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Abnormal error processing in individuals with major depressive disorder

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Abstract of the Dissertation

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Major depressive disorder (MDD) is one of the most common and devastating psychiatric disorders. Behavioral studies have found that individuals with MDD are characterized by decreased accuracy after incorrect trials compared to correct trials, suggesting poor performance adjustments following errors. Recently, event-related potentials (ERPs) have been used to elucidate neural indices of response monitoring. The error-related negativity (ERN) is an ERP that presents as a negative deflection approximately 50 ms following an erroneous response, whereas the correct-response negativity (CRN) occurs following a correct response. The current study investigated the ERN and CRN in individuals with current MDD (CD), remitted MDD (RD) and healthy controls (HC) in order to elucidate deficits in response monitoring. By incorporating a RD group, we sought to determine whether deficits were related to current, state levels of depression. Participants performed an arrow version of the flanker task and a short/long mouth task that included trial-to-trial feedback. There were no group differences in the ERN or CRN in the flanker task,

however individuals with more severe depressive symptoms had a larger CRN and smaller ERN-CRN difference. In the short/long mouth task, individuals in the CD group had a smaller ERN compared to the HC group, and the RD group had an ERN that was numerically between the HC and CD groups. Additionally, the CD group had significantly lower accuracy compared to both the HC and RD groups. Overall, these results suggest that trial-to-trial feedback may affect performance monitoring in individuals with current MDD, such that they performed worse and had a reduced error signal in the brain. Individuals with remitted MDD performed as well as healthy controls, but they also had a slightly smaller ERN in the short/long mouth task. Additionally, individuals with current MDD appeared to have increased performance monitoring on correct trials in the flanker task. This study indicates that individuals with MDD have abnormal processing of both error and correct responses, however task-related differences – in particular the presence of trial-to-trial feedback – may moderate these abnormalities.

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INTRODUCTION

Recent research has confirmed the clinical intuition that individuals with major depressive disorder (MDD) are characterized by excessive reactions to errors and negative feedback. It is possible that the everyday occurrence of making an error or receiving a negative performance evaluation at work is amplified in these individuals, leading to continued impairment in basic functioning. Therapeutic techniques could be utilized to specifically address responsivity to these negative events, which may help to enhance future performance. Although imaging studies have elucidated neural substrates of performance monitoring, few studies have investigated these processes in individuals with MDD. More importantly, because imaging techniques have poor temporal resolution, they may not be able to capture the accurate timeline of neural activity following errors and negative feedback. Thus, by utilizing event-related potentials (ERPs), these processes can by studied on the scale of milliseconds.

The current study reviews clinical, behavioral, imaging and event-related potential studies that each contributes to the current knowledge about how individuals with MDD process errors and negative feedback. We set forth to study error and negative feedback processing in individuals with current MDD using ERPs in order identify indices of abnormal performance monitoring. Specifically, clinical features, such as symptom severity and chronic depression, will be assessed in order to determine their relationship to response monitoring ERPs. Additionally, this investigation will assess error and negative feedback processing in individuals who have recovered from a major

depressive episode in order to determine whether or not depression related performance abnormalities are still present after symptom resolution. This may allow us to identify a biological measure that can be used to identify individuals who are at risk for developing MDD.

Major Depressive Disorder (MDD)

Clinical characteristics

MDD is characterized by a persistent depressed mood or loss of pleasure (anhedonia), and is often accompanied by a myriad of other symptoms that include physical (changes in appetite, weight, number of hours sleeping, and motor activation) and cognitive symptoms (feelings of worthlessness, guilt, inability to concentrate and suicidal ideation; American Psychiatric Association, 1994). Lifetime prevalence of MDD in the general population is 16% (Kessler, et al., 2003; Kessler, et al., 2005). The most frequent age of onset is between 25-32 years of age (Kessler, et al., 2005), although it commonly occurs in adolescence (Kessler, Avenevoli, & Ries Merikangas, 2001). There is a high rate of comorbidity between MDD and other disorders (72.1%), with anxiety disorders co-occurring most often (Kessler, et al., 2003). Not only is MDD debilitating, with approximately 60% of individuals reporting severe to very severe impairment in their daily lives (Kessler, et al., 2003), but MDD is also related to increased mortality risk comparable to that of stroke or congestive heart failure (Schulz, et al., 2000). Unfortunately, only about 50% of individuals with MDD respond to various forms of psychotherapy (Roth & Fonagy, 2005) or antidepressant treatment (Casacalenda, Perry, & Looper, 2002) and at least two out of every three individuals who experience a

depressive episode will have a recurrence (N. Kennedy, Abbott, & Paykel, 2003; Solomon, et al., 2000).

MDD is a heterogeneous disorder that is likely caused by a combination of factors, including genetic vulnerability, environment and stress (Caspi, et al., 2003; Lesch & Mossner, 2006; Nestler, et al., 2002; Van Os & Jones, 1999). It has been estimated that 33% of the risk for developing MDD is genetic (Fava & Kendler, 2000). In fact, one of the strongest known risk factors for MDD is having a parent with the disorder (Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Sullivan, Neale, & Kendler, 2000; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). Additionally, personality traits, such as high levels of negative affect place individuals at risk for developing MDD (Kendler, Kessler, Neale, Heath, & Eaves, 1993; Ormel, Oldehinkel, & Brilman, 2001; Ormel, Oldehinkel, & Vollebergh, 2004; Van Os & Jones, 1999). Due to the genetic complexity of most psychiatric disorders (J. L. Kennedy, Farrer, Andreasen, Mayeux, & St George-Hyslop, 2003), it is highly unlikely that one distinct genetic factor will account for the heterogeneity of the disorder; however some efforts have been made to identify endophenotypes, or characteristics that mediate the relationship between genes and a given behavioral phenotype (Gottesman & Gould, 2003).

Negativity bias

A negatively biased view of the environment is thought to be a strong factor in the development of depression (Beck, 1967; Leppanen, 2006). Behavioral studies suggest that individuals with MDD are unable to inhibit the processing of negative faces (Goeleven, De Raedt, Baert, & Koster, 2006), have difficulty disengaging attention from

negative words (Koster, De Raedt, Goeleven, Franck, & Crombez, 2005), and show an attentional bias toward sad faces (Gotlib, Krasnoperova, Yue, & Joormann, 2004). Additionally, after receiving negative feedback, individuals with high depression scores report increased self-focus (Greenberg & Pyszczynski, 1986), amplification of the significance of failure (Wenzlaff & Grozier, 1988), increased depressed mood (Abela & D'Alessandro, 2002; Henriques & Leitenberg, 2002), and difficulty suppressing failure-related thoughts (Conway, Howell, & Giannopoulos, 1991). Therefore, not only are individuals with MDD more focused on negative stimuli, they have difficulty recovering after receiving negative feedback.

Sensitivity to mistakes and negative feedback

Making a mistake is an aversive event (Hajcak & Foti, 2008), and mistakes may be processed similar to negative feedback (cf. Holroyd & Coles, 2002). For individuals with MDD, such internal negative feedback will likely affect them in an amplified manner (i.e. they will exhibit an increased sensitivity to negative feedback). Indeed, individuals who report high levels of depressive symptoms are characterized by decreased accuracy after incorrect trials compared to correct trials (Holmes & Pizzagalli, 2007; Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). It has been suggested that the increased frequency of these double errors (i.e. errors after errors) is evidence of poor performance adjustments following an error (Pizzagalli, et al., 2006). Therefore, consistent with the negativity bias literature, individuals with MDD have difficulty recovering after committing an initial error.

Behavioral evidence also suggests that depressed individual's exhibit increased sensitivity to negative feedback, as evidenced by subsequent error commission. For example, individuals with depression are more likely to make an error after receiving feedback on their poor performance (Beats, Sahakian, & Levy, 1996; Compton, et al., 2008; Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997; Elliott, Sahakian, Michael, Paykel, & Dolan, 1998; Holmes & Pizzagalli, 2008b; Steffens, Wagner, Levy, Horn, & Krishnan, 2001). Moreover, these findings extend to individuals with remitted MDD (Elliott, Sahakian, et al., 1997), suggesting that this sensitivity to negative feedback is a trait-like characteristic that may be independent of current depressive symptoms.

Initially, it was suggested that these results represent a 'catastrophic response to failure' in individuals with MDD (Beats, et al., 1996; Elliott, et al., 1996); that is, once an individual with MDD has committed an error, their sensitivity to negative feedback causes them to become further impaired, which increases their likelihood of committing a subsequent error. However, a recent theory suggests that there is impairment in performance monitoring, such that individuals with MDD are unable to use information about their performance in order to improve on subsequent trials (Elliott, Sahakian, et al., 1997; Steffens, et al., 2001). This theory has received support by recent neurobiological studies of individuals with MDD (Holmes & Pizzagalli, 2008b).

Neural substrates of response monitoring

Brain regions involved in response monitoring

In order to investigate response monitoring, it is important to understand the neural substrates underlying these processes. A number of brain regions are involved in

response monitoring. The basal ganglia (BG) include dopaminergic (DA) cell bodies in the ventral tegmental area (VTA) and the substantia nigra (SN), which project to subcortical structures, such as the caudate, putamen and the nucleus accumbens. The BG are involved in learning, as evidenced by increased activation in the subcortical structures in response to learning signals in functional magnetic resonance imaging (fMRI) studies (Haruno, et al., 2004; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Seymour, et al., 2004; Tanaka, et al., 2006; Yacubian, et al., 2006). It has been suggested that the phasic activation of DA neurons serves as an error signal in order to facilitate learning (Schultz & Dickinson, 2000). Neurons in the BG monitor for differences between expected and actual outcomes, resulting in either an increase (after a better than expected outcome) or a decrease in phasic DA (after a worse than expected outcome; Schultz, 2002; Schultz, Dayan, & Montague, 1997).

Imaging studies in healthy individuals have also supported BG activation and deactivation during positive and negative feedback, respectively (Bray & O'Doherty, 2007; Delgado, Locke, Stenger, & Fiez, 2003; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). Some studies find that the ventral striatum even activates to gain related predictions (Yacubian, et al., 2006). Additionally, the VTA activates to rewarding, but not non-rewarding, events (D'Ardenne, McClure, Nystrom, & Cohen, 2008).

Substantial evidence of anterior cingulate cortex (ACC) activity on error trials has been reported. FMRI studies in humans have shown that the rostral ACC is activated after an error is committed (Braver, Barch, Gray, Molfese, & Snyder, 2001; Kiehl, Liddle, & Hopfinger, 2000; Mathalon, Whitfield, & Ford, 2003; Menon, Adleman,

White, Glover, & Reiss, 2001; Ullsperger & von Cramon, 2004). Another subregion of the ACC that has also been implicated in error detection is the caudal ACC (Carter, et al., 1998; Holroyd, et al., 2004; Ullsperger & von Cramon, 2001). It is likely that multiple subregions of the ACC are involved in error processing (Mathalon, Whitfield, et al., 2003), however it may be difficult to determine the temporal specificity of these activations due to the limited temporal resolution of imaging techniques such as fMRI.

Imaging studies have also shown that negative feedback activates either the rostral (Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Ullsperger & von Cramon, 2003) or the dorsal ACC (Bush, et al., 2002; Holroyd, et al., 2004). In animal studies, the rostral ACC is sensitive to reward expectancy and delivery (S. Ito, Stuphorn, Brown, & Schall, 2003; Shidara & Richmond, 2002). The activation of the ACC may be due to the unexpected or aversive nature of the feedback, thus signaling for behavioral adjustments.

After the brain detects an error, it is important to prevent an error from occurring again. The dorsolateral prefrontal cortex (DLPFC) plays a role in cognitive control as evidenced by its increased activation during task switching (Meyer, et al., 1998) or in response to instructions that indicate the need for increased cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000). Imaging studies have also shown increased activity of the DLPFC on trials after errors (Garavan, Ross, Murphy, Roche, & Stein, 2002; Kerns, et al., 2004). Source localization studies have also confirmed these findings (Holmes & Pizzagalli, 2008b). Interestingly, the activation of the DLPFC is closely tied to behavioral changes that occur after an error (i.e. post-error slowing),

suggesting its role in behavioral adjustments and not merely error detection (Kerns, et al., 2004).

Deficits in error-related brain activity assessed by fMRI in individuals with MDD

There have been few imaging studies that have assessed changes in brain activity in response to errors and negative feedback in individuals with MDD. In one study, Langenecker and colleagues (2007) found that increased activity in the rostral ACC during error trials predicted treatment response. In another study, Fales and colleagues (2008) found that individuals with MDD failed to activate the pregenual ACC compared to healthy controls in response to an error. They also found that individuals with MDD failed to recruit DLPFC on post-error trials. Finally, two studies have assessed brain activation in response to negative feedback in individuals with MDD (Elliott, et al., 1998; Taylor Tavares, et al., 2008), however neither of these studies looked at ACC activation. Overall, the studies that have assessed errors in individuals with MDD suggest that although there is decreased activation in the ACC in response to errors, individuals who ultimately respond to treatment have increased activation in the ACC. Therefore, ACC activity in response to errors may be a sensitive index of specific clinical features, such as treatment response. However, other clinical features have yet to be investigated, such as symptom severity and chronicity of MDD, which may also moderate the relationship between ACC activation in response to errors and depression.

Error-related negativity (ERN) and related components

Imaging studies have provided insight into brain regions that are involved in performance monitoring – regions that are similarly abnormally activated in individuals

with MDD. Another way to investigate these abnormalities is through the use of event-related potentials (ERPs). Unlike imaging techniques, which are optimal for obtaining spatial information, ERPs directly reflect neural activity and have excellent temporal resolution – tracking brain activity on the scale of milliseconds. One such ERP, the error-related negativity (ERN), has been extensively utilized in the study of errors. The ERN is an ERP component that presents as a negative deflection approximately 50 ms after the commission of an error (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN has been observed across tasks that employ a variety of stimulus and response modalities (Bernstein, Scheffers, & Coles, 1995; Holroyd, Dien, & Coles, 1998; Van't Ent & Apkarian, 1999) and task difficulty (Band & Kok, 2000; Mathalon, Bennett, et al., 2003; Mathewson, Dywan, & Segalowitz, 2005; Moser, Hajcak, & Simons, 2005; Themanson, Hillman, & Curtin, 2006). Additionally, the ERN has high test-retest reliability (Olvet & Hajcak, submitted-b), becomes stable after just 6 error trials are included in the average (Olvet & Hajcak, in press) and has a moderate heritability rate (Anokhin, Golosheykin, & Heath, 2008).

The ERN is typically measured at midline frontal or central electrode sites where the ERN is largest (i.e., FCz). The source of the ERN is thought to be in the rostral ACC (Laurens, Ngan, Bates, Kiehl, & Liddle, 2003; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003), however some source localization studies report the source of the ERN in the caudal ACC (O'Connell, et al., 2007; van Veen & Carter, 2002) and the supplemental motor area (Herrmann, Rommler, Ehlis, Heidrich, & Fallgatter, 2004). In a novel attempt to make sense of these findings, Mathalon and colleagues (2003) had subjects perform a

Go/No-Go task while recording brain activity with EEG and fMRI. They found that both the caudal and rostral ACC activity significantly correlated with ERN. It has been suggested that the ERN could represent a combination of signals from multiple subregions within the ACC (Gehring & Knight, 2000). Additionally, intracerebral ERP recordings show that although the source of the ERN is likely the ACC, several other regions are involved in error processing, such as the DLPFC, the orbitofrontal cortex, and the hippocampus (Brazdil, Roman, Daniel, & Rektor, 2005; Brazdil, et al., 2002).

An ERN-like component is sometimes evident on correct response trials (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Ford, 1999; Gehring & Knight, 2000; Scheffers & Coles, 2000; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). This component has been referred to as the correct response negativity (CRN; Ford, 1999). Authors have suggested that the CRN reflects an emotional reaction (Luu, Collins, & Tucker, 2000), uncertainty of a correct response (Coles, Scheffers, & Holroyd, 2001; Pailing, Segalowitz, Dywan, & Davies, 2002), or the coactivation of correct and incorrect responses (Luu, et al., 2000; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996). Although these ideas are plausible, they do not necessarily explain the phenomena of CRNs on simple tasks with clear stimuli. Therefore, it is likely that the CRN merely represents response monitoring activity in the ACC, which can be present on both correct and error trials (Falkenstein, et al., 2000; Vidal, et al., 2000).

Functional significance of the ERN

Several theories and models have been put forth to explain the functional significance of the ERN. One of the more prominent computational models is the

reinforcement learning theory of the ERN (RL-ERN; Holroyd & Coles, 2002). According to the RL-ERN, the BG monitor information from both the environment (external) and self-generated actions (internal), and evaluate on-going events based on learned expectations (Holroyd & Coles, 2002). The RL-ERN is rooted in the temporal difference theory which states that the BG induce an increase or decrease in phasic midbrain DA activity when events are better or worse than expected, respectively (for review see Barto, 1995; Houk, Adams, & Barto, 1995; Schultz, 2002). The RL-ERN theory proposes that the ERN is the result of disinhibition of the ACC by DA neurons signaling events as worse than anticipated. From this perspective, error signals are important for learning because they are used to predict future rewards and non-rewards and to modify ongoing behavior (Barto, 1995; Montague, Dayan, & Sejnowski, 1996; Schultz, 2002).

A major shortcoming of the RL-ERN model is that it does not account for motivational and individual differences. Errors are motivationally salient events that prompt psychophysiological changes that include skin conductance and heart rate deceleration (Hajcak, McDonald, & Simons, 2003b, 2004). Although these peripheral responses are consistent with both a defensive and orienting response, a recent study from our lab found that the defensive startle reflex was larger following errors than correct responses (Hajcak & Foti, 2008). Collectively, these data suggest that the ERN might reflect error-detection that is utilized for motivational ends. Thus, the amplitude of the ERN might relate to the *significance* of an error. This possibility was first suggested by Gehring and colleagues (1993) who reported that the amplitude of the ERN was larger

when participants were told to be more accurate, whereas the ERN was smaller when participants were told to respond faster. Therefore, by emphasizing accuracy, the authors could have made errors more salient which in turn could have made them more important (Hajcak, Moser, Yeung, & Simons, 2005). Other studies have supported these findings by explicitly manipulating error value (Chiu & Deldin, 2007; Hajcak, Moser, et al., 2005; Kim, Iwaki, Uno, & Fujita, 2005).

Feedback negativity (FN)

Consistent with the theory that reward prediction error should be elicited when events are first detected as worse than expected, there is an ERP component, the feedback negativity (FN) that peaks approximately 250 ms following the onset of feedback, and is larger (e.g., more negative) following feedback that represents negative outcomes, such as errors or monetary loss (Gehring & Willoughby, 2002; Hajcak, Holroyd, Moser, & Simons, 2005; Hajcak, Moser, Holroyd, & Simons, 2006; Holroyd & Coles, 2002; Holroyd, Hajcak, & Larsen, 2006; Miltner, Lemke, et al., 1997; Yeung, Holroyd, & Cohen, 2005; Yeung & Sanfey, 2004). The FN is maximal at frontal or central electrode sites and is not contingent on active responding (Donkers, Nieuwenhuis, & van Boxtel, 2005; Potts, Martin, Burton, & Montague, 2006; Yeung, et al., 2005). The FN is also thought to originate in the ACC, however like the ERN, it is unclear which subregion of the ACC is responsible for the generation of the FN. Source localization studies generally report the ACC (Gehring & Willoughby, 2002), or more specifically the dorsal ACC (Holroyd & Coles, 2002; Luu, et al., 2003; Miltner, Lemke, et al., 1997). Another study

found that the source of the FN is the medial prefrontal cortex (PFC) and the posterior cingulate cortex (Muller, Moller, Rodriguez-Fornells, & Munte, 2005).

In light of their similarities, it has been hypothesized that the ERN and the FN reflect the activity of the same monitoring system (Holroyd & Coles, 2002). Holroyd and colleagues (2002; 2004) found that the source of both the ERN and the FN is the dorsal ACC. However, other studies have shown that the scalp topography of the FN is more widely distributed, especially into parietal regions (Gehring & Willoughby, 2004; Miltner, Braun, & Coles, 1997; Muller, et al., 2005). In addition, the ERN appears to be sensitive to error value (Hajcak, Moser, et al., 2005), whereas the FN seems to represent a binary distinction between favorable and unfavorable outcomes (Hajcak, et al., 2006). Therefore, it is unclear whether or not these components derive from the same source, although they certainly share many apparent similarities.

The ERN in anxiety disorders and related personality characteristics

Both depression and anxiety disorders are characterized by high negative affect (Brown, Chorpita, & Barlow, 1998) and have a high rate of comorbidity (Kessler, et al., 2003). Studies showed an increased ERN amplitude in adult obsessive-compulsive disorder (OCD) patients relative to controls (Gehring, Himle, & Nisenson, 2000) and in children with either generalized anxiety disorder (GAD) or OCD (Hajcak, Franklin, Foa, & Simons, 2008; Johannes, et al., 2001; Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2006). Additionally, two studies to date have shown that the ERN does not change after successful treatment for anxiety disorders in children (Hajcak, et al., 2008; Ladouceur, Dahl, Birmaher, Axelson, & Ryan, 2007) and another study conducted with spider phobic

individuals found that the ERN amplitude did not change during symptom provocation with the presence of a tarantula (Moser, et al., 2005). Combined, these studies suggest that the ERN is enhanced in individuals with anxiety disorders and the ERN is a trait marker that is not affected by state-related changes in anxious symptoms.

Some studies have shown an increased CRN in certain psychiatric populations. For example, one study found increased error-related activity in high obsessive-compulsive trait subjects on both error and correct trials (Hajcak & Simons, 2002), which was confirmed in an fMRI study that found increased ACC activity in both error and correct trials in OCD patients (Ursu, et al., 2001). An increased CRN has also been found in schizophrenic patients compared to controls (Mathalon, et al., 2002; Morris, Yee, & Nuechterlein, 2006), individuals with PFC lesions (Gehring & Knight, 2000) and individuals with PFC white matter infarctions (Hogan, Vargha-Khadem, Saunders, Kirkham, & Baldeweg, 2006). These findings suggest that increased error monitoring on correct trials may result from frontal cortex abnormalities.

ERP research on individual differences has also provided some evidence that the ERN is related to personality traits that vary with both anxiety and depression. Two studies have found that subjects who scored high in negative affect have significantly larger ERN amplitudes compared with subjects who scored low on negative affect (Hajcak, et al., 2004; Luu, et al., 2000). Additionally, individuals who report high levels of OC traits, worry and anxiety have been associated with increased ERN amplitude (Hajcak, McDonald, & Simons, 2003a; Hajcak & Simons, 2002). An fMRI study also found increased ACC activity on error trials in individuals with high trait anxiety (Paulus,

Feinstein, Simmons, & Stein, 2004). Hajcak and colleagues (2004) argued that abnormal ERN amplitude may reflect an underlying characteristic that is central to disorders characterized by negative affect.

The ERN in MDD

Consistent with the notion that both anxiety disorders and MDD are characterized by high negative affect, some studies have identified an increased ERN in individuals with MDD when utilizing speeded response tasks that incorporate trial-to-trial feedback. For example, Holmes & Pizzagalli (2008b) found that individuals with MDD had a larger ERN amplitude compared to healthy controls. Another study found that depressed individuals had a larger ERN amplitude in a punishment condition compared to controls, but no difference in ERN amplitude during a reward condition, which supports the notion that depressed individuals are especially sensitive to negative feedback (Chiu & Deldin, 2007). These initials studies lend some support to the hypothesis that an increased ERN is related to high negative affect (Hajcak, et al., 2004). However, Schrijvers and colleagues (2008; 2009) reported no differences in ERN amplitude comparing individuals with MDD and healthy controls. Additionally, Compton and colleagues (2008) found no difference in ERN amplitude in undergraduate students endorsing low vs. high depression scores. Thus, although there is some evidence to suggest that individuals with MDD have increased ERNs, not all studies have confirmed these findings.

The FN in MDD

There has only been one study that has assessed the FN in individuals with MDD. Tucker and colleagues (2003) showed that individuals with MDD have a larger FN not

only to negative feedback, but to *all* types of feedback. A recent study, however, suggests that undergraduates who report high depression scores have a decreased FN (Foti & Hajcak, 2008). This is contrary to behavioral studies which show that individuals with MDD are more sensitive to negative *performance* feedback. However, Foti & Hajcak used a gambling paradigm which may elicit a different response; individuals with MDD may be *less* sensitive to feedback indicating monetary rewards or losses, and *more* sensitive to feedback that reflects performance evaluation. For the purposes of the current study, we focused on errors and negative performance feedback – which are personally relevant – rather than including monetary based feedback – which is not necessarily personally relevant and may be tapping into altered reward-based processes.

One study has looked at the FN in remitted depression (Santesso, et al., 2008). Although the findings suggest that individuals with remitted MDD had an increased FN amplitude compared to healthy controls, this study did not include a currently depressed group therefore it is unclear whether or not the remitted group was comparable to individuals who are currently depressed. Another limitation of these findings is that the authors did not include positive feedback in the task, so it is uncertain whether these differences are due purely to negative feedback or if the remitted MDD group is sensitive to feedback, in general. Finally, the area that they chose to analyze the FN extends beyond the typical FN window (i.e. 250 – 350 ms; whereas they analyzed it from 200 – 500 ms).

The relationship between depressive symptom severity and the ERN/FN

It is possible that depressive symptom severity may be the key to understanding the discrepancies in the ERN literature. For example, the clinical populations studied vary on symptom severity, with numerically larger ERNs in individuals suffering from mild (Compton, et al., 2008) or moderate depression (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b) and numerically smaller ERNs in individuals suffering from severe depression (Schrijvers, et al., 2008; Schrijvers, et al., 2009). Therefore, there may be a non-linear relationship between symptom severity and the ERN. In fact, this had been suggested by Tucker and colleagues (2003) in relation to the FN; they reported that individuals who had no depressive symptoms or severe depressive symptoms had a small FN, whereas individuals who had mild or moderate depressive symptoms had a large FN. A similar relationship between the ERN and symptom severity has been reported with anxiety symptoms in individuals with OCD (Nieuwenhuis, Nielen, Mol, Hajcak, & Veltman, 2005). Thus, the relationship between the ERN and depressive symptom severity needs to be further investigated. In addition, the relationship between the ERN and other clinical characteristics, such as chronic depression and the presence of anxiety symptoms, are important areas for future research.

Summary

There have been few studies that have investigated the ERN and the FN in individuals with MDD. In general, it appears that individuals with moderate MDD have an increased ERN following mistakes and a larger FN following all types of feedback. Additionally, individuals with remitted MDD may have a larger ERN compared to

healthy controls, but these results should be interpreted with caution due to the study's methodological limitations. In order to fully understand error and feedback processing deficits in individuals with MDD, it would be ideal to obtain both the ERN and FN in individuals who are currently depressed, individuals with remitted depression, and healthy controls. Additionally, by incorporating a remitted depressed group, it is possible to determine whether altered performance monitoring is a stable trait characteristic that may be useful for assessing risk.

Aims of the present research

The present study was developed to investigate response monitoring abnormalities in individuals with MDD, as well as in individuals with remitted MDD. Few studies have investigated the ERN and the FN in individuals with MDD—and none have assessed them simultaneously or included a comparison group with remitted depression. Therefore, this study provides insight into how individuals with current and past MDD process mistakes (i.e. ERN) and how they respond to negative performance feedback (i.e. FN) using behavioral and ERP measures. Although these processes may be related, they reflect internal vs. external negative feedback signals, and might differ from one another in MDD. Additionally, this study investigated whether or not these components represent a trait risk factor for depression by comparing currently versus formerly depressed individuals. There is an abundance of evidence to suggest that the ERN is a trait risk marker in anxiety disorders, however little work has been done in depression. In order to further elucidate these findings, individuals with current MDD, remitted MDD, and healthy controls performed two speeded response tasks: the flanker

task (Eriksen & Eriksen, 1974) and the short/long mouth task (adapted from Pizzagalli, Jahn, & O'Shea, 2005). The flanker task is a commonly used simple speeded response task that is used to elicit errors and the ERN. The short/long mouth task is a signal detection task that incorporates trial-to-trial feedback in order to inform the participants as to whether or not they made the correct choice. By using these two tasks, we can study both the ERN and the FN, as well as to determine whether or not differences in task paradigm (i.e. the incorporation of trial-to-trial feedback) will affect the ERN. The following specific aims were investigated:

Aim 1: To evaluate error-related ERPs in individuals with MDD.

Although two studies have reported increased ERNs in individuals with MDD, others have failed to replicate these findings. Additionally, no study to date has assessed the CRN in individuals with MDD. The clinical populations in these studies varied in their depressive symptom severity, which may actually be the key to understanding the relationship between MDD and the ERN. Therefore, the aim of this study was to evaluate the ERN and the CRN in individuals with MDD. Additionally, we evaluated the relationship between the ERPs and clinical measures, including symptom severity, anxiety, and a history of chronic depression, as well as behavioral measures, such as accuracy. Based on the literature, we hypothesized that the ERN and the CRN would be increased in individuals with moderate MDD, but decreased in individuals with severe MDD.

Aim 2: To evaluate the FN in individuals with MDD.

Only one study has examined the FN elicited by performance feedback in individuals with MDD; Tucker and colleagues found that individuals with MDD had an increased FN overall in response to feedback. Based on the literature then, it is unclear whether or not individuals with MDD would have an increased FN compared to healthy controls. However, based on both the ERN and FN literatures, we hypothesized that the FN would be increased in individuals with moderate MDD, but decreased in individuals with severe MDD.

Aim 3: To evaluate the relationship between the ERN and the FN across tasks.

Investigators have found that within a single task, there is an inverse relationship between the ERN and the FN as participants learn stimulus-response mappings (Holroyd & Coles; Nieuwenhius 2002). However, no one has looked at the relationship between the ERN and the FN across tasks. The question remains whether individuals with an increased ERN in one task will also have an increased FN in another. To this end, we sought to compare the ERN in the flanker task with the FN in the short/long mouth task.

Aim 4: To evaluate whether differences in the ERN and FN are also observed in remitted MDD.

Treatment studies in individuals with anxiety disorders have shown that enhanced error-related activity does not change with successful treatment or with symptom provocation. Further support that the ERN may represent a trait-like marker is found in non-clinical populations that are characterized by personality traits that are risk factors

for MDD, such as high negative affect. However, no studies to date have examined the ERN among individuals with a history of depression.

One recent study found that individuals with remitted MDD had increased FN compared to healthy controls; yet this study did not investigate individuals with current MDD, nor did this study include positive feedback. These limitations make it difficult to interpret the results. This proposal will address both of these issues and we hypothesized that there would be no difference in the ERN or the FN when comparing current and remitted depressed individuals, however the remitted depressed individuals should have a significantly different ERN or FN when compared to healthy controls.

METHODS

Participants

22 individuals with current MDD, 24 individuals with remitted MDD and 25 individuals with no current or past psychiatric disorder participated in the current experiment. All participants were recruited from the community and university by posting flyers and placing advertisements on the internet, screening university students in the Psychology Department's approved mass testing session, and contacting patients who participated in a treatment study of chronic depression; additionally, participants were recruited through a Seed Grant for Survey Research—the Survey Research Center randomly called 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 screening to assess for inclusion/exclusion criteria, including the administration of the Mini-International Neuropsychiatric Interview (MINI; Sheehan, et al., 1998) to initially assess for Axis I disorders. Individuals who were eligible based on the phone screen were invited for a 3 hour 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. Individuals in the currently depressed (CD) group met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a current major depressive episode (MDE) and scored greater than 24 on the Inventory of Depressive Symptomatology, Self-Report (IDS-SR). The individuals in the remitted depressed (RD) group met DSM-IV criteria for at least one past MDE and scored less

than 15 on the IDS-SR. Participants were excluded if they were currently on antidepressant medications or met DSM-IV criteria for another current Axis I disorder (excluding specific phobia: N = 1 CD). All participants had stopped antidepressant medication at least one month prior to participating in the study. These exclusion criteria were included in order to avoid potential effects of medication or the diagnosis of another psychiatric disorder which is associated with an altered ERN/FN. Individuals in the healthy control (HC) group were excluded if they met criteria for any past or current DSM-IV Axis I diagnosis. For each group, 5 diagnostic interviews were recorded for inter-rater reliability assessment; all 15 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.

Stimulus Materials

All tasks were 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 in (48.26 cm) monitor. Participants were seated at a viewing distance of approximately 24 in (60.96 cm).

One task was an arrow version of the flanker task (Eriksen & Eriksen, 1974). 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 2,300 to 2,800 ms.

The short/long mouth task was a modified signal-detection task (adapted from Pizzagalli, et al., 2005) in which subjects were briefly shown a schematic face with either a short (11 mm) or long (12 mm) mouth and were asked to identify which type of mouth was presented by pressing the right or left mouse button (mouse button response sides were counterbalanced across subjects). The stimuli were presented equally often in a randomized sequence. Stimuli appeared in the following order and remained on screen for the following durations: (i) a fixation cross for 500 ms, (ii) a mouthless schematic face for 500 ms, (iii) the addition of either a short mouth (11 mm) or a long mouth (12 mm) for 100 ms, (iv) the mouthless schematic face remained on the screen until the subjects made a response, and (v) feedback on their accuracy was presented for 1750 ms (a cartoon image of a thumbs up if correct and a thumbs down if incorrect).

Procedure

After obtaining informed consent, participants were asked to fill out the IDS-SR_{30}. Participants who met IDS-SR_{30} criteria were administered the Structured Clinical Interview for DSM-IV Axis I Disorders – Non-Patient Edition, Version 2 (SCID-I/NP; Spitzer, Williams, Gibbon, & First, 1992) in order to determine the presence of Axis I disorders. If participants continued to meet eligibility criteria after the clinical interview, they participated in the electroencephalograph (EEG) session. EEG sensors were attached and the participant was given detailed task instructions. The two tasks were presented in a random order.

In the flanker task, participants 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.

In the short/long mouth task, participants were instructed to press one mouse button if they thought the mouth was short, the other if they thought the mouth was long (mouse button response sides were counterbalanced across subjects). Participants performed a practice block of 10 trials; the actual experiment consisted of 3 blocks of 100 trials (300 trials total) with each block initiated by the participant.

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 32 scalp electrodes based on the 10/20 system, 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).

Off-line analysis was performed using Brain Vision Analyzer software (Brain Products, Gilohing, Germany). EEG data were re-referenced to the numeric mean of the mastoids and band-pass filtered with cutoffs of 4 and 7 Hz (i.e. in the theta range). Theta activity is thought to arise from either the ACC (Asada, Fukuda, Tsunoda, Yamaguchi, & Tonoike, 1999; Gevins, Smith, McEvoy, & Yu, 1997; Ishii, et al., 1999) or the DLPFC (Sasaki, Tsujimoto, Nishikawa, Nishitani, & Ishihara, 1996). In addition, data supports the notion that the ERN represents theta activation (Luu & Tucker, 2001; Luu, et al., 2003; Luu, Tucker, & Makeig, 2004; Makeig, 2002; Makeig, et al., 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.

For the flanker task and the short/long mouth task, 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. For the short/long mouth task, the EEG was also segmented for each trial beginning 400 ms before each feedback onset and continuing for 1000 ms; thus, the 600 ms after feedback onset was represented in the ERP averages. The EEG was corrected for blinks and eye movements using the method developed by Gratton, Coles, and Donchin (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.

For the flanker task, response-locked ERPs were averaged separately for error and correct trials. The ERN was evaluated as the average activity on error trials from response onset to 100 ms (i.e. 0 – 100 ms) and the CRN was evaluated in the same time window on correct trials. The electrode site was chosen based on where the ERN was maximal (see Results section). A 200 ms window prior to response onset (-400 to -200 ms) 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).

For the short/long mouth task, response and feedback-locked ERPs were averaged for error and correct trials. For response-locked ERP averages, the ERN was evaluated as the average activity on error trials from response onset to 100 ms (i.e. 0 – 100 ms) and the CRN was evaluated in the same time window on correct trials. A 200 ms window prior to response onset (-400 to -200 ms) served as the baseline. For feedback-locked ERP averages, the FN was evaluated as the average activity on error trials between 250-350 ms following feedback onset. A 200 ms window prior to feedback onset (-200 to 0 ms) served as the baseline for the FN. The electrode site for the ERN and the FN was chosen based on where they were maximal (see Results section).

Behavioral measures included both the number of error and correct 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, RT and accuracy on trials following errors were also evaluated to determine if there were group differences in post-error behavior. For the flanker task, trials were removed from the analysis if reaction times were faster than 200 ms or slower than 800 ms (1.52% of all trials). For the short/long mouth task, trials were removed if reaction times were faster than 200 ms or slower than 1500 ms (1.58% of all trials). The number of trials removed did not differ among the groups for either the flanker ($F(2,65) = 1.36$, $p > .05$) or the short/long mouth task ($F(2,68) < 1$).

Clinical measures

The Inventory for Depressive Symptomatology, Self-Rated (IDS-SR; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) was used to assess depressive symptom severity. The IDS-SR is a 30-item scale in which participants were asked to rate their response from 0 to 3 based on how the item best describes them for the past seven days. The items asked about a variety of depressive symptoms, such as mood (e.g. "Feeling sad"), anhedonia (e.g. "Capacity for pleasure or enjoyment"), and physical symptoms (e.g. "Leaden paralysis"). Only 28 items were included in the total score because one item in a pair asked for either increased or decreased "appetite disturbance" and "body weight disturbance." The IDS-SR has good internal consistency and concurrent validity (Biggs, et al., 2000; Rush, et al., 1996; 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 & 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 each in the past week, using a scale from 1 = "not at all" to 5 = "extremely." The MASQ has five subscales: 1. General Distress Mixed Symptoms (15 items), 2. General Distress Depressive Symptoms (12 items), 3. General Distress Anxious Symptoms (11 items), 4. Anhedonic Depression (22 items), and 5. Anxious Arousal (17 items). The General Distress Mixed Symptom subscale contained items that were more physical or cognitive (e.g. "Got fatigued easily", "Trouble paying attention"). The General Distress Depressive Symptoms subscale contained items that were related to sad or negative mood (e.g. "Felt sad", "Pessimistic about the future"). The General Distress Anxious subscale contained items that were related to anxiety (e.g. "Felt nervous", "Unable to relax"). The Anhedonic Depression subscale contained items that were related to anhedonia (e.g. "Felt nothing was enjoyable", "Felt slowed down"). Finally, the Anxious Arousal subscale contained items that were related to panic symptoms (e.g. "Short of breath", "Cold or sweaty hands"). MASQ subscales have good internal consistency, and convergent and discriminant validity (Watson, et al., 1995).

The Temporal Experience of Pleasure Scale (TEPS; Gard, Gard, Kring, & John, 2006) is an 18-item self-report measure of trait anticipatory and consummatory pleasure. Participants were asked to rate how true each item is for them, in general, using a scale from 1 = "Very false for me" or 5 = "Very true for me." The anticipatory subscale contained items that were related to anticipating future events (e.g. "When something

exciting is coming up in my life, I really look forward to it"), whereas the consummatory subscale contained items that were related to enjoying sensory stimuli (e.g. "I enjoy taking a deep breath of fresh air when I walk outside"). The TEPS has good internal consistency, test–retest reliability, and convergent and discriminant validity (Gard, et al., 2006).

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. For the clinical measures, the MASQ scores were log transformed. For the flanker task, the following measures were log transformed: reaction time, post-error accuracy, and post-error reaction time. For the short/long mouth task, post-error accuracy measures were log transformed. Averages and figures 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); Greenhouse-Geisser correction was applied to *p* values associated with multiple-df, repeated measures comparisons when appropriate. Group differences were assessed using either a one-way analysis of variance (ANOVA) with Group (HC, CD, and RD) as the between-subjects factor, or a mixed ANOVA with Trial Type (Error and Correct) as the within-subjects factor and Group (HC, CD, and RD) as between-subjects factors. Post-hoc *t*-tests were used to follow up significant ANOVA results. Analysis of covariance (ANCOVA) was used to account for variability between the groups that could be

attributed to a third factor that the groups differed on. The Pearson correlation coefficient (r) was used to examine the relationship between the ERP and clinical measures. For brevity, only significant correlations between ERP and self report measures are reported.

RESULTS

Sample Characteristics

The final sample consisted of 22 CD (13 female), 24 RD (17 female), and 25 HC (18 female). Demographic information is presented in Table 1. A one-way ANOVA indicated that there were no differences among the groups on age ($F(2,68) < 1$) or years of education ($F(2,68) = 1.32$, $p > .05$). Chi-square analysis also indicated that there were no differences among the groups on gender ($\chi^2(2) = 1.06$, $p > .05$) or ethnicity ($\chi^2(2) = 1.65$, $p > .05$). When comparing the CD and RD groups, there were no differences in the number of MDE episodes ($F(1,42) = 2.79$, $p > .05$), age of onset of first MDE ($F(1,44) < 1$) or prior antidepressant use ($\chi^2(1) = 2.09$, $p > .05$). Five participants were currently receiving psychotherapy (N = 4 for the CD group; N = 1 for the RD group).

The average score on the IDS-SR in the CD group was 43.82 (SD=10.99) indicating severe MDD (this score is roughly equivalent to a 34 on the Beck Depression Inventory; BDI). The average score for the HC group was 5.72 (SD=3.55) and for the RD group was 7.50 (SD=3.99). Both the HC and RD groups had an IDS-SR score below 15 indicating no clinically significant MDD symptomatology. A one-way ANOVA indicated that IDS-SR score differed as a function of group ($F(2,68) = 223.67$, $p < .001$). Post-hoc comparisons confirmed that the CD group had significantly higher scores than both the HC ($t(45) = -15.56$, $p < .001$) and RD ($t(44) = 14.64$, $p < .001$) groups, whereas the HC and RD groups did not differ ($t(47) = -1.65$, $p > .05$).

The average scores on each of the MASQ and TEPS subscales are presented in Table 2. For the MASQ subscales, a one-way ANOVA indicated that the groups differed

on the Distress Mixed ($F(2,68) = 138.56$, $p < .001$), Distress Depression ($F(2,68) = 164.76$, $p < .001$), Distress Anxiety ($F(2,68) = 115.02$, $p < .001$), Anhedonic Depression ($F(2,68) = 102.75$, $p < .001$), and Anxious Arousal subscales ($F(2,68) = 37.05$, $p < .001$). Post-hoc comparisons confirmed that the CD group had significantly higher scores than both the HC and RD groups on all MASQ subscales (all ps < .001). The RD group had significantly higher scores than the HC on the Distress Mixed ($t(47) = -3.04$, p < .01), Distress Depressed ($t(47) = -2.7$, $p < .01$), Distress Anxious subscales ($t(47) = -4.02$, $p < .001$), but not on the Anhedonic Depression ($t(47) = -1.26$, $p > .05$) and Anxious Arousal subscales ($t(47) = -1.44$, $p > .05$). For the TEPS subscales, a one-way ANOVA indicated that the groups differed on the Anticipatory ($F(2,68) = 14.30$, $p < .001$) and Consummatory subscales ($F(2,68) = 16.39$, $p < .001$). Post-hoc comparisons confirmed that the CD group had significantly lower scores than both the HC and RD groups on all TEPS subscales (all ps < .01). The RD group had significantly lower scores than the HC on the Anticipatory ($t(47) = 2.09$, $p < .05$), but not on the Consummatory subscale ($t(47) = -.33$, $p > .05$).

Table 1

Demographic data means (and standard deviations)

	Current MDD (N = 22)	Remitted MDD (N = 24)	Healthy Controls (N = 25)
Age, mean	37.05 (16.14)	38.25 (15.64)	40.84 (13.16)
Years of Education, mean	15.77 (2.94)	14.71 (2.20)	15.60 (2.08)
Female, %	59.1%	70.8%	72.0%
Caucasion, %	68.2%	83.3%	80.0%
IDS-SR, mean[a]	43.82 (10.99)	7.50 (3.99)	5.72 (3.55)
Length of current episode, weeks, mean	171.64 (319.12)	N/A	N/A
Number of episodes[b], mean	5.14 (8.34)	2.17 (1.72)	N/A
Age of onset of MDD, mean	22.18 (10.63)	25.38 (14.60)	N/A
Prior antidepressant use, %	50.0%	29.2%	N/A

[a] CD vs. RD and HC $p < .001$

[b] One subject from each group reported having too many episodes to count.

Table 2

MASQ and TEPS data means (and standard deviations)

	Current MDD (N = 22)	Remitted MDD (N = 24)	Healthy Controls (N = 25)
	MASQ		
Distress: Mixed	50.82 (12.01)[a]	22.83 (5.21)[b]	19.16 (3.25)
Distress: Depression	43.59 (11.21)[a]	15.75 (3.29)[b]	13.64 (2.20)
Distress: Anxious	27.41 (5.80)[a]	15.25 (3.17)[c]	12.52 (1.61)
Anhedonic Depression	86.23 (13.30)[a]	45.96 (8.60)	42.88 (7.85)
Anxious Arousal	31.86 (13.29)[a]	19.00 (2.15)	18.28 (1.28)
	TEPS		
Anticipatory	38.55 (6.31)[d]	44.88 (7.69)[e]	48.96 (5.93)
Consummatory	33.09 (8.08)[d]	41.54 (3.50)	41.16 (33.09)

[a]CD vs. HC and RD $p < .001$
[b]RD vs. HC $p < .01$
[c]RD vs. HC $p < .001$
[d]CD vs. HC and RD $p < .001$
[e]RD vs. HC $p < .05$

Flanker Task

Based on the literature (Olvet & Hajcak, in press), participants who made fewer than 6 errors in the flanker task were excluded (N = 3 in the HC group). The final sample for the flanker task consisted of 22 HC, 22 CD, and 24 RD participants.

Performance measures

Accuracy and RT data are presented in Table 3. A 2 (Trial Type) x 3 (Group) mixed model ANOVA indicated that participants were faster on error than on correct trials ($F(1,65) = 263.09$, $p < .001$), however the groups did not differ in RT ($F(2,65) < 1$), nor was there a significant interaction between Trial Type and Group ($F(2,65) = 1.03$, $p > .05$). A one-way ANOVA indicated that the three groups did not differ on the number of errors ($F(2,65) < 1$) nor on the percent of correct trials ($F(2,65) < 1$).

Post-error accuracy and RT data are presented in Table 3. A 2 (Trial Type) x 3 (Group) mixed model ANOVA indicated that participants were slower on trials that occurred after an initial error than after an initial correct trial ($F(1,65) = 8.69$, $p < .01$), however the groups did not differ in post-error RT ($F(2,65) = 1.01$, $p > .05$) nor was there a significant interaction between Trial Type and Group ($F(2,65) < 1$). A one-way ANOVA indicated that the three groups did not differ on the number of errors following error trials ($F(2,65) < 1$) nor on the percent correct trials after error trials ($F(2,65) = 1.33$, $p > .05$).

Error-related brain activity

The average number of epochs included in the ERP averages for correct trials was 289.72 (SD = 26.37) and for error trials was 28.36 (SD = 14.26). As expected,

participants had more correct than error epochs ($F(1, 65) = 3599.44$, $p < .001$), however there was no significant difference in the number of ERP epochs between the groups ($F(2,65) = .50$, $p > .05$), nor was there an interaction between Trial Type and Group ($F(2,65) = .19$, $p > .05$).

In order to determine the location where the ERN was maximal, a 2 (Trial Type) x 4 (Electrode Site: Fz, FCz, Cz, and Pz) repeated measures ANOVA was performed. The magnitude of the ERN was significantly more negative than the CRN ($F(1,67) = 124.34$, $p < .001$), and both the ERN and CRN were more negative at frontal sites ($F(3,201) = 134.51$, $p < .001$). There was also an interaction between Trial Type and Electrode Site ($F(3,201) = 40.14$, $p < .001$). Post-hoc paired comparisons confirmed that the ERN was maximal at FCz compared to Fz ($t(67) = 6.72$, $p < .001$), Cz ($t(67) = 6.64$, $p < .001$), and Pz ($t(67) = 12.70$, $p < .001$). Thus, the following analyses were performed using the FCz electrode site[1].

Grand average response-locked ERPs are presented in Figure 1 and the average ERP values are presented in Table 4. A 2 (Trial Type) x 3 (Group) mixed model ANOVA indicated that the ERN was significantly more negative than the CRN ($F(1,65)=165.16$, $p < .001$), but the groups did not differ in ERPs ($F(2,65) < 1$) nor was there a significant interaction between Trial Type and Group ($F(2,65) < 1$).

ERPs by severity, anxiety, and chronicity

Although there were no differences in ERPs between the groups, we sought to determine if there was a relationship between symptom severity and the ERPs. The CD group was divided using a median split on the IDS-SR scale (median = 40) yielding 9

individuals with low and 10 individuals with high depression severity. The two groups did not differ on demographic variables that are known to affect the ERN (i.e. age). ERPs are presented in Figure 2 for low and high severity groups. A 2 (Trial Type) x 2 (Severity Group) ANOVA indicated that there was no significant effect of Severity Group ($F(1,17) = 1.04$, $p > .05$), however the ERN was significantly more negative than the CRN ($F(1,17) = 58.44$, $p < .001$) and there was a significant interaction between Trial Type and Severity Group ($F(1,17) = 5.05$, $p < .05$). Post-hoc comparisons indicated that there was no difference in the ERN between the Severity Groups (High severity: -2.16 (1.56); Low severity: -2.72 (2.27); $t(17) = -.63$, $p > .05$), however the high severity group did have a larger (i.e. more negative) CRN than the low severity group (High severity: .57 (.59); Low severity: 2.29 (1.81); $t(17) = 2.71$, $p < .05$) and a smaller difference between the ERN and the CRN (ERN-CRN; High severity: -2.84 (1.58); Low severity: -5.01 (2.74); $t(17) = -2.18$, $p < .05$).

The anxiety subscales of the MASQ were also used to determine whether anxiety severity was related to the ERPs. The CD, RD and HC groups were divided using a median split on the Distress Anxious and the Anxious Arousal subscales of the MASQ, however there were no significant differences between the ERN or CRN based on anxiety scores (all ps $> .05$).

Since there were many participants in the CD and RD group that suffered (either currently or in the past) from chronic depression (defined as: total duration of at least 2 years of a MDE, double depression, or recurrent MDD without recovery between episodes), we also sought to determine if there was a relationship between chronicity and

the ERPs. The RD and CD groups were divided (based on criteria above) into chronic (N = 18) and non-chronic depression groups (N = 28). ERPs are presented in Figure 3 for chronic and non-chronic groups and ERN magnitudes are presented in Figure 4. A 2 (Trial Type) x 2 (Chronicity Group) ANOVA indicated that there was no significant effect of Chronicity Group ($F(1,44) < 1$), however the ERN was significantly more negative than the CRN ($F(1,44) = 113.29$, $p < .001$) and there was a significant interaction between Trial Type and Chronicity Group ($F(1,44) = 2.09$, $p < .05$). Post-hoc comparisons indicated that there was no difference in the ERN between the groups (Chronic: -2.05 (1.80); Non-chronic: -2.44 (1.84); $t(44) = .72$, $p > .05$), however the chronic group did have a larger (i.e. more negative) CRN than the non-chronic group (Chronic: .56 (1.32); Non-Chronic: 1.57 (1.25); $t(44) = -2.61$, $p < .05$) and the ERN-CRN was significantly smaller in the chronic group compared to the non-chronic group (Chronic: -2.62 (1.56); Non-chronic: -4.02 (2.32); $t(44) = 2.25$, $p < .05$). Based on the developmental literature which suggests that, in adulthood, the ERN decreases with age (Band & Kok, 2000; Falkenstein, Hoormann, & Hohnsbein, 2001; Mathalon, Bennett, et al., 2003; Mathewson, et al., 2005; Nieuwenhuis, et al., 2002; Themanson, et al., 2006), we examined whether these two groups differed on age. Indeed, the two chronicity groups differed on age ($t(44) = 2.22$, $p < .05$), with the chronic group being older than the non-chronic group (Chronic: 43.83 (16.45); Non-chronic: 33.71 (14.13)). Therefore, age was included as a covariate in the analysis. A 2 (Trial Type) x 2 (Chronicity Group) ANCOVA indicated that the ERN was significantly more negative than the CRN ($F(1,43) = 50.09$, $p < .001$), but there was no significant effect of Chronicity Group ($F(1,43) < 1$),

nor an interaction between Trial Type and Chronicity Group ($F(1,43) = 1.85$, $p > .05$). Thus, it is possible that age related differences between the two groups may account for the differences in the ERP components.

Relationship between ERPs and accuracy

Studies suggest that the ERN is significantly related to accuracy, such that individuals who are more accurate have larger ERNs than individuals who are less accurate (Gehring, et al., 1993; Hajcak, et al., 2003b). Overall, there was a significant correlation between the ERN and accuracy ($r = -.25$, $p < .05$) and the ERN-CRN and accuracy ($r = -.28$, $p < .05$), however this relationship did not reach significance when the groups were examined separately (all ps $> .05$).

Relationship between ERPs and clinical measures

In order to further explore the relationship between ERPs and clinical measures, Pearson correlations were performed with the IDS-SR total score, MASQ subscales and TEPS subscales. There were no significant correlations when including all participants in the analysis. There was a significant correlation in the CD group between the CRN and the IDS-SR ($r = -.42$, $p = .05$), the MASQ Distress Mixed ($r = -.61$, $p < .01$), Distress Depression ($r = -.64$, $p < .001$) and Anhedonic Depression subscales ($r = -.68$, $p < .001$), but not in the HC or RD groups (ps $> .05$). Figure 5 presents the correlation between the CRN and the MASQ Distress Mixed subscale in the CD, RD and HC groups. A similar relationship emerged in the CD group when comparing the ERN-CRN to the IDS-SR ($r = .41$, $p = .06$), and MASQ subscales (Distress Mixed: $r = .45$, $p < .05$; Distress Depression: $r = .40$, $p = .07$); Anhedonic Depression: $r = -53$, $p < .05$). The relationship between

depression scores and both the CRN and the ERN-CRN indicate that individuals who had more significant depressive symptoms had a larger CRN and a smaller ERN-CRN. This finding is consistent with the median-split analysis (see above). There was no significant correlation between the ERN, CRN or ERN-CRN and the MASQ Distress Anxious and Anxious Arousal subscales in any group (*p*s > .05), suggesting that this finding was specific to depressive, but not anxiety, symptoms.

There was also a significant correlation between the CRN and the TEPS Consummatory subscale ($r = .60$, $p < .01$) and a trend correlation between the CRN and the TEPS Anticipatory subscale ($r = .41$, $p = .06$) in the CD group. In the HC and RD groups, there was also a significant correlation between the CRN and the Anticipatory subscale (HC: $r = .49$, $p < .05$; RD: $r = .47$, $p < .05$), but not with the Consummatory subscale (HC: $r = .17$, $p > .05$; RD: $r = .13$, $p > .05$). Similar results emerged between the ERN-CRN and the Consummatory subscale in the CD group ($r = -.48$, $p < .05$) and the Anticipatory subscale in the HC ($r = -.39$, $p = .07$) and RD groups ($r = -.39$, $p = .06$). Therefore, individuals who scored low on anticipatory pleasure measures (i.e. endorsing little pleasure) also had a large CRN and small ERN-CRN. In addition, in the HC group there was a significant correlation between the ERN and the Consummatory subscale ($r = .49$, $p < .05$).

Table 3

Performance data means (and standard deviations) for the flanker task

	Current MDD (N = 22)	Remitted MDD (N = 24)	Healthy Controls (N = 22)
	Reaction time (ms)		
Error trials	344.10 (46.84)	344.61 (59.02)	341.90 (53.97)
Correct trials	443.65 (80.57)	426.63 (58.21)	416.48 (56.78)
	Accuracy		
No. of errors	31.86 (16.27)	31.17 (15.24)	30.32 (14.97)
% correct	90.29 (4.97)	90.53 (4.66)	90.80 (4.54)
	Post-trial reaction time (ms)		
Post-error trials	452.38 (83.40)	426.56 (66.72)	416.68 (51.23)
Post-correct trials	432.93 (78.77)	418.72 (59.02)	408.81 (58.01)
	Post-error accuracy		
No. of errors	3.59 (5.52)	4.33 (7.63)	4.32 (5.29)
% correct	91.56 (9.58)	89.99 (13.73)	87.99 (10.43)

Table 4

ERP data means (and standard deviations) for the flanker task

	Current MDD (N = 22)	Remitted MDD (N = 24)	Healthy Controls (N = 22)
ERN	-2.31 (1.93)	-2.28 (1.75)	-2.14 (1.65)
CRN	1.24 (1.49)	1.12 (1.25)	1.18 (1.24)

Short/Long Mouth Task

All participants made at least 6 errors, therefore the final sample for the short/long mouth task consisted of 25 HC, 22 CD, and 24 RD participants.

Performance measures

Accuracy and RT data are presented in Table 5. A 2 (Trial Type) x 3 (Group) mixed model ANOVA indicated that participants were faster on correct than on error trials ($F(1,68) = 62.51$, $p < .001$). The groups did not differ overall in RT ($F(2,68) < 1$), but there was a significant interaction between Trial Type and Group ($F(2,68) = 3.42$, $p < .05$). Post-hoc comparisons indicated a greater difference between error and correct RT between the CD and RD groups ($t(44) = -2.73$, $p < .01$), but not the HC and the CD or RD (ps > .05). These data indicate that the RD group had a larger difference in reaction time compared to the CD group, which may be explained by the fact that the RD group was slower to respond to errors than the CD group.

A one-way ANOVA indicated that the three groups did differ on the number of errors ($F(2,68) = 6.32$, $p < .01$). Post-hoc comparisons indicated that the CD group made significantly more errors than the HC group ($t(45) = -3.00$, $p < .01$) and the RD group ($t(44) = 2.69$, $p < .05$), whereas there was no difference between the HC and RD groups ($t(47) = -.53$, $p > .05$). Similar findings emerged when analyzing the percent of correct trials ($F(2,68) = 6.25$, $p < .01$), with the CD group having a lower accuracy than HC ($t(45) = 2.98$, $p < .01$) and RD groups ($t(44) = -2.69$, $p < .01$); the HC and RD groups had comparable accuracy ($t(47) = .51$, $p > .05$).

Post-error accuracy and RT data are presented in Table 5. A 2 (Trial Type) x 3 (Group) mixed model ANOVA indicated that participants were slower on trials that occurred after an initial error than after an initial correct trial ($F(1,68) = 56.89$, $p < .001$), however the groups did not differ in post-error RT ($F(2,68) < 1$), nor was there a significant interaction between Trial Type and Group ($F(2,68) = 1.17$, $p > .05$). A one-way ANOVA indicated that the three groups did differ on the number of errors following errors ($F(2,68) = 7.20$, $p < .001$). Post-hoc comparisons indicated that the CD group made significantly more errors after errors than the HC group ($t(45) = -3.75$, $p < .001$) and the RD group ($t(44) = 3.13$, $p < .01$), whereas there was no difference between the HC and RD groups ($t(47) = -.85$, $p > .05$). These findings were confirmed when analyzing the percent of correct trials after an error ($F(2,68) = 6.38$, $p < .01$), with the CD group having a lower accuracy after errors than HC ($t(45) = 3.67$, $p < .001$) and RD groups ($t(44) = -2.99$, $p < .01$), and the HC and RD groups having comparable accuracy after errors ($t(47) = 1.15$, $p > .05$). Overall, the CD group performed worse than the HC and RD groups and they had impaired post-error accuracy.

Error-related brain activity

Response-locked ERPs

The average number of epochs included in the ERP averages for correct trials was 244.91 (SD = 22.93) and for error trials was 49.59 (SD = 22.34). As expected, participants had more correct than error epochs ($F(1,68) = 1532.36$, $p < .001$) and there was a significant interaction between Trial Type and Group ($F(2,68) = 6.74$, $p < .01$), but not a main effect of Group ($F(2,68) = .77$, $p > .05$). Consistent with the behavioral

findings, post-hoc comparisons indicated that there was a significant difference in the number of error and correct epochs when comparing the HC and CD groups (error epochs: $t(45) = -2.98$, $p < .01$; correct epochs: $t(45) = 3.14$, $p < .01$) and RD and CD groups (error epochs: $t(44) = 2.69$, $p < .05$; correct epochs: $t(45) = -2.98$, $p < .01$), but not between HC and RD groups (error epochs: $t(47) = -.51$, $p > .05$; correct epochs: $t(47) = .30$, $p > .05$).

In order to determine the electrode location where the ERN was maximal, a 2 (Trial Type) x 4 (Electrode Site: Fz, FCz, Cz, and Pz) repeated measures ANOVA was performed. The ERN was more negative than the CRN ($F(1,70) = 67.22$, $p < .001$), and the ERN and CRN were more negative at frontal sites ($F(3,201) = 82.95$, $p < .001$); additionally, there was an interaction between Trial Type and Electrode Site ($F(3,201) = 17.08$, $p < .001$). Post-hoc comparisons confirmed that the ERN was maximal at Fz compared to Cz ($t(70) = -4.79$, $p < .001$) and Pz ($t(70) = 8.18$, $p < .001$), but Fz was not significantly different from FCz ($t(70) = -1.62$, $p > .05$). Thus, the following analyses were performed using the Fz electrode site where the ERN was numerically maximal[2].

Grand average response-locked ERPs and scalp topographies are presented in Figure 6 and ERN magnitudes are presented in Figure 7. Average ERP values are presented in Table 6. A 2 (Trial Type) x 3(Group) mixed model ANOVA indicated that the ERN was significantly more negative than the CRN at Fz ($F(1,68)=52.31$, $p < .001$). There was no overall effect of Group ($F(2,68) = 2.34$, $p > .05$), however there was a significant interaction between Trial Type and Group ($F(2,68) = 3.44$, $p < .05$). Post-hoc comparisons indicated that the CD group had a significantly smaller ERN (i.e., less

negative ERN) compared to the HC group ($t(45) = -2.97$, $p < .01$)[3]. There were no significant differences between the HC and RD ($t(47) = -1.72$, $p > .05$) or the CD and RD groups ($t(44) = 1.04$, $p > .05$). The groups did not differ, however, with respect to the CRN (all ps > .05).

ERPs by severity, anxiety, and chronicity

We sought to determine if there was relationship between symptom severity and the ERPs. The CD group was divided using a median split on the IDS-SR scale (median = 40) yielding 9 individuals with low severity and 10 individuals with high severity. A 2 (Trial Type) x 2 (Severity Group) ANOVA indicated that the ERN was significantly more negative than the CRN ($F(1,17) = 20.34$, $p < .001$), but there was no significant effect of Severity Group ($F(1,17) < 1$), nor was there a significant Trial Type and Severity Group interaction ($F(1,17) = 1.88$, $p > .05$).

The anxiety subscales of the MASQ were also used to determine whether anxiety severity was related to the ERPs. The CD, RD, and HC groups were divided using a median split on the Distress Anxious and the Anxious Arousal subscales of the MASQ, however there were no significant differences in the ERN or CRN based on anxiety (all ps > .05).

We also sought to determine if there was a relationship between chronicity and the ERPs. The RD and CD groups were divided into chronic (N = 18) and non-chronic depression (N = 28). A 2 (Trial Type) x 2 (Chronicity Group) ANOVA indicated that the ERN was significantly more negative than the CRN ($F(1,44) = 22.16$, $p < .001$), but there was no significant effect of Chronicity Group ($F(1,44) = 2.64$, $p > .05$), nor was there an

interaction between Trial Type and Chronicity Group ($F(1,44) = 1.14$, $p > .05$). Due to the significant age difference between these two groups (see above) age was included as a covariate in the analysis. A 2 (Trial Type) x 2 (Chronicity Group) ANCOVA confirmed the ANOVA results (Trial Type: ($F(1,43) = 5.70$, $p < .05$); Chronicity Group ($F(1,43) = 1.60$, $p > .05$); Trial Type x Chronicity Group ($F(1,43) < 1$).

Relationship between ERPs and accuracy

Since the CD group performed significantly worse than the HC and RD groups, correlational analyses were performed in order to explore the relationship between the ERPs and accuracy. Overall, there was a significant correlation between the ERN and accuracy ($r = -.29$, $p < .05$) and the ERN-CRN and accuracy ($r = -.30$, $p < .05$). There was also a significant correlation between the ERN and accuracy ($r = -.42$, $p < .05$) and the ERN-CRN and accuracy in the HC group ($r = -.53$, $p < .01$), such that better performance predicted an increased ERN. However, the correlation between the ERN and accuracy or the ERN-CRN and accuracy did not reach significance for either the CD or RD groups (all ps $> .05$).

Relationship between ERPs and clinical measures

In order to further explore the relationship between ERPs, accuracy and clinical measures, Pearson correlations were performed with the IDS-SR total score, MASQ subscales and TEPS subscales. Overall, there were significant correlations between the ERN and the IDS-SR ($r = .29$, $p < .05$), Distress Mixed ($r = .30$, $p < .05$), Distress Depression ($r = .24$, $p < .05$) and the Distress Anxious ($r = .31$, $p < .01$) subscales of the MASQ. Thus, more depressive symptoms were related to a smaller their ERN. There was

also a significant correlation between the ERN-CRN and Anhedonic Depression in the CD group ($r = .44$, $p < .05$), However, there were no other significant correlations between the ERPs and the MASQ when looking at the three groups individually.

Overall, the ERN and CRN were unrelated to the TEPS. The only significant correlations for the CD group were between the TEPS Anticipatory subscale and the ERN ($r = .50$, $p < .05$) and the CRN ($r = .51$, $p < .05$). Additionally, in the HC group there was a significant correlation between the TEPS Consummatory subscale and the ERN ($r = .41$, $p < .05$). No correlations reached significance in the RD group.

Accuracy was related to the Distressed Mixed ($r = -.45$, $p < .001$), Distress Depression ($r = -.46$, $p < .001$), Distress Anxiety ($r = -.47$, $p < .001$), Anhedonic Depression ($r = -.46$, $p < .001$) and Anxious Arousal ($r = -.37$, $p < .001$) subscales of the MASQ. Looking at the three groups individually, these correlations were only present for the CD group (Distress Mixed: $r = -.57$, $p < .01$; Distress Depression: $r = -.41$, $p = .06$; Distress Anxiety: $r = -.47$, $p < .05$; Anhedonic Depression: $r = -.48$, $p < .05$). Figure 8 presents the correlation between accuracy and the MASQ Distress Mixed subscale in the CD, RD and HC groups. Additionally, accuracy significantly correlated with the TEPS Consummatory subscale, but only in the CD group ($r = .63$, $p < .01$). These findings suggest that individuals reporting more significant depression symptoms performed the worst and had the smallest ERN.

Feedback-locked ERPs

Visual inspection of the feedback-locked ERP (i.e. the FN) initially suggested that there was a FN approximately 250 ms after feedback onset. However, upon inspection of

the scalp distribution of the FN, it did not appear to have the frontocentral distribution that is characteristic of the FN. However, we performed statistical analyses on the data to investigate this further. In order to determine the location where the FN was maximal, a 2 (Trial Type) x 4 (Electrode Site: Fz, FCz, Cz, and Pz) repeated measures ANOVA was performed. The magnitude of the FN was significantly more negative in response to negative than to positive feedback ($F(1,70) = 73.56$, $p < .001$), and both the components were more negative at posterior sites ($F(3,210) = 18.52$, $p < .001$). There was also an interaction between Trial Type and Electrode Site ($F(3,210) = 118.24$, $p < .001$). Post-hoc paired comparisons confirmed that the FN was maximal at Pz compared to Fz ($t(70)= -9.07$, $p < .001$), Cz ($t(70) = -6.26$, $p < .001$), and FCz ($t(70) = 6.84$, $p < .001$). Thus, the following analyses were performed using the Pz electrode site[4].

Overall grand average response-locked ERPs and the scalp distribution are presented in Figure 9. A 2 (Trial Type) x 3 (Group) mixed model ANOVA indicated that the FN was significantly more negative in response to negative compared to positive feedback trials ($F(1,68)=188.51$, $p < .001$), but the groups did not differ in ERPs ($F(2,68) < 1$) and there was only a trend interaction between Trial Type and Group ($F(2,68) = 2.95$, $p = .06$). Post-hoc comparisons did not reveal any significant group differences ($ps > .05$).

Table 5

Performance data means (and standard deviations) for the short/long mouth task

	Current MDD (N = 22)	Remitted MDD (N = 24)	Healthy Controls (N = 25)
	Reaction time (ms)		
Error trials	628.61 (128.53)	693.72 (137.32)	655.87 (135.77)
Correct trials	597.74 (104.52)	617.34 (105.78)	594.38 (109.21)
	Accuracy		
No. of errors	63.68 (26.57)[a]	46.13 (15.89)	43.40 (19.58)
% correct	78.77 (8.86)[b]	84.63 (5.30)	85.49 (6.55)
	Post-trial reaction time (ms)		
Post-error trials	627.17 (118.46)	669.92 (114.48)	643.71 (134.51)
Post-correct trials	593.29 (110.11)	596.40 (106.77)	620.90 (110.54)
	Post-error accuracy		
No. of errors	18.63 (14.29)[c]	9.46 (6.88)	8.56 (7.25)
% correct	73.55 (10.62)[c]	82.03 (9.10)	83.70 (9.28)

[a]CD vs. HC and RD $p < .01$

[b]CD vs. HC $p < .01$, CD vs. RD $p < .05$

[c]CD vs. HC $p < .001$, CD vs. RD $p < .01$

Table 6

ERP data means (and standard deviations) for the short/long mouth task

	Current MDD (N = 22)	Remitted MDD (N = 24)	Healthy Controls (N = 25)
ERN (uV)	-.25 (.54)[a]	-.46 (.82)	-.87 (.84)
CRN (uV)	.42 (.72)	-.00 (1.04)	.22 (.71)

[a]CD vs. HC $p < .01$

Across task comparison

In the short/long mouth task, there was no FN in response to negative feedback, therefore we were unable to directly compare the ERN (in the flanker task) and the FN (in the short/long mouth task). However, we did observe an ERN in short/long mouth task and there was a significant difference in the ERN when comparing the HC and CD groups; an effect that was not seen in the flanker task. Therefore, we wanted to directly compare the ERN and CRN on the two tasks statistically. To this end, we performed a 2 (Task: flanker and short/long mouth) x 2 (Trial: error and correct) x 6 (Electrode site: Fz, FCz, Cz, Pz, Oz, and Iz) x 3 (Group: HC, CD and RD) mixed ANOVA. Figure 10 presents these data by component (top) and by task (bottom) in order to illustrate the complex relationship among the factors. Results indicated that the ERN was significantly larger than the CRN ($F(1,65) = 143.92$, $p < .001$) and both components were larger at frontal sites compared to posterior sites ($F(5,325) = 73.93$, $p < .001$). A significant interaction between Electrode x Trial ($F(5,325) = 87.29$, $p < .001$) confirmed that the ERN was larger at frontal sites compared to the CRN.

A significant Task x Trial interaction ($F(1,65) = 113.04$, $p < .001$) indicated that the ERN was larger in the flanker task compared to the short/long mouth task, whereas the CRN was larger in the short/long mouth task compared to the flanker task. Additionally, a significant interaction between Electrode x Task ($F(5,325) = 19.44$, $p < .001$) indicated that both the ERN and CRN were larger at frontal sites in the flanker task compared to the short/long mouth task, and smaller at parietal sites in the flanker task compared to the short/long mouth task. Finally, a significant Electrode x Trial x Task

interaction ($F(5,325) = 72.07$, $p < .001$) indicated that the ERN was larger in the flanker task compared to the short/long mouth task, but only at frontal sites, whereas the CRN was smaller in the flanker task compared to the short/long mouth task, but only at parietal sites.

There were no main effects of Task ($F(1,65) = 1.07$, $p > .05$) or Group ($F(2,65) = .11$, $p > .05$), nor were there any significant interactions including Group (Task x Group: $F(2,65) = 1.77$, $p > .05$; Trial x Group: $F(2,65) = .18$, $p > .05$; Electrode x Group: $F(10,325) = 1.18$, $p > .05$; Task x Trial x Group: $F(2,65) = 1.35$, $p > .05$; Task x Electrode x Group: $F(10,325) = .43$, $p > .05$; Trial x Electrode x Group: $F(10,325) = .82$, $p > .05$; Trial x Task x Electrode x Group: $F(10,325) = 1.05$, $p > .05$).

Overall, these data suggest that: 1) the ERN was larger in the flanker task compared to the short/long mouth task at frontal sites, 2) the CRN was smaller in the flanker task compared to short/long mouth task at parietal sites, and 3) the ERN had a different scalp distribution in the flanker task (i.e. more fronto-central, clearly maximal at FCz) compared to the short/long mouth task (i.e. maximal at Fz, but generally larger than the CRN across all electrode sites). There was also no significant group effects, therefore the groups did not differ as a function of task. However, it is important to note that comparing the ERN/CRN at the same electrode site across tasks may not be feasible due to the differences in their scalp distribution.

DISCUSSION

The ERN and CRN in individuals with MDD

Flanker task

ERP findings

In the flanker task, we found no difference in the ERN among the CD, RD and HC groups. However, we did find that individuals with severe depressive symptoms had a smaller difference between the ERN and CRN, suggesting diminished error-related brain activity. This is contrary to what other researchers have found, including an increased ERN in individuals with MDD (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b) or an ERN comparable to healthy controls (Schrijvers, et al., 2008; Schrijvers, et al., 2009). Additionally, one study found that the ERN of undergraduates who reported depressive symptoms was similar to those not reporting depressive symptoms (Compton, et al., 2008).

Schrijvers and colleagues (Schrijvers, et al., 2008; Schrijvers, et al., 2009) have argued that the discrepancies in the depression ERN literature may be attributable to differences in symptom severity. For instance, in their patient samples, individuals were more severely depressed than other samples (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b). In fact, from the ERPs in Schrivers's studies, it appears that the depressed participants had a numerically smaller ERN compared to the healthy control group. This is consistent with the findings in the current study, in which the depressed sample was also in the moderate to severe range and participants with more severe depressive

symptoms had a smaller difference between the ERN and CRN. Thus, the current results might be more comparable to the Schrijvers papers.

Although it is possible that severity may impact the ERN, Schrivers and colleagues did not find a correlation between symptom severity and the ERN (Schrijvers, et al., 2008). The current study found a significant relationship between the ERN-CRN and depressive severity; the ERN-CRN difference was significantly smaller in the high severity group compared to the low severity group. A nearly significant correlation was also found between depressive severity and the ERN-CRN difference. While assessing the FN, Tucker and colleagues (2003) found that the FN was small for individuals who scored low and high on a depression scale, whereas individuals who scored in the middle had a large FN. Niewenhuis and colleagues (2005) also found a similar pattern while studying the ERN in individuals with OCD: individuals with severe OCD symptoms had smaller ERNs than those with milder OCD symptoms. If this is the case, the literature is rather consistent in showing that individuals with mild (Compton, et al., 2008) or moderate depressive symptoms (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b) have a large ERN and those with severe depression have a small ERN (Schrijvers, et al., 2008; Schrijvers, et al., 2009). The current results are also in line with these findings.

Additionally, we examined preliminary data from 6 individuals reporting mild depressive symptoms (IDS-SR > 15), but who did not meet criteria for a current MDE (although they did meet criteria for at least 1 past MDE). These individuals appear to have an increased ERN in the flanker task compared to those of the HC, CD and RD

groups. Overall, it appears that symptom severity may be the key to explain the discrepant findings in the literature.

In the flanker task, individuals in the CD group who had more severe depressive symptoms also had a larger CRN. Although the CRN has not been extensively investigated, researchers suggest that the CRN reflects an emotional reaction (Luu, et al., 2000), uncertainty of a correct response (Coles, et al., 2001; Pailing, et al., 2002), or the coactivation of correct and incorrect responses (Luu, et al., 2000; Scheffers, et al., 1996). It is likely that the CRN represents response monitoring activity elicited in 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 that they have increased error monitoring on correct trials. This has been shown in anxiety disorders; some studies have shown that OCD patients have increased ACC activity on both error and correct trials (Ursu, et al., 2001), which was substantiated in an ERP study that showed increased error-related activity in high-OC trait subjects on both error and correct trials (Hajcak & Simons, 2002). Although most researchers have focused on an increased ERN to identify excessive performance monitoring, the CRN may also provide important information about abnormal performance monitoring processes.

Another explanation for the increased CRN is that severely depressed individuals may be more uncertain when they make a correct response. An increased CRN has been reported when participants were uncertain about their response (Coles, et al., 2001; Pailing & Segalowitz, 2004). These findings suggest that the subjective assessment of

performance is more important than actual performance (Pailing & Segalowitz, 2004). This is in line with a behavioral study which showed that individuals with MDD underestimated the number of correct trials they had on a working memory task, but they correctly estimated the number of error trials (Dunn, Dalgleish, Lawrence, & Ogilvie, 2007). Therefore, individuals with MDD may expect to make errors and not expect to make correct responses.

Some data suggests that the PFC is important in the modulation of the CRN. Gehring and Knight (2000) found that individuals with PFC lesions had an increased CRN which was equal in size to the ERN. Hogan and colleagues (2006) examined ERPs in individuals with white matter infarctions in the PFC and found that these individuals had a smaller difference between the ERN and CRN compared to healthy controls. Although this difference was mostly driven by a smaller ERN, individuals with white matter infarctions appeared to have a larger CRN than controls (Hogan, et al., 2006). These findings are in contrast with what is seen in individuals with ACC lesions, who have completely abolished ERNs (Stemmer, Segalowitz, Witzke, & Schonle, 2004). A larger CRN may be indicative of diminished cortical control, whereas a smaller ERN may be indicative of diminished ACC monitoring. This is especially of interest because studies have shown that individuals with MDD have decreased PFC volume (Botteron, Raichle, Drevets, Heath, & Todd, 2002; Coffey, et al., 1993; Drevets, et al., 1997) and activity (Drevets, 1998, 2000; H. Ito, et al., 1996; Kimbrell, et al., 2002; Oda, et al., 2003; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). These studies drive home the

notion that the PFC is essential to successful performance monitoring (see Koski & Paus, 2000; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004).

We also found that individuals with a history of chronic depression had a larger CRN and smaller ERN-CRN difference compared to individuals without a history of chronic depression, however these group differences may be reflecting group differences in age. Studies have consistently found a decreased ERN in older (54-85 years old) compared to younger adults (18-28 years old; Band & Kok, 2000; Falkenstein, et al., 2001; Mathalon, Bennett, et al., 2003; Mathewson, et al., 2005; Nieuwenhuis, et al., 2002; Themanson, et al., 2006). This is consistent with the current study in that the individuals with a history of chronic depression were older and had smaller ERNs compared to individuals without a history of chronic depression. However, it is important to note that the average age of individuals with a history of chronic depression was only 10 years older than those without a history of chronic depression. This is in contrast to developmental studies which compare individuals who are 30 years apart.

If, however, these ERP differences are reflecting abnormal processes unique to chronic depression, it is interesting to note that the chronic depression group comprised both CD and RD participants. This suggests that an increased CRN and decreased ERN-CRN difference could be a trait characteristic that remains even after symptom resolution. Additionally, Figure 4 shows the same pattern in both groups (i.e. a larger CRN in individuals regardless of when their chronic depressive episode occurred – either past or current). This study is unable to ascertain whether or not the increased CRN and decreased ERN-CRN is a risk factor for depression or if it represents a scar or

consequence of the MDE; additionally it is unclear if these findings are better accounted for by group difference in age. Nonetheless, the finding suggests that abnormal response monitoring in chronic depression is an important factor to further investigate.

Short/long mouth task

ERP findings

In the short/long mouth task, the CD group had significantly *smaller* ERNs than the HC group. We did not find a significant interaction between group and task in the across-task analysis, but the results suggest that the ERNs in the tasks had a different scalp distribution, which makes them difficult to directly compare.

Recent evidence suggests that the presence of trial-to-trial feedback moderates the relationship between anxiety and the ERN (Olvet & Hajcak, submitted-a). In particular, the ERN correlated with anxiety scores when using a flanker task without feedback; however when trial-to-trial feedback was included in the flanker task, the ERN was uncorrelated with anxiety scores. Nieuwenhuis and colleagues (2005) suggested that in individuals with anxiety disorders, trial-to-trial feedback may reduce the burden of internal monitoring, thus decreasing the ERN.

The reduced ERN in the short/long mouth task, and not the flanker task, suggest that trial-to-trial feedback may be an important factor to consider in MDD, too. This is supported by a study in which each participant performed multiple versions of a flanker task with either feedback that signaled a monetary reward when participants were correct, feedback that signaled a monetary punishment when participants were incorrect, or a neutral version without feedback (Chiu & Deldin, 2007). The authors found that

depressed individuals had a larger the ERN amplitude in the punishment condition compared to controls, but there was no difference in the ERN amplitude during a reward condition. Therefore, the negative feedback (i.e. monetary loss) may have played a role in accentuating the ERN among individuals with MDD.

Although the primary purpose of the short/long mouth task was to assess the FN in MDD, there was no clear FN component in the data. There was a component that occurred around the time that the FN was expected (i.e. 250 – 350 ms after feedback onset), which was larger (i.e. more negative) to negative than positive feedback, however the scalp distribution of that ERP appeared to be much more posterior than the FN (which is typically frontal). We analyzed the area measure of the component, however did not find any significant group differences. It is difficult to make any conclusions based on these findings because it is unclear whether or not this component is truly a FN.

According to the TD theory, the learned DA signal propagates back from the time of reward to the time of the conditioned stimulus (Ljungberg, Apicella, & Schultz, 1992; Schultz, Apicella, & Ljungberg, 1993). Therefore, there is an inverse relationship between the DA response at the time of reward and at the time of the conditioned stimulus. This relationship is typically evident between the ERN and the FN. Two studies have shown that as subjects learn a series of stimulus-response mappings which became increasingly consistent, the ERN becomes more evident at the time of response and the FN, when feedback is presented, becomes smaller (Holroyd & Coles, 2002; Nieuwenhuis, et al., 2002). In other words, the FN was initially present following negative feedback, but as the subjects learned what stimulus-response mappings were

correct, the ERN was present following incorrect responses. This has been confirmed in a fMRI study that showed that activation in the rostral ACC shifted in time after participants learned the task (Mars, et al., 2005). Therefore, it is likely that participants were aware of committing an error since there was a clear ERN in this task, as such the feedback was irrelevant and the component we analyzed was most likely not the FN.

Behavioral findings

The main behavioral finding in the short/long mouth face task was that the CD group had decreased accuracy and decreased post-error accuracy compared to both the HC and the RD groups. This finding supports a number of studies that find that individuals with MDD and those who report high levels of depressive symptoms had decreased accuracy after incorrect trials compared to correct trials (Holmes & Pizzagalli, 2007, 2008b; Pizzagalli, et al., 2006) and after receiving feedback on their poor performance (Beats, et al., 1996; Compton, et al., 2008; Elliott, Sahakian, et al., 1997; Elliott, et al., 1998; Steffens, et al., 2001). Interestingly, in the flanker task (i.e. without trial-to-trial feedback) there were no performance differences among the groups. Therefore, it is possible that the trial-to-trial feedback in the short/long mouth task was essential for affecting performance measures as a function of current depression.

In order to explain these behavioral findings, it was originally hypothesized that poor performance after negative feedback represented a 'catastrophic response to failure' in individuals with MDD (Beats, et al., 1996; Elliott, et al., 1996). However, more recently it has been suggested that negative feedback results in impaired performance monitoring, which prevents individuals with MDD from improving on subsequent trials

(Elliott, Sahakian, et al., 1997; Pizzagalli, et al., 2006; Steffens, et al., 2001). Neurobiological studies support this, which find decreased frontocingulate activation in individuals with depression who exhibit poor performance (Audenaert, et al., 2002; Elliott, Baker, et al., 1997; Elliott, Sahakian, et al., 1997; Holmes & Pizzagalli, 2008a; Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003).

In the CD group, there were also significant correlations between accuracy in the short/long mouth task and all MASQ subscales except for Anxious Arousal. The Consummatory subscale of the TEPS was also correlated with accuracy. These data suggest that individuals who are currently experiencing more severe depressive symptoms performed the worst. Similar results were reported by Pizzagalli and colleagues (2006); they found a significant correlation between MASQ scores and post-error accuracy, such that individuals with more severe depression performed the worst on post-error trials. In the current study, there was no correlation between the ERN and accuracy in the CD group, therefore it seems that behavioral findings might be more sensitive than ERPs to gradations of depressive severity.

One possible limitation of the current findings is that both ERN and performance differences were found between groups. Two prominent computational models of the ERN suggest that the ERN should be smaller when more errors are committed (Holroyd & Coles, 2002; Yeung, Cohen, & Botvinick, 2004). In the current study, we performed an additional analysis based on performance matched participants and still found a smaller ERN in the CD group. Therefore, performance differences alone do not seem to explain the group differences in the ERN. Further evidence suggests that the relationship between

performance measures and the ERN are not straight forward; in a study where participants performed two versions of the flanker task (one with trial-to-trial feedback and one without), there was no difference in the ERN across tasks even though participants performed worse on the version without feedback (Olvet & Hajcak, submitted-a).

In depression, feedback may disrupt internal monitoring. After receiving negative feedback, individuals with high depression scores increase their self-focus (Greenberg & Pyszczynski, 1986), amplify the significance of the failure (Wenzlaff & Grozier, 1988), report an increase in depressed mood (Abela & D'Alessandro, 2002; Henriques & Leitenberg, 2002), and have difficulty suppressing failure-related thoughts (Conway, et al., 1991). Behaviorally, those who report high levels of depressive symptoms also have decreased accuracy after incorrect trials compared to correct trials (Holmes & Pizzagalli, 2007; Pizzagalli, et al., 2006). Also, individuals with MDD are more likely to make an error after receiving negative feedback on their poor performance (Beats, et al., 1996; Compton, et al., 2008; Elliott, Sahakian, et al., 1997; Elliott, et al., 1998; Holmes & Pizzagalli, 2008b; Steffens, et al., 2001). The current study found that individuals with MDD have decreased response monitoring, as well as decreased accuracy overall and after a subsequent error in a task that incorporates trial-to-trial feedback. Therefore, in individuals with MDD, the presence of feedback may impede their ability to properly monitor performance, leading to poorer subsequent performance.

Task difficulty

It is important to note that although we found different results in the two ERN tasks, which may be attributed to the presence of trial-to-trial feedback, the two tasks differed in their level of difficulty. The flanker task was an easy task with a high rate of accuracy (approximately 90%), whereas the short/long mouth task resulted in a slightly lower accuracy rate (approximately 80%). Additionally, the ERN overall was smaller in the short/long mouth task (approximately -0.5 uV) compared to the flanker task (approximately -2 uV). When individuals are uncertain of their response, the ERN is smaller than when individuals are certain of the accuracy of their response (Pailing & Segalowitz, 2004). Also, the behavioral finding that individuals were *slower* to respond to error trials compared to correct trials may also be an indicator of response uncertainty. Therefore, it is possible that the overall reduced ERN in the short/long mouth task may indicate that this task was more difficult for participants.

Neurobiological deficits in MDD and anxiety disorders related to error-related brain regions

We recently suggested that the ERN may be a useful endophenotype for internalizing disorders, such as MDD and anxiety (Hajcak, et al., 2008; Olvet & Hajcak, 2008). Both MDD and anxiety disorders are characterized by high negative affect (Brown, et al., 1998; Clark & Watson, 1991) and high levels of negative affect predict the onset of anxiety and MDD in prospective studies (Kendler, et al., 1993; Ormel, et al., 2001; Ormel, et al., 2004; Van Os & Jones, 1999). Based on initial studies of the ERN in MDD (Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008b), it appeared that these results

matched the increased ERN reported in anxiety disorders. However, recent findings, including the current study, command a more comprehensive understanding of the relationship between the ERN and internalizing disorders.

One possible avenue is to evaluate neurobiological abnormalities in MDD and anxiety disorders in comparison to one another. For example, frontocingulate dysfunction plays a significant role in the pathophysiology of MDD (Davidson, Pizzagalli, Nitschke, & Putnam, 2002; Mayberg, 1997). Both decreased PFC volume (Botteron, et al., 2002; Coffey, et al., 1993; Drevets, et al., 1997) and ACC volume (Drevets, et al., 1997; Hastings, Parsey, Oquendo, Arango, & Mann, 2004) are evident in MDD. In accordance with volume decrements, decreases in activation are also seen in the PFC and the ACC (Drevets, 1998, 2000; H. Ito, et al., 1996; Kimbrell, et al., 2002; Oda, et al., 2003; Siegle, et al., 2007). There is also some evidence to suggest that individuals with MDD also have reduced BG volume (Husain, et al., 1991; Krishnan, et al., 1992) and metabolism (Baxter, et al., 1987; Mayberg, Lewis, Regenold, & Wagner, 1994). These deficits in BG regions are especially indicative of psychomotor symptomatology (see Sobin & Sackeim, 1997 for a review). Individuals with psychomotor retardation also have decreased DA function (Martinot, et al., 2001) and D2R binding (Shah, Ogilvie, Goodwin, & Ebmeier, 1997).

In contrast to abnormalities seen in individuals with MDD, individuals with anxiety disorders are typically characterized by corticostriatal hyperactivity (Baer, et al., 1995; Baxter, et al., 1987; Insel, 1992; Saxena, Brody, Schwartz, & Baxter, 1998). ACC volume (Rosenberg & Keshavan, 1998) and glucose metabolism (Breiter, et al., 1996; Swedo, et al., 1989) are increased in individuals with OCD. Even in individuals with

MDD, sadness was associated with decreased ACC activity, whereas anxiety was associated with increased ACC activity (Brody AL et al 2001). In OCD especially, the BG is hyperactive (Nakatani, et al., 2003; Rosenberg & Hanna, 2000) and symptom severity is significantly correlated with BG activation (Kwon, et al., 2003; Lacerda, et al., 2003).

In sum, it appears that individuals with MDD are characterized by decrements in PFC and ACC activity, as well as decreases in BG activity, especially in relation to psychomotor retardation. These findings are consistent with a recent report that the ERN was smaller in individuals with psychomotor retardation (Schrijvers, et al., 2008). This is in contrast to what is seen in individuals with anxiety disorders; namely increased ACC and BG activation. In light of this neurobiological evidence, it is possible that the smaller ERN in the CD group is reflecting neurobiological deficits in individuals with MDD.

The ERN as a risk factor for MDD

Another major aim of this study was to assess whether the ERN represents a risk factor for MDD. In MDD, behavioral studies have found that sensitivity to negative feedback is still present in individuals with remitted MDD (Elliott, Sahakian, et al., 1997). However, one study found that as symptoms decreased, the ERN increased (Schrijvers, et al., 2009). In the short/long mouth task, individuals with remitted depression had an ERN that was numerically in between the HC and CD groups (see Figure 7), although it was not significantly different from either group. These data suggest that in depression, the ERN may increase slightly with symptom resolution, but not completely. This parallels findings in a study that assessed the ERN in individuals

with schizophrenia both during an acute psychotic episode and after 6 weeks of treatment (Bates, Liddle, Kiehl, & Ngan, 2004). This study found that schizophrenic patients had decreased ERN amplitudes when compared to controls at both time points, however, ERN amplitude in the schizophrenic patients significantly increased from time-point 1 to time-point 2.

It is also important to mention that, in the current study, although depressive symptoms assessed by the IDS-SR were not significantly different between the HC and RD groups, the RD group did report significantly more general depressive and anxiety symptoms on the MASQ scale than the HC group. The RD group also reported less trait anticipatory pleasure than the HC group. Therefore, the mild symptoms present in the RD group may also account for the slightly smaller ERN compared to the HC group.

There have been several studies in anxiety disorders which suggest that the ERN is a trait characteristic in anxiety disorders. For example, children with anxiety disorders have an increased ERN both before and after successful treatment (Hajcak, et al., 2008; Ladouceur, et al., 2006). Additionally, there is no change in the ERN after symptom provocation in individuals who are spider phobic (Moser, et al., 2005). Individuals with the personality trait of high negative affect also have an increased ERN (Hajcak, et al., 2004; Luu, et al., 2000). Overall, it appears that the ERN is a stable trait characteristic in anxiety disorders.

Imaging studies show that individuals with MDD who are more likely to respond to antidepressant treatment have increased pretreatment activity in the rostral ACC (Mayberg, et al., 1997; Mayberg, et al., 1999; J. Wu, et al., 1999; J. C. Wu, et al., 1992).

The relationship between treatment response and rostral ACC activity is also sensitive to the *degree* of clinical response (Pizzagalli, et al., 2001). Additionally, increased rostral ACC activation *after errors* is also predictive of better treatment response (Langenecker, et al., 2007). Although this activation is an important predictor of treatment response, this increased activation does not necessarily change with successful treatment (Mayberg, et al., 2000). Therefore, in the current study, those who successfully responded to treatment in the past or spontaneously remitted (i.e. the RD group) had a slightly larger ERN than the CD group. This would indicate that these "responders" have slightly more ACC activation to errors compared with the "non-responders" (i.e. the CD group). Although this idea is consistent with the literature, it is also important to note that the current study assessed the ERN after a MDE in the RD group, not before, therefore it is difficult to know whether or not this is truly the case.

Methodological considerations

Theta filtering

In the current study, the EEG data were filtered in the theta range, ultimately diminishing any potential slow wave activity in the ERP data. Filtering the data using a more liberal range (0.1-30 Hz) yielded a similar pattern of results in both tasks, which just fell short of significance in the short/long mouth task. In the Holmes and Pizzagalli (2008b) study, which found an increased ERN in individuals with MDD, there is a visible (but not significant) difference in the CRN between the groups, likely resulting from the pre-response P300. Therefore, it is possible that group differences may result from differences in the P300—especially in light of the fact that studies have consistently

reported a smaller P300 in individuals with MDD (Anderer, Saletu, Semlitsch, & Pascual-Marqui, 2002; Karaaslan, Gonul, Oguz, Erdinc, & Esel, 2003; Kawasaki, Tanaka, Wang, Hokama, & Hiramatsu, 2004; Kemp, et al., 2008; Roschke & Wagner, 2003; Urretavizcaya, et al., 2003). Additionally, there was a difference in the CRN between groups in another recent publication (Schrijvers, et al., 2009), however this group did not find group differences in the ERN.

It has been suggested that theta activity is indicative of transmission between brain structures (Vinogradova, 1995). Theta activity is thought to arise from either the ACC (Asada, et al., 1999; Gevins, et al., 1997; Ishii, et al., 1999) or the DLPFC (Sasaki, et al., 1996). These two structures are highly interconnected (Barbas, 1992; Petrides & Pandya, 1999) and theta activity within these structures is positively correlated in healthy participants (Pizzagalli, Oakes, & Davidson, 2003). In addition, data supports the notion that the ERN represents theta activation (Luu & Tucker, 2001; Luu, et al., 2003; Luu, et al., 2004; Makeig, 2002; Makeig, et al., 2002).

Interestingly, there are parallels between the ERN and theta activity in individuals with MDD. Holmes and Pizzagalli (2008b) found that current density in the ACC and PFC was positively correlated in healthy participants after they committed an error, whereas there was no such correlation in the individuals with MDD. The same group showed that theta activity in the ACC and PFC were positively correlated in healthy participants, whereas there was no such correlation in the individuals with MDD (Pizzagalli, et al., 2003). Therefore, these results suggest that the ERN and theta activity are both assessing similar brain activity and confirming a dysfunctional connection

between these structures in individuals with MDD. The added benefit is that theta filtering removes potential interference from other components that may occur at overlapping points in time with the ERN.

Comparing clinical samples

There are some important differences to note when comparing the clinical sample in the current study to other studies that have assessed the ERN in individuals with MDD. One study reported that 5 of their 18 depressed participants had a comorbid anxiety disorder (social phobia (N=1), panic disorder (N=1), social phobia and panic disorder (N=2), and PTSD (N=1); Chiu & Deldin, 2007), another reported 1 of their 15 depressed participants had a comorbid diagnosis of PTSD (Schrijvers, et al., 2009), and another did not report whether their participants had a comorbid anxiety disorder (Schrijvers, et al., 2008). Only one study reported excluding participants with comorbid anxiety disorder (Holmes & Pizzagalli, 2008b), with the exception of specific phobia (N=1), which makes this sample the most comparable to the current study.

In the current study, participants were excluded if they had a comorbid anxiety disorder (with the exception of specific phobia) because of the well documented increased ERN in anxiety disorders (Gehring, et al., 2000; Hajcak, et al., 2008; Johannes, et al., 2001; Ladouceur, et al., 2006). Even though participants did not meet criteria for a current anxiety disorder, the CD group scored higher on the anxiety subscales on the MASQ than the HC and RD groups. There was no relationship in the CD group between anxiety and the ERN in either task, even when splitting the CD group based on a median split on both anxiety subscales of the MASQ. In fact, Nieuwenhuis and colleagues (2005)

found that individuals with OCD who scored high on a depression scale had a smaller ERN compared with those who scored low. Therefore, it is possible that the debilitating apathy and anhedonia found in depression trump the effect of anxiety on the ERN.

Another major difference between the current study and some of the previous studies (Chiu & Deldin, 2007; Schrijvers, et al., 2008; Schrijvers, et al., 2009; but see Holmes & Pizzagalli 2008) was that our participants were not currently on antidepressant medication. Some antidepressants directly affect DA (i.e. norepinephrine dopamine reuptake inhibitors, or NDRIs, such as buproprion), whereas SSRIs might also indirectly affect DA (Sekine, Suzuki, Ramachandran, Blackburn, & Ashby, 2007). It has been shown that acute administration of the SSRI paroxetine does not affect the ERN (de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006), but it is unclear if these findings extend to chronic SSRI administration. Additionally, Jocham and Ullsperger (2009) suggest that several neurotransmitter systems are affected in performance monitoring, therefore it is difficult to determine what effect chronic use of antidepressants may have on the ERN.

Future directions

The relationship between ERPs and symptom severity is certainly a topic of research to be further explored. To date, studies have examined individuals with either moderate or severe MDD, with varying results. If the relationship between the ERN and symptom severity is non-linear, then it would be interesting to assess individuals with MDD across a range of symptom severity. We have preliminary data from 6 individuals with mild depression appear to have an increased ERN in the flanker task compared to HC, CD and RD groups. What is especially interesting about this group is that although

they have significant depressive symptoms, their symptoms are not debilitating enough to interfere with their daily lives. It is possible that symptom interference in daily activity is a key factor in affecting the ERN. Additionally Compton and colleagues (2008) found that depressed undergraduates had a numerically larger (although not significantly larger) ERN compared to non-depressed undergraduates. These data provide us with strong preliminary evidence that the relationship between the ERN and depressive symptom severity is non-linear.

The relationship between the CRN and depression severity should also be further explored. For example, one possible explanation for the increased CRN is that individuals with severe MDD were uncertain of their correct responses. If this was the case, then obtaining confidence ratings on each trial would confirm that. Imaging studies could also identify brain regions that are active on correct trials; specifically focusing on activity in the ACC (which may be increased) and the PFC (which may be decreased).

Another avenue to explore is the difference between individuals with MDD and individuals with GAD. Although most of the ERN research has been done in OCD, there is one study looking at a pediatric population of mixed anxiety disorders, including GAD (Ladouceur, et al., 2006). The results suggest that anxiety disorders, in general, are characterized by an increased ERN. Therefore, it would be interesting to directly compare individuals with MDD and GAD on similar tasks. If there are differences between MDD and GAD participants, it would suggest that the ERN is not sensitive to the common construct of negative affect, per se, but more specific to features of anxiety disorders.

Finally, we were unable to assess the FN in the current study, however studying performance feedback processes in individuals who may be especially sensitive to feedback is a significant avenue of further research. Only one study to date has assessed the FN in individuals with MDD (Chiu & Deldin, 2007), and the results from that study are unclear. Understanding the neural processes underlying the brains response to negative feedback in individuals with MDD may help to explain the behavioral deficits that subsequently occur.

Conclusions

In the current study, we set forth to examine error-related abnormalities in individuals with current MDD, remitted MDD and healthy controls. A primary hypothesis was that the ERN and the CRN would be increased in individuals with moderate MDD, but decreased in individuals with severe MDD. This hypothesis was supported by the finding that individuals with high severity symptoms had a smaller ERN-CRN and larger CRN compared to individuals with low severity symptoms. Furthermore, we hypothesized that individuals with RD would have comparable ERNs to the CD group. This hypothesis was not supported, however the RD group's ERN was numerically between the HC and CD groups, which suggest some ERN abnormality in the RD group. Finally, we sought to evaluate the FN in MDD, however the task that we utilized did not elicit a typical FN component, therefore we were unable to evaluate it. Overall, this study suggests that individuals with MDD have abnormal error processing, but the presence of trial-to-trial feedback may moderate the relationship between the ERN and MDD. Additionally, the CRN appears to be sensitive to symptom severity.

Footnotes

[1] The same pattern of results is found when comparing the ERN at Fz and Cz. Using a more liberal filtering range (0.1 – 30 Hz) the pattern of the results were similar for the CRN, but the comparisons were not significant.

[2] The same pattern of results is found when comparing the ERN at FCz and Cz. Using a more liberal filtering range (0.1 – 30 Hz) the pattern of the results were similar for the ERN, although the comparison between the HC and CD group just fell short of significance.

[3] The significantly smaller ERN in the CD group may be related to poorer performance. However, when matching participants based on performance (N = 18 per group) in order to eliminate performance differences ($F(2,51) < 1$), the CD group still had a significantly smaller ERN compared to the HC group ($t(34) = -2.34$, $p < .05$), but similar CRNs ($t(34) = -1.33$, $p > .05$). There was no difference in ERN or CRN area when comparing the HC and RD groups or the CD and RD groups (all ps $> .05$).

[4] The same pattern of results is found when comparing the FN at Fz, FCz and Cz, as well as using data filtered in a more liberal range (0.1 – 30 Hz).

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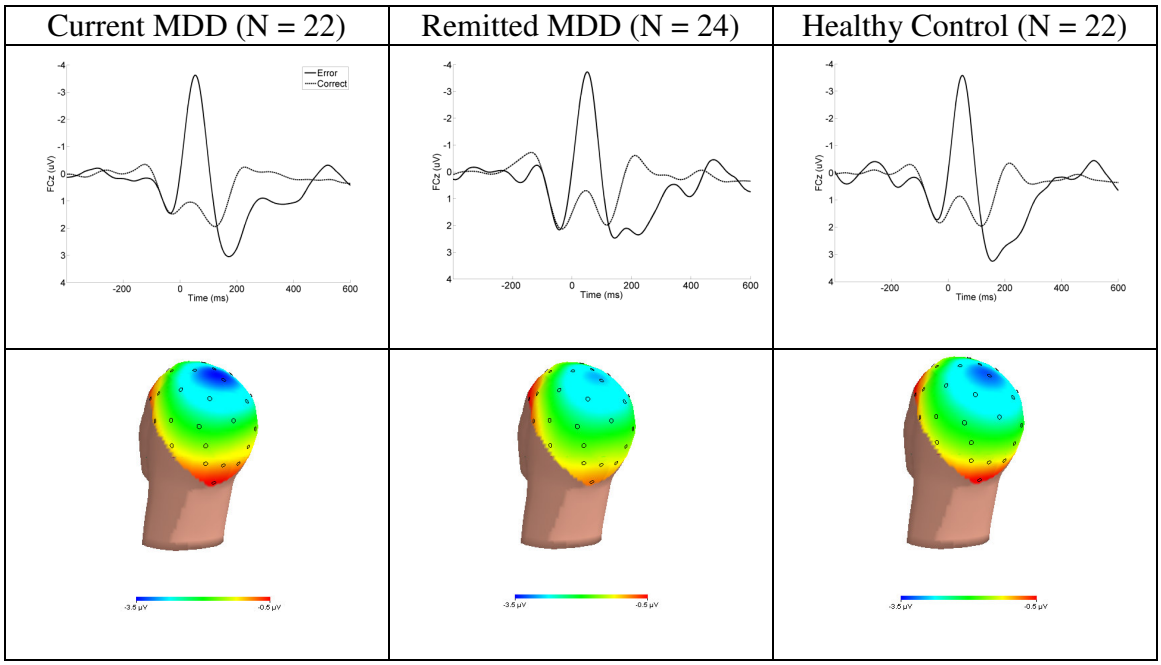


Figure 1. Response-locked ERPs for error and correct trials for CD (top left), RD (top middle) and HC groups (top right) and scalp topography of error-related brain activity from 0 to 100 ms post-response for CD (bottom left), RD (bottom middle) and HC groups (bottom right) at FCz for the flanker task.

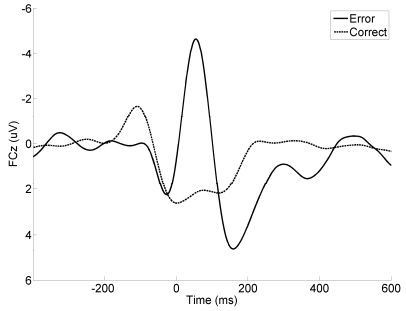
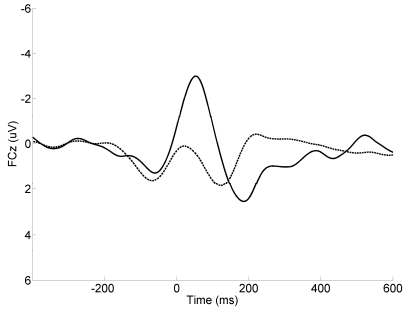
Low Depressive Symptom Severity (N = 9)	High Depressive Symptom Severity (N = 10)
	

Figure 2. Response-locked ERPs for error and correct trials for individuals with low depressive symptom severity (left) and high depressive symptom severity groups (right) at FCz for the flanker task.

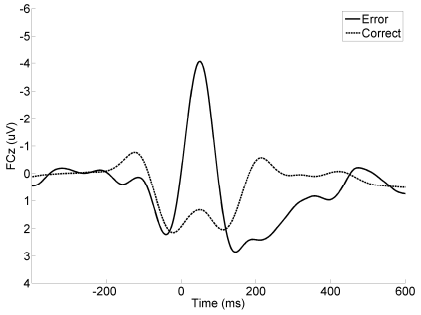
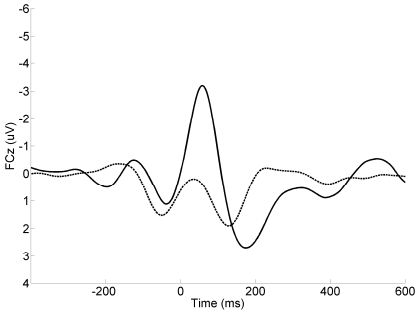
History of Non-chronic Depression (N = 28)	History of Chronic Depression (N = 18)
	

Figure 3. Response-locked ERPs for error and correct trials for individuals with a history of non-chronic (left) and chronic depression (right) at FCz for the flanker task.

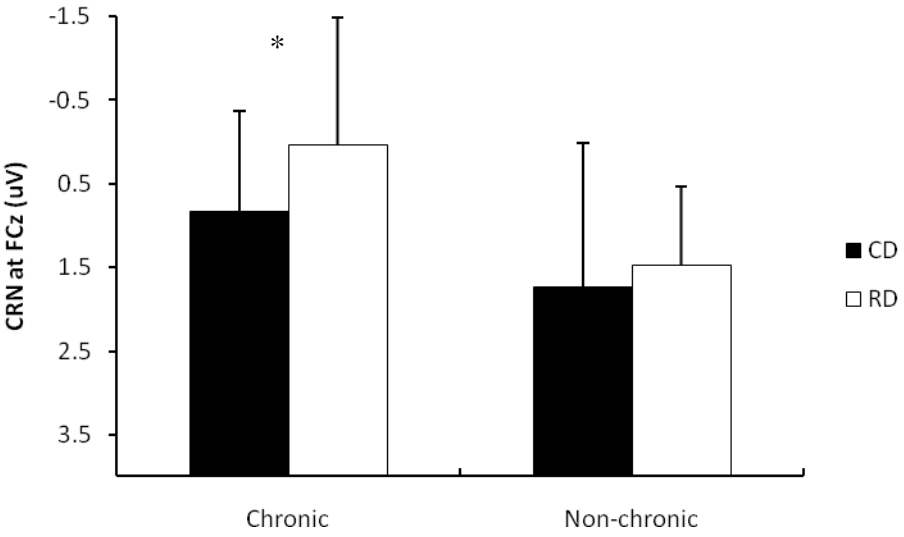


Figure 4. CRN magnitudes at FCz for CD and RD participants based on a history of chronic or non-chronic depression for the flanker task

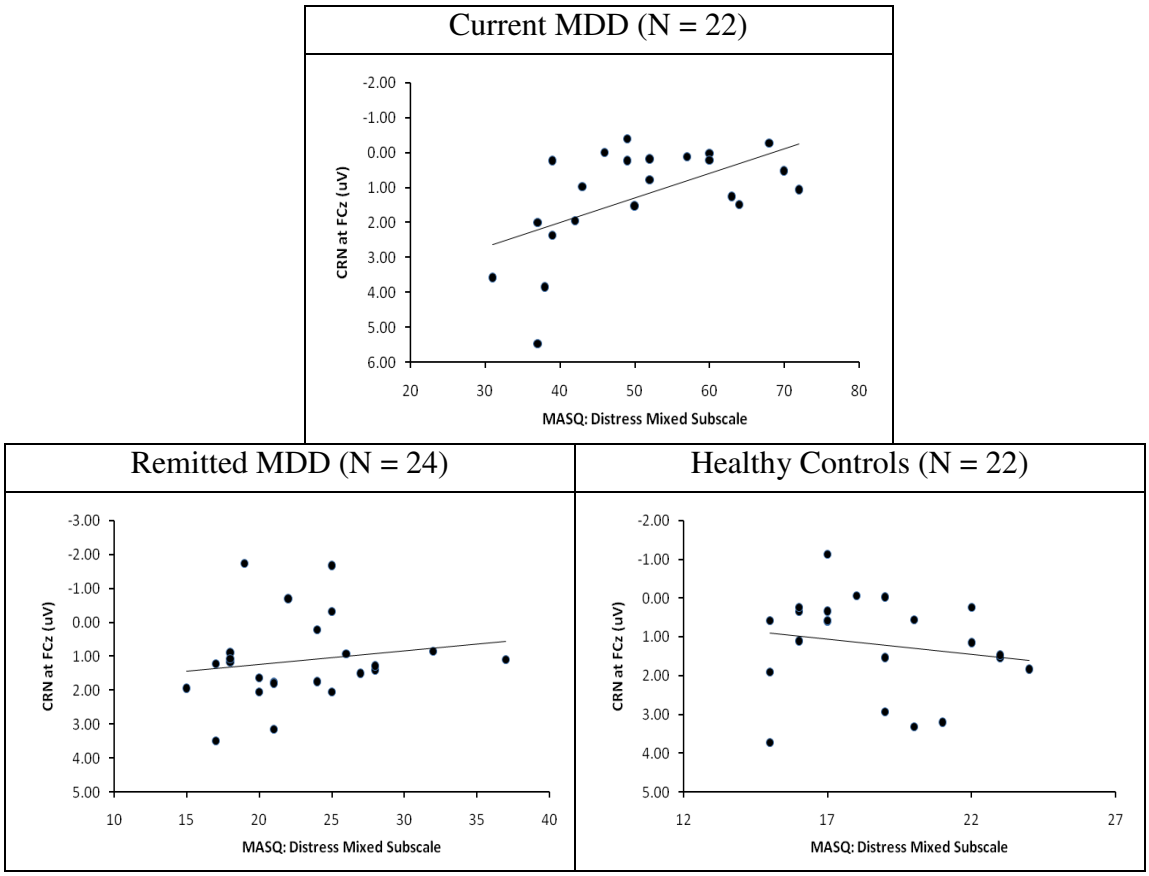


Figure 5. Scatterplots depicting the Pearson correlation between the CRN at FCz and MASQ: Depressed Mixed scores in the CD (top), RD (bottom left) and HC groups (bottom right) for the flanker task.

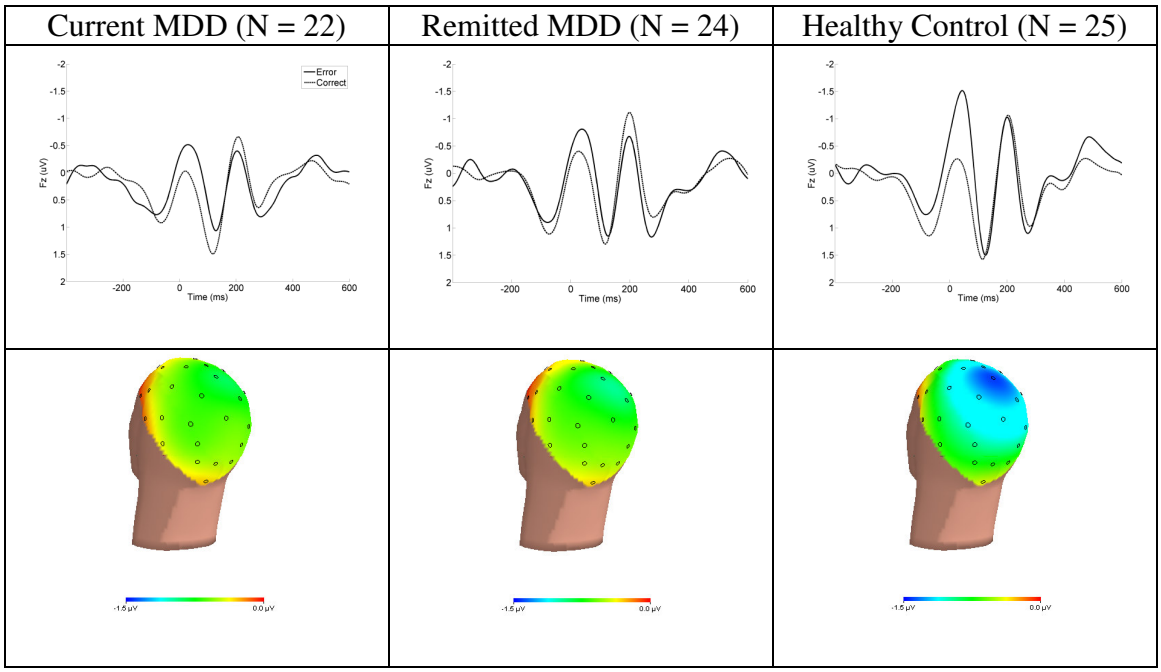


Figure 6. Response-locked ERPs for error and correct trials for CD (top left), RD (top middle) and HC groups (top right) and scalp topography of error-related brain activity from 0 to 100 ms post-response for CD (bottom left), RD (bottom middle) and HC groups (bottom right) at Fz for the short/long mouth task.

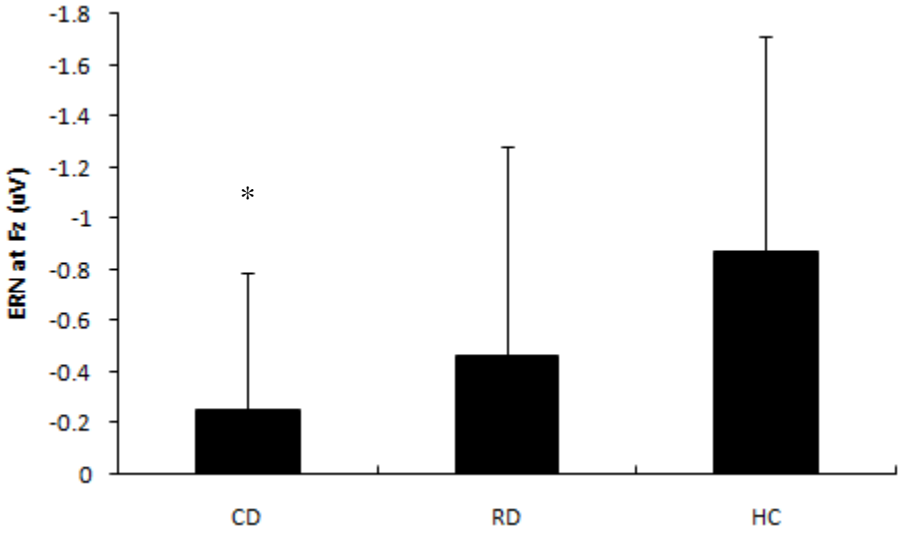


Figure 7. ERN magnitudes at Fz for the short/long mouth task.

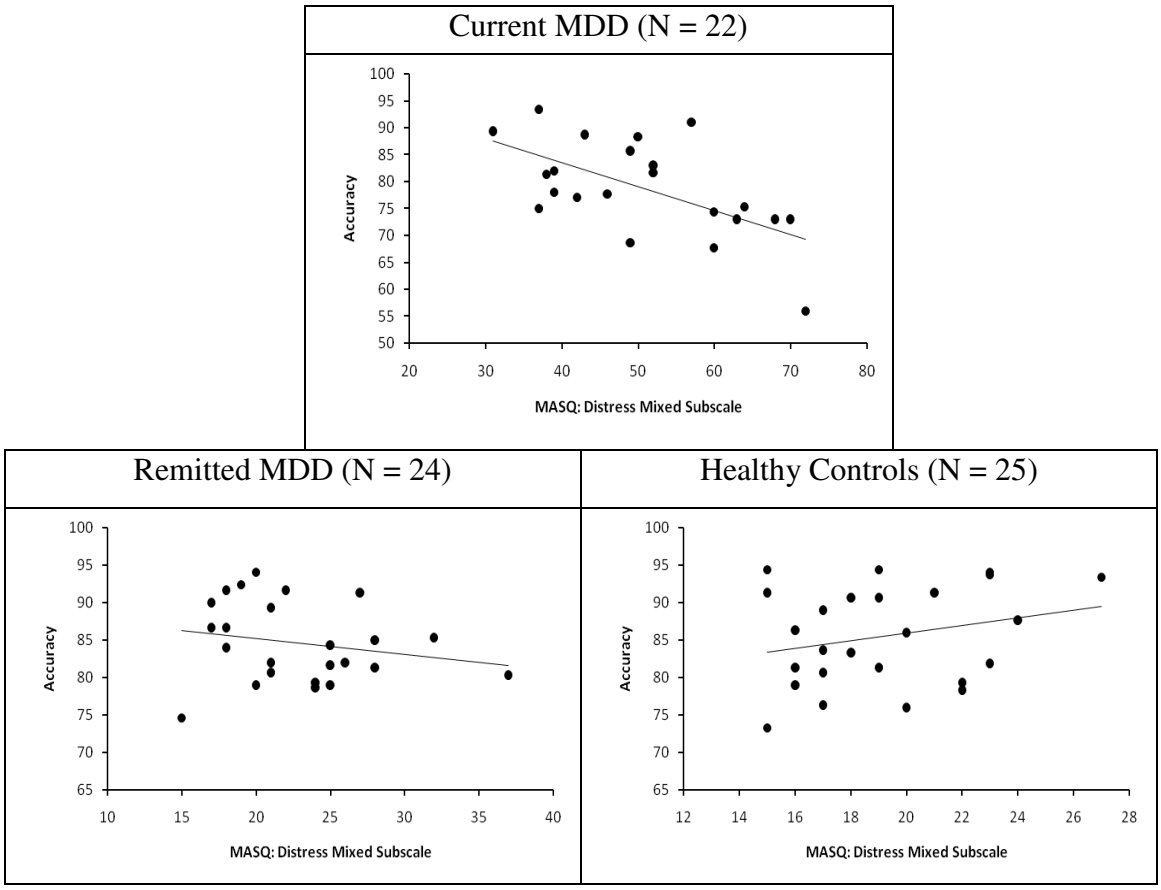


Figure 8. Scatterplots depicting the Pearson correlation between the accuracy and MASQ: Depressed Mixed scores in the CD (top), RD (bottom left) and HC groups (bottom right) for the short/long mouth task.

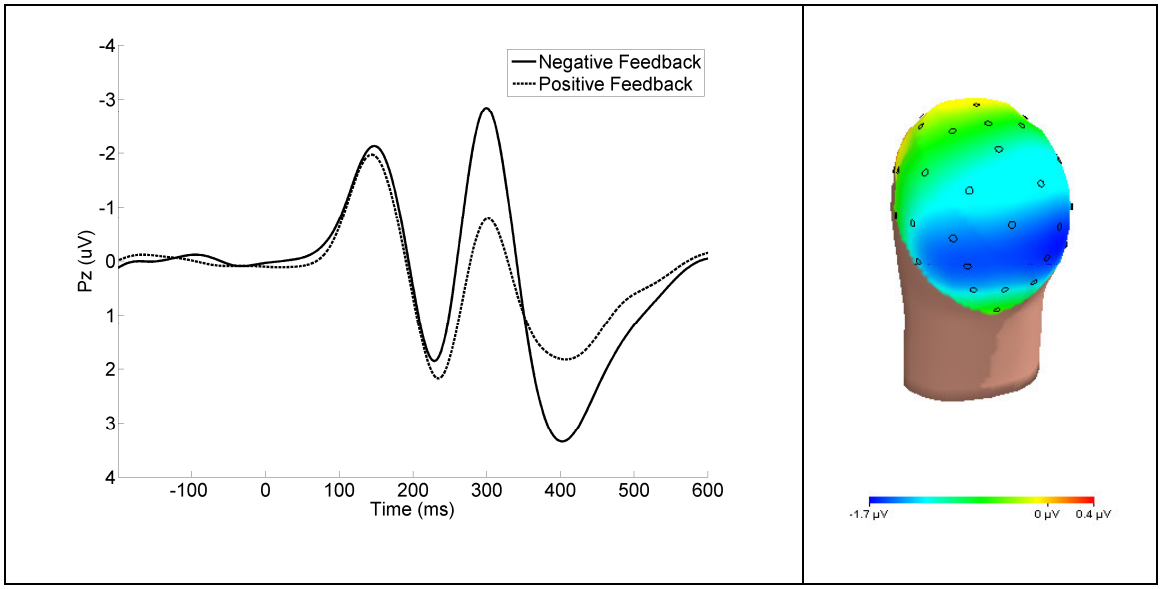


Figure 9. Feedback-locked ERPs for incorrect and correct feedback trials for all participants (left) at Pz for the short/long mouth task and the scalp distribution (right) for 250 – 350 ms after feedback onset.

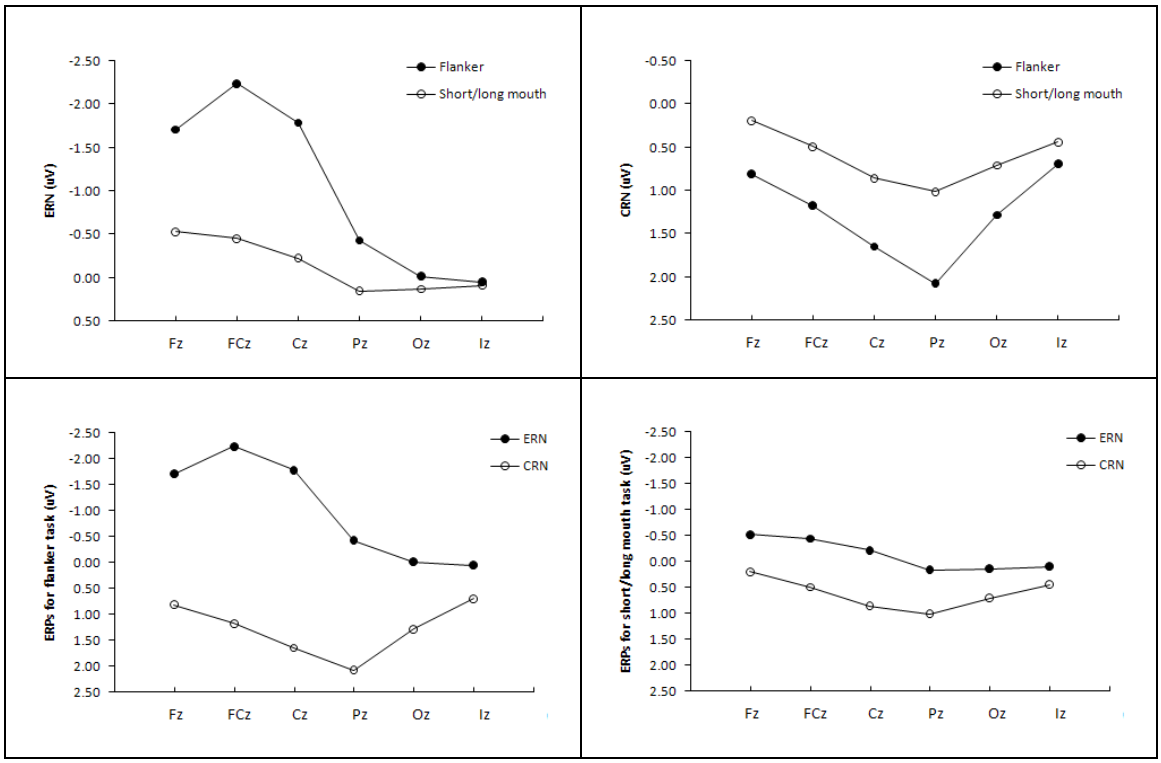


Figure 10. The average ERN (top left) and CRN (top right) by task across the 6 midline electrode sites. The average ERPs for the flanker (bottom left) and short/long mouth task (bottom right) by task across the 6 midline electrode sites.