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Abnormal Emotional Reactivity and Reward Sensitivity in Major Depressive Disorder: Evidence from Event-Related Potentials

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Abstract of the Dissertation

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Major depressive disorder (MDD) is associated with abnormal neural activity elicited by affective stimuli and reward, yet results have been inconsistent across studies and have at times been contradictory. Discrepancies may be due in part to the wide range of laboratory paradigms and stimuli that have been used. The current study examined this issue by recording event-related potentials across a battery of four tasks within a single MDD sample. First, using two emotional reactivity tasks, the moderating effect of the personal relevance of stimuli was examined; normative and idiographic affective stimuli were contrasted. Second, using two environmental feedback tasks, monetary and performance feedback were contrasted. ERPs were collected from adult females with current unipolar depression (n=36) and never-depressed controls (n=44). Across the two emotional reactivity tasks, distinct abnormalities were observed: The late positive potential elicited by normative unpleasant images, as well as normative pleasant and unpleasant words, was blunted in the MDD compared to the control group. By contrast, the

late positive potential elicited by idiographic pleasant and unpleasant words—stimuli describing participants' own moods—was increased in the MDD compared to the control group. This pattern suggests that MDD is associated with neither a global increase nor decrease in emotional reactivity, but that abnormalities are context-specific and relate to the personal relevance of stimuli. Group effects were also observed across the two feedback tasks: The feedback negativity elicited by monetary outcomes was blunted in the MDD group, but the response elicited by performance feedback was intact and comparable in magnitude to controls. This suggests that impaired feedback processing in MDD is specific to reward information. Group differences in emotional reactivity and reward sensitivity were largely unrelated across individuals, suggesting the presence of relatively unique neural deficits that may relate to clinically distinct subgroups. Consistent with this possibility, the blunted neural response to monetary reward was specific to those MDD participants reporting impaired mood reactivity, a core symptom of melancholic depression. Future research will be necessary to clarify how each of these abnormal neural responses may uniquely relate to MDD onset, course, and treatment outcome.

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List of Abbreviations

AA	Anxious Arousal subscale
ACC	anterior cingulate cortex
AD	Anhedonic Depression subscale
ANEW	Affective Norms for English Words
ANOVA	analysis of variance
ECI	emotion context insensitivity
EEG	electroencephalogram
ERP	event-related potential
fMRI	functional magnetic resonance imaging
FN	feedback negativity
GDA	General Distress: Anxious Symptoms subscale
GDD	General Distress: Depressive Symptoms subscale
IAPS	International Affective Picture System
LPP	late positive potential
MASQ	Mood and Anxiety Symptom Questionnaire
MDD	major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
ms	millisecond
SCID	Structured Interview for DSM Disorders
SHAPS	Snaith-Hamilton Pleasure Scale
μV	microvolt

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Introduction

With a lifetime prevalence rate of approximately 16%, major depressive disorder (MDD) ranks among the world's most common illnesses (R. C. Kessler & Wang, 2009). MDD is associated with an increased rate of mortality (Cuijpers & Smit, 2002), as well as an annual economic burden in the tens of billions of dollars (Berto, D'Ilario, Ruffo, Di Virgilio, & Rizzo, 2000; Luppa, Heinrich, Angermeyer, Konig, & Riedel-Heller, 2007). MDD is defined as a disturbance in mood—a pervasive feeling of sadness, a diminished interest in pleasurable activities, or both—and presents with a range of other cognitive and physical symptoms including insomnia, difficulty concentrating, and suicidality (American Psychiatric Association, 2000).

Incorporating approaches from cognitive and affective neuroscience, there has been a recent emphasis on examining information processing abnormalities in MDD, particularly with regard to neural activity elicited by emotional stimuli (Fitzgerald, Laird, Maller, & Daskalakis, 2008) and reward (Forbes, 2009; Nestler & Carlezon, 2006). Studies have generally shown that emotional reactivity and reward sensitivity are affected in MDD, identifying patterns of abnormal neural activity that may contribute to the onset and maintenance of the illness. Applying neural measures to the study of MDD in this manner has the potential to yield tools that can be used to objectively quantify psychological dysfunction. For example, limbic hyperactivity to negative stimuli has been related to rumination (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002) and predicts treatment response to cognitive behavioral therapy (Siegle, Carter, & Thase, 2006). In addition, striatal hypoactivity to monetary reward has been uniquely related to anhedonia severity and not other concurrent symptoms of depression or anxiety (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Wacker, Dillon, & Pizzagalli, 2009).

Results have not always been consistent across studies, however, and have at times been contradictory. Discrepancies across studies may be due in part to the wide range of laboratory paradigms and stimuli that have been used: Some studies have reported hypoactivity to normative affective stimuli in MDD, whereas others have reported hyperactivity to idiographic stimuli—suggesting that the personal relevance of stimuli may influence the directionality of abnormal emotional reactivity in MDD. Studies of reward sensitivity, meanwhile, have generally reported hypoactivity in MDD, yet some studies that have conflated reward and performance feedback have reported hyperactivity—suggesting that the type of information conveyed by feedback on reward tasks may influence the directionality of group differences. Responses to stimuli varying in personal relevance or in reward information have yet to be directly compared, though, and it remains unclear whether these task differences moderate patterns of abnormal neural activity in MDD. The current study seeks to address this question by recording neural activity across a battery of four tasks within a single MDD sample. These tasks are designed to examine whether MDD is characterized by both hypoactivity in specific experimental contexts and hyperactivity in others, with *decreased* reactivity to normative affective stimuli and monetary reward, as well as *increased* reactivity to idiographic affective stimuli and performance feedback. Below, we review the current state of the literature on abnormal emotional reactivity and reward processing in MDD, and we identify specific methodological differences across studies that could account for some of the divergent findings.

Emotional Reactivity

One influential account of abnormal emotional reactivity in MDD is Mayberg's limbic-cortical dysregulation model, by which depressive symptoms are attributable to underactive prefrontal and overactive limbic regions (Mayberg, 1997, 2003; Mayberg et al., 1999).

Consistent with this model, a meta-analysis of neuroimaging studies concluded that MDD is consistently characterized reduced activity in the dorsolateral prefrontal cortex (DLPFC) both during rest and while viewing negative stimuli, and that activity in this region increases following successful treatment with antidepressant medication (Fitzgerald et al., 2008). This is in contrast to evidence of hyperactivity in MDD during cognitively demanding paradigms, potentially reflecting cortical inefficiency (Harvey et al., 2005). Together, this pattern of disrupted activity in the DLPFC is thought to relate to cognitive symptoms of MDD as well as the impaired regulation of negative emotional responses (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007).

On the other hand, neuroimaging studies of emotional reactivity in limbic regions, particularly the amygdala, have been less consistent (Townsend et al., 2010). Some studies have found evidence of hyperactivity in MDD, with relatively increased amygdala activity while viewing negative compared to neutral stimuli (Anand et al., 2005; Dichter, Felder, & Smoski, 2009; Hamilton & Gotlib, 2008; Sheline et al., 2001; Surguladze et al., 2005; Suslow et al., 2010). Other studies have found either the opposite pattern, with *blunted* amygdala reactivity to negative stimuli (Lawrence et al., 2004; Moses-Kolko et al., 2010; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Silverman et al., 2011; Thomas et al., 2001), or have found null effects, with comparable levels of amygdala reactivity across depressed and healthy samples (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010; Davidson, Irwin, Anderle, & Kalin, 2003; Townsend et al., 2010). Further, one study found a moderating effect of directed attention, such that amygdala reactivity to fearful faces was blunted when the stimuli were task-relevant but was increased when they were task-irrelevant (Fales et al., 2008). These discrepant findings suggest

that MDD is not characterized by a global dysfynction in amygdala reactivity to affective stimuli, but rather a more complex pattern that may depend on experimental context.

One methodological factor that may account for some of these discrepancies is that some studies have used paradigms that do not reliability elicit amygdala activation in controls. In three studies reporting amygdala hyperactivity in MDD, the between-group difference was driven by either a lack of activation or deactivation in the control sample (Hamilton & Gotlib, 2008; Sheline et al., 2001; Surguladze et al., 2005; Suslow et al., 2010)—suggesting that it is not increased emotional modulation of amygdala activity in MDD per se, but rather inappropriate amygdala recruitment. In other words, individuals with MDD exhibited increased amygdala activity to stimuli that ought not to have elicited such activity at all. Similarly, there is some evidence of increased amygdala activation to both negative and neutral stimuli, again suggesting inappropriate recruitment (Gaffrey et al., 2011; Sheline et al., 2001). Finally, three other studies reported increased amygdala activity to negative stimuli but did not consider neutral stimuli, leaving it unclear whether group differences reflect increased emotional modulation or simply increased activity overall (Fu et al., 2004; van Wingen et al., 2011; Yang et al., 2010).

This pattern raises the possibility that, at least in certain contexts, abnormal amygdala activity in MDD may manifest as a failure to properly discriminate affective from neutral information. That is, apparent amygdala hyperactivity in some studies may be better understood as inappropriate activity elicited by stimuli that ought not to have elicited amygdala activation, based on the patterns observed among healthy controls. Indeed, in one recent study using stimuli high in emotional arousal, healthy controls exhibited robust amygdala activation in response to both negative and positive but not neutral stimuli compared to the implicit baseline; by comparison, depressed individuals exhibited a relatively inflexible pattern of amygdala

recruitment, with comparable activation in response to all stimuli, regardless of the emotional content (Ritchey et al., 2011). The MDD group was characterized by a combination of inappropriately increased activity to neutral stimuli and reduced activity to positive and negative stimuli, resulting in less emotional modulation of amygdala activity. Notably, in a second assessment following successful treatment with cognitive behavioral therapy, amygdala activity in the depressed sample followed the normal pattern of affective discrimination (i.e., increased responses to positive and negative compared to neutral stimuli).

This inflexible pattern of neural activity observed by Ritchey and colleagues (2011)—indicating a failure in MDD to properly differentiate affective from neutral stimuli—is consistent with the emotion context insensitivity (ECI) model, an alternate account of emotional reactivity in MDD that has been advanced outside the neuroimaging literature. The ECI model postulates that MDD is primarily characterized by a broad disengagement with one's environment and blunted reactivity to both positive and negative compared to neutral stimuli (Rottenberg, Gross, & Gotlib, 2005). A subsequent meta-analysis found the ECI model to be well-supported across a number of different paradigms using measures of self-report, behavior, and peripheral physiology (Bylsma, Morris, & Rottenberg, 2008). For example, individuals with MDD exhibit less affective modulation of the startle reflex while viewing pleasant, neutral, and unpleasant images (Allen, Trinder, & Brennan, 1999; Dichter & Tomarken, 2008; Dichter, Tomarken, Shelton, & Sutton, 2004); they exhibit less facial muscle activity while viewing both positive and negative facial expressions (Wexler, Levenson, Warrenburg, & Price, 1994); and they report blunted emotional experiences while viewing sad or amusing film clips (Rottenberg et al., 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002).

Integrating this evidence with the neuroimaging findings described above, it appears that there are two conceptually distinct issues at play that have not been well separated in the literature: impaired reactivity versus inappropriate reactivity. Impaired reactivity would imply that the response to emotional stimuli in MDD is inhibited under conditions that ought to elicit such reactivity. That is, in experimental manipulations that elicit robust neural activity associated with affective processing in healthy individuals, that response would be abnormal in MDD. The ECI model predicts that neural activity will be blunted, and some fMRI studies have lent support to this perspective (Lawrence et al., 2004; Moses-Kolko et al., 2010; Ritchey et al., 2011; Thomas et al., 2001).

By contrast, inappropriate reactivity would imply an emotional response in MDD under conditions that ought *not* to elicit such reactivity. That is, in experimental manipulations that do not elicit neural activity associated with affective processing in healthy individuals, is neural activity inappropriately elicited in MDD? We propose here that some neuroimaging studies reporting increased emotional reactivity in MDD may be better understood as supporting *inappropriate* reactivity, with affective modulation of neural activity observed only among individuals with MDD and not in controls (Fales et al., 2008; Gaffrey et al., 2011; Hamilton & Gotlib, 2008; Sheline et al., 2001; Surguladze et al., 2005; Suslow et al., 2010).

It stands to reason that this exaggerated and inappropriate emotional reactivity will be most apparent in response to stimuli that are uniquely salient for depressed but not healthy individuals, and, along these lines, several neuroimaging studies have focused on amygdala reactivity to sad images, with somewhat mixed results (Almeida et al., 2010; Dichter, Felder, & Smoski, 2009; Fu et al., 2004; Gaffrey et al., 2011; Surguladze et al., 2005; Suslow et al., 2010). A more powerful manipulation may be to incorporate idiographic stimuli that directly target

negative mood states in a manner that is tailored for each participant (Rottenberg et al., 2005). Consistent with this notion, Siegle and colleagues have used a paradigm in which participants generate a set of words to describe their own negative, neutral, and positive moods: Among individuals with MDD but not healthy controls, amygdala activity was enhanced while viewing the idiographic negative words alongside other normative words (Siegle et al., 2006; Siegle et al., 2002; Siegle et al., 2007), indicating that this is an effective experimental manipulation for eliciting *inappropriate emotional reactivity* in MDD; this effect was replicated in another recent study using a similar paradigm (H. Kessler et al., 2011). In spite of these promising findings, these studies did not directly compare neural responses to idiographic and normative stimuli, leaving it unclear whether the personal relevance of stimuli is a key determining factor of inappropriate emotional reactivity in MDD.

To pursue this question, we measured in the current study event-related potentials (ERPs) while individuals with MDD viewed normative and idiographic affective stimuli. In particular, we focus on the late positive potential (LPP), a well-established electrocortical measure that is sensitive to the affective content of stimuli. The LPP is observed as a sustained positivity in the ERP waveform that is enhanced for both pleasant and unpleasant compared to neutral stimuli, including images (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000), faces (Schupp et al., 2004), and words (Fischler & Bradley, 2006). It is maximal at centroparietal recording sites, is evident as early as 200 ms following stimulus onset, and is sustained throughout stimulus presentation (Cuthbert et al., 2000; Foti, Hajcak, & Dien, 2009; Hajcak, Dunning, & Foti, 2009; Schupp et al., 2000).

The LPP is thought to reflect increased attention to and facilitated processing of emotionally salient stimuli (Bradley, 2009), and it has been linked through source localization to

activity in occipital and parietal brain regions (Keil et al., 2002). Furthermore, two studies combining fMRI and ERP approaches found that LPP amplitude corresponded to increased blood flow in temporal, parietal, and occipital visual cortical structures (Sabatinelli, Lang, Keil, & Bradley, 2007) and the amygdala (Sabatinelli, Keil, Frank, & Lang, 2012), indicating contributions of cortical and limbic structures involved in emotional processing. Consistent with the notion that the LPP indexes increased attention to emotional stimuli, manipulations that increase or decrease the salience of aversive stimuli modulate the LPP (Foti & Hajcak, 2008; Hajcak & Nieuwenhuis, 2006; Krompinger, Moser, & Simons, 2008; Moser, Hajcak, Bukay, & Simons, 2006). Importantly, the LPP also provides precise information about the time-course of emotional processing that is not feasible with neuroimaging techniques. For example, in one study of directed attention, individuals exhibited a sustained reduction in LPP amplitude beginning just 620 ms after an instruction to attend to less arousing aspects of unpleasant pictures (Hajcak et al., 2009).

In two studies to date, the LPP has been shown to be an effective measure for examining abnormal emotional reactivity in MDD. In one recent study from our group, we recorded the LPP in response to emotional faces among currently- and never-depressed adults (Foti, Olvet, Klein, & Hajcak, 2010). Among controls, the LPP was significantly modulated by fearful and angry compared to neutral faces, but in the MDD group the LPP was insensitive to face type. In a separate study, a blunted LPP to emotional compared to neutral faces was also found among young children with a maternal history of MDD (Kujawa, Hajcak, Torpey, Kim, & Klein, 2011). These two studies provide ERP evidence consistent with the ECI model, such that robust affective modulation of LPP amplitude was observed in control but not depressive samples in both studies, indicating impaired emotional reactivity. The LPP has yet to be applied as a

measure of *inappropriate* emotional reactivity in MDD, though, and it would be important to evaluate whether the modulation of LPP amplitude by negative idiographic stimuli is increased among individuals with MDD compared to controls.

In the current study, we sought to build upon these preliminary findings by recording the LPP across two tasks designed to examine the influence of personal relevance of stimuli on electrocortical measures of emotional reactivity in MDD. In the first task, we examined whether emotional reactivity, as indicated by LPP amplitude, is impaired in MDD while viewing high-arousal, normative stimuli that are known to elicit robust neural activity in healthy populations. We used pleasant, neutral, and unpleasant images drawn from the International Affective Picture System (IAPS), a standardized set of images with normative ratings on emotional arousal and valence (Lang, Bradley, & Cuthbert, 2005). We used specific semantic categories of IAPS images known to maximize the affective modulation of the LPP in unselected samples: unpleasant images depicting mutilation and threat, and pleasant images depicting erotic and affiliative scenes (Weinberg & Hajcak, 2010). Insofar as viewing IAPS images elicits amygdala activation and increased activity in the visual cortex compared to viewing faces (Britton, Taylor, Sudheimer, & Liberzon, 2006), this task is a more robust experimental manipulation and is a stronger test of the ECI model compared to the previous study that used face stimuli (Foti et al., 2010). Based on that prior result as well as recent neuroimaging evidence from Ritchey and colleagues (2011), we predicted that the LPP would be significantly increased for pleasant and unpleasant compared to neutral stimuli among controls, whereas in the MDD group the affective modulation of LPP amplitude by normative stimuli would be reduced.

In the second task, we examined whether emotional reactivity is inappropriately increased in MDD while viewing negative stimuli high in personal relevance. We used the

paradigm originally developed by Siegle and colleagues (2002) and recorded the LPP elicited by both normative and idiographic affective words. All participants viewed the same set of pleasant, neutral, and unpleasant normative words drawn from the Affective Norms for English Words (ANEW; Bradley & Lang, 1999). In addition, participants generated a separate set of personally relevant words that best represent their own happy, neutral, and sad moods. Although Siegle and colleagues (2002) did not analyze the normative and idiographic stimuli separately, this contrast is of interest in the current study in order to test whether the affective modulation of the LPP is moderated by the personal relevance of stimuli within the MDD group. Consistent with the ECI model, we predicted that the affective modulation of the LPP by normative words would be blunted in the MDD group compared to controls, but that the opposite pattern would be apparent for negative idiographic words, with *increased* affective modulation of the LPP in the MDD group. In this way, the current study is well-suited to provide a comprehensive assessment of emotional reactivity in MDD, as indicated by the abnormal modulation of the LPP across these two experimental paradigms.

Reward Sensitivity

Anhedonia, defined as a pervasive lack of reactivity to pleasurable stimuli, is one of the cardinal symptoms of MDD (American Psychiatric Association, 2000). Indeed, factor analysis of self-report data suggests that this deficit in positive affect may be what distinguishes MDD from frequently comorbid anxiety disorders (Joiner, Catanzaro, & Laurent, 1996; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995). Extending this work to behavioral correlates of anhedonia, a number of studies have demonstrated that depression is associated with impaired responsiveness to rewards. For example, studies using signal-detection approaches have shown that healthy individuals exhibit a response bias under conditions of monetary reward in order to

maximize their earnings; dysphoric (Henriques, Glowacki, & Davidson, 1994) and depressed (Henriques & Davidson, 2000) individuals do not exhibit this bias, showing instead a relatively inflexible response style that is not modulated by reward contingencies. This behavioral inflexibility—with reduced differentiation between rewards and non-rewards—is consistent with the ECI model. Blunted reward responsiveness on laboratory tasks is associated with self-reported anhedonia severity (Pizzagalli, Jahn, & O'Shea, 2005), and it appears to be driven by impaired reinforcement learning across trials, such that individuals with MDD respond to single rewards but fail to maintain a normal response bias over time in the absence of immediate reward (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008).

Converging with this line of behavioral evidence, biological studies have shed light on the pathophysiology of impaired reward sensitivity in MDD. For example, the approach-related motivational system, which sustains goal-directed behavior and certain forms of positive affect, has been related to relatively increased activity in the left prefrontal cortex (Davidson, 1992, 1998). Consistent with the notion that anhedonia is a key aspect of MDD, electroencephalograph (EEG) studies have shown that individuals with MDD exhibit reduced activity in the left prefrontal cortex while at rest (Debener et al., 2000; Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990, 1991; Stewart, Bismark, Towers, Coan, & Allen, 2010) and while anticipating monetary reward (Shankman, Klein, Tenke, & Bruder, 2007), indicating an underactive approach system.

In addition to these studies on hypoactive prefrontal regions, recent work has focused on the mesocorticolimbic reward circuit, particularly dopaminergically-mediated activity in the striatum and the anterior cingulate cortex (ACC) during reward processing. A meta-analysis of the neuroimaging literature on reward processing in healthy adults found that the striatum is a

core area that consistently shows increased activation in response to rewards (Liu, Hairston, Schrier, & Fan, 2011). Although less consistently observed across studies, the authors also found evidence that the dorsal ACC is activated by non-rewards; other work has implicated the dorsal ACC in the integration of reinforcement history (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). Converging with behavioral evidence of reward insensitivity, several neuroimaging studies have found reduced striatal reactivity to monetary gains in MDD (Forbes et al., 2006; Forbes et al., 2009; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Pizzagalli et al., 2009; Smoski et al., 2009; Steele, Kumar, & Ebmeier, 2007). Further, this striatal hypoactivity relates specifically to self-reported anhedonia severity rather than other depressive symptoms or anxiety (Keedwell et al., 2005; Wacker et al., 2009), and striatal reactivity to rewards increases upon recovery from depression (Dichter, Felder, Petty, et al., 2009). Similarly, dorsal ACC activity elicited by monetary loss also appears to be blunted in MDD (Forbes et al., 2006; Knutson et al., 2008; Smoski et al., 2009; Steele et al., 2007). Consistent with the ECI model, these studies indicate that MDD is associated with blunted neural differentiation between positive and negative monetary outcomes, with reduced reward-related activity in the striatum and reduced loss-related activity in the dorsal ACC.

Building upon this neuroimaging evidence, complementary information about the time course of impaired reward processing in MDD may be obtained from electrophysiological measures of neural activity. ERP studies have focused primarily on the feedback negativity (FN; also referred to as the feedback-related negativity or the medial frontal negativity), a negative deflection in the ERP that differentiates feedback indicating favorable (e.g., monetary gain, correct feedback) from unfavorable outcomes (e.g., monetary loss, error feedback). The FN

peaks at approximately 300 ms following feedback presentation and is maximal at frontocentral recording sites (Miltner, Braun, & Coles, 1997). The FN has been localized to a source in the dorsal ACC (Gehring & Willoughby, 2002), and variation in FN amplitude has been interpreted as reflecting changes in mesencephalic dopamine activity when reward prediction errors occur (Holroyd & Coles, 2002). Consistent with this perspective, FN amplitude is increased in response to unexpected reward outcomes (Hajcak, Moser, Holroyd, & Simons, 2007; Holroyd, Nieuwenhuis, Yeung, & Cohen, 2003). The FN also tracks the relative valence of outcomes within the immediate context, such that the amplitude of the FN elicited by neutral feedback depends on whether the alternative outcome would have been a monetary gain or loss (Holroyd, Hajcak, & Larsen, 2006; Holroyd, Larsen, & Cohen, 2004). On the other hand, FN amplitude is insensitive to outcome magnitude; the FN distinguishes between monetary gains and losses but is equivalent for larger compared to smaller losses (Hajcak, Moser, Holroyd, & Simons, 2006; Sato et al., 2005; Yeung & Sanfey, 2004). These results indicate that the FN reflects early neural activity associated with a binary evaluative process of reward outcomes that are either better or worse than expected.

The FN takes its name from the fact that it is observed as a negative-going ERP component that is increased (i.e., more negative) for monetary losses compared to gains. Several recent studies, however, have provided evidence that variation in FN amplitude may be driven instead by rewards (Baker & Holroyd, 2011; Holroyd, Krigolson, & Lee, 2011; Holroyd, Pakzad-Vaezi, & Krigolson, 2008). Consistent with this interpretation, in a recent study, we used temporospatial principal components analysis (PCA) to parse the ERP waveform and identified the FN as an absolute positivity that was increased (i.e., more positive) in response to monetary gains compared to losses (Foti, Weinberg, Dien, & Hajcak, 2011). In other words, the

FN may be better understood as a *reward-related positivity*, reflecting increased neural activity to rewards compared to non-rewards. In that same study, we also applied source localization techniques to the PCA-derived response and identified a source in the striatum. In a follow-up study combining ERP and fMRI measures in a single sample, we replicated the PCA solution and the striatal source of the FN, and we found that FN amplitude correlated directly with the hemodynamic response in the striatum to monetary gain (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011). These data indicate that, in addition to the ACC, the FN may partly reflect reward-related striatal activity.

Based on these results, the FN appears as a neural measure well-suited to further examine impaired reward processing in MDD. In one study to date using an unselected adult sample, we found that depressive symptom severity was inversely related to FN amplitude, quantified as the difference between monetary loss and gain (Foti & Hajcak, 2009). We subsequently replicated this finding in a child sample and found that depressive symptoms were uniquely associated with a blunted response to monetary gain, and not losses (Bress, Smith, Foti, Klein, & Hajcak, 2012). To clarify this link between depressive symptoms and FN amplitude, we also conducted two studies using a negative mood induction. A blunted FN was associated with self-reported sadness following the mood induction (Foti & Hajcak, 2010), and the association between negative mood state and blunted FN amplitude was particularly strong among individuals at increased risk for MDD (Foti, Hajcak, Kotov, & Klein, 2011). Together, these findings are consistent with the aforementioned neuroimaging studies showing blunted striatal and ACC activity during reward processing in MDD, and they show that the FN is an effective tool for quantifying neural insensitivity to rewards.

In these four ERP studies linking a blunted FN to depressive symptoms and induced sadness (Bress et al., 2012; Foti & Hajcak, 2009, 2010; Foti, Hajcak, et al., 2011), a simple gambling task was used in which participants won or lost a nominal amount of money on each trial; reward outcomes were randomly determined on a trial-wise basis and not tied to behavioral performance. On the other hand, in one other study to date examining the FN in MDD, a speeded response task was used (Tucker, Luu, Frishkoff, Quiring, & Poulsen, 2003). On each trial, participants were asked to quickly respond to a visual stimulus and were then presented with a letter grade evaluating their performance; slow responses received a grade of "F" and were associated with a monetary loss. Compared to healthy controls, individuals with MDD exhibited a larger (i.e., more negative) FN in response to negative feedback, and this increased ERP response was localized to the dorsal ACC. A similar pattern has also been observed in remitted depression (Santesso et al., 2008). These results are interpreted as indicating hypersensitivity to negative feedback in MDD, which is consistent with neuropsychological evidence that perceived failure after receiving negative feedback has a detrimental effect on subsequent task performance in MDD (Elliott et al., 1996).

In these two ERP tasks reporting an increased FN in MDD (Santesso et al., 2008; Tucker et al., 2003), however, the feedback conflated reward and performance information, with monetary outcomes contingent on task success. This raises the possibility that neural responses to reward and performance feedback are differentially affected in MDD: The FN elicited by monetary feedback may be decreased in MDD, with reduced differentiation between monetary gain and loss. This is consistent with the ECI model and reflects impaired reward sensitivity. Conversely, the FN elicited by performance feedback may be increased in MDD, reflecting increased and inappropriate sensitivity to perceived failure. Consistent with this possibility, in

one recent study using a purely behavioral task—without monetary reward—the FN elicited by negative feedback was increased among individuals with MDD (Mies et al., 2011). To date, however, no study has directly compared the FN elicited by reward and performance information in a single MDD sample. We sought to address this gap in the literature by recording the FN across two tasks: The first task was the same gambling paradigm we have used previously (Bress et al., 2012; Foti & Hajcak, 2010; Foti, Hajcak, et al., 2011; Foti, Weinberg, et al., 2011), where reward outcomes are randomly determined and not tied to behavioral performance. This task ought to isolate neural activity associated specifically with the processing of reward information. We predicted that the FN elicited by reward feedback would be blunted among individuals with MDD compared to controls, thereby extending our prior findings to a clinical population. Of interest is also whether the blunted FN in MDD would be driven primarily by an impaired response to monetary gain, rather than loss (Bress et al., 2012), and whether this blunted neural activity would be related to self-reported anhedonia severity (Wacker et al., 2009)

Second, we used a time estimation task that has also been shown to be effective for eliciting an FN (Miltner et al., 1997). In this task, participants were asked to press a button when exactly one second has elapsed following an auditory cue, and they were presented with feedback regarding the accuracy of their response on each trial. Participants did not win or lose money on this task—feedback was indicative solely of behavioral performance. Unlike the gambling task, we predicted that the FN elicited on this time estimation task would be increased among individuals with MDD compared to controls, as shown previously (Mies et al., 2011). Of interest here is whether the increased FN in MDD would be driven primarily by an enhanced response to negative performance feedback. By recording the FN across these two tasks in a single sample, our overarching goal was to dissociate the putative effects of reward and

performance information on FN amplitude and further clarify the nature of reduced reward sensitivity in MDD.

Summary

The current research project seeks to advance the existing literature on abnormal emotional reactivity and reward sensitivity in MDD by differentiating between impaired and inappropriate neural reactivity. Across two tasks, we examined whether the abnormal affective modulation of LPP amplitude is influenced by the personal relevance of stimuli. Across two additional tasks, we examined whether abnormal FN amplitude is differentially influenced by reward and performance information. We predicted that individuals with MDD would exhibit impaired neural responses to normative affective compared to neutral stimuli (i.e., blunted LPP amplitude) and to monetary gain compared to loss (i.e., blunted FN amplitude). Conversely, we predicted that individuals with MDD would exhibit increased and inappropriate neural responses to idiographic affective compared to neutral stimuli (i.e., increased LPP amplitude) and to negative compared to positive performance feedback (i.e., increased FN amplitude).

Methods

Participants

The depressed group consisted of 36 female adults recruited from within Stony Brook University and the surrounding communities. Only female participants were recruited for the current study given that prevalence rates of MDD are significantly higher in women than in men (R. C. Kessler et al., 2003). The inclusion criterion for the depressed group was a clinical diagnosis of unipolar depression (i.e., current MDD and/or dysthymic disorder); exclusion criteria were the diagnosis of current generalized anxiety disorder (i.e., past six months), lifetime obsessive compulsive disorder, lifetime substance abuse/dependence, or more than one other current comorbid Axis I disorder. Individuals with generalized anxiety disorder, obsessive compulsive disorder, and substance use disorders were excluded from the current study in consideration of data linking these disorders to abnormal emotional reactivity, reward sensitivity, and performance monitoring (Diekhof, Falkai, & Gruber, 2008; MacNamara & Hajcak, 2010; Olvet & Hajcak, 2008; Weinberg & Hajcak, 2011; Weinberg, Olvet, & Hajcak, 2010); the goal of the current study was to assess the relatively unique impact of unipolar depression on neural activity associated with the processing of affective stimuli and reward, independent of these other frequently comorbid psychiatric conditions. In light of research that antidepressant medication alters the latency and amplitude of ERPs (Rinaudo, Soufflet, Toussaint, & Macher, 1999), current prescription of antidepressants (i.e., past two months) was also an exclusion criterion; prior history of pharmacological treatment was not assessed. Following data showing that 60-70% of total symptom improvement in treating MDD with cognitive behavioral therapy occurs within the first four weeks (Ilardi & Craighead, 1994), participants currently receiving psychotherapy were required to have been in treatment for at least one month on the ground that

most symptom change would have occurred prior to that point. The healthy control group consisted of 44 female adults with no history of any diagnosable Axis I disorder, no current prescription of psychiatric medication, and no history of any neurological illness.

Psychological evaluations of all participants were made using a two-step process: At an initial telephone contact, eligibility was determined using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to assess for Axis I disorders. Eligible participants who attended the laboratory session were then evaluated with the more extensive Structured Interview for DSM Disorders (SCID; First, Spitzer, Gibbon, & Williams, 2001). The MINI and SCID were completed by master's level graduate students with extensive clinical experience with these instruments.

Participants were recruited using fliers posted in the Psychological Center at Stony Brook University, campus announcements made via email, and internet advertisements posted in the Long Island section of www.craigslist.org. This research protocol was approved by the institutional review board at Stony Brook University, and written informed consent was obtained from all participants.

Symptom Measures

Symptoms of depression and anxiety. Symptom severity was assessed using the Mood and Anxiety Symptom Questionnaire (MASQ), a 90-item scale designed in accordance with the tripartite model of depression and anxiety (Watson, Clark, et al., 1995; Watson, Weber, et al., 1995). Each item is rated on a five-point scale representing the presence and severity of that symptom over the preceding week (1 = *not at all*, 5 = *extremely*). Of interest were the following four subscales: the Anhedonic Depression (AD) and Anxious Arousal (AA) subscales capture symptoms thought to be relatively specific to depression and anxiety, respectively; the General

Distress: Depressive Symptoms (GDD) and General Distress: Anxious Symptoms (GDA) capture symptoms thought to be relatively common to both disorders. The four scales possess good internal consistency in student, adult, and patient samples (α >.80), and the disorder-specific AD and AA subscales exhibit convergent and discriminant validity (Watson, Weber, et al., 1995). In light neuroimaging evidence showing a unique association between AD score and blunted striatal response to monetary gain (Wacker et al., 2009), it was of particular interest here to test where there would be an analogous association with the FN elicited in the monetary feedback task.

Hedonic capacity. The ability to experience pleasure was measured using the Snaith-Hamilton Pleasure Scale (SHAPS), a 14-item self-report scale designed for use in general psychiatric populations (Snaith et al., 1995). The SHAPS contains items that assess pleasure derived from four categories of experience: interests/hobbies, social interaction, sensory experience, and food/drink. Each item is rated on a four-point scale representing the ability to experience pleasure from a specific experience over the preceding few days (1 = *strongly agree*, 4 = *strongly disagree*). It is recommended that responses be scored in a dichotomous fashion, with either of the "disagree" responses scored as 1 and either of the "agree" responses as a 0; the range of possible scores is 0-14, with higher scores indicating increasing impairment in hedonic capacity. The SHAPS possesses excellent internal consistency in both non-clinical and patient samples (α >.80), and it exhibits convergent and discriminant validity, with MDD patients yielding higher scores compared to patients with psychosis and substance abuse (Franken, Rassin, & Muris, 2007). For the current study, only the depressed group completed the SHAPS.

In addition to the SHAPS, hedonic capacity was also measured using the features of the current depressive episode determined by the SCID. Of interest were two depressive subtypes:

(1) melancholic depression, which is characterized primarily by anhedonia, impaired mood reactivity to pleasurable events, a worsening of symptoms in the morning, early-morning wakening, psychomotor retardation, weight loss, and excessive guilt; and (2) atypical depression, which is characterized by intact mood reactivity to pleasurable events, weight gain, hypersomnia, leaden paralysis, and hypersensitivity to interpersonal rejection (American Psychiatric Association, 2000). Separate from meeting the full criteria for these subtypes, mood reactivity to pleasurable events was considered as a distinct index of hedonic capacity, as this is the single clinical feature that differentiates melancholic from atypical depression (i.e., intact mood reactivity precludes a diagnosis of melancholic depression, and impaired mood reactivity precludes a diagnosis of atypical depression).

Emotional Reactivity Tasks: Late Positive Potential

Normative images. The first task used normative, high-arousal affective stimuli to elicit the LPP. Participants passively viewed 60 images drawn from the IAPS (20 each of pleasant, neutral, and unpleasant).[1] Within each valence category, images were selected in order to maximize the affective modulation of the LPP: pleasant images depicted erotic and affiliative scenes (e.g., babies, cute animals), unpleasant images depicted mutilation and threatening scenes (e.g., guns, animal attack), and neutral images depicted objects and scenes without people (Weinberg & Hajcak, 2010). Based on normative ratings, the selected pleasant images (M=7.19, SD=.47) were rated as more pleasant than the neutral images (M=5.05, SD=.35; t(38)=16.30, p<.001), which in turn were more pleasant than the unpleasant images (M=2.66, SD=.64; t(38)=14.71, p<.001). Both the selected pleasant (M=5.94, SD=.73) and unpleasant images

[1] The following IAPS images were used: pleasant (1463, 1710, 1722, 2045, 2208, 2303, 2345, 2346, 2347, 2550, 4608, 4643, 4659, 4660, 4664, 4668, 4670, 4690, 4694, 4695), unpleasant (1050, 1300, 1525, 1930, 3001, 3015, 3019, 3051, 3069, 3101, 3185, 3195, 3213, 3215, 6242, 6244, 6250, 6370, 6550, 6571) and neutral (5471, 5500, 5531, 5731, 7000, 7002, 7004, 7006, 7050, 7053, 7055, 7056, 7150, 7161, 7491, 7495, 7500, 7595, 7700).

(*M*=6.23, *SD*=.58) were higher in emotional arousal compared to the neutral images (*M*=2.97, *SD*=.48; pleasant vs. neutral: $t(38)=15.24$, $p<.001$; unpleasant vs. neutral: $t(38)=19.45$, $p<.001$), but they did not differ from one another ($t(38)=1.41$, $p=.17$).

Image presentation was blocked by valence, and each image was presented exactly once for 60 total trials. The order of image presentation within each block and the order of blocks were randomized across participants. In each trial, the image was presented in the center of the computer screen against a black background for 2000 ms, followed by a fixation point ('+') displayed for a random interval varying from 2000-2500 ms. At a viewing distance of approximately 24 in (60.96 cm), the images occupied approximately 40° of the visual field horizontally and vertically. At the beginning of each block, participants were presented with the following instructions: "The following pictures will be more pleasant to view," "The following pictures will be more unpleasant to view," or "The following pictures will be more neutral to view." Participants were instructed to simply view the images, and they first completed nine practice trials with IAPS images not included in the main task. At the end of each block, participants received a short break.

Idiographic and normative words. The second task used affective words to elicit the LPP, modeled after the paradigm developed by Siegle and colleagues (2002). Thirty normative words were drawn from the ANEW (10 each of pleasant, neutral, and unpleasant).[2] Within each category, the selected words were balanced for emotional arousal, word frequency, and character length using a computer program (Siegle, 1994). Based on normative ratings, the selected pleasant words (*M*=7.85, *SD*=.28) were rated as more pleasant than the neutral words (*M*=5.10, *SD*=.48; $t(18)=15.70$, $p<.001$), which were in turn rated as more pleasant than the unpleasant

[2] The following ANEW words were used: pleasant (birthday, cheer, fireworks, flirt, glory, joyful, rescue, sexy, sunlight, treasure), unpleasant (blood, brutal, despise, hatred, hostage, rage, scared, ulcer, unfaithful, vandal) and neutral (barrel, bland, curtains, salad, subdued, elbow, umbrella, vest, violin, windmill).

words (*M*=2.36, *SD*=5.10; *t*(18)=13.75, *p*<.001). Both the selected pleasant (*M*=6.51, *SD*=.45) and unpleasant words (*M*=6.63, *SD*=.59) were higher in emotional arousal compared to the neutral words (*M*=3.57, *SD*=.31; pleasant vs. neutral: *t*(18)=16.91, *p*<.001; unpleasant vs. neutral: *t*(18)=14.57, *p*<.001), but they did not differ from one another (*t*(18)=.53, *p*=.60). An analogous set of thirty idiographic words (10 each of pleasant, neutral, and unpleasant) were generated by each participant, based on the following descriptions: "10 personally relevant negative words that best represent what you think about when you are upset, down, or depressed," "10 personally relevant positive words that best represent what you think about when you are happy or in a good mood," and "10 personally relevant neutral (i.e., not positive or negative) words that best represent what you think about when you are neither very happy nor very upset, down, or depressed." Participants were instructed to generate words that are between three and 11 letters long.

The structure of the words task paralleled that of the images task described above. Word presentation was blocked by valence and personal relevance (i.e., separate blocks for normative unpleasant and idiographic unpleasant words). Each word was presented exactly twice in each block for a total of 120 trials (60 idiographic, 60 normative). The order of word presentation within each block and the order of blocks were randomized across participants. In each trial, the word was presented in the center of the computer screen against a black background for 2000 ms, followed by a fixation point ('+') displayed for a random interval varying from 2000-2500 ms. On average, the words occupied approximately 6° of the visual field horizontally and 2° vertically. At the beginning of each block, participants were presented with the following instructions: "The following words will be more pleasant to view," "The following words will be more unpleasant to view", or "The following words will be more neutral to view." Participants

were instructed to simply view the words, and they first completed nine practice trials with ANEW words not included in the main task. At the end of each block, participants received a short break. In order to reduce the novelty of the normative stimuli relative to the idiographic stimuli, prior to completing the task participants read a list of all 30 normative words. After completing the task, participants were asked to rate all word stimuli on valence and emotional arousal using the nine-point self-assessment manikin (Bradley & Lang, 1994).

Reward Sensitivity Tasks

Monetary feedback. The first task used reward information to elicit the FN, identical to the simple gambling paradigm that we have used previously (Carlson et al., 2011; Foti, Weinberg, et al., 2011). On each trial, participants were shown a graphic displaying two doors (occupying 6° of the visual field vertically and 8° horizontally) and were told to choose which door they wanted to open using either the left or right mouse button. Participants were told that one of the two doors contained a prize on each trial. Following each choice, a feedback stimulus appeared on the screen informing participant whether they won or lost money on that trial. A green '↑' indicated a correct guess and a gain of $0.40, while a red '↓' indicated an incorrect guess and a loss of $0.20 (each occupying 3° of the visual field vertically and 1° horizontally). A fixation mark (+) was presented before the onset of each stimulus. At the end of each trial, participants were presented with the instruction "Click for the next round." The task consisted of 50 trials total, with positive feedback given on exactly 25 trials (i.e., 50%). Feedback was presented in a random order for each participant. The order and timing of all stimuli was as follows: (i) the graphic of two doors was presented until a response is made, (ii) a fixation mark was presented for 1000 ms, (iii) a feedback arrow was presented for 2000 ms, (iv) a fixation mark was presented for 1500 ms, and (v) "Click for the next round" was presented until a

response was made. Prior to the main task, participants completed five practice trials. Halfway through the task, participants received a short break and the total amount of money won at that point was displayed on the screen.

Performance feedback. The second task used performance information to elicit the FN, modeled after the time estimation task that has been used previously (Miltner et al., 1997). On each trial, participants were presented with an auditory cue (1000 Hz tone, 65 dB) and instructed to estimate when exactly one second had elapsed following the cue by pressing the left mouse button. A fixation mark ('+') appeared in the center of the screen during the estimation period. Following the button press, a happy or sad cartoon face (occupying 7° of the visual field vertically and horizontally) appeared on the screen informing participants whether their estimate was accurate or not. A happy face indicated that their response fell within the designated time window for that trial, whereas the sad face indicated that their response was outside the window. At the beginning of the task, the time window had an initial length of 400 ms centered around the one-second mark (i.e., 800-1200 ms following the auditory cue). In order to maintain an approximate success rate of 50%, the window was dynamically adjusted throughout the task for each participant. After each accurate response, the window was shortened by 20 ms, and after each inaccurate response the window was lengthened by 20 ms. The order and timing of all stimuli was as follows: (i) the auditory cue was presented for 50 ms, (ii) a fixation mark was presented until a response was made and then for an additional 1200 ms afterward, (iii) a feedback face was presented for 1500 ms, and (iv) a fixation mark was presented for 2500 ms. Participants first completed 20 practice trials; the adjusted time window at the end of the practice was carried over to the start of the main task, which consisted of 60 trials. Participants received a short break halfway through the task.

Procedure

The experiment was conducted in a single laboratory session lasting approximately three hours. Following a brief description of the experiment, participants signed a consent form. The SCID was then administered to confirm all psychiatric diagnoses and study eligibility. Next, the EEG recording session was conducted by a research assistant blind to group membership. Participants completed the four tasks in counterbalanced order, and prior to each task instructions were provided. The tasks were administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) to control the presentation and timing of all stimuli. Following the EEG recording session, participants completed the MASQ (depressed and control groups) and SHAPS (depressed group only only). All participants were paid their winnings from the monetary feedback task ($5.00), as well as an additional $75 as compensation for their time.

Psychophysiological Recording and Data Reduction

The continuous EEG was recorded using a custom cap (Cortech Solutions, Wilmington, NC, USA) and the ActiveTwo Biosemi system (BioSemi, Amsterdam, Netherlands). The signal was preamplified at the electrode with a gain of one, and the EEG was digitized at 24-bit resolution with a least significant bit value of 31.25 nV and a sampling rate of 1024 Hz, using a low-pass fifth-order sinc filter with a -3 dB cutoff of 204.8 Hz. Recordings were taken from 34 scalp electrodes based on the 10/20 system (including FCz and Iz), as well as two electrodes placed on the left and right mastoids. The electrooculogram was recorded from electrodes 1 cm above and below the left eye, 1 cm to the left of the left eye, and 1 cm to the right of the right eye. Each electrode was measured online with respect to a common mode sense electrode forming a monopolar channel. Off-line analysis was performed using Brain Vision Analyzer

software (Brain Products, Munich, Germany). All data were re-referenced to the average of the two mastoid electrodes and band-pass filtered with cutoffs of 0.01 and 30 Hz. The EEG was segmented for each trial as follows: For the LPP, epochs began 500 ms prior to image/word onset and continued for 2000 ms afterward; for the FN, epochs began 500 ms prior to feedback onset and continued for 1000 ms afterward. Each trial was corrected for blinks and eye movements using the method developed by Gratton and colleagues (1983). Specific channels in each trial were rejected using a semi-automated procedure, with physiological artifacts identified by the following criteria: a step of more than 50 μV between sample points, a difference of 300 μV within a trial, and a maximum difference of less than 0.5 μV within 100-ms intervals. Additional artifacts were identified using visual inspection.

Stimulus-locked ERPs were averaged separately for each trial type within each task. The LPP is maximal at centroparietal sites (Cuthbert et al., 2000; Foti et al., 2009; Keil et al., 2002; Schupp et al., 2000; Weinberg & Hajcak, 2010), and it was scored as the average activity at a pooling of representative electrodes (Pz, CPz, Cz, CP1, CP2). While the LPP is apparent in the ERP waveform as a sustained positive deflection, studies have demonstrated that the LPP represents the summed activity of posterior components that overlap in time (Foti et al., 2009; Weinberg & Hajcak, 2010). Taking this into account, the LPP was scored across two time windows: 400-1000 and 1000-2000 ms. The FN, meanwhile, is maximal at frontocentral sites (Carlson et al., 2011; Foti, Weinberg, et al., 2011; Gehring & Willoughby, 2002; Miltner et al., 1997), and it was scored as the average activity at a pooling of representative electrodes (Fz, FCz, Cz, FC1, FC2) in a window spanning 250-350 ms. For both the LPP and the FN, the activity in a 200-ms window prior to stimulus onset served as the baseline.

Data Analysis

Effects of interest on the LPP and FN were examined using mixed design ANOVAs, with Greenhouse-Geisser correction where appropriate. The within-subjects factor for each task was trial type: For the affective images task, the within-subjects factor compared LPP amplitude across pleasant, neutral, and unpleasant images. For the affective words task, the omnibus ANOVA included within-subjects factors of Picture (pleasant, neutral, unpleasant) and Personal Relevance (normative, idiographic). For the monetary feedback task, the within-subjects factor compared FN amplitude across gain and loss trials. For the time estimation task, the within-subjects factor compared FN amplitude across positive and negative feedback. In each case, the between-subjects factor was group (Depressed vs. Control). In a separate step, comorbidity (presence vs. absence of a comorbid Axis I disorder) and psychotherapy status (past month treatment vs. not) were added as additional predictors to assess whether adjusting for these variables influenced the pattern of results.

Of interest was the statistical significance of the interaction between trial type and group, indicating a moderating effect of MDD on ERP amplitude across stimuli. Significant interactions were pursued with between-subjects tests. With regard to the LPP tasks, interaction contrasts were performed by testing whether the pleasant minus neutral and unpleasant minus neutral difference scores significantly varied by group. With regard to the FN tasks, simple effects tests were performed by comparing positive and negative feedback separately across groups. Of particular interest was whether the predicted reduction in FN amplitude on the monetary feedback task was driven by a reduced response to rewards, as well as whether the predicted increase in FN amplitude on the time estimation task was driven by an increased response to negative feedback.

Exploratory analyses were also conducted to relate abnormal ERP responses to symptoms (MASQ subscale scores) and impaired hedonic capacity (SHAPS score, depression subtype, and mood reactivity). At the bivariate level, correlations were performed to examine whether the LPP and FN relate specifically to scores on the SHAPS and the AD subscale—indicating an association with symptoms thought to be relatively specific to MDD—or relate to symptoms of anxiety and psychological distress more broadly. Considering previous work, it was also of interest to examine the cumulative contributions of the ERP variables as predictors of AD and SHAPS scores using multiple linear regression (cf. Pizzagalli et al., 2008; Wacker et al., 2009). This analysis revealed the total percentage of variance in self-reported anhedonia that can be accounted for by ERP measures, as well as whether any individual ERPs uniquely and significantly predicted anhedonia severity. The impacts of depression subtype and mood reactivity, both of which are categorical predictors, were assessed using one-way ANOVAs. All statistical analyses were performed using PASW Statistics (Version 18.0; SPSS, Inc., Chicago, IL, USA).

Results

Sample Characteristics

Demographic and clinical characteristics of the depressed and control groups are presented in Table 1. Seven control participants did not indicate an ethnicity, and 10 total participants (1 depressed, 9 control) did not indicate a race. There was a trend toward a group difference in race, with a somewhat greater number of Caucasian participants in the depressed group compared to the control group ($\chi^2(1)=2.95$, $p=.09$); group differences in age, ethnicity, and education level were not significant (p's>.20).

With regard to clinical characteristics, MDD participants were more likely to be receiving current (i.e., past month) psychotherapy. Ten participants declined to complete the MASQ (1 depressed, 9 control). Individuals in the depressed group reported more severe symptoms of depression and anxiety compared to the control group, with significant group differences on all four MASQ subscales. The SHAPS was completed only by the depressed group; SHAPS data was available for 27 depressed participants. A majority of these depressed participants (n=20, 74.1%) received a score of 1 or higher on the SHAPS, indicating at least mild impairment in hedonic capacity, which is consistent with prior research using this measure (Snaith et al., 1995).

Diagnostic characteristics of the depressed group are presented in Table 2. A majority of depressed participants (58.3%) met criteria for current MDD with no comorbid disorders. With regard to the features of the current depressive episode, one participant had missing data on the current depression subtype and two had missing data on mood reactivity. A majority of participants (51.4%) did not meet full criteria for either melancholic or atypical depression, and depression subtype was not associated with symptom severity on the four MASQ subscales or SHAPS score (all p's>.20). One third of the depressed group (32.3%) reported having impaired

mood reactivity during the current depressive episode, with blunted reactivity to pleasurable events. Impaired mood reactivity was specifically associated with self-reported anhedonia, as indicated by AD ($t(31)=2.33$, $p<.05$) and SHAPS scores ($t(25)=2.46$, $p<.05$); associations with GDD, AA, and GDA scores were not significant (all p's>.10).

Emotional Reactivity

Normative images. All 36 depressed subjects had usable ERP data on the normative images task. Of the 44 controls, 5 were not administered the task and 4 had unusable ERP data (>50% artifacts), leaving 35 in the final sample. As seen in Figure 1, affective modulation of the LPP was apparent as early as 300 ms after stimulus onset and was sustained throughout stimulus presentation. Below, analysis of LPP amplitude is presented separately for the early (400-1000 ms) and late (1000-2000 ms) time windows (cf. Foti et al., 2009; Weinberg & Hajcak, 2010).

Early time window, 400-1000 ms. The mixed-model ANOVA yielded a significant effect of Picture Type ($F(2,138)=93.51$, $p<.001$) that was qualified by an interaction with Group ($F(2,138)=4.88$, $p<.01$). Both effects remained significant after adjusting for comorbidity and treatment status (Picture Type: $F(2,134)=75.83$, $p<.001$; Picture Type × Group: $F(2,134)=4.71$, $p<.05$). Follow-up contrasts for the early time window revealed that within the control group, the LPP was increased for pleasant ($t(34)=7.62$, $p<.001$) and unpleasant ($t(34)=9.40$, $p<.001$) compared to neutral images. Within the depressed group, the LPP was also increased for pleasant ($t(35)=7.52$, $p<.001$) and unpleasant ($t(35)=7.43$, $p<.001$) compared to neutral images. To further examine the interaction effect, difference scores were used (i.e., unpleasant – neutral, pleasant – neutral): the effect of unpleasant vs. neutral images was blunted among the depressed group compared to the control group ($t(69)=2.74$, $p<.01$); the effect of pleasant vs. neutral images, on the other hand, was comparable across groups ($p=.54$).

Late time window, 1000-2000 ms. The mixed-model ANOVA again yielded a significant effect of Picture Type ($F(2,138)=53.41$, $p<.001$); the interaction with Group, however, was not significant in this window ($p=.24$). Across the full sample, the LPP was increased for pleasant ($t(70)=9.57$, $p<.001$) and unpleasant ($t(70)=7.97$, $p<.001$) compared to neutral images. Unlike the early time window, the modulation of the LPP by unpleasant and pleasant images (i.e., difference scores) was comparable across groups (both p's>.30).

Unlike the early time window, the affective modulation of the LPP in the late time window was maximal at frontal sites. To examine whether this frontal modulation of the LPP by picture type varied across groups, a separate pooling of electrodes was formed (Fz/FCz/1/2). The mixed-model ANOVA at frontal sites yielded a significant main effect of Picture Type ($F(2,138)=50.46$, $p<.001$), but the interaction with Group was not significant ($p=.28$). As was observed for the centroparietal electrode pooling, the affective modulation of the LPP (i.e., difference scores) was comparable across both groups (both p's>.20).

Associations with clinical characteristics. Across the full sample, AA severity was associated with a blunted LPP to pleasant compared to neutral stimuli in the early time window ($r=-.26$, $p<.05$). This association remained significant after controlling for AD severity ($\beta=-.33$, $p<.05$) but was no longer significant when adding all four subscales as simultaneous predictors ($\beta=-.32$, $p=.12$). There was also a trend toward AD severity associated with a blunted LPP to unpleasant stimuli in the early time window ($r=-.23$, $p=.07$). Other associations with MASQ subscales did not reach significance (all p's>.10). Within the depressed group, SHAPS score, depression subtype, and mood reactivity were unrelated to LPP amplitude (all p's>.30).

Idiographic and normative words. The affective words task was not administered to three control participants. With regard to ERP data, three control participants were excluded for

a poor quality signal (>50% artifacts), and three additional participants were excluded for being statistical outliers (>3 standard deviations from the grand mean); two depressed participants were excluded for a poor quality signal, and one for being a statistical outlier. As a result, usable ERP data were available for 35 controls and 33 depressed participants. Ratings of valence and emotional arousal were available for 31 controls and 32 depressed participants. Analyses of ERP data are presented below, followed by self-report ratings of valence and arousal for all word stimuli.

Early time window, 400-1000 ms. LPP amplitude across conditions and groups was examined using a mixed-model ANOVA with Word Type (three levels: pleasant, neutral, unpleasant) and Personal Relevance (two levels: normative, idiographic) as the within-subjects factors, and Group (two levels: control, depressed) as the between-subjects factor. In the early time window, a significant main effect of Word Type was present ($F(2,132)=8.93$, $p<.001$); regardless of personal relevance, the LPP was increased overall for pleasant ($F(1,66)=12.64$, $p<.001$) and unpleasant ($F(1,66)=14.67$, $p<.001$) compared to neutral words. A main effect of Personal Relevance was also present, with the LPP being increased for idiographic compared to normative words overall ($F(1,66)=55.34$, $p<.001$). There were no significant interactions with Group (all p's>.25). Considering normative and idiographic words separately, main effects of Picture Type were observed in each case (Normative: $F(2,132)=7.00$, $p<.001$; Idiographic: $F(2,132)=3.34$, $p<.05$), but neither interaction with Group was significant (both p's>.70).

Late time window, 1000-2000 ms. Using the same mixed-model ANOVA as described above, an identical pattern was observed in the late time window: There was a significant main effect of Word Type ($F(2,132)=5.10$, $p<.01$), with the LPP increased for pleasant ($F(1,66)=10.00$, $p<.01$) and unpleasant ($F(1,66)=5.72$, $p<.05$) compared to neutral words. There

was also a significant main effect of Personal Relevance with the LPP increased for idiographic words overall ($F(1,66)=11.82$, $p<.001$). Once again, there were no significant interactions with Group (all p's>.30). Considering normative and idiographic words separately, a main effect of Picture Type was observed for normative words ($F(2,132)=5.30$, $p<.01$) but not idiographic words ($p=.72$); neither interaction with group was significant (both p's>.40).

Narrower time window, 600-800 ms. Within the images task, the modulation of LPP amplitude by picture type was apparent as early as 300 ms and sustained throughout stimulus presentation. Within the words task, however, a different pattern was apparent: Affective modulation of the LPP was smaller overall, and a ceiling effect was present for idiographic stimuli. Within the depressed group, affective modulation of the LPP to idiographic stimuli was maximal in a relatively circumscribed portion of the LPP, from approximately 600-800 ms. Later in the epoch, the LPP was increased for all idiographic stimuli, including neutral words. Whereas the predefined time windows were effective for capturing the temporal dynamics of the LPP elicited by affective images, they were less effective for assessing the LPP elicited by affective words.

In light of this observation, an exploratory analysis was conducted by focusing on the narrower time window of 600-800 ms, where affective modulation of the LPP was apparent for both normative and idiographic stimuli. The mixed-model ANOVA once again yielded significant main effects of Word Type ($F(1,132)=6.26$, $p<.01$) and Personal Relevance ($F(1,66)=34.31$, $p<.001$). Unlike in the pre-defined time windows described above, however, a significant three-way interaction with group was also observed: The emotional vs. neutral contrast (i.e., pleasant/unpleasant vs. neutral) significantly interacted with Group and Personal Relevance ($F(1,66)=5.48$, $p<.05$); the effect persisted after adjusting for comorbidity and

treatment status ($F(1,64)=3.81$, $p=.05$). This three-way interaction indicates that group differences in the affective modulation of the LPP varied as a function of the personal relevance of stimuli. Specifically, among controls the LPP was significantly increased for *normative* pleasant ($t(34)=3.34$, $p<.01$) and unpleasant ($t(34)=2.66$, $p<.05$) compared to neutral words, but did not differ for idiographic words (both p's$>.70$). The opposite pattern was observed for depressed participants, with the LPP increased for *idiographic* pleasant ($t(32)=2.34$, $p<.05$) and unpleasant ($t(32)=2.40$, $p<.05$) compared to neutral words, but comparable in amplitude for normative words (both p's$>.25$).

Valence and arousal ratings. Group means of ratings for all word stimuli are presented in Figure 4. The mixed-model ANOVA for valence ratings yielded a significant main effect of Personal Relevance ($F(1,61)=20.19$, $p<.001$), indicating that idiographic words overall were rated as more pleasant than normative words. There was also a significant main effect of Word Type ($F(2,122)=863.62$, $p<.001$), a significant two-way interaction between Personal Relevance and Word Type ($F(2,122)=19.71$, $p<.001$), and a significant three-way interaction between Personal Relevance, Word Type, and Group ($F(2,122)=3.63$, $p<.05$). Across groups, the normative pleasant vs. neutral contrast was blunted in the depressed group compared to controls ($t(61)=2.27$, $p<.05$); group differences in the normative unpleasant vs. neutral contrast and the two idiographic contrasts were not significant (all p's$>.50$). Of note, the three-way interaction was no longer significant after adjusting for comorbidity and treatment status ($p=.14$). While statistical power was limited, there was a trend toward a blunted effect of pleasant vs. neutral words among depressed individuals with a current comorbid Axis I disorder ($t(61)=1.72$, $p=.09$), suggesting that this subgroup of participants was driving the between-subjects difference in valence ratings.

The mixed-model ANOVA for arousal ratings yielded a significant main effect of Personal Relevance ($F(1,61)=47.92$, $p<.001$), indicating that idiographic words were rated as more arousing than normative words overall. There was also a significant main effect of Word Type ($F(2,122)=120.41$, $p<.001$) and an interaction between Word Type and Personal Relevance that approached significance ($F(2,122)=2.83$, $p=.06$). Across the full sample, there was a trend toward normative unpleasant words being rated as more arousing than normative pleasant words ($t(63)=1.75$, $p=.09$), whereas this was not the case for idiographic words ($p=.74$). None of the interactions with Group were significant (all p's>.20).

Associations with clinical characteristics. For individual difference comparisons, the LPP in the narrower time window was used (i.e., 600-800 ms). Across the full sample, AA severity was associated with an increased LPP to normative pleasant vs. neutral words ($r=.28$, $p<.05$). This association remained significant after controlling for AD severity ($\beta=.38$, $p<.05$) and was marginally significant after adding all four subscales as simultaneous predictors ($\beta=.38$, $p=.08$). Other associations with MASQ subscales did not reach significance (all p's>.10). Within the depressed group, SHAPS score, depression subtype, and mood reactivity were unrelated to LPP amplitude (all p's>.10).

Reward Sensitivity

Monetary feedback. Two control participants were excluded for a poor quality signal (>50% artifacts). Usable ERP data was available for 42 controls and 36 depressed participants. As seen in Figure 5, monetary gain elicited a positive deflection in the ERP waveform and monetary loss elicited a negative deflection; the difference between losses and gains was maximal at approximately 300 ms at frontocentral sites.

Feedback negativity. The mixed-model ANOVA yielded a significant effect of Feedback Type ($F(1,76)=78.04$, $p<.001$) that was qualified by an interaction with Group ($F(1,76)=5.45$, $p<.05$), indicating that the difference between loss and gain trials was blunted in the depressed compared to the control group; the main effect of Group was not significant ($p=.77$). The interaction with Group remained significant after adjusting for comorbidity and treatment status ($F(1,74)=5.01$, $p<.05$). Considering loss and gain trials separately, group differences in FN amplitude were not significant (both *p*'s>.30). Within groups, the loss vs. gain contrast was significant for both controls ($t(41)=9.28$, $p<.001$) and depressed participants ($t(35)=3.96$, $p<.001$).

Associations with clinical characteristics. Across the full sample, blunted FN amplitude (loss minus gain) was associated with symptom severity on all four subscales (AD: $r=.30$, $p<.05$; GDD: $r=.41$, $p<.001$; AA: $r=.37$, $p<.01$; GDA: $r=.37$, $p<.01$). The FN is numerically negative when using the difference score, so positive correlation coefficients here indicate that greater symptom severity was associated with reduced differentiation between losses and gains. Adding all four subscales as simultaneous predictors of FN amplitude, none of the unique associations were statistically significant (all *p*'s>.10).

FN amplitude was also significantly associated with mood reactivity (Figure 6): Among depressed individuals reporting intact mood reactivity, the difference between loss and gain was significant ($t(23)=5.71$, $p<.001$) and comparable in amplitude to controls ($p=.59$). Among depressed individuals reporting impaired mood reactivity, the difference between loss and gain was not significant ($p=.42$), and FN amplitude (loss minus gain) was blunted compared to both depressed individuals with intact mood reactivity ($t(32)=3.96$, $p<.001$) and controls ($t(51)=4.96$, $p<.001$). This group effect was driven specifically by a reduced response to monetary gain

(impaired vs. intact: $t(51)=2.77$, $p<.01$; impaired vs. controls: ($t(32)=2.74$, $p<.01$), and not loss (both p's>.30). FN amplitude was unrelated to depression subtype and SHAPS score (both p's>.50).

Performance feedback. The time estimation task was not administered to four control participants. Usable ERP data was available for 40 controls and 36 depressed participants. As seen in Figure 7, error feedback elicited a negative deflection and correct feedback elicited a positive deflection in the ERP waveform; similar to the gambling task, the difference between error and correct feedback was maximal at approximately 300 at frontocentral sites.

Feedback negativity. The mixed model ANOVA yielded a significant effect of Feedback Type ($F(1, 74)=22.99$, $p<.001$), indicating that the FN differed across error and correct feedback trials. Unlike the gambling task, the interaction with Group was not significant ($p=.95$). Within groups, the error vs. correct contrast was significant for both the control ($t(39)=3.74$, $p<.001$) and MDD groups ($t(35)=3.08$, $p<.01$). The main effect of Group was not significant ($p=.17$).

Associations with clinical characteristics. Across the full sample, FN amplitude was not associated with symptom severity on any of the four MASQ subscales (all p's>.30). Within the depressed sample, FN amplitude was not associated with SHAPS score, depression subtype, or mood reactivity (all p's>.40).

Convergence Across Tasks

Bivariate associations between ERP variables are presented in Table 3. *Within* each class of affective stimuli (i.e., normative images, normative words, and idiographic words considered separately), significant correlations were observed for the modulation of LPP amplitude by pleasant and unpleasant compared to neutral stimuli. The same was not true *across* classes of affective stimuli, such that LPP amplitudes elicited by normative images, normative words, and

idiographic words were not correlated with one another. Similarly, FN amplitude was uncorrelated across the monetary and performance feedback tasks. Across the LPP and FN tasks, a significant inverse association was observed only between the LPP elicited by idiographic negative stimuli and the FN elicited by monetary feedback, with an increased LPP associated with a blunted FN.

To examine the unique associations between ERP variables and clinical characteristics, multiple regression was used. Three ERP variables that demonstrated significant between-groups effects were included as simultaneous predictors: the LPP elicited by unpleasant vs. neutral normative images (400-1000 ms), the LPP elicited by normative (pleasant/unpleasant vs. neutral) vs. idiographic words (600-800 ms), and the FN elicited by monetary feedback. Significant unique effects of FN amplitude were observed in predicting scores on the four MASQ subscales, controlling for the LPP variables (AD: β=.28, p<.05; GDD: β=.39, p<.01; AA: β=.36, p<.01; GDA: β=.33, p<.05); effects of the two LPP variables were not significant (all p's>.10). Similarly, FN amplitude to monetary feedback significantly predicted blunted mood reactivity as a categorical outcome variable using logistic regression (OR=1.64, p<.01), controlling for the two LPP variables; effects of the two LPP variables were not significant (both p's>.50).

Discussion

The current study extends the existing literature on information processing abnormalities associated with MDD by clarifying the experimental contexts and classes of stimuli that are associated with specific neurobiological differences. With regard to emotional reactivity, a moderating effect of the personal relevance of stimuli was observed. Individuals with MDD exhibited *blunted* reactivity to normative stimuli and *increased* reactivity to idiographic stimuli, as indicated by the affective modulation of LPP amplitude. With regard to reward sensitivity, individuals with MDD exhibited a *blunted* FN only to feedback indicating monetary outcomes; the FN elicited by performance feedback was intact and comparable to controls. Furthermore, the reduction in FN amplitude to monetary feedback was driven by a subgroup of individuals with MDD who also reported impaired mood reactivity, a key feature of melancholic depression. The current study demonstrates that MDD is characterized by neither a global decrease nor increase in neural activity elicited by motivationally salient stimuli, but rather a more complex pattern of dysregulated information processing in which the directionality of effects depends on the specific methods and type of stimuli used.

Emotional Reactivity

By considering the impact of the personal relevance of stimuli on abnormal emotional reactivity in MDD, the current study offers a possible explanation for inconsistent findings in the extant neuroimaging literature. Whereas the limbic-cortical dysregulation model postulates that depression is characterized by *hyperactivity* in brain regions associated with emotional processing (Mayberg, 1997, 2003; Mayberg et al., 1999), the emotion context insensitivity model postulates that depression is characterized by *hypoactivity* (Rottenberg et al., 2005)—yet neither model completely accounts for the current data. Instead, evidence in support of both types of

abnormalities was observed: Idiographic affective words, generated by participants to describe their own positive and negative moods, modulated LPP amplitude in the MDD group only, indicating increased and inappropriate emotional reactivity in that context. On the other hand, normative affective words modulated LPP amplitude in the control group only, indicating that emotional reactivity was blunted within the MDD group in this context. These group differences in the processing of idiographic and normative stimuli were not explained by self-reported ratings of arousal, which were comparable for depressed and healthy participants. Taken together, this pattern indicates that abnormal emotional reactivity in MDD may be better characterized as a dual abnormality in emotional reactivity, consisting of both a disengagement from one's emotional environment and an increase in self-focused emotional attention. As such, MDD is characterized by reduced reactivity to motivationally salient stimuli that are not directly relevant to one's internal state and enhanced reactivity to personally relevant stimuli.

A ruminative cognitive style, marked by excessive self-focused attention on emotional states, has been related to the onset and course of MDD (Nolen-Hoeksema, 2000). Consistent with that finding, a subsequent meta-analysis of over two hundred studies observed that a tendency to engage in increased self-focus was associated with negative affect and depressive symptoms, in both clinical and nonclinical samples (Mor & Winquist, 2002). Linking these data on cognitive biases in MDD with neurobiological measures, there is an emerging literature examining the impact of MDD on activity within the default mode network, a neural circuit spanning prefrontal, posterior cingulate, parietal, and temporal brain regions. The default mode network is typically characterized by a high level of activity at rest and inhibition during engagement with external stimuli (Raichle et al., 2001). It has been proposed that the cognitive biases and excessive self-focused attention that are often observed in MDD may be related to

dysregulation in the default mode network, whereby there is a failure to inhibit activity in this default network and recruit goal-directed neural activity when transitioning from rest to task engagement (Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012). In other words, MDD is thought to be characterized by a failure to properly redirect attention away from one's internal state and toward goal-directed or motivational salient external stimuli. The LPP data in the current study are consistent with this perspective, offering converging electrophysiological evidence of increased and inflexible self-focused attention, with potentiated neural activity to self-relevant emotional stimuli and blunted neural activity to normative emotional stimuli. Given that increased amygdala reactivity to personally-relevant emotional stimuli in MDD has been previously shown to predict a greater response to cognitive behavioral therapy (Siegle et al., 2006), it is of interest whether this analogous bias in LPP amplitude toward idiographic stimuli may also predict response to psychological intervention, a direction which warrants further investigation.

In addition to these LPP data on the processing of idiographic and normative words, the MDD group also exhibited abnormal reactivity to normative affective images. As with the effect of normative words, the LPP elicited by unpleasant images was blunted in the MDD group compared to the control group. The unpleasant images used in the current study were selected to maximize the affective modulation of the LPP, and all of the images used depicted scenes of environmental threat, either in the form of an imminent physical attack or a mutilated body (Weinberg & Hajcak, 2010). Consistent with the current finding of a blunted LPP to unpleasant images, previous research has found that MDD is associated with a blunted LPP (Foti et al., 2010) and blunted amygdala activation (Lawrence et al., 2004; Moses-Kolko et al., 2010;

Thomas et al., 2001) to emotional facial expressions that signal environmental threat (i.e., angry and fearful).

An unexpected finding in the current study, however, was that the LPP elicited by normative pleasant images was intact in the MDD group and comparable to that of controls. Whereas the blunted LPP to normative words was observed for both pleasant and unpleasant stimuli, the blunted LPP to images was specific to unpleasant stimuli. Of note, abnormalities in LPP amplitude across tasks were largely unrelated; affective modulation of the LPP to normative words was not associated with modulation of the LPP to unpleasant images across individuals. This suggests that reductions in LPP amplitude to specific classes of stimuli represent distinct affective deficits, rather than a general reduction in reactivity to normative stimuli. In particular, the reduced LPP to unpleasant images may relate more closely to a deficit in defensive motivation to stimuli signaling environmental threat. The reduced LPP to normative words, however, may instead be driven by a failure to *differentiate* neutral from affective stimuli, with the group difference in LPP amplitude driven largely by an increased response to neutral words in the MDD group, rather than a decreased response to affective words per se.

Further underscoring the point that the affective words and images tasks may have tapped unique abnormalities associated with MDD, the timing of the LPP differed across classes of stimuli. In response to unpleasant images, the LPP within the MDD group was blunted from approximately 400-1000 ms. On the other hand, the increase in LPP amplitude to idiographic stimuli within the MDD group was apparent within a more narrow time window, from approximately 600-800 ms. Lastly, it is worth noting that affective images yielded a substantially larger effect size across the full sample, with the affective modulation larger than that of words by a factor of five. While the LPP elicited by unpleasant images was blunted in the

MDD group compared to the control group, there was still significant affective modulation of the LPP among depressed individuals. This indicates that emotional reactivity to normative stimuli is impaired but not absent in MDD and that, unlike words and facial stimuli, high-arousal affective images elicit robust neural activity in MDD. One possibility is that the threshold of emotional arousal necessary to elicit significant allocation of attention to external stimuli is higher in MDD, perhaps due in part to the co-occurring increase in self-focused attention.

Reward Sensitivity

Previous studies examining abnormal FN amplitude in MDD have yielded conflicting results, with alternating reports of a blunted FN to positive feedback (Bress et al., 2012; Foti & Hajcak, 2009; Foti, Hajcak, et al., 2011) and an increased FN to negative feedback (Mies et al., 2011; Santesso et al., 2008; Tucker et al., 2003). The current study clarifies this discrepancy by demonstrating that the blunted FN in MDD is specific to feedback indicating reward. Individuals with MDD exhibited a blunted FN to feedback indicative of monetary outcomes, yet the FN to performance feedback was intact and comparable to that of controls. Accordingly, MDD is not associated with a global impairment in environmental feedback processing per se, but rather a more specific deficit in reward sensitivity, as evidenced by blunted FN amplitude in our doors task.

The current study also extends previous reports of a blunted FN in MDD by relating this electrophysiological measure to a more specific clinical phenotype: impaired mood reactivity to pleasurable events, a core feature of melancholic depression. While the FN elicited by monetary feedback was blunted among the MDD group as a whole compared to controls, this group difference was driven specifically by a reduced response to monetary gain among those depressed individuals reporting impaired mood reactivity. By contrast, those depressed

individuals reporting *intact* mood reactivity to pleasurable events also exhibited an intact FN, comparable in amplitude to controls. Here, two homogenous subgroups of MDD participants were identified based on the presence of neurobiological impairment in reward sensitivity, as captured by FN amplitude. Using neurobiological data to inform the classification of psychopathology in this way is consistent with the Research Domain Criteria Project recently launched by the National Institute of Mental Health (Insel et al., 2010). Rather than seeking to elucidate the neural substrates of MDD, mapping dysfunction within a well-characterized neural measure of reward sensitivity onto specific clinical phenomenon may be an effective approach to further refine the definition of the anhedonic phenotype in MDD. In this regard, the FN elicited by monetary feedback appears to be a promising tool.

This preliminary finding linking FN amplitude to mood reactivity in MDD stands as a potential validation of impaired mood reactivity as an illness characteristic that distinguishes between melancholic and atypical depression. Notably, Holtzheimer and Mayberg (2011) recently argued that progress in developing more successful treatments for MDD may be hampered by an overly broad and heterogeneous set of symptoms, as well as a misguided research focus on the negative mood state associated with major depressive episodes. The authors argue that, rather than the presence of a negative mood state per se, MDD may be uniquely characterized by the inability to disengage from that state, a definition which resonates well with the current FN data. In future research, it will be important to consider how this specific illness characteristic, in conjunction with impaired FN amplitude, might be used to guide treatment selection. For example, behavioral activation, a psychosocial intervention designed to increase the frequency of pleasurable daily activities, might be particularly effective for individuals with intact mood reactivity and an intact FN (Weinstock, Munroe, & Miller, 2011).

For individuals with impaired mood reactivity and blunted FN amplitude—potentially indicating dopamingergic dysfunction—a dopamine agonist that specifically targets hypoactivity in the mesocortolimbic reward circuit may be uniquely effective (Lemke, Brecht, Koester, & Reichmann, 2006). In this way, considering ERP data on conjunction with other sources of clinical information may be used to develop more precise treatment selection algorithms, matching interventions with subgroups of patients exhibiting specific behavioral and neurobiological profiles of impairment.

The clinical utility of melancholia as a distinct construct remains contentious, with inconsistent evidence that the melancholic subtype of MDD uniquely predicts differences in course and pathophysiology (Hadzi-Pavlovic & Boyce, 2012). Along these lines, in the current sample, FN amplitude was not predicted by full diagnostic criteria for either the melancholic or atypical subtype. Similarly, FN amplitude in the current study was not associated with two other deficits in self-reported hedonic capacity: symptoms of anhedonic depression as measured by the MASQ, as well as social and physical anhedonia as measured by the SHAPS. These null effects are consistent with a recent report demonstrating intact FN amplitude on a gambling task among individuals high in self-reported physical anhedonia (Padrao, Mallorqui, Cucurell, Marco-Pallares, & Rodriguez-Fornells, 2012).

Overall, this pattern of null findings highlights the fact that reward is not a unitary construct, but rather is comprised of distinct processes including anticipatory pleasure, consummatory pleasure, and reward learning—each of which is associated with distinct neural circuitry and behavior (Pizzagalli, Dillon, Bogdan, & Holmes, 2011; Treadway & Zald, 2011). By extension, anhedonia is also a heterogeneous construct, and a deficit in one aspect of reward processing may not necessarily generalize to others. FN amplitude has been interpreted as

reflecting phasic changes in midbrain dopamine signals related to reward learning (Holroyd & Coles, 2002), which appears to be distinct from either motivational or consummatory deficits in subjective pleasure. Here, a reduced FN to random monetary feedback was related specifically to impairment in mood reactivity, a relatively circumscribed clinical phenomenon. This association did not generalize to other, more global assessments of depressive symptoms and self-reported hedonic capacity. Likewise, it may not generalize to other experimental contexts. In particular, the anhedonic depression subscale of the MASQ has previously been related to reduced behavioral response bias to reward on a probabilistic learning task (Pizzagalli et al., 2008) and reduced striatal activation to reward on a monetary incentive delay task (Wacker et al., 2009), yet in the current study this MASQ subscale was unrelated to FN amplitude. One possibility is that these tasks may be tapping into distinct facets of reward processing; each of these faces may be impaired in MDD, but they may not necessarily relate to one another across individuals. To pursue this topic further, it would be of interest to combine behavioral and electrophysiological information from multiple reward tasks, examining whether individual differences converge upon a latent factor or instead provide unique sources of information regarding more narrowly-defined deficits in reward processing.

In contrast with three previous reporting an increased FN to performance feedback in MDD (Mies et al., 2011; Santesso et al., 2008; Tucker et al., 2003), the FN elicited in the time estimation task was comparable across the MDD and control groups. One possible explanation for this discrepancy is that two of the aforementioned studies failed to control for the presence of comorbid symptoms of anxiety (Mies et al., 2011; Tucker et al., 2003), which is associated with potentiated neural activity associated with error processing (Weinberg, Riesel, & Hajcak, 2012). The third study, while controlling for individual differences in anxiety, only considered the FN

elicited by negative feedback; positive feedback was not considered, leaving it unclear whether the group difference in FN amplitude was indicative of increased differentiation across feedback type (Santesso et al., 2008). Regardless, the current result supports the notion that the processing of performance feedback is intact in MDD, and that impairment in FN amplitude is specific to reward information.

Strengths, Limitations, and Future Directions

A strength of the current study is the use of a battery of ERP tasks within a single MDD sample, allowing for a more thorough assessment of the specificity of observed information processing abnormalities. Indeed, ERP amplitudes were largely uncorrelated across tasks, suggesting that each measure provided a unique source of information with regard to affective and anhedonic deficits associated with MDD. LPP amplitude elicited by images did not predict that elicited by words, and the FN to monetary feedback did not predict the FN to performance feedback. This lack of associations between ERP measures across tasks demonstrates the importance of interpreting individual differences in a neurobiological measure only with regard to the specific experimental context used.

A second strength of the current study is the use of a relatively pure MDD sample, with limited psychiatric comorbidity and no antidepressant medication usage. Indeed, heterogeneity in symptom profiles and in treatment status have been identified as likely contributors to inconsistent findings within the neuroimaging literature in MDD (Townsend et al., 2010). Here, comorbid diagnoses of generalized anxiety disorder, obsessive compulsive disorder, and substance use disorders were used as exclusion criteria, enhancing the internal validity of the current results as being associated specifically with MDD.

One important limitation of the current study is that the course of depressive illness was not thoroughly assessed, leaving it unclear whether FN and LPP amplitude are impacted by illness features such as age of onset, number of major depressive episodes, and the length of the current episode. While both the FN and LPP appear to be promising biomarkers for information processing abnormalities in MDD, further work is necessary to clarify what aspects of the illness is captured by these neural responses. For example, a recent study observed that a blunted FN amplitude in response to monetary reward prospectively predicted the onset of a first major depressive episode within an adolescent sample, over and above other known risk factors of past subthreshold symptoms, familial history, and neuroticism (Bress et al., 2012). This finding suggests that the FN in particular may relate not to the current depressed state per se, but may rather reflect a trait-like vulnerability for developing MDD. Future studies may shed further light on this topic by examining the moderating role of illness trajectory, such as comparing single-episode and recurrent MDD. In addition, it will be valuable to incorporate a longitudinal design to assess what specific neurobiological responses normalize upon recovery, and how these ERP data may be harnessed to better predict remission of symptoms.

Conclusions

The current study sheds new light on the impact of MDD on the processing of motivationally salient stimuli, elucidating the conditions in which abnormal emotional reactivity and reward sensitivity are present. With regard to the processing of affective stimuli, MDD is characterized by two distinct abnormalities: increased reactivity to idiographic stimuli, and decreased reactivity to normative stimuli. With regard to the processing of environmental feedback, MDD is characterized by a unique deficit in reward sensitivity that may specifically relate to impaired mood reactivity; the processing of performance feedback is unaffected. Group

differences in emotional reactivity and reward sensitivity were largely unrelated across individuals, suggesting the presence of relatively unique neural deficits that may relate to clinically distinct subgroups. By considering multiple ERP components within a single depressed sample, the coherence across measures was examined, thereby providing a richer understanding of the neurobiological profile of MDD than would be attained by considering any single ERP component alone. Future research is necessary to clarify the diagnostic specificity of each of these abnormal neural responses, as well as how each may relate to MDD onset, course, and treatment outcome.

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Table 1

Sample Characteristics

	Depression (*n*=36)		Controls (*n*=44)		Group Comparison
	N	%	N	%	
Ethnicity					
Hispanic/Latino	2	5.6	4	10.8	$\chi^2(1)=.67$
Other	34	94.4	33	89.2	
Race					
Caucasian	25	71.4	18	51.4	$\chi^2(1)=2.95^{\dagger}$
Other	10	28.6	17	48.6	
Education					
Part College or Less	23	63.9	32	72.7	$\chi^2(1)=.72$
College Degree	13	36.1	12	27.3	
Current Psychological Treatment	5	13.9	1	2.3	$\chi^2(1)=3.85^{*}$
	M	*SD*	*M*	*SD*	
Age	25.64	8.76	23.59	7.02	$F(1,78)=1.35$
Symptoms					
Anhedonic Depression	64.46	12.38	39.86	10.97	$F(1,68)=77.46^{***}$
General Distress, Depression	37.69	11.67	18.91	5.74	$F(1,68)=72.79^{***}$
Anxious Arousal	30.14	10.77	20.89	4.58	$F(1,68)=21.91^{***}$
General Distress, Anxiety	24.74	8.67	16.34	4.69	$F(1,68)=25.43^{***}$
Hedonic Capacity	3.78	3.53	—	—	N/A

Note: Symptoms are subscale scores from the Mood and Anxiety Symptom Questionnaire. Hedonic capacity is the total score on the Snaith-Hamilton Pleasure Scale.
$^{\dagger}p<.10$, $^{*}p<.05$ $^{***}p<.001$

Table 2

Diagnostic Characteristics of Depressed Group

Diagnosis	N	%
Major Depressive Disorder		
No comorbid disorders	21	58.3
Panic Disorder	2	5.6
Social Phobia	1	2.8
Specific phobia	5	13.9
Dysthymic Disorder		
No comorbid disorders	4	11.1
Double Depression		
No comorbid disorders	1	2.8
Body Dysmorphic Disorder	1	2.8
Specific phobia	1	2.8
Features of Current Episode	**N**	**%**
Depression Subtype		
Melancholic	11	34.1
Atypical	6	17.1
Neither	18	51.4
Mood Reactivity		
Intact	23	67.6
Impaired	11	32.3

Note: Double depression indicates a current diagnosis of both major depressive disorder and dysthymic disorder.

Table 3

Associations Between Event-Related Potential Variables

	Late Positive Potential						Feedback Negativity	
	Normative Images[a]	Normative Images[b]	Normative Words[a]	Normative Words[b]	Idiographic Words[a]	Idiographic Words[b]	Monetary Outcomes[c]	Performance Feedback[d]
Normative Images[a]	—	.53***	-.19	.00	.22	-.01	.18	-.11
Normative Images[b]		—	-.07	.17	-.06	-.11	.10	-.19
Normative Words[a]			—	.49***	.09	.02	-.13	.00
Normative Words[b]				—	.03	-.06	-.11	-.13
Idiographic Words[a]					—	.30*	-.05	-.11
Idiographic Words[b]						—	-.29*	-.04
Monetary Outcomes[c]							—	.17
Performance Feedback[d]								—

Note: Superscripts indicate contrast type (a = pleasant vs. neutral, b = unpleasant vs. neutral, c = loss vs. gain, d = error vs. correct). The late positive potential was scored from 400-1000 ms for images and from 600-800 ms for words, corresponding to the time windows where group differences in amplitude were observed. Feedback negativity values were converted to a positive number, such that positive correlation coefficients indicate a direct association, and vice versa. *p<.05, ***p<.001

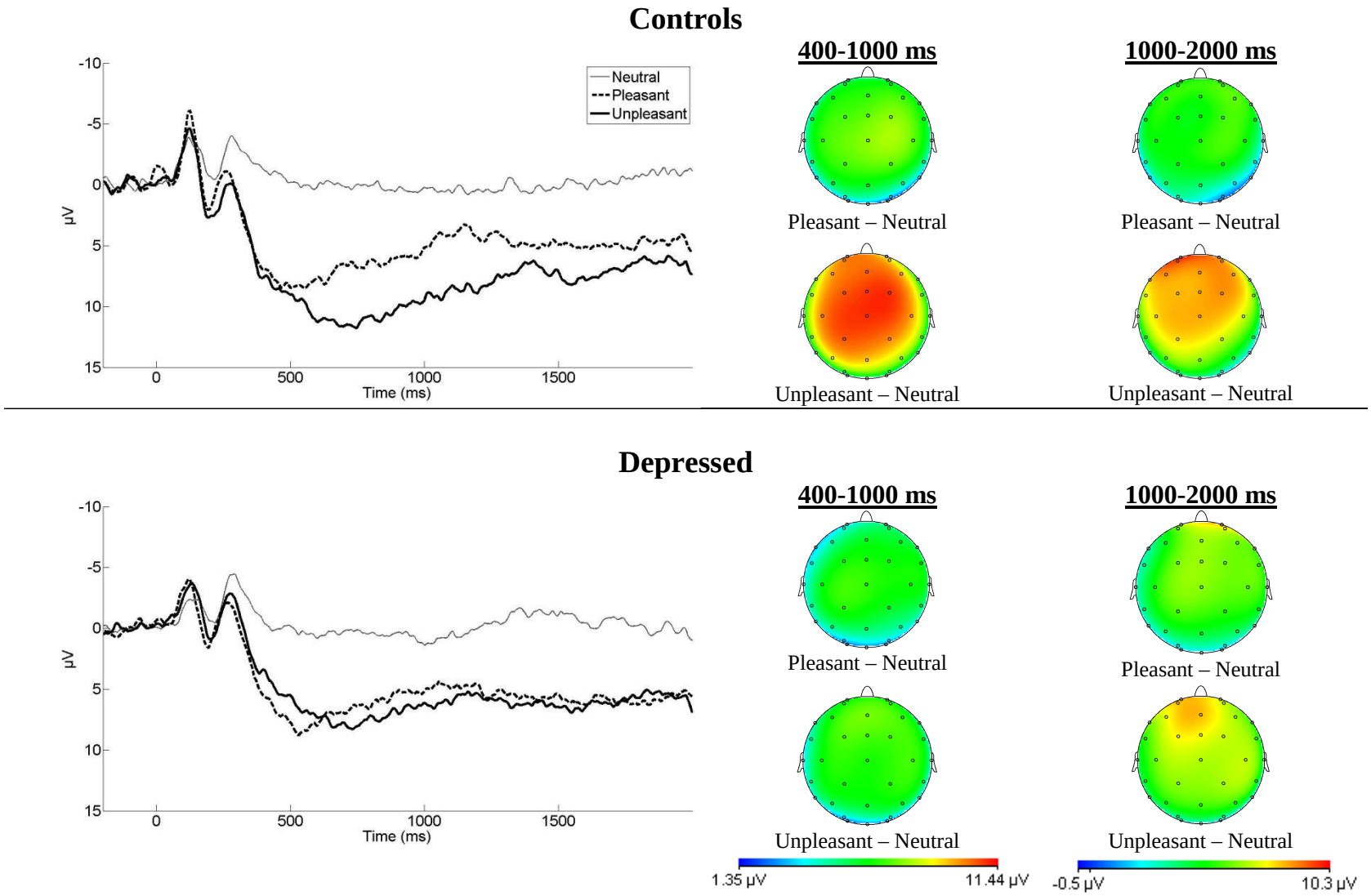

Figure 1. The late positive potential elicited by affective images among control (top) and depressed participants (bottom). Waveforms depict activity at a pooling of electrodes Cz/CP1/CP2/Pz.

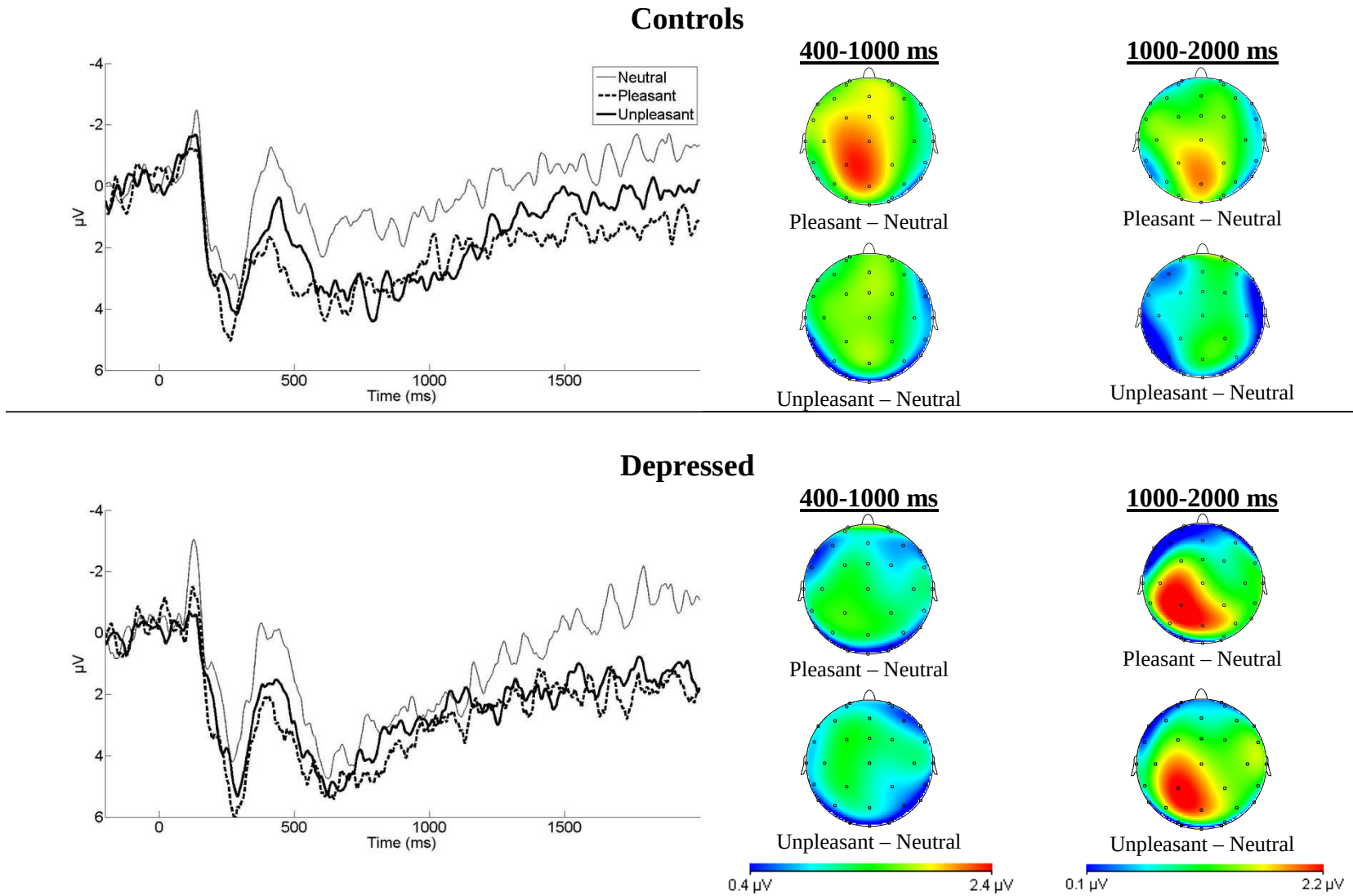

Figure 2. The late positive potential elicited by normative words among control (top) and depressed participants (bottom). Waveforms depict activity at a pooling of electrodes Cz/CP1/CP2/Pz.

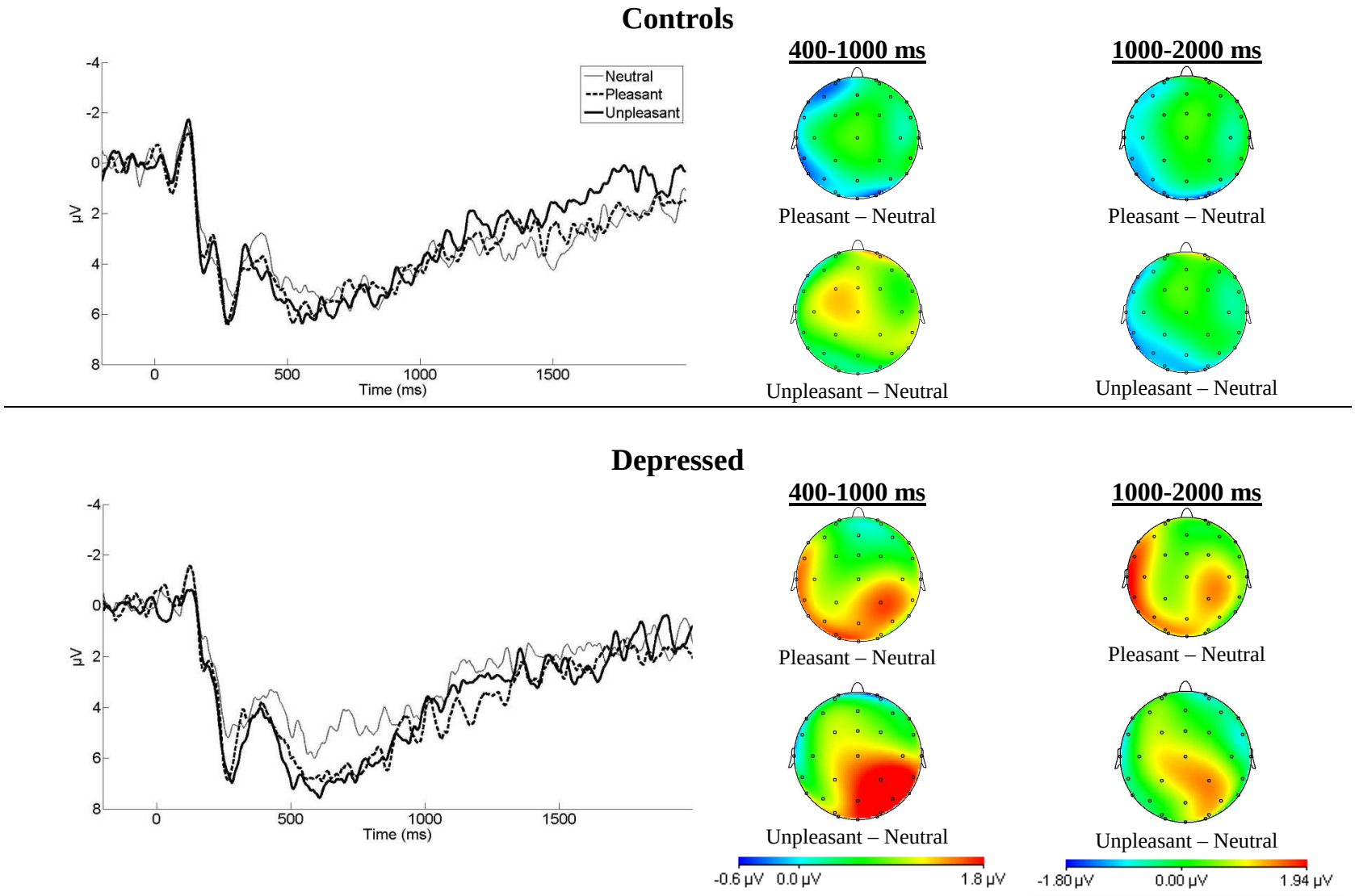

Figure 3. The late positive potential elicited by idiographic words among control (top) and depressed participants (bottom). Waveforms depict activity at a pooling of electrodes Cz/CP1/CP2/Pz.

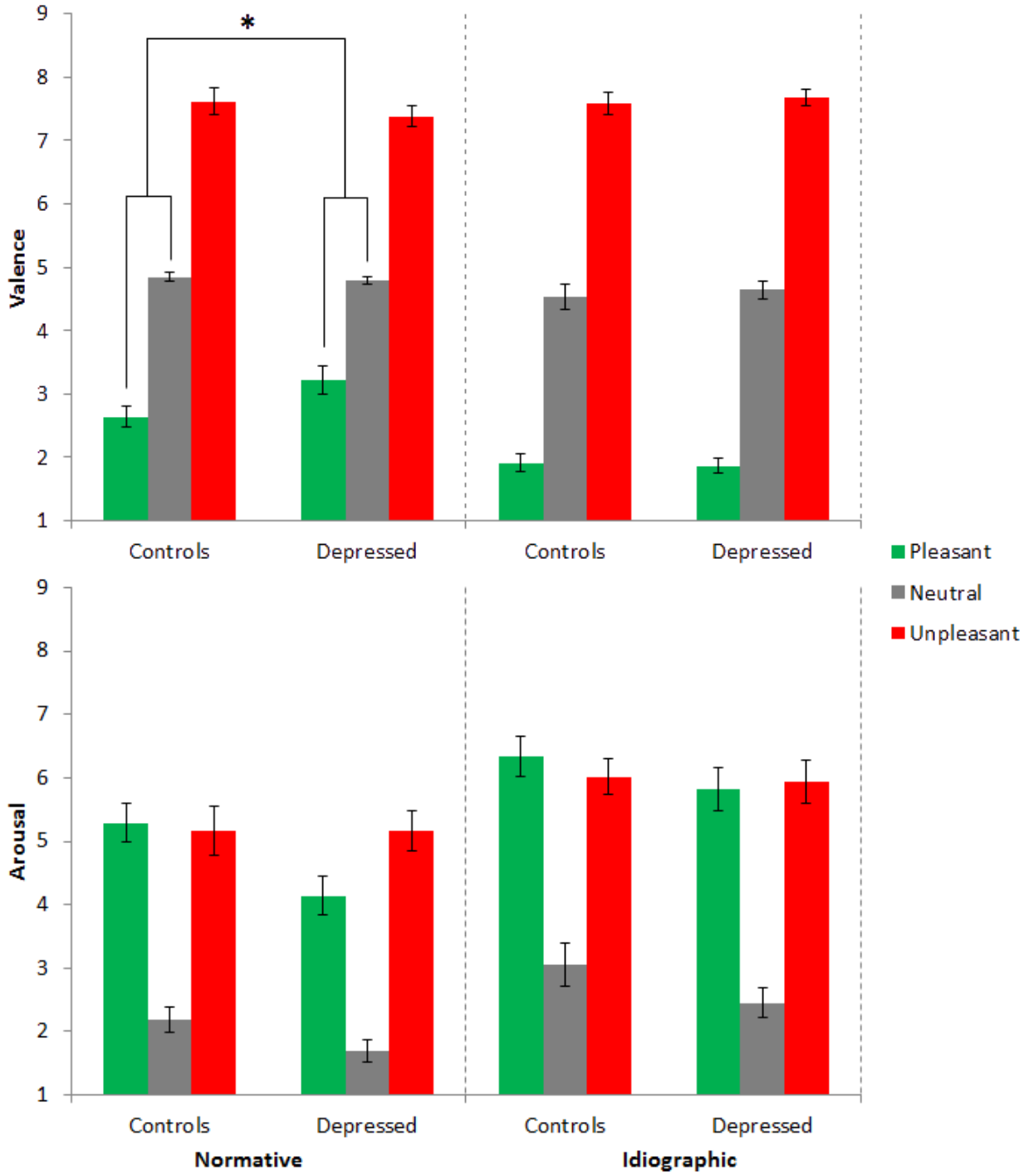

Figure 4. Participant ratings of valence and emotional arousal for affective words. Numerically greater valence ratings indicate increasing unpleasantness. Error bars represent the standard error of the mean. *p<.05

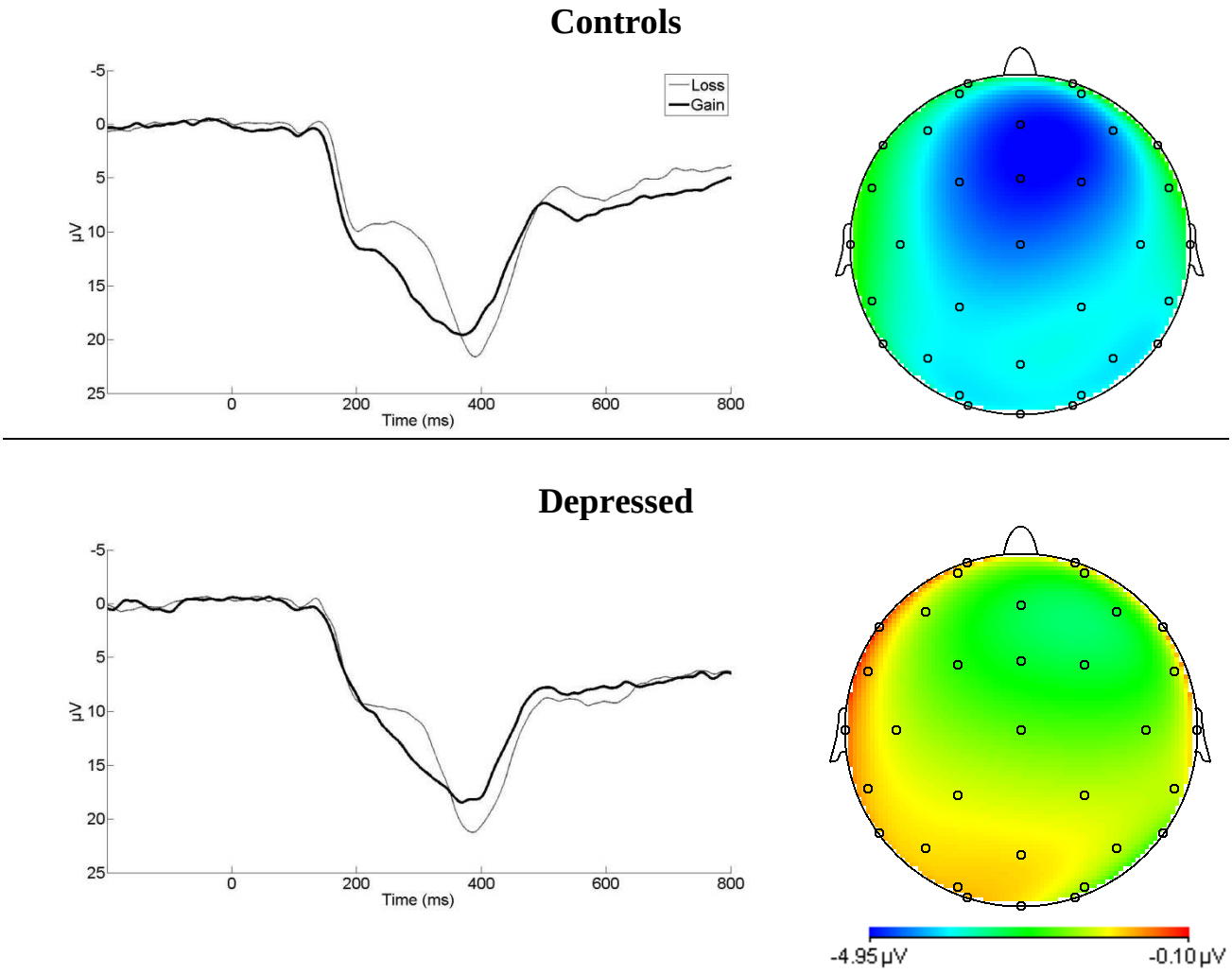

Figure 5. The feedback negativity elicited by monetary loss and gain among control (top) and depressed participants (bottom). Waveforms depict activity at a pooling of Fz/FCz/FC1/FC2/Cz, and headmaps depict the loss minus gain difference from 250-350 ms.

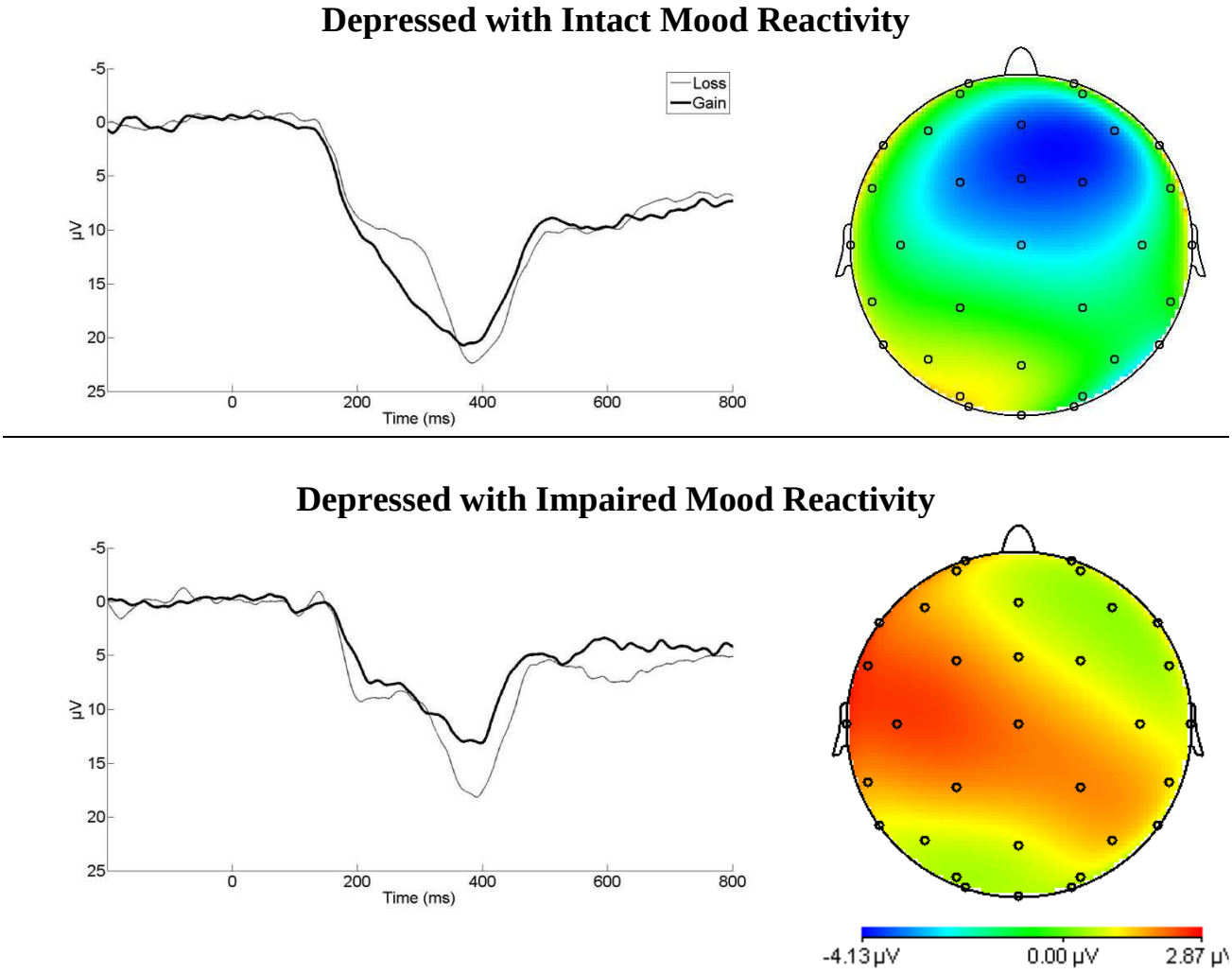

Figure 6. The feedback negativity elicited by monetary loss and gain among depressed participants reporting intact mood reactivity to pleasurable events (top) or impaired mood reactivity (bottom). Waveforms depict activity at Fz/FCz/FC1/FC2/Cz, and headmaps depict the loss minus gain difference from 250-350 ms.

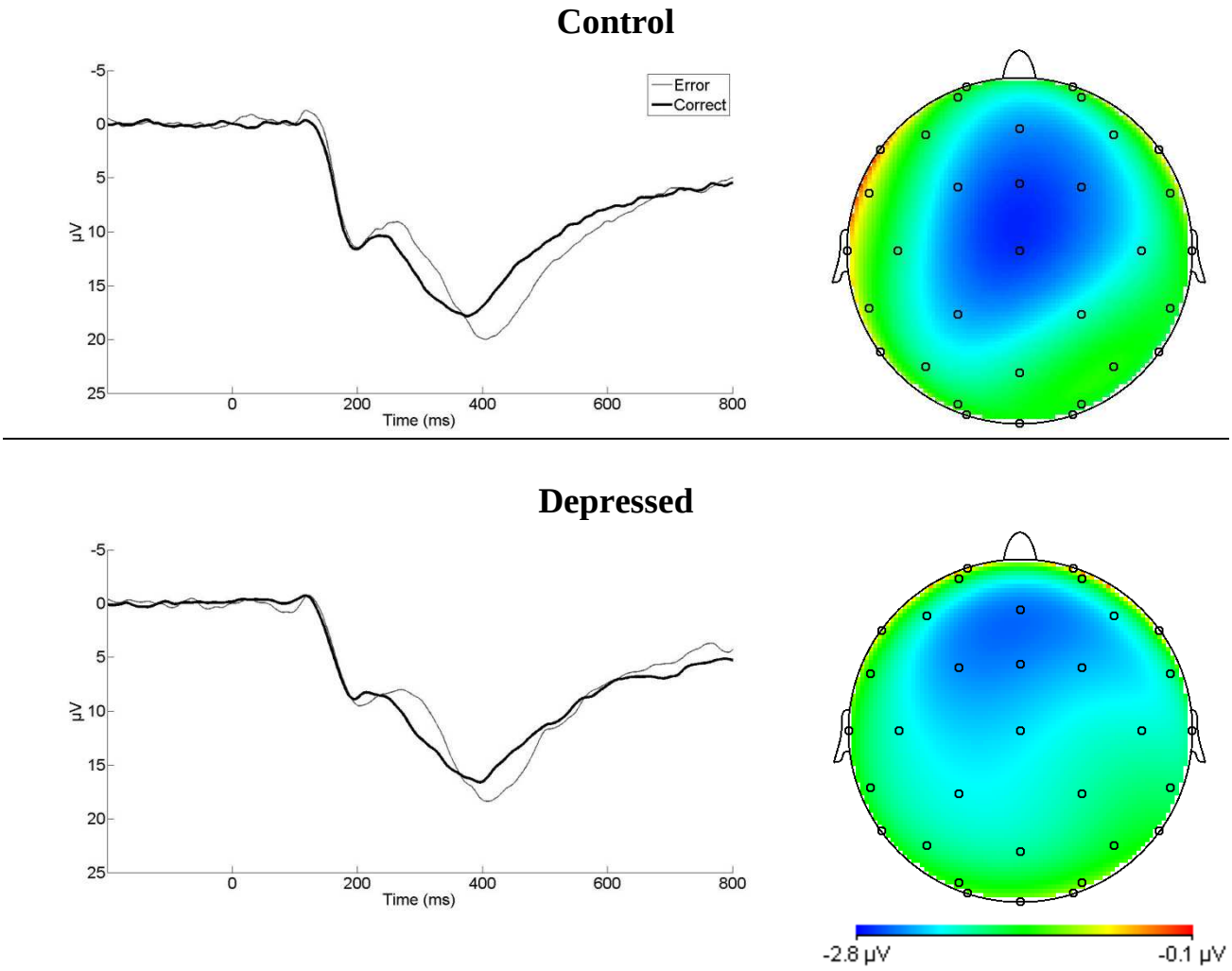

Figure 7. The feedback negativity elicited by performance feedback among control (top) and depressed participants (bottom). Waveforms depict activity at Fz/FCz/FC1/FC2/Cz, and headmaps depict the loss minus gain difference from 250-350 ms.