Published in final edited form as:

Biol Psychol. 2016 January ; 113: 100–107. doi:10.1016/j.biopsycho.2015.11.012.

Blunted neural response to errors as a trait marker of melancholic depression

Anna Weinberg¹, Huiting Liu, and Stewart A. Shankman

University of Illinois at Chicago

Abstract

Identification of biomarkers of vulnerability for Major Depressive Disorder is a high priority, but heterogeneity of the diagnosis can hinder research. Biomarkers of vulnerability should also be present in the absence of the diagnosis. The present study examined the magnitude of the error-related negativity (ERN), an event-related potential component following errors in a sample with remitted melancholic depression (N=17), remitted non-melancholic depression (N=33), and healthy controls (N=55). Remitted melancholic depression was uniquely characterized by a blunted ERN relative to the other two groups. Individuals with remitted non-melancholic depression did not differ from controls in the magnitude of the ERN. This was the case despite the fact that the melancholic and non-melancholic groups did not differ in course or severity of their past illnesses, or in their current functioning. Results suggest that the blunted ERN may be a viable vulnerability marker for melancholia.

Keywords

Error-related Negativity; melancholia; vulnerability; Depression

Major Depressive Disorder (MDD) is one of the most common and costly forms of illness worldwide (Greenberg, Stiglin, Finkelstein, & Berndt, 1993; Mathers, Fat, & Boerma, 2008; Murray et al., 2013). Yet, despite its prevalence and considerable public health impact, the pathophysiology of depression is not well understood (Krishnan & Nestler, 2008). Efforts to identify reliable and stable biomarkers of vulnerability for the disorder have often been inconclusive due, in part, to the heterogeneity of diagnostic categories (Cuthbert, 2014; Cuthbert & Insel, 2013; Helzer, Kraemer, & Krueger, 2006; Klein, 2008). Different symptoms and symptom clusters subsumed under the MDD diagnosis appear to have distinct etiologies (Day et al., 2015), clinical features (Kendler, 1997), courses (Angst, Gamma, Benazzi, Ajdacic, & Rössler, 2007; Lux & Kendler, 2010), and biological

Correspondence should be addressed to Stewart Shankman, Department of Psychology, University of Illinois at Chicago, Chicago, IL, 60607. stewarts@uic.edu.

¹Present Address: Department of Psychology, McGill University, Stewart Biology Building, 1205 Dr. Penfield Avenue, Montreal, Quebec H3A 1B1

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

conflicts of interest The authors report no conflicts of interest.

correlates (Pizzagalli et al., 2004), which are likely obscured in studies that only compare those with MDD to controls. Examining more specific processes and symptom clusters may help bridge biological and psychological data and identify vulnerability markers (Insel et al., 2010; Shankman & Gorka, 2015).

Neural response to errors appears to be a viable neurobiological marker of psychopathology (Manoach & Agam, 2013; Vaidyanathan, Nelson, & Patrick, 2012; Weinberg, Dieterich, & Riesel, 2015). In particular, the error-related negativity (ERN; Falkenstein et al., 1990; Gehring, et al., 1993), an event-related potential (ERP) response to errors, may be useful in research concerned with the pathophysiology of depression (Weinberg, Dieterich, & Riesel, 2015). The ERN appears as a negative-going deflection in the ERP waveform at frontocentral sites, between 0 and 100 ms following the commission of an error. There are multiple functional explanations for the ERN, the majority of which agree that the ERN reflects an alarm signal following error commission—a call to increase cognitive control and adjust behavior (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Holroyd & Coles, 2002; Holroyd & Yeung, 2012).

Multiple lines of research strongly implicate the ACC, a part of the frontostriatal system, as the neural generator of the ERN (Brázdil, Roman, Daniel, & Rektor, 2005; Debener et al., 2005; Ito, Stuphorn, Brown, & Schall, 2003; Miltner et al., 2003; Reinhart & Woodman, 2014; Stemmer, Segalowitz, Witzke, & Schönle, 2004). However, the ACC is richly innervated by dopaminergic neurons (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001), and neurotransmission of dopamine (DA), which mediates stimulus salience as well as motoric control, influences the magnitude of the ERN. For instance, DA agonists enhance the ERN (De Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004), while DA antagonists attenuate it (De Bruijn et al., 2004; Zirnheld et al., 2004). Similarly, neuropsychological diseases in which dysfunction of the mesencephalic DA system plays a central role, like Parkinson's (Falkenstein, Willemsen, Hohnsbein, & Hielscher, 2006) and Huntington's disease (Beste, Saft, Andrich, Gold, & Falkenstein, 2006) have been associated with attenuated ERN amplitudes. Genetic polymorphisms governing DA neurotransmission can also influence error processing in both healthy and neuropsychiatric populations (Manoach & Agam, 2013). Moreover, there is evidence that the magnitude of the ERN depends in part on efference motor signals from the cerebellum, routed through the thalamus, that adaptively adjust basal ganglia activity on the basis of a perceived mismatch between desired and actual response (i.e., an error) and adjust behaviors accordingly (e.g., Peterburs et al., 2011, 2012, 2015; Seifert et al., 2011). Studies of patients with either cerebellar or thalamic lesions, for instance, have demonstrated that disturbed communication between the basal ganglia, cerebellum, and thalamus and the frontal cortex is reflected in a blunted ERN (Peterburs et al., 2011; 2012).

Abnormalities in the magnitude of the ERN have been identified in diverse forms of psychopathology, including depression (Weinberg, Dieterich, & Riesel, 2015). However, the literature on the ERN in depression is far from consistent. For instance, though several studies have demonstrated that a diagnosis of depression is associated with a blunted ERN (Ladouceur et al., 2012; Schoenberg, 2014; Schrijvers et al., 2008; Weinberg, Meyer, et al., 2015), others have demonstrated an enhanced ERN in depression (Aarts, Vanderhasselt,

Otte, Baeken, & Pourtois, 2013; Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008a, 2010; Tang et al., 2013). Still others have found no evidence of difference from controls (Olvet, Klein, & Hajcak, 2010; Ruchow et al., 2006; Schrijvers et al., 2009; Weinberg, Klein, & Hajcak, 2012; Weinberg, Kotov, & Proudfit, 2015). One possibility underlying these mixed results is that the aforementioned diagnostic heterogeneity within MDD is obscuring meaningful variation in neural response. For instance, even within depressed groups, there is evidence that symptom profiles associated with reduced DA functioning and motoric disturbances, particularly psychomotor retardation, uniquely predict a reduced ERN (Schrijvers et al., 2008; Weinberg, Kotov, & Proudfit, 2015). Other studies in depressed populations have also found that more severe symptoms of anhedonia predicted a more blunted ERN (Olvet, Klein, & Hajcak, 2010).

Depression in general has often been associated with reduced DA transmission (Dunlop & Nemeroff, 2007). Yet this impairment may be most pronounced in melancholic depression (Baumeister & Parker, 2012; Parker, 2007; Parker et al., 1995), a specifier within the MDD category which has long been thought to have a more neurobiological etiology than other depressive subtypes (Baumeister & Parker, 2012; Fava et al., 1997; Klein, 1974; Pizzagalli et al., 2004). Indeed, the cardinal symptoms of melancholia are pervasive anhedonia and psychomotor disturbances, in particular psychomotor retardation, which typically manifests as slowing across one or more of the following domains: facial movements, gait, speech and thought processes (Parker, 2007; Parker et al., 1995). This neurocognitive retardation also may persist at a discernable level even after recovery from depression, and relate to the severity of depression (e.g., Gorwood, Richard-Devantoy, Bayle, & Clery-Melun, 2014). Given the association between DA functioning, motoric disturbances, and the ERN, and evidence that melancholic depression might be more strongly characterized by DA dysfunction and motor disturbances than other depressive subtypes, the present study sought to examine the ERN in individuals who met criteria for melancholic and non-melancholic forms of depression.

In addition to examining the effect of diagnostic heterogeneity, we were interested in whether the ERN might represent a viable *vulnerability* marker for some depressive phenotypes but not others. Research on the psychometric properties of the ERN suggest that it is relatively trait-like, in that it is a stable (Foti, Kotov, & Hajcak, 2013; Meyer, Riesel, & Proudfit, 2013; Olvet & Hajcak, 2009c) and reliable neural signal (Olvet & Hajcak, 2009b; Segalowitz et al., 2010; Weinberg & Hajcak, 2011) with excellent internal consistency (Riesel, Weinberg, Endrass, Meyer, & Hajcak, 2013). Additionally, there is evidence that the magnitude of the ERN is subject to substantial genetic influence (Anokhin, Golosheykin, & Heath, 2008), and abnormalities in the ERN have been observed in unaffected family members of individuals with psychopathology (Carrasco et al., 2013; Euser, Evans, Greaves-Lord, Huizink, & Franken, 2013; Riesel, Endrass, Kaufmann, & Kathmann, 2011; Torpey et al., 2013), as well as other high-risk populations (Lahat et al., 2014; Meyer et al., 2014). Combined, these data suggest the ERN is a viable candidate for a heritable, trait-like risk marker (Manoach & Agam, 2013; Vaidyanathan et al., 2012; Weinberg, Riesel, & Hajcak, 2012).

If the ERN does represent a stable vulnerability factor, abnormalities in the magnitude of the ERN should also be primarily state-independent, and not linked to changes in symptom severity. Thus, if a blunted ERN is a potential trait marker of melancholic depression, it should also be evident in those with remitted melancholic depression. To date, three studies have examined the ERN in remitted MDD, and have found mixed results (Alexopoulos et al., 2007; Georgiadi, Liotti, Nixon, & Liddle, 2011; Schoenberg, 2014). One of these found that individuals with current MDD exhibited a blunted ERN relative to controls, but those with remitted MDD did not (Schoenberg, 2014). Another found a reduced ERN in a group who had remitted from depression relative to those who did not remit (Alexopoulos et al., 2007). The third found that remitted MDD was characterized by an *enhanced* ERN relative to controls, but that current MDD did not differ from controls (Georgiadi et al., 2011). Yet each of these studies only examined MDD as a single category, suggesting again that diagnostic heterogeneity within the depressive category can hinder research on biomarkers for depression.

The present study therefore had two goals: the first was to examine whether inconsistencies regarding the ERN in depression could be resolved by studying the subtype of melancholic depression. The second was to examine whether the ERN might represent a state-independent vulnerability marker. To meet these goals, we examined the magnitude of the ERN in a sample of individuals with remitted MDD (melancholic type), remitted MDD (non-melancholic type), and healthy controls (HC). We predicted that the magnitude of the ERN would be blunted in remitted melancholic depression relative to both controls and remitted non-melancholic depression. In order to explore whether the magnitude of the ERN related more to current functioning, or might instead represent a vulnerability marker, we also examined current symptoms and functioning between the two remitted depressed groups.

Method

Participants

The participants in the current sample were selected from a larger sample of siblings, recruited to have a broad spectrum of psychopathology. In the analyses described below, only one sibling per pair was included (see Weinberg, Liu, Hajcak, & Shankman, 2015, for details on the larger sample). Participants were recruited from the community and area mental health clinics (via fliers, Internet postings, etc.), on the basis of symptoms of anxiety and depression, and were screened via telephone using the Depression, Anxiety, and Stress Scale (DASS; Lovibond & Lovibond, 1995). Because manic and psychotic symptoms have been shown to be separable from internalizing disorders (Watson, 2005), participants were excluded if they had a history of a manic/ hypomanic episode or psychotic symptoms. Participants were also excluded if they were unable to read or write English; had a history of head trauma with loss of consciousness; or were left-handed.

Participants were included in the current analyses if a) they did not meet criteria for any current or lifetime Axis I disorder (Healthy Controls; HC; $N = 55$), or b) they did not meet criteria for current MDD, but did meet criteria for past MDD ($N = 50$). The remitted depressed group was then divided into individuals who met lifetime criteria for DSM-IV

melancholic depression (rMD, $N = 17$), and those who did not meet criteria for melancholic depression (rNMD, $N = 33$). Of those with remitted non-melancholic depression, 8 met criteria for atypical depression, and the remaining 23 met criteria for unspecified MDE episodes. The final sample was 68% female, and was racially diverse (42.3% Caucasian-American, 28.5% Hispanic, 5.7% African-American, 16.3% Asian, 4.9 % Middle Eastern, . 8% “Other”, and 1.6 % Mixed Race), well-educated (54.5% had completed at least some college education; 18.7% had completed four years of college) and relatively young (Age $M = 22.10$, $SD = 2.98$). All procedures were approved by the University of Illinois–Chicago Institutional Review Board.

Measures

All clinical diagnoses of current and lifetime Axis I disorders were assessed via the Structured Clinical Interview for DSM–IV (SCID; First, Gibbon, Spitzer, & Williams, 1996). The SCID included items that assessed melancholic MDD using DSM-IV criteria (which is nearly identical to DSM-V criteria). Current clinician-rated global assessment of functioning (GAF) was also made in the course of the SCID. The SCID was also used to assess number of past episodes, the time since the most recent episode, and age of onset of the first episode of depression. Diagnosticians were trained to criterion on the SCID and supervised by a licensed clinical psychologist. In addition to diagnoses, interviewers dimensionally assessed functional impairment and subjective distress during the past depressive episode that the remitted depressed participants identified as their most severe. Interviewers made ratings for impairment in the domains of social, occupational, and daily life, as well as perceived distress, along a nine-point scale ranging from 0 (None) to 8 (Severe). The anchors for the scale were adopted from the Anxiety Disorders Interview Schedule (ADIS-IV; Brown, DiNardo, Barlow, & DiNardo, 1994) in which a 2 or higher was clinically significant distress or impairment. Overall severity of worst past episode was calculated as the mean of these impairment ratings.

Current depression and anxiety symptoms (past two weeks) were also assessed in all participants using the expanded Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012). We report here on the following subscales associated with unipolar depression and DSM-V anxiety disorders: General Depression, Dysphoria, Lassitude, Insomnia, Appetite Loss, Appetite Gain, Ill-Temper, Well-Being, Social Anxiety, and Panic.

Task and Materials

Participants completed a battery of tasks and the order was counterbalanced across subjects. Results from other tasks will be reported elsewhere (Weinberg, Liu, et al., 2015). The present task was administered on a Pentium class computer, using the stimulus presentation software Presentation (Neurobehavioral Systems, Inc.). Participants completed an arrowhead version of the flanker task (Eriksen & Eriksen, 1974) while their brain activity was recorded using an electroencephalograph (EEG). On each trial of the task, participants were shown a row of 5 simultaneously-presented arrowheads and were instructed to indicate the direction the center arrow was pointing by responding with the left or right mouse button. Half of all trials were compatible (“<<<<<” or “>>>>>”) and half were incompatible (“<<><<” or “>><>>”); the order of compatible and incompatible trials was randomized. 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 2,300 to 2,800 ms. Participants completed a practice block of 30 trials to ensure they understood the task. Both speed and accuracy were emphasized during task instruction, and throughout the experiment. The actual task consisted of 11 blocks of 30 trials (330 trials total) with each block initiated by the participant, and took approximately 15 minutes to complete. After each block of trials, participants received one of three types of performance feedback: if performance was 75% correct or lower, the message “Please try to be more accurate” was displayed; if accuracy was above 90%, participants were told “Please try to respond faster”; finally, if performance was between 75 and 90% correct, the message “You’re doing a great job” was displayed. All participants included in the present analyses committed 8 or more errors, the number necessary to obtain a reliable ERN (Olvet & Hajcak, 2009c).

Psychophysiological Recording, Data Reduction and Analysis

Continuous EEG recordings were collected using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Sixty-four electrodes 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 three facial electrodes: horizontal eye movements were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes (HEO). Vertical eye movements and blinks were measured via one electrode placed approximately 1 cm below the left eye and electrode FP1 (VEO). The data were digitized at a sampling rate of 1024 Hz, using a low-pass fifth order sinc filter with -3dB 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 (non-differential) channel. CMS forms a feedback loop with a paired driven right leg (DRL) electrode, located between POz and PO4, reducing the potential of the participants and increasing the common mode rejection rate. Offline, all data were analyzed in Brain Vision Analyzer and 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 using VEO and HEO channels per a modified version of the algorithm discussed in Gratton, Coles, and Donchin (1983).

A semi-automatic procedure was employed to detect and reject artifacts. The criteria applied were a voltage step of more than $50.0\text{ }\mu\text{V}$ between sample points, a voltage difference of $300.0\text{ }\mu\text{V}$ within a trial, and a maximum voltage difference of less than $.50\text{ }\mu\text{V}$ within 100 ms intervals. Visual inspection of the data was then conducted to detect and reject any remaining artifacts.

The EEG was segmented into 1,500 ms windows for each trial, beginning 500 ms before each response onset and continuing for 1,000 ms. Error and correct trials were then separately averaged. The mean activity in a 200-ms window from -500 to -300 ms prior to response onset served as the baseline and was subtracted from each data point. Based on a visual inspection of the data, and in line with previous work (Simons, 2010; Weinberg & Hajcak, 2011), the ERN was quantified on error trials as the average activity from 0 to 80

ms at electrode site Cz, where error-related brain activity was maximal across groups (Holroyd & Coles, 2002; Moser, Moran, & Jendrusina, 2012; Riesel et al., 2013; Weinberg, Klein & Hajcak, 2012; Weinberg, Kotov, Proudfit, 2015; Weinberg, Olvet, & Hajcak, 2010). In addition, the correct response negativity (CRN) was evaluated in the same time window and sites on correct trials. Because the CRN appears to measure generic response monitoring (Simons, 2010), and a negative deflection is typically present on both error and correct trials (Burle, Roger, Allain, Vidal, & Hasbroucq, 2008), it is often critical to examine the difference between the ERN and CRN (i.e., $ERN - CRN$) in order to quantify neural activity unique to error-processing. Difference scores for error minus correct trials ($ERN - CRN$) were therefore calculated for each subject subtracting the CRN from ERN (Riesel et al., 2013).

A parietal positive-going deflection in the waveform is also observed following the ERN, called the error positivity (Pe; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). Relative to the ERN, the Pe is less well-understood (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005), but increasing evidence suggests the component may be related to error awareness (Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). The Pe was evaluated at channel Pz, between 200 and 400 ms.

Behavioral measures included the number of error trials for each subject, and accuracy expressed as a percentage of trials with correct responses (out of total number of trials, including non-responses). Accuracy was also calculated for responses following erroneous and correct responses (post-error accuracy and post-correct accuracy). Average reaction times (RTs) on error and correct trials were also calculated separately. Post-error RT (average of $[RT(E+1) - RT(E-1)]$ for all errors E; Dutilh et al., 2012) was also evaluated to examine post-error behavior. Trials were removed from analysis if reaction times were faster than 200 ms or slower than 1,000 ms.

All statistical analyses were conducted using SPSS (Version 22.0) General Linear Model software. Group scores on each subscale of the IDAS, as well as # of past depressive episodes, age of onset, severity of worst past episode, current clinician-rated GAF scores, post-error slowing, and accuracy 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. In order to evaluate differences in reaction time, post-error accuracy, and activity in the time-window of the ERN/CRN, three 2 (response type: correct or error) $\times$ 3 (group: HC, rNMD, and rMD) mixed-model ANOVAs were conducted, followed by post-hoc Tukey's t-tests.

Results

Behavioral Data

Accuracy and RT data are presented in Table 1. Reaction time varied as a function of accuracy $F(1, 102) = 374.23, p < .0001, \eta_p^2 = .79$, such that participants were faster on error $M = 358.01, sd = 48.01$ than correct trials $M = 428.13, sd = 43.60$. The groups did not differ in terms of their overall RT $F(2, 102) = 1.99, p = .14, \eta_p^2 = .04$, nor did Group interact with Trial Type to determine RT $F(2, 102) < 1, p = .64, \eta_p^2 = .01$. However, the HC, rMD and rNMD groups did differ on accuracy at a trend level $F(2, 102) = 2.73, p = .07, \eta_p^2 = .05$.

Post-hoc comparisons revealed that the rNMD group had significantly higher accuracy than the HC group $D = 2.34$ $SE = 1.02$, $p = .02$. The rMD and HC groups did not significantly differ from one another in terms of accuracy $D = 1.47$ $SE = 1.29$, $p = .26$, nor did the rMD and rNMD groups $D = .87$ $SE = 1.39$, $p = .53$. The groups did not differ significantly in post-error RT, $F(2, 102) = .11$, $p = .90$, $\eta_p^2 = .002$. Participants were equally accurate following correct $M = 90.87$, $sd = .87$ and incorrect $M = 89.7$, $sd = .51$ trials $F(1, 102) = 2.75$, $p = .10$, $\eta_p^2 = .03$, and this did not differ as a function of group $F(2, 102) = 1.62$, $p = .20$, $\eta_p^2 = .03$.

Error-related brain activity

Figure 1 displays grand average response-locked ERPs at Cz, where the error minus correct difference was maximal across groups. Topographic maps from left to right for the HC, rNMD and rMD groups, depicting voltage differences (in μV) across the scalp for error minus correct responses in the time window of the ERN are also presented in Figure 1. Average ERN values are listed in Table 1.

Confirming the impression from Figure 1, the ERN $M = .74$, $sd = 8.39$ was more negative relative to the CRN $M = 9.73$, $sd = 6.43$ across all groups $F(1, 102) = 140.05$, $p < .0001$, $\eta_p^2 = .58$. There was no main effect of group in the magnitude of the overall electrocortical response (i.e., collapsing across the ERN and CRN; $F(2, 102) = .32$, $p = .73$, $\eta_p^2 = .01$). However, the difference between the ERN and CRN (ERN) varied according to group, reflected in a significant group by response interaction $F(2, 102) = 3.68$, $p = .03$, $\eta_p^2 = .07$ ¹. Post hoc tukey's tests indicated that the ERN was smaller in the rMD compared to the HC group $D = 4.72$ $SE = 1.55$, $p = .003$, as well as compared to the rNMD group $D = 4.07$ $SE = 1.92$, $p = .04$. The HC and rNMD groups did not differ from one another in terms of the ERN $D = .64$ $SE = 1.42$, $p = .65$ ².

In the time-window of the Pe, the neural response to errors was more positive (i.e., larger) $M = 15.74$, $sd = 9.06$ than the neural response to correct $M = 3.23$, $sd = 5.05$ across all groups $F(1, 102) = 237.07$, $p < .001$, $\eta_p^2 = .70$. However, there was no main effect of group $F(2, 102) = 2.12$, $p = .13$, $\eta_p^2 = .04$, nor was the effect of response type qualified by an interaction with group $F(2, 102) = 2.12$, $p = .13$, $\eta_p^2 = .04$.

Participant Characteristics

Means for current Global Assessment of Functioning and current symptoms endorsed on the IDAS are presented in Table 1. As indicated in Table 1, although both remitted depressed groups differed from the HC group in reporting lower GAF and more symptoms of depression, social anxiety and panic, current symptoms for the two remitted groups were within one standard deviation of the means for non-clinical samples reported on in Watson and colleagues (2007). The two remitted depressed groups did not differ from one another on any variables related to current functioning, course of the disorder, the severity of their worst episode, or time spent in remission (all p values $> .20$).

¹The interaction of group and response type remained significant when including accuracy as a covariate in the model: $F(2, 101) = 3.76$, $p = .03$, $\eta_p^2 = .07$.

²Gender was also not associated with the magnitude of the ERN ($r = .08$, $p = .42$), CRN ($r = -.04$, $p = .66$), or ERN ($r = .15$, $p = .14$), nor did it differ significantly between groups; gender was therefore not included in the analyses.

Discussion

In the present study, we sought to explore the possibility that a blunted ERN might be a vulnerability marker for a specific depressive subtype: melancholic depression. Our results demonstrate that the ERN was blunted only in the subset of individuals with remitted melancholic depression, and not in individuals with remitted non-melancholic depression. Indeed, among individuals with non-melancholic depression, the ERN was comparable to that observed in never-depressed controls. Moreover, individuals with remitted melancholic depression exhibited a blunted ERN relative to individuals with remitted non-melancholic depression, and this blunting was observed despite the fact that the melancholic and non-melancholic groups did not differ in terms of symptom severity or impairment at the time of the visit or previous course of their depression. These data suggest that the blunted ERN we observed was not a state-effect reflecting the severity of subclinical symptoms of depression at the time of the assessment. These findings extend previous evidence for impairments in error-monitoring in MDD, and link the blunted ERN to the more specific phenotype of melancholic depression.

In addition, the present results may be useful in examinations of the ERN as a potential vulnerability marker for melancholic depression. We examined the ERN in remitted depression in order to understand whether abnormalities in the magnitude of the ERN are evident even when clinical levels of depressive psychopathology are not. Combined with previous evidence that the ERN is heritable (Anokhin et al., 2008), trait-like (Olvet & Hajcak, 2009b; Segalowitz et al., 2010; Weinberg & Hajcak, 2011), insensitive to changes in symptom reduction (Hajcak, Franklin, Foa, & Simons, 2008; Riesel, Endrass, Auerbach, & Kathmann, 2015), and evident in unaffected first-degree relatives of patients (Carrasco et al., 2013; Riesel et al., 2011), the present results suggest that the blunted ERN in melancholia might be a marker of enduring vulnerability for the disorder, that predates observable psychopathology and persists in the face of remission.

Because these individuals have already experienced at least one clinically-significant depressive episode, however, we cannot make the claim that the blunted ERN represents vulnerability to *first* onset of melancholic depression. In light of evidence that past depressive illness is a robust predictor of future episodes (Kendler, Thornton, & Gardner, 2001), it is also possible that the blunted ERN observed in the present paper most accurately reflects risk for an exacerbation of symptoms and an increase in severity, not vulnerability to the first emergence of symptoms. This is still an important form of vulnerability, and may inform prevention studies. However, prospective studies targeting vulnerable populations prior to the onset of depression will be necessary to adjudicate this question. Additionally, future studies should compare remitted to current depressive cases to establish the stability of the effect.

These results also have the potential to explain the mixed results from previous investigations of the magnitude of the ERN in depression, and highlight the capacity for diagnostic heterogeneity to obscure meaningful differences in neural response. Specifically, whereas some studies have found a blunted ERN in clinically depressed groups or in association with symptoms of depression (Ladouceur et al., 2012; Schoenberg, 2014;

Schrijvers et al., 2008; Weinberg, Meyer, et al., 2015), many others have not (Aarts et al., 2013; Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b, 2010; Tang et al., 2013; Schroder et al., 2013). It is possible that these mixed results are the result of diagnostic heterogeneity. The blunted ERN in depression may only be evident for those with melancholic subtype, as we observed in this study. This is consistent with previous evidence indicating that psychomotor retardation, a cardinal symptom of melancholic depression (but not all depression), is associated with a blunted ERN (Bates, Kiehl, Laurens, & Liddle, 2002; Foti, Kotov, Bromet, & Hajcak, 2012; Schrijvers et al., 2008; Weinberg, Kotov, & Proudfit, 2015), as well as evidence from lesion studies that impaired communication between motor centers and frontal regions is associated with a blunted ERN (Peterburs et al., 2011; 2012).

However, several studies have also found an increased ERN in depression (Aarts et al., 2013; Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b, 2010). We did not observe this in the non-melancholic depression subtypes in the present study—instead, remitted non-melancholic depressed individuals had an ERN that was comparable to controls (Olvet et al., 2010; Ruchow et al., 2006; Weinberg, Klein & Hajcak, 2012; Weinberg, Kotov, & Proudfit, 2015). It may be the case that, in addition to diagnostic heterogeneity, differences in tasks used to elicit the ERN may have contributed to the mixed results in depression (Weinberg, Dieterich, et al., 2015). In particular, factors like incentive conditions and trial-to-trial feedback may play an important role. For instance, in the present study, participants engaged in a simple flanker task, in which global feedback on performance was provided only between blocks. In some studies that have identified an enhanced ERN in depression, participants' responses were followed by immediate performance feedback (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b), which appears to influence the association between individual differences and the magnitude of the ERN (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 both the magnitude of the ERN (Hajcak, Moser, Yeung, & Simons, 2005) and the association of the ERN with depression (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b). Future studies might examine subtypes of depression under different task conditions in order to better identify specific impairments and deficits (Weinberg, Dieterich, et al., 2015).

Similarly, whereas some work in clinical populations has demonstrated that increased anhedonia is associated with a blunted ERN (Olvet, Klein, & Hajcak, 2010), other research in non-clinical undergraduate samples have found no such association with symptoms of anhedonia (Schroder et al., 2013). It is possible that a limited range within the anhedonia subscale in non-clinical samples reduces power to detect effects. Alternatively, some have proposed that a nonlinear association may exist between depression severity and the magnitude of the ERN such that less severe depression or depressive symptoms are associated with a larger ERN (Endrass, Riesel, Kathmann, & Buhlmann, 2014) and more severe symptoms are associated with a blunted ERN (e.g., Olvet, Klein, & Hajcak, 2010). The results of the current study may indicate a threshold, such that a trait-like tendency towards clinically-significant levels of anhedonia are associated with a blunted ERN.

It is worth noting here that, despite evidence for a blunted ERN in the remitted Melancholic Depression group, the groups did not differ on the majority of the performance variables,

with the exception that the remitted non-Melancholic Depression group was more accurate relative to the Healthy Control group. This disconnect between neural and behavioral responses in the flanker task is consistent with a substantial body of clinical literature suggesting at least a partial dissociation between the magnitude of the ERN and behavioral measures (for a review, see Weinberg, Riesel, & Hajcak, 2012), and suggests that the magnitude of the ERN does not simply reflect performance-related variables (Weinberg, Meyer, et al., 2015; Weinberg, Riesel & Hajcak, 2012).

In conclusion, the present study found that melancholic depression was specifically related to a blunted ERN, and, further, that this blunted ERN was evident even in the absence of clinically-significant levels of pathology. Combined, this suggests the blunted ERN may be a viable vulnerability marker for a particularly pernicious subtype of depression (Angst et al., 2007). Previous work has successfully used ERPs in low-symptom individuals to identify those individuals who would go on to meet criteria for Alzheimer's (e.g., Lai, et al., 2010; Parra et al., 2012) and in asymptomatic children to predict who would go on to meet criteria for an anxiety disorder (Lamm et al., 2014; Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015). The ERN may also be a valuable measure in future studies that seek to identify vulnerable individuals, and may be helpful in informing prevention efforts and tracking treatment response..

Acknowledgments

This work was supported by National Institute of Mental Health Grants RO1 MH098093 to Stewart A. Shankman.

References

- Aarts K, Vanderhasselt M-A, Otte G, Baeken C, Pourtois G. Electrical brain imaging reveals the expression and timing of altered error monitoring functions in major depression. *Journal of Abnormal Psychology*. 2013; 122(4):939–950. [PubMed: 24364597]
- Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Kalayam B, Katz R, Kanellopoulos D, Foxe JJ. Event-related potentials in an emotional go/nogo task and remission of geriatric depression. *Neuroreport*. 2007; 18(3):217–221. [PubMed: 17314660]
- Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P. The anterior cingulate cortex. *Annals of the New York Academy of Sciences*. 2001; 935(1):107–117. [PubMed: 11411161]
- Angst J, Gamma A, Benazzi F, Ajdacic V, Rössler W. Melancholia and atypical depression in the Zurich study: epidemiology, clinical characteristics, course, comorbidity and personality. *Acta Psychiatrica Scandinavica*. 2007; 115(s433):72–84. [PubMed: 17280573]
- Anokhin AP, Golosheykin S, Heath AC. Heritability of frontal brain function related to action monitoring. *Psychophysiology*. 2008; 45(4):524–534. [PubMed: 18503487]
- Bates AT, Kiehl KA, Laurens KR, Liddle PF. Error-related negativity and correct response negativity in schizophrenia. *Clinical Neurophysiology*. 2002; 113(9):1454–1463. [PubMed: 12169328]
- Baumeister H, Parker G. Meta-review of depressive subtyping models. *Journal of Affective Disorders*. 2012; 139(2):126–140. [PubMed: 21885128]
- Beste C, Saft C, Andrich J, Gold R, Falkenstein M. Error processing in Huntington's disease. *PLoS One*. 2006; 1(1):e86. [PubMed: 17183717]
- Botvinick MM, Braver TS, Barch D, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychological Review*. 2001; 108:624–652. [PubMed: 11488380]
- Brázdil M, Roman R, Daniel P, Rektor I. Intracerebral error-related negativity in a simple go/nogo task. *Journal of Psychophysiology*. 2005; 19(4):244–255.

- Brown, TA.; DiNardo, P.; Barlow, DH.; DiNardo, PA. Anxiety disorders interview schedule adult version (ADIS-IV). Oxford University Press; 1994.
- Burle B, Roger C, Allain S, Vidal F, Hasbroucq T. Error negativity does not reflect conflict: a reappraisal of conflict monitoring and anterior cingulate cortex activity. *Journal of Cognitive Neuroscience*. 2008; 20(9):1637–1655. [PubMed: 18345992]
- Carrasco M, Harbin SM, Nienhuis JK, Fitzgerald KD, Gehring WJ, Hanna GL. Increased Error-Related Brain Activity In Youth With Obsessive-Compulsive Disorder And Unaffected Siblings. *Depression and Anxiety*. 2013; 30(1):39–46. [PubMed: 23225541]
- Chiu PH, Deldin PJ. Neural evidence for enhanced error detection in major depressive disorder. *The American Journal of Psychiatry*. 2007; 164(4):608–616. [PubMed: 17403974]
- Cuthbert B. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry*. 2014; 13(1):28–35. [PubMed: 24497240]
- Cuthbert B, Insel T. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC medicine*. 2013; 11(1):126. [PubMed: 23672542]
- Day CV, Rush AJ, Harris AW, Boyce PM, Rekshan W, Etkin A, Williams LM. Impairment and distress patterns distinguishing the melancholic depression subtype: An iSPOT-D report. *Journal of Affective Disorders*. 2015; 174:493–502. [PubMed: 25554994]
- De Bruijn ER, Hulstijn W, Verkes RJ, Ruigt GS, Sabbe BG. Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology*. 2004; 177(1–2): 151–160. [PubMed: 15578258]
- Debener S, Ullsperger M, Siegel M, Fiehler K, Von Cramon DY, Engel AK. Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *The Journal of Neuroscience*. 2005; 25(50):11730–11737. [PubMed: 16354931]
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry*. 2007; 64(3):327–337. [PubMed: 17339521]
- Dutilh G, van Ravenzwaaij D, Nieuwenhuis S, van der Maas HL, Forstmann BU, Wagenmakers E-J. How to measure post-error slowing: a confound and a simple solution. *Journal of Mathematical Psychology*. 2012; 56(3):208–216.
- Endrass T, Riesel A, Kathmann N, Buhlmann U. Performance monitoring in obsessive-compulsive disorder and social anxiety disorder. *Journal of Abnormal Psychology*. 2014; 123(4):705–714. [PubMed: 25286372]
- Endrass T, Reuter B, Kathmann N. ERP correlates of conscious error recognition: aware and unaware errors in an antisaccade task. *European Journal of Neuroscience*. 2007; 26(6):1714–1720. [PubMed: 17880402]
- Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*. 1974; 16(1):143–149.
- Euser AS, Evans BE, Greaves Lord K, Huizink AC, Franken IH. Diminished error-related brain activity as a promising endophenotype for substance-use disorders: evidence from high-risk offspring. *Addiction Biology*. 2013; 18(6):970–984. [PubMed: 23145495]
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. *Psychophysiological Brain Research*. 1990; 1:192–195.
- Falkenstein M, Hoormann J, Christ S, Hohnsbein J. ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology*. 2000; 51:87–107. [PubMed: 10686361]
- Falkenstein M, Willemsen R, Hohnsbein J, Hielscher H. Effects of stimulus-response compatibility in Parkinson's disease: a psychophysiological analysis. *Journal of Neural Transmission*. 2006; 113(10):1449–1462. [PubMed: 16465455]
- Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava JA, Rosenbaum JF. Major depressive subtypes and treatment response. *Biological Psychiatry*. 1997; 42(7):568–576. [PubMed: 9376453]
- First, M.; Gibbon, M.; Spitzer, RL.; Williams, J. User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. Biometrics Research Department, New York State Psychiatric Institute; New York: 1996.

- Foti D, Kotov R, Bromet E, Hajcak G. Beyond the broken error-related negativity: functional and diagnostic correlates of error processing in psychosis. *Biological Psychiatry*. 2012; 71(10):864–872. [PubMed: 22336564]
- Foti D, Kotov R, Hajcak G. Psychometric considerations in using error-related brain activity as a biomarker in psychotic disorders. *Journal of Abnormal Psychology*. 2013; 122(2):520–531. [PubMed: 23713506]
- Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E. A neural system for error detection and compensation. *Psychological Science*. 1993; 4:385–390.
- Georgiadi E, Liotti M, Nixon NL, Liddle PF. Electrophysiological evidence for abnormal error monitoring in recurrent major depressive disorder. *Psychophysiology*. 2011; 48(9):1192–1202. [PubMed: 21446996]
- Gorwood P, Richard-Devantoy S, Baylé F, Cléry-Melun ML. Psychomotor retardation is a scar of past depressive episodes, revealed by simple cognitive tests. *European Neuropsychopharmacology*. 2014; 24(10):1630–1640. [PubMed: 25129432]
- Gratton G, Coles M, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*. 1983; 55(4):468–484. [PubMed: 6187540]
- Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER. The economic burden of depression in 1990. *Journal of Clinical Psychiatry*. 1993; 54:405–418. [PubMed: 8270583]
- Gründler TO, Cavanagh JF, Figueroa CM, Frank MJ, Allen JJ. Task-related dissociation in ERN amplitude as a function of obsessive-compulsive symptoms. *Neuropsychologia*. 2009; 47(8):1978–1987. [PubMed: 19428431]
- Hajcak G, Franklin ME, Foa EB, Simons RF. Increased error-related brain activity in pediatric obsessive-compulsive disorder before and after treatment. *American Journal of Psychiatry*. 2008; 165:116–123. [PubMed: 17986681]
- Hajcak G, Moser JS, Yeung N, Simons RF. On the ERN and the significance of errors. *Psychophysiology*. 2005; 42(2):151–160. [PubMed: 15787852]
- Helzer JE, Kraemer HC, Krueger RF. The feasibility and need for dimensional psychiatric diagnoses. *Psychological Medicine*. 2006; 36(12):1671–1680. [PubMed: 16907995]
- Holmes AJ, Pizzagalli DA. Response conflict and frontocingulate dysfunction in unmedicated participants with major depression. *Neuropsychologia*. 2008a; 46(12):2904–2913. [PubMed: 18577391]
- Holmes AJ, Pizzagalli DA. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Archives of General Psychiatry*. 2008b; 65(2):179–188. [PubMed: 18250256]
- Holmes AJ, Pizzagalli DA. Effects of task-relevant incentives on the electrophysiological correlates of error processing in major depressive disorder. *Cognitive, Affective, & Behavioral Neuroscience*. 2010; 10(1):119–128.
- Holroyd C, Coles M. The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological review*. 2002; 109(4):679–709. [PubMed: 12374324]
- Holroyd CB, Yeung N. Motivation of extended behaviors by anterior cingulate cortex. *Trends in Cognitive Sciences*. 2012; 16(2):122–128. [PubMed: 22226543]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine D, Quinn K, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*. 2010; 167(7):748–751. [PubMed: 20595427]
- Ito S, Stuphorn V, Brown JW, Schall JD. Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science*. 2003; 302(5642):120–122. [PubMed: 14526085]
- Kendler KS. The diagnostic validity of melancholic major depression in a population-based sample of female twins. *Archives of General Psychiatry*. 1997; 54(4):299–304. [PubMed: 9107145]
- Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *American Journal of Psychiatry*. 2001; 158(4):582–586. [PubMed: 11282692]
- Klein D. Endogenomorphic depression: a conceptual and terminological revision. *Archives of General Psychiatry*. 1974; 31(4):447–454. [PubMed: 4420562]

- Klein D. Classification of depressive disorders in the DSM-V: proposal for a two-dimension system. *Journal of Abnormal Psychology*. 2008; 117(3):552–560. [PubMed: 18729608]
- Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008; 455(7215):894–902. [PubMed: 18923511]
- Ladouceur CD, Slifka JS, Dahl RE, Birmaher B, Axelson DA, Ryan ND. Altered error-related brain activity in youth with major depression. *Developmental Cognitive Neuroscience*. 2012; 2(3):351–362. [PubMed: 22669036]
- Lahat A, Lamm C, Chronis-Tuscano A, Pine DS, Henderson HA, Fox NA. Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2014; 53(4):447–455. [PubMed: 24655654]
- Lai CL, Lin RT, Liou LM, Liu CK. The role of event-related potentials in cognitive decline in Alzheimer's disease. *Clinical Neurophysiology*. 2010; 121(2):194–199. [PubMed: 20005164]
- Lamm C, Walker OL, Degnan KA, Henderson HA, Pine DS, McDermott JM, Fox NA. Cognitive control moderates early childhood temperament in predicting social behavior in 7-year-old children: an ERP study. *Developmental Science*. 2014; 17(5):667–681. [PubMed: 24754610]
- Lovibond, S.; Lovibond, P. Manual for the depression anxiety stress scales. The Psychology Foundation of Australia: Inc.; Sydney: 1995.
- Lux V, Kendler K. Deconstructing major depression: a validation study of the DSM-IV symptomatic criteria. *Psychological medicine*. 2010; 40(10):1679–1690. [PubMed: 20059797]
- Manoach DS, Agam Y. Neural markers of errors as endophenotypes in neuropsychiatric disorders. *Frontiers in Human Neuroscience*. 2013; 7
- Mathers, CD.; Fat, DM.; Boerma, J. The global burden of disease: 2004 update. World Health Organization; 2008.
- Meyer A, Hajcak G, Torpey-Newman DC, Kujawa A, Klein DN. Enhanced error-related brain activity in children predicts the onset of anxiety disorders between the ages of 6 and 9. *Journal of Abnormal Psychology*. 2015; 124(2):266–274. [PubMed: 25643204]
- Meyer A, Proudfit G, Bufferd S, Kujawa A, Laptook R, Torpey D, Klein D. Self-Reported and Observed Punitive Parenting Prospectively Predicts Increased Error-Related Brain Activity in Six-Year-Old Children. *Journal of Abnormal Child Psychology*. 2014; 43(5):821–829. [PubMed: 25092483]
- Meyer A, Riesel A, Proudfit G. Reliability of the ERN across multiple tasks as a function of increasing errors. *Psychophysiology*. 2013; 50(12):1220–1225. [PubMed: 24730035]
- Miltner W, Lemke U, Weiss T, Holroyd C, Scheffers M, Coles M. Implementation of error-processing in the human anterior cingulate cortex: a source analysis of the magnetic equivalent of the error-related negativity. *Biological Psychology*. 2003; 64(1):157–166. [PubMed: 14602360]
- Moser J, Moran T, Jendrusina A. Parsing relationships between dimensions of anxiety and action monitoring brain potentials in female undergraduates. *Psychophysiology*. 2012; 49(1):3–10. [PubMed: 21895687]
- Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Abdalla S. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*. 2013; 380(9859):2197–2223.
- Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GPH, Kok A. Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*. 2001; 38:752–760. [PubMed: 11577898]
- Olvet D, Hajcak G. The effect of trial-to-trial feedback on the error-related negativity and its relationship with anxiety. *Cognitive, Affective, & Behavioral Neuroscience*. 2009a; 9(4):427–433.
- Olvet D, Hajcak G. Reliability of error-related brain activity. *Brain research*. 2009b; 1284:89–99. [PubMed: 19501071]
- Olvet D, Hajcak G. The stability of error related brain activity with increasing trials. *Psychophysiology*. 2009c; 46(5):957–961. [PubMed: 19558398]
- Olvet D, Klein D, Hajcak G. Depression symptom severity and error-related brain activity. *Psychiatry Research*. 2010; 179(1):30–37. [PubMed: 20630603]

- Overbeek TJM, Nieuwenhuis S, Ridderinkhof KR. Dissociable components of error processing: On the functional significance of the Pe vis-a-vis the ERN/Ne. *Journal of Psychophysiology*. 2005; 19:319–329.
- Parker G. Defining melancholia: the primacy of psychomotor disturbance. *Acta Psychiatrica Scandinavica*. 2007; 115(s433):21–30. [PubMed: 17201862]
- Parker G, Hadzi-Pavlovic D, Austin M, Mitchell P, Wilhelm K, Hickie I, Eyers K. Sub-typing depression, I. Is psychomotor disturbance necessary and sufficient to the definition of melancholia? *Psychological Medicine*. 1995; 25(4):815–823. [PubMed: 7480459]
- Parra MA, Ascencio LL, Urquina HF, Manes F, Ibáñez AM. P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. *Frontiers in Neurology*. 2012; 3:1–10. [PubMed: 22279441]
- Peterburs J, Gajda K, Koch B, Schwarz M, Hoffmann KP, Daum I, Bellebaum C. Cerebellar lesions alter performance monitoring on the antisaccade task—an event-related potentials study. *Neuropsychologia*. 2012; 50(3):379–389. [PubMed: 22227094]
- Peterburs J, Thürling M, Rustemeier M, Göricke S, Suchan B, Timmann D, Bellebaum C. A cerebellar role in performance monitoring—Evidence from EEG and voxel-based morphometry in patients with cerebellar degenerative disease. *Neuropsychologia*. 2015; 68:139–147. [PubMed: 25592368]
- Peterburs J, Pergola G, Koch B, Schwarz M, Hoffmann KP, Daum I, Bellebaum C. Altered error processing following vascular thalamic damage: evidence from an antisaccade task. *PLoS One*. 2011; 6(6):e21517–e21517. [PubMed: 21731771]
- Pizzagalli D, Oakes T, Fox A, Chung M, Larson C, Abercrombie H, Davidson R. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Molecular psychiatry*. 2004; 9(4):393–405.
- Reinhart RM, Woodman GF. Causal control of medial–frontal cortex governs electrophysiological and behavioral indices of performance monitoring and learning. *The Journal of Neuroscience*. 2014; 34(12):4214–4227. [PubMed: 24647942]
- Riesel A, Endrass T, Auerbach L, Kathmann N. Overactive Performance Monitoring as an Endophenotype for Obsessive-Compulsive Disorder: Evidence From a Treatment Study. *American Journal of Psychiatry*. 2015; 172(7):665–673. [PubMed: 25783756]
- Riesel A, Endrass T, Kaufmann C, Kathmann N. Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: evidence from unaffected first-degree relatives. *American Journal of Psychiatry*. 2011; 168(3):317–324. [PubMed: 21123314]
- Riesel A, Weinberg A, Endrass T, Meyer A, Hajcak G. The ERN is the ERN is the ERN? Convergent validity of error-related brain activity across different tasks. *Biological Psychology*. 2013; 93(3):377–385. [PubMed: 23607999]
- Ruchow M, Herrnberger B, Beschoner P, Grön G, Spitzer M, Kiefer M. Error processing in major depressive disorder: Evidence from event-related potentials. *Journal of Psychiatric Research*. 2006; 40(1):37–46. [PubMed: 15882872]
- Schoenberg PL. The error processing system in major depressive disorder: Cortical phenotypal marker hypothesis. *Biological Psychology*. 2014; 99:100–114. [PubMed: 24680837]
- Schrijvers D, de Bruijn ER, Maas Y, De Grave C, Sabbe BG, Hulstijn W. Action monitoring in major depressive disorder with psychomotor retardation. *Cortex*. 2008; 44(5):569–579. [PubMed: 18387589]
- Schrijvers D, De Bruijn ER, Maas YJ, Vancoillie P, Hulstijn W, Sabbe BG. Action monitoring and depressive symptom reduction in major depressive disorder. *International Journal of Psychophysiology*. 2009; 71(3):218–224. [PubMed: 18926863]
- Schroder HS, Moran TP, Infantolino ZP, Moser JS. The relationship between depressive symptoms and error monitoring during response switching. *Cognitive, Affective, & Behavioral Neuroscience*. 2013; 13(4):790–802.
- Segalowitz SJ, Santesso DL, Murphy TI, Homan D, Chantziantoniou DK, Khan S. Retest reliability of medial frontal negativities during performance monitoring. *Psychophysiology*. 2010; 47(2):260–270. [PubMed: 20030755]

- Seifert S, von Cramon DY, Imperati D, Tittgemeyer M, Ullsperger M. Thalamocingulate interactions in performance monitoring. *The Journal of Neuroscience*. 2011; 31(9):3375–3383. [PubMed: 21368049]
- Shankman S, Gorka S. Psychopathology research in the RDoC era: Unanswered questions and the importance of the psychophysiological unit of analysis. *International Journal of Psychophysiology*. 2015 in press.
- Simons RF. The way of our errors: theme and variations. *Psychophysiology*. 2010; 47(1):1–14. [PubMed: 19929897]
- Stemmer B, Segalowitz SJ, Witzke W, Schönle PW. Error detection in patients with lesions to the medial prefrontal cortex: an ERP study. *Neuropsychologia*. 2004; 42(1):118–130. [PubMed: 14615082]
- Tang Y, Zhang X, Simmonite M, Li H, Zhang T, Guo Q, Wang J. Hyperactivity within an extensive cortical distribution associated with excessive sensitivity in error processing in unmedicated depression: a combined event-related potential and sLORETA study. *International Journal of Psychophysiology*. 2013; 90(2):282–289. [PubMed: 24056021]
- Torpey D, Hajcak G, Kim J, Kujawa A, Dyson M, Olino T, Klein D. Error related brain activity in young children: associations with parental anxiety and child temperamental negative emotionality. *Journal of Child Psychology and Psychiatry*. 2013; 54(8):854–862. [PubMed: 23294040]
- Vaidyanathan U, Nelson LD, Patrick CJ. Clarifying domains of internalizing psychopathology using neurophysiology. *Psychological medicine*. 2012; 42(3):447–459. [PubMed: 21854683]
- Watson D. Rethinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. *Journal of Abnormal Psychology*. 2005; 114(4):522–536. [PubMed: 16351375]
- Watson D, O'Hara MW, Simms LJ, Kotov R, Chmielewski M, McDade-Montez EA, Stuart S. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). *Psychological Assessment*. 2007; 19(3):253–268. [PubMed: 17845118]
- Watson D, O'Hara M, Naragon-Gainey K, Koffel E, Chmielewski M, Kotov R, Ruggero C. Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment*. 2012; 19(4):399–420. [PubMed: 22822173]
- Weinberg A, Dieterich R, Riesel A. Error-related brain activity in the age of RDoC: A review of the literature. *International Journal of Psychophysiology*, in press. 2015
- Weinberg A, Hajcak G. Longer term test-retest reliability of error related brain activity. *Psychophysiology*. 2011; 48(10):1420–1425. [PubMed: 21496055]
- Weinberg A, Klein D, Hajcak G. Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *Journal of Abnormal Psychology*. 2012; 121(4):885–896. [PubMed: 22564180]
- Weinberg A, Kotov R, Proudfit G. Neural Indicators of Error Processing in Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, and Major Depressive Disorder. *Journal of Abnormal Psychology*. 2015; 124(1):172–185. [PubMed: 25384068]
- Weinberg A, Liu H, Hajcak G, Shankman S. Blunted Neural Response to Rewards as a Vulnerability Factor for Depression: Results from a Family Study. *International Journal of Psychophysiology*. 2015 in press.
- Weinberg A, Meyer A, Hale-Rude E, Perlman G, Kotov R, Klein D, Hajcak G. Error-related negativity and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology*, revise and resubmit. 2015
- Weinberg A, Olvet D, Hajcak G. Increased error-related brain activity in generalized anxiety disorder. *Biological Psychology*. 2010; 85(3):472–480. [PubMed: 20883743]
- Weinberg A, Riesel A, Hajcak G. Integrating multiple perspectives on error-related brain activity: the ERN as a neural indicator of trait defensive reactivity. *Motivation and Emotion*. 2012; 36(1):84–100.
- Zirnheld PJ, Carroll CA, Kieffaber PD, O'donnell BF, Shekhar A, Hetrick WP. Haloperidol impairs learning and error-related negativity in humans. *Journal of Cognitive Neuroscience*. 2004; 16(6):1098–1112. [PubMed: 15298795]

Highlights

- Blunted neural response to errors in remitted melancholic depression.
- Neural response to errors intact in remitted non-melancholic depression.
- The two remitted groups did not differ in current functioning or past course.
- May help refine our understanding of the depression-ERN association.

Figure 1.

(Top) Scalp topographies representing the error-related negativity. These maps are derived from the average difference (error minus correct response) between 0 and 80 ms following response onset, and represent the ERN for Healthy Control (HC), remitted Non-Melancholic Depression (rNMD), and remitted Melancholic Depression (rMD) groups. (Bottom) Response-locked ERP waveforms at electrode site Cz for HC, rNMD, and rMD groups. For each panel, response onset occurred at 0 ms. In addition to raw waveforms for correct and error responses, each panel also depicts the error-correct difference (solid grey line). Per ERP convention, negative voltages are plotted up.

Table 1

Demographic information, performance variables, neural responses, means for subscales of the Inventory of Depression and Anxiety Symptoms (IDAS-II), and clinical characteristics of worst past episode for the three groups.

	Healthy Controls (N = 55)	Non-Melancholic Depression (N = 33)	Melancholic Depression (N = 17)
Demographics			
Age	21.41 (2.70)	23.15 (3.01)	22.83 (3.28)
Sex (% female)	64.79%	73.53%	66.67%
Behavior			
Correct RT	423.64 (39.49)	427.63 (44.76)	443.64 (52.53)
Error RT	353.32 (45.53)	354.59 (42.35)	379.80 (61.61)
Accuracy (%)	88.96 (4.91) ^a	91.29 (4.64) ^a	90.43 (3.60)
Post-error accuracy	90.58 (7.60)	90.65 (9.20)	91.37 (7.92)
Post-correct accuracy	88.28 (4.97)	90.90 (4.56)	89.92 (3.84)
PES	34.75 (28.91)	33.60 (30.23)	38.07 (44.45)
ERPs (μV)			
ERN	−.24 (6.42)	1.21 (9.96)	3.02 (10.53)
CRN	9.72 (5.66)	10.52 (5.82)	8.26 (9.46)
ERN	−9.96 (5.54) ^a	−9.31 (7.71) ^b	−5.24 (5.68) ^{ab}
Pe (error)	15.30 (8.27)	16.01 (7.48)	16.63 (13.72)
Pe (correct)	4.054 (5.47)	1.32 (3.05)	4.30 (5.93)
Current Functioning			
GAF	84.18 (9.51) ^{ab}	67.85 (11.14) ^a	62.71 (12.49) ^b
IDAS Scales			
General Depression	31.60 (7.04) ^{ab}	41.82 (12.31) ^a	40.35 (10.28) ^b
Dysphoria	14.15 (4.12) ^{ab}	20.97 (7.91) ^a	19.24 (5.77) ^b
Lassitude	10.80 (3.36) ^{ab}	14.15 (4.72) ^a	14.00 (4.74) ^b
Insomnia	9.67 (3.33) ^{ab}	11.39 (5.25) ^a	12.59 (5.71) ^b
Appetite Loss	4.04 (1.59) ^{ab}	5.24 (2.28) ^a	4.82 (2.04) ^b
Appetite Gain	4.16 (1.80) ^{ab}	4.97 (1.53) ^a	4.59 (1.66) ^b
Ill Temper	6.23 (2.67)	6.83 (2.53)	7.09 (2.77)
Well-Being	27.04 (6.14)	24.94 (5.67)	25.59 (6.72)
Social Anxiety	7.13 (1.40) ^{ab}	10.97 (4.48) ^a	10.53 (4.33) ^b
Panic	9.29 (2.21) ^{ab}	11.63 (4.24) ^a	11.21 (3.81) ^b
Course			
# of MDD Episodes	--	2.06 (1.36)	2.53 (1.51)
MDD age of onset	--	17.27 (5.04)	15.29 (4.01)
Severity of worst past episode	--	3.73 (.90)	3.99 (.73)
Time in remission (months)	--	26.72 (23.96)	24.53 (28.97)

Note. Values with common superscripts were significantly different at $p < .05$ using χ^2 or Tukey tests; IDAS = Inventory of Depression and Anxiety Symptoms; RT = Reaction Time; PES = Post-Slowing; ERP = Event-Related Potential; ERN = error-related negativity, CRN = correct-response negativity; ERN = ERN minus CRN; GAF = Global Assessment of Functioning; MDD = Major Depressive Disorder