponds to a moderate-severe level of depressive symptomatology. An independent samples t-test indicated that there were no differences between the groups on age (t (42) = 0.42, P = 0.68) or years of education (t (42) = −0.18, P = 0.86). Chi-square analysis also indicated that there were no differences between the groups on gender (χ² (1) = 0.39, P = 0.53) or ethnicity (χ² (1) = 0.46, P = 0.50). The MDD group had significantly higher scores on the IDS-SR (t (42) = −15.68, P < 0.001), and on the MASQ General Distress Mixed (t (42) = −16.30, P < 0.001), General Distress Depression (t (42) = −15.80, P < 0.001), General Distress Anxiety (t (42) = −15.40, P < 0.001), Anhedonic Depression (t (42) = −13.04, P < 0.001), and Anxious Arousal (t (42) = −6.32, P < 0.001) subscales compared to the HC group.

### Table 1

| Demographic and clinical data means (and standard deviations). |
|-----------------|-----------------|
| **MDD** (N = 22) | **Healthy Controls** (N = 22) |
| Age             | 37.05 (16.14)   | 38.86 (12.59)   |
| Years of Education | 15.77 (2.94)   | 15.64 (1.99)   |
| Female, %       | 59.1%           | 68.2%           |
| Caucasian, %    | 68.2%           | 77.3%           |
| **IDS-SR**      |                 |                 |
| General Distress Mixed Symptoms | 43.82 (10.99) | 54.3 (3.35) |
| General Distress Depressive Symptoms | 43.59 (11.21) | 121.14 (1.65) |
| General Distress Anxious Symptoms | 27.41 (5.80) | 124.11 (1.50) |
| Anhedonic Depression | 86.21 (13.33) | 42.77 (8.10) |
| Anxious Arousal  | 31.86 (13.29)  | 18.23 (1.19)   |

### Table 2

| Performance and ERP data means (and standard deviations). |
|-----------------|-----------------|
| **MDD** (N = 22) | **Healthy controls** (N = 22) |
| Reaction time (ms) |                 |                 |
| Error trials     | 344.10 (46.84)  | 341.89 (53.97)  |
| Correct trials   | 443.65 (80.57)  | 416.48 (56.78)  |
| **Accuracy**     |                 |                 |
| No. of errors    | 31.86 (16.27)   | 30.32 (14.97)   |
| % correct        | 90.29 (4.97)    | 90.80 (4.54)    |
| **Post-trial reaction time (ms)** |                 |                 |
| Post-error trials | 452.38 (83.40)  | 416.68 (51.23)  |
| Post-correct trials | 432.93 (78.77)  | 408.81 (58.01)  |
| **Post-error accuracy** |                 |                 |
| No. of errors    | 3.59 (5.52)     | 4.32 (5.30)     |
| % correct        | 91.56 (9.58)    | 87.99 (10.43)   |
| **ERN (µV)**     |                 |                 |
| ERN              | −2.31 (1.93)    | −2.14 (1.65)    |
| CRN              | 1.24 (1.49)     | 1.18 (1.24)     |
| **ΔERN**         | −3.54 (2.46)    | −3.32 (2.22)    |
| **Pe (error trials)** | 11.24 (8.34)    | 14.90 (7.82)    |
| **Pe (correct trials)** | 4.98 (8.06)     | 3.04 (4.47)     |
| **ΔPe**          | 6.26 (8.45)     | 11.86 (8.28)    |

### Notes

- a MDD vs. HC: *P* < 0.001.
- b Participants were faster on correct trials, *P* < 0.001.
- c The ERN was more negative than the CRN, *P* < 0.001.
- d The Pe was more positive on error trials, *P* < 0.001.
- e The MDD group had a smaller ΔPe than the HC group, *P* < 0.005.
trials ($t(142) = 0.76, P = 0.58$), and had comparable accuracy after error trials ($t(142) = -1.12, P = 0.27$).

### 3.3. ERPs

Grand average response-locked ERPs at FCz are presented in Fig. 1 and the average ERP values are presented in Table 2. A 2 (Trial Type) × 2 (Group) mixed model ANOVA indicated that the ERN at FCz was significantly more negative than the CRN ($F(1,42) = 94.26, P < 0.001$), the MDD and HC groups did not differ from one another ($F(1,42) = 0.03, P = 0.86$), and there was no Trial Type × Group interaction ($F(1,42) = 0.10, P = 0.75$). Thus, both the ERN and the CRN were similar in the MDD and HC groups.¹

Grand average response-locked ERPs at Pz are presented in Fig. 2. A 2 (Trial Type) × 2 (Group) mixed model ANOVA indicated that the Pe at Pz was significantly more positive on error than correct trials ($F(1,42) = 51.60, P = 0.001$), and the MDD and HC groups had comparable ERPs overall ($F(1,42) = 0.22, P = 0.64$), but there was a Trial Type × Group interaction ($F(1,42) = 4.94, P < 0.05$). Post-hoc comparisons confirmed that the MDD group had a smaller ΔPe compared to the HC group ($t(42) = 2.22, P = 0.05$), however there were no group differences on error ($t(42) = 1.50, P = 0.14$) or correct trials alone ($t(42) = -0.99, P = 0.33$). Therefore, individuals with MDD appear to have less differentiation of error versus correct trials when examining post-error activity in the time-range of the Pe.

### 3.4. Correlations with symptom severity

In order to test the relationship between ERPs and symptom severity, Pearson correlations were performed between ERPs and clinical measures. Table 3a presents the Pearson correlation coefficients for the MDD group and Table 3b presents Pearson correlation coefficients for the HC group. Fig. 3 presents scatter plots for significant correlations between ERPs and symptom severity in the MDD group. Significant correlations (with familywise error correction, $P < 0.016$) are presented below.

#### 3.4.1. CRN

In the MDD group, there were significant correlations between the CRN and the General Distress Mixed Symptom ($r = -0.61, P < 0.01$), General Distress Depressive Symptom ($r = -0.64, P < 0.001$), and the Anhedonic Depression ($r = -0.68, P < 0.001$) subscales of the MASQ. The results indicate that as depression scores increased, the CRN increased (i.e. was more negative).²

#### 3.4.2. ΔERN

In the MDD group, there were significant correlations between the ΔERN and the Anhedonic Depression subscale of the MASQ ($r = 0.53, P < 0.01$), and trend-level correlations with the General Distress Mixed Symptom ($r = 0.45, P = 0.05$) and the General Distress Depressive Symptom subscale ($r = 0.40, P = 0.07$). The results indicate that as depression scores increased, there was a smaller differentiation between error and correct trials. To appreciate the impact of depression severity on the differentiation between the ERN and CRN, Fig. 4 presents ERPs for the HC group, as well as the MDD group divided by a median split based on IDS-SR score (median = 40).

¹ Using data filtered in the 0.1–30 Hz range for the group comparisons, the ANOVA results are consistent with the theta filtered data. The ERN is significantly more negative than the CRN ($F(1,42) = 58.29, P < 0.001$), with no effect of Group ($F(1,42) = 1$), nor a Trial Type × Group interaction ($F(1,42) = 2.74, P = 0.11$).

² Using data filtered in the 0.1–30 Hz range, the correlations between ERPs and symptom severity in the MDD group were in the same direction, but failed to reach significance (Ps ranged from 0.07 to 0.54).

### 3.4.3. Pe

In the MDD group, there was a significant correlation between the Pe on error trials and the General Distress Anxious Symptom subscale ($r = -0.55, P < 0.01$), such that more severe anxiety was related to a smaller Pe.

### 4. Discussion

In the present study, the ERN was comparable in the MDD and HC groups. Moreover, similar results were obtained for two common data filtering ranges (i.e. 4–7 Hz and 0.1–30 Hz). This is consistent with some published data demonstrating comparable ERNs among MDD and control participants (Compton et al., 2008; Schrijvers et al., 2008; Schrijvers et al., 2009), but not other studies which have reported an enhanced ERN in MDD (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Holmes and Pizzagalli, 2010).

It is unclear why the current study, as well as others (Compton et al., 2008b; Schrijvers et al., 2008; Schrijvers et al., 2009), did not find a significantly different ERN among MDD subjects compared to healthy controls. Schrijvers and colleagues have argued that the discrepancies in the depression ERP literature may be attributable to differences in symptom severity. For instance, in Schrijvers’s patient samples, individuals were more severely depressed than other samples (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Holmes and Pizzagalli, 2010), and it appears that the depressed participants in the Schrijvers et al. studies had a numerically smaller ERN compared to the healthy control group. Indeed, results from the current study are consistent with the possibility that an enhanced ERN might characterize mild MDD, whereas a reduced ERN might be evident among those with more severe MDD. The mean symptom severity of the depressed sample in the current study was in the moderate to severe range—and participants with more severe depression symptoms on the MASQ Anhedonic Depression subscale had a smaller ΔERN.

In addition, relatively heterogeneous samples have been used across studies. For example, some studies have included severely depressed individuals on an inpatient unit (e.g. Schrijvers et al., 2008; Schrijvers et al., 2009), non-clinical undergraduates (e.g. Compton et al., 2008), and severely depressed non-treatment seeking individuals (e.g. current study). Variability in medication status and psychiatric comorbidity further complicates comparisons across studies. Specifically, some studies included patients who were taking psychotropic medication (Chiu and Deldin, 2007; Schrijvers et al., 2008; Schrijvers et al., 2009) or had concurrent comorbid anxiety disorders (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Schrijvers et al., 2009; Holmes and Pizzagalli, 2010; current study). Finally, it is also worth noting that documented differences in the ERN related to MDD have not been especially robust. For example, Chiu and Deldin (2007) found a significantly increased ERN in MDD subjects in two of three task conditions (i.e. neutral and punishment, but not reward, conditions); Holmes and Pizzagalli (2008b) found an overall effect of group—suggesting that performance monitoring, in general, was altered in the MDD group.

While assessing a related ERP component associated with error processing, the feedback negativity (FN), Tucker et al. (2003) found that the FN was small both for individuals who scored low and high on a depression scale, whereas individuals who scored in the middle were characterized by a large FN. Thus, individuals with mild (Compton et al., 2008) or moderate depressive symptoms (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Holmes and Pizzagalli, 2010) may be characterized by a numerically large ERN, whereas those with severe depression appear to have a small ERN (Schrijvers et al., 2008; Schrijvers et al., 2009). The current results are also in line with these findings. It is possible that the debilitating apathy and anhedonia found in more severe depression diminish the abnormally large ERN that might typically characterize individuals with depression (Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Holmes and Pizzagalli, 2010) and those who report high negative affect more...
generally (Luu et al., 2000; Hajcak et al., 2004). Alternatively, because MDD is a heterogeneous and polygenic disorder (Pettit et al., 2006; McMahon et al., 2010), it is possible that variability in the ERN across MDD studies may reflect similar variability in the disorder itself. For example, it is possible that a subset of individuals with a common symptom profile may be driving positive results. In line with this notion, Schrijvers et al. (2008) reported that individuals who reported severe psychomotor retardation had a smaller ERN.

Individuals in the MDD group who had more severe depression symptoms on the General Distress Mixed Symptom, General Distress Depressive Symptom, and Anhedonic Depression MASQ subscales also had a larger (i.e. more negative) CRN. Although the CRN has not been extensively investigated, it is likely that the CRN represents response monitoring activity of the ACC on correct trials, and is similar in nature to the ERN (Falkenstein et al., 2000; Vidal et al., 2000). The increased CRN in severely depressed individuals, therefore, may indicate increased error monitoring on correct trials. An increased CRN has been reported when participants were uncertain about their response (Coles et al., 2001; Pailing and Segalowitz, 2004), therefore, it is possible that severely depressed individuals may be more uncertain about the veracity of their correct responses. Moreover, depressed individuals may expect to make more errors. This is in line with a behavioral study which showed that individuals with MDD underestimated their number of correct responses on a working memory task, results that were not found for estimations of errors (Dunn et al., 2007). Another study confirmed that depression scores predicted subjective reports of cognitive failures (Farrin et al., 2003). Although the current study is unable to address whether or not this is the case, it is possible that individuals with MDD may simply expect to make more errors—which could relate to both the increased CRN and the reduced differentiation of the ERN and CRN.

The $\Delta$Pe was smaller among individuals with MDD compared to the healthy controls. These data are consistent with some studies which have found a smaller Pe in individuals with severe MDD (Schrijvers et al., 2008; Schrijvers et al., 2009; however see Chiu and Deldin, 2007; Holmes and Pizzagalli, 2008b; Compton et al., 2008). Recently, Holmes and Pizzagalli (2010) showed that the Pe was smaller in individuals with MDD in a reward, but not a no incentive, condition. Insofar as the Pe represents error awareness (Leuthold and Sommer, 1999; Nieuwenhuis et al., 2001) or an orienting response to errors (Davies et al., 2001; Hajcak et al., 2003; Ridderinkhof et al., 2004), decreased Pe may indicate that MDD individuals have a reduced orienting response to errors.

Table 3a
Pearson correlation coefficients assessing the relationship between ERPs and clinical measures in the MDD group.

<table>
<thead>
<tr>
<th>MASQ subscales</th>
<th>General Distress Mixed Symptoms</th>
<th>General Distress Depressive Symptoms</th>
<th>General Distress Anxious Symptoms</th>
<th>Anhedonic Depression</th>
<th>Anxious Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>ERN</td>
<td>0.11</td>
<td>0.64</td>
<td>0.01</td>
<td>0.95</td>
<td>0.15</td>
</tr>
<tr>
<td>CRN</td>
<td>-0.61*</td>
<td>0.002</td>
<td>-0.64*</td>
<td>-0.001</td>
<td>-0.32</td>
</tr>
<tr>
<td>$\Delta$ERN</td>
<td>0.45</td>
<td>0.03</td>
<td>0.40</td>
<td>0.07</td>
<td>0.31</td>
</tr>
<tr>
<td>Pe (error)</td>
<td>-0.25</td>
<td>0.26</td>
<td>-0.13</td>
<td>0.56</td>
<td>-0.55*</td>
</tr>
<tr>
<td>Pe (correct)</td>
<td>0.06</td>
<td>0.79</td>
<td>-0.09</td>
<td>0.70</td>
<td>-0.30</td>
</tr>
<tr>
<td>$\Delta$Pe</td>
<td>-0.31</td>
<td>0.17</td>
<td>-0.05</td>
<td>0.84</td>
<td>-0.26</td>
</tr>
</tbody>
</table>

* Indicates a significant difference.
2009), individuals with MDD may have reduced awareness and orienting to their own failures. The finding of a diminished $\Delta$Pe is also consistent with the idea that the Pe is comparable to a P300-like orienting response (Davies et al., 2001; Hajcak et al., 2003; Ridderinkhof et al., 2009), as studies have consistently shown that individuals with MDD have a reduced P300 (Anderer et al., 2002; Karaaslan et al., 2003; Roschke and Wagner, 2003; Urretavizcaya et al., 2003; Kawasaki et al., 2004; Kemp et al., 2009). Additionally, it has been hypothesized that the Pe represents the affective appraisal of an error (Falkenstein et al., 2000). In this context, the decreased Pe in the current study might suggest that individuals with severe MDD were relatively indifferent to making errors.

Both the ERN and Pe were smaller in individuals with severe MDD based on the difference measures; in other words, they have a reduced differentiation between error and correct trials. It is also important to note that the correlations between depressive symptoms and both the CRN and the $\Delta$ERN, coupled with the lack of correlation between depressive symptoms and the ERN, all point towards the notion that the CRN was driving the $\Delta$ERN correlation. Indeed, a multiple linear regression analysis revealed that the CRN was a significant predictor of Anhedonic Depression ($\beta = -0.57, P < 0.05$), whereas the $\Delta$ERN was not ($\beta = 0.18, P = 0.42$). Again, this may be due to the increased expectation to make errors (Farrin et al., 2003; Dunn et al., 2007), or an overall negatively biased view among individuals with MDD (Beck, 1967; Leppanen, 2006). Other studies that examine the ERN or Pe in individuals with MDD did not report difference measures; therefore, the direct comparison to the current findings should be done with caution.

Although some studies have found that individuals who report high levels of depressive symptoms are characterized by decreased accuracy after incorrect trials compared to correct trials (Pizzagalli et al., 2006; Holmes and Pizzagalli, 2007; Holmes and Pizzagalli, 2008b), the current study did not find such a relationship. It is possible that task difficulty plays a role in these discrepant findings. In the current study, an arrowhead version of the flanker task was utilized, which is a fairly easy task, compared to more difficult tasks used in prior studies (Pizzagalli et al., 2006; Holmes and Pizzagalli, 2007; Holmes and Pizzagalli, 2008b).

There are other possible explanations regarding the discrepancy between the current study and previous studies assessing the ERN in individuals with MDD. Unlike the current study, all previous studies incorporated trial-to-trial feedback in speeded response tasks. Recent evidence suggests that the presence of trial-to-trial feedback moderates the relationship between anxiety and the ERN (Olvet and Hajcak, 2009a), however it is unclear whether feedback might similarly alter the
relationship between depression and the ERN. Indeed, Chiu and Deldin (2007) found that depressed individuals had a larger ERN amplitude in the punishment and neutral conditions of their task compared to healthy controls, but there was no difference in the ERN amplitude during the reward condition. On the other hand, Holmes and Pizzagalli (2010) found that the ERN was larger among individuals with MDD compared to healthy controls, and that this difference was apparent across both reward and no incentive conditions. Given the varied findings, further study is required to clarify the effect of positive and negative feedback on the relationship between the ERN and MDD. Finally, we were unable to separately examine compatible and incompatible errors because there were relatively few error trials, especially on compatible trials. Because conflict-related components on correct trials (i.e. the N2), have been found to be abnormal among individuals with MDD (Holmes and Pizzagalli, 2008a; Vanderhasselt and De Raedt, 2009), it might be important for future studies to examine whether the relationship between ERN and MDD varies on high versus low conflict trials.

In the current study, we set forth to examine error-related abnormalities in non-medicated individuals with MDD. A primary hypothesis was that the ERN would be increased in individuals with MDD compared to healthy controls. Although this hypothesis was not supported, we did find that the ΔERN was moderated by symptom severity on the Anhedonic Depression subscale of the MASQ, such that individuals with moderate MDD had a larger ΔERN and individuals with severe MDD had a smaller ΔERN. Additionally, it appears that individuals with severe depressive symptoms also have excessive error processing on correct trials. Another hypothesis was that individuals with MDD would have a smaller Pe compared to healthy controls. This hypothesis was supported, such that individuals with MDD had a smaller ΔPe compared to healthy controls. Overall, this study suggests that individuals with MDD have less differentiation of errors versus correct trials on ERPs that index both error monitoring and error awareness.

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References


Fig. 4. Response-locked ERPs at FCz for error and correct trials for individuals with low depressive symptom severity (left), high depressive symptom severity (middle) and healthy control groups. Data were band-pass filtered between 4 and 7 Hz. Response onset occurred at 0 ms and negative is plotted up.


Leuthold, H., Sommer, W., 1999. ERP correlates of error processing in spatial S-P.


