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Emotional Reactivity and Regulation in Current and Remitted Depression:

An Event Related Potential Study

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
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Date of Approval:
July 18, 2011

Keywords: major depression, mood disorders, emotion regulation, reappraisal, late
positive potential

ACKNOWLEDGEMENTS

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ABSTRACT

Major Depressive Disorder (MDD) is thought to be characterized by emotion regulation deficits, including decreased use of adaptive strategies such as reappraisal, but little is known about the exact nature of these deficits and whether or not they are specific to the depressed mood state. The late positive potential (LPP) is a sustained positive deflection of the event-related potential (ERP) associated with responding to emotionally-valenced stimuli, and reappraisal strategies have been found to reduce LPP magnitude in response to emotional stimuli in healthy individuals, but this effect has not been examined in MDD. This study utilized ERPs to examine emotional reactivity to positive and negative pictures during passive viewing and a reappraisal condition in a sample 25 of individuals with current MDD, 26 with remitted depression (RMD), and 26 healthy controls. The LPP was greater for passive viewing of positive and negative relative to neutral pictures in all groups, with no significant group findings emerging. For positive pictures, all groups showed reduced LPP's for positive reappraisal relative to passive viewing with no group by condition interactions. For negative pictures, both the MDD and RMD groups exhibited abnormalities, with the MDD group failing to show a reduction in LPP for reappraised pictures relative to passive viewing and the RMD group demonstrating an unexpected increase in LPP magnitude for reappraised negative pictures. The LPP for emotional pictures and reappraisal instructions may reveal deficits in emotional reactivity and regulation among mood-disordered individuals, particularly for negative stimuli, and may suggest targets for clinical intervention.

INTRODUCTION

Major Depressive Disorder (MDD) is a debilitating disorder that affects as many as 10-25% of women and 9-12% of men at some point in their lifetime (Murray and Lopez, 1997). MDD is classified as a mood disorder by The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 2000), reflecting the profound disturbance of affective functioning. *DSM–IV* diagnostic criteria specify symptoms of at least 2 weeks duration that implicate deficient positive affect and loss of interest in pleasurable activities (e.g., anhedonia), excessive negative affect (e.g., sadness), or both. Indeed, patients diagnosed with depression reliably report low positive affect (PA) and elevated negative affect (NA) on a variety of questionnaire and interview measures (e.g., Clark, Watson, and Mineka, 1994). Durable disturbance of mood is thus one of the most salient features of MDD. MDD symptoms also include several associated somatic and cognitive symptoms, such as loss or increase in appetite, weight gain or loss, sleep disturbance, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, concentration or decision-making difficulties and suicidal ideation or behavior (DSM-IV; APA, 2000).

One strand of research has sought to clarify how MDD influences different aspects of affective functioning. Given that MDD is quintessentially a disorder of mood, one natural question is how the pervasive mood disturbance in MDD influences ongoing emotional reactivity (i.e., a positive or negative emotional response to a

stimulus in the environment). Addressing this question requires a distinction between the constructs mood and emotion (e.g., Rottenberg and Gross, 2003).

Definition of affect-related constructs

Moods have been defined as diffuse, slow-moving feeling states that are weakly tied to specific stimuli in the environment (e.g., Watson, 2000). By contrast, emotions have been defined as quick-moving reactions that occur when an individual processes a meaningful stimulus and typically involve coordinated changes in subjective feelings, behavior and physiology (Ekman, 1992; Keltner and Gross, 1999; Lang, Bradley and Cuthbert, 1998). When mood and emotion are so distinguished, it is apparent that the various diagnostic criteria for depression, such as pervasive sadness or anhedonia, refer to moods, not emotions. Thus, how MDD alters emotions is an open empirical question.

Although the constructs are distinguishable, moods and emotions are generally seen as interconnected, with moods altering the probability of having specific emotions (e.g., Rosenberg, 1998). A growing body of work has attempted to specify exactly how the mood disturbance in MDD influences emotional functioning (e.g., Golin, Hartman, Klatt, Munz and Wolfgang, 1977; Lewinsohn, Lobitz and Wilson, 1973; Berenbaum and Oltmanns, 1992; Sloan, Strauss, Quirk and Sajatovic, 1997; Sloan, Strauss and Wisner, 2001; Bylsma, Morris and Rottenberg, 2008). Although there have been surprisingly few empirical demonstrations of explicit links between moods and emotions, it is often assumed that moods will potentiate like-valenced or matching emotions (e.g., irritable mood facilitates angry reactions, an anxious mood facilitates panic, etc; Rottenberg, 2005). By extension, excessive negative mood in depression would potentiate negative

emotional reactivity and/or a lack of positive mood would attenuate positive emotional reactivity.

Traditionally, the presumed indices of emotional reactivity include responses in experiential, behavioral and physiological response systems (e.g., Lang, 1998; Ekman, 1992; Izard, 1977; Levenson, 1977). Emotions are viewed as sets of organized responses that involved coordinated changes in a variety of bodily systems to prepare an organism to respond appropriately to environmental changes. Human emotional responses are thought to have evolved in phylogeny from the more basic patterns of approach to appetitive stimuli and withdrawal from aversive stimuli that are conserved across species (Schneirla, 1959). One complexity in studying these emotional responses is that emotional impulses are generated across multiple systems (behavior, physiology, phenomenology) and activity in these systems is imperfectly yoked (e.g., Mauss, Levenson, McCarter and Gross, 2005; Lang, 1998; Lacey and Lacey, 1970). A second complexity in interpreting emotion data is that emotion is subject to regulatory processes that will typically alter the magnitude and trajectory of a response, in ways that are just beginning to be understood (Gross, 2008).

Does depression enhance or blunt emotional reactions?

Based in part upon the prevalent assumption that moods facilitates emotions when the mood and emotion are matching in valence (Rosenberg, 1998), researchers have suggested that negative mood in MDD may potentiate negative emotional reactions (e.g., Golin, et al., 1977; Lewinsohn, et al., 1973) and the absence of positive mood may attenuate positive emotional reactions (Berenbaum and Oltmanns, 1992; Sloan, et al.,

1997; Sloan, et al., 2001). Thus far there is little empirical research that supports

negative potentiation in diagnosed samples; interestingly, however, there appears to be

some support for negative potentiation in dysphoric (non-diagnosed) samples (Golin, et

al., 1977; Lewinsohn, et al., 1973). By contrast, there is fairly consistent empirical

support for the positive attenuation theory and accumulating evidence from laboratory

studies indicates that MDD may actually involve blunted emotional reactivity

independent of valence, a pattern that has been labeled emotion context insensitivity

(ECI; Rottenberg, 2005; Rottenberg, Gross and Gotlib, 2005).

In a meta-analysis of 19 laboratory studies of emotional reactivity in MDD

(Bylsma, et al., 2008), ECI was consistently demonstrated across behavioral,

physiological and experiential response systems; however, there was a significant degree

of heterogeneity in effect sizes even within response systems, suggesting that differences

in the experimental design, such as the specific stimuli used and the timing in which the

responses are measured may play an important role in understanding differences in

emotional reactivity between persons with MDD and healthy individuals. Further,

results from small number of naturalistic studies of emotion in every day life settings

have not been consistent with laboratory findings of ECI. For example, two experience-

sampling studies of emotional reactions to daily life events in MDD found that,

unexpectedly, MDD individuals reported greater reductions in NA than controls when

responding to positive events (Bylsma, Clift and Rottenberg, 2011; Peeters, Nicolson,

Berkhof, Delespaul and De Vries, 2003). Although there are many possible explanations

for these lab-life discrepancies, variations in the context and the time course of the

emotional reactions may be especially important.

Is ECI mood state dependent or trait-like?

Although a growing area of research has examined emotional reactivity in individuals with current major depression, emotional reactivity has been little studied in remitted depression. Such investigations are critical for clarifying the relation between emotional reactivity and vulnerability to depression. For example, if ECI contributes to depression onset, it should exhibit a trait-like quality and should be evident among formerly depressed individuals when they are currently euthymic; therefore, currently and formerly depressed individuals should exhibit similar patterns of emotional responding. However, if ECI were specific to a depressed mood state, ECI would be expected to be observed only among currently depressed individuals.

A small body of studies has begun to examine emotional reactivity in remitted depression. Consistent with the possibility that ECI is trait-like, Iacono et al. (1984) found that currently and formerly depressed participants exhibited similarly attenuated electrodermal responding across both emotional and non-emotional stimuli relative to control participants. Sigmon and Nelson-Gray (1992) also found that formerly and currently depressed individuals more closely resembled each other and were both different from controls; however, formerly depressed and currently depressed persons were characterized by an opposite pattern of potentiated electrodermal responding to negative stimuli. In a treatment study, Dichter, Tomarken, Shelton and Sutton (2004) found that prior to beginning antidepressant treatment, emotion-startle modulation in depressed individuals was attenuated relative to control participants and remained attenuated even after symptomatic improvement. However, in a more recent study using

stricter criteria for defining remitted depression (e.g., excluding individuals with current

subthreshold symptoms), Rottenberg, et al. (2005) examined emotional reactivity to

normative and idiographic films in individuals with current and remitted depression.

Currently depressed individuals reported less sadness reactivity and less happiness

experience across all conditions relative to both controls and formerly depressed.

Overall, the results suggest that depression may produce mood-state-dependent changes

in emotional reactivity that are most pronounced in emotion experience reports. Given

the conflicting findings, data are currently inconclusive whether the emotional

dysfunction observed in MDD is more clearly due to the current mood state or a trait-

like vulnerability to developing depression, or some combination of both state and trait

effects.

Affective style and the time course of emotion

The inconsistent findings in studies examining group differences may be due, in

part, to the considerable variation in individual's emotional reactivity and regulation.

These variations have been referred to as affective style (e.g., Davidson, 1998). One

important aspect of affective style is known as affective chronometry, which involves

the study of individual differences in the temporal dynamics of affect. Affective

chronometry includes measures such as the rate of change of an emotional response (rise

time to peak of the response and recovery following the response), the magnitude or

peak of the emotional response and the duration of the response (Davidson, 1998).

Other related features of affective style that influence the temporal dynamics of emotion

include the threshold to respond and emotion regulation (both conscious and unconscious processes).

Variations in affective style may comprise key individual differences that underlie vulnerability to psychopathology, such as mood disorders. For example, Davidson, Jackson and Kalin (2000) proposed that individuals with mood disorders may have an abnormally early response onset to a negative stimulus that may bypass normal regulatory constraints or may be abnormally slow to recover once a negative emotional response has been generated. While these proposals are intriguing, few tests of these ideas have been performed. Given that there are often differences in the emotional responses of mood disordered individuals relative to healthy individuals, it becomes particularly important to examine where the differences arise in the time course of emotional responding, as well as other features of affective style. Another consideration is that differences in emotional responding between mood-disordered and healthy individuals could reflect, in part, variations in the temporal resolutions of measures used in experimental studies. Specifically, emotional stimuli of varying durations and intensities have been used, with emotional response measures generally being retrospective (in the case of self-report) or averaged over periods of time varying in duration, which may obscure important differences in the time course of emotional responding.

Some work has begun to examine the time course of emotion and variables, such as appraisals, emotion regulation strategies, personality and psychopathology, that affect the temporal dynamics of emotional responses, including the duration and rates of decay of emotional responses. For example, Hemenover (2003) examined self-reported

affective responses at two time points during an emotional film and found that extraverts, emotionally stable participants and those with high negative mood regulation expectancies showed slow rates of positive and rapid rates of negative self-reported affective decay. In contrast, individuals high on neuroticism or introversion and those with low negative mood regulation expectancies showed slow rates of negative and rapid rates of positive decay.

Perhaps most germane here, Dichter and Tomarken (2008) examined the chronometry of the affective startle modulation in MDD and found that MDD individuals did not exhibit the normal modulation in startle response as a function of stimulus valence, and, importantly, valence effects were dependent on the particular measures and time points assessed before and after the onset of the stimuli. Specifically, MDD individuals failed to appropriately modulate their startle response according to valence for the 2000ms anticipatory probe before the stimulus and the 3500-4500ms probe while viewing the stimulus; however, they demonstrated normal startle responses at the 750ms probe as well as on self reported and behavioral reactivity. Further, for the 300ms probe during stimulus viewing, all groups demonstrated a lack of affective modulation. One reading of Dichter and Tomarken (2008)'s findings is that depressed and healthy individuals might have similar initial early emotional responses, which begin to diverge later in the time course as emotion regulatory processes begin to have an impact. Results such as these highlight the importance of close attention to the time course of emotional responding in individual difference studies. More studies with assessment at various points in time before, during and after exposure to stimuli are needed to fully understand these phenomena.

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Examining emotional responding with ERPs

Event Related Potentials (ERPs) have been utilized in a large number of studies to examine the time course of emotional responding due to the high temporal resolution of ERP, allowing for examination of responses in the millisecond range. ERPs are electrophysiological signals in the brain that have the ability to measure the sequence of constituent operations that are involved in the processing and acting on of incoming information. As researchers have noted, examining ERPs are ideal for investigating the unfolding of different processes across time (Moser, Krompinger, Dietz and Simons, 2009; Dien, Spencer and Donchin, 2004). Specifically, Dien and colleagues (2004) outlined a model suggesting the time course and ERP correlates of different information processing stages that progress from simpler processes (earlier in the time course after a stimulus onset) to more complex (later in the time course). Similarly, researchers examining affective stimuli note that characterizing the temporal order of affective ERP components contributes to the understanding of affective time course (Olofsson, Nordin, Sequeira and Polich, 2008; Codispoti, Ferrari and Bradley, 2007).

Emotion-modulated ERPs in healthy individuals. ERP components have been used to study emotional processing and responding in healthy individuals. Olofsson, Nordin, Sequeira and Polich (2008) described a review of over 50 studies using ERP to examine emotional processing and reactivity of healthy individuals. As reviewed by Olofsson et al. (2008), a variety of ERP components have been implicated in emotional reactivity in healthy individuals, beginning around 100-200ms post-stimulus, with differences found in these components varying by arousal and, less consistently, by

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valence of the stimuli. ERP studies of affective processing examining early latency

components reveal inconsistent findings due to the sensitivity of these components to

perceptual features of the stimuli and to other task demands. However, some relatively

consistent findings have revealed that the arousing unpleasant images may produce

larger P1 amplitudes (~100-200ms) relative to unpleasant and neutral stimuli, suggesting

selection attention to negatively valenced stimuli, and, further, examination of middle-

latency components (~200-300ms) reveal that P2 and N2 components are sensitive to

arousing pleasant images (for review, see Olofsson et al., 2008).

The Late Positive Potential (LPP), a relatively late component which begins

around 200-300ms latency, has been found to be particularly relevant for emotional

responding to affective pictures (for review, see Olofsson et al., 2008).   The LPP was

initially identified in affective oddball paradigms, in which a rare pleasant or unpleasant

target is presented within a series of pictures of the opposite or neutral valence (e.g.,

Cacioppo, Crites, Bernnston and Coles, 1993). The greater the affective target differed

from the series, the larger the LPP response (e.g., Cacioppo, Crites, Gardner and

Bernston, 1994). More recently, an affective picture-processing paradigm has been used

in which pleasant, neutral and unpleasant pictures occur with equal probability in a

random sequence, with pictures presented for a sustained period over several seconds

(i.e., in contrast to oddball tasks in which stimuli are typically presented for less than 1

second). Most of these studies have used the standardized emotion-eliciting picture

stimuli due to the ability to systematically vary stimulus valence and arousal and display

positive, negative and neutral pictures. In studies using this paradigm, the magnitude of

the LPP over the centroparietal cortex reliably and consistently increases in magnitude

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as arousal levels increase for both positively and negatively valenced stimuli (e.g., Cuthbert et al., 2000; Codispoti et al., 2007; Schupp, Junghofer, Weike and Hamm, 2004; Cacioppo, Crites, Gardner and Bernston, 1994; Keil et al., 2002; Palomba, Angrilli and Milli, 1997; Pastor et al., 2008; e.g., Flaisch, Junghoffer, Bradley, Schupp and Lang, 2008). This positive slow wave is found to develop around 200-400ms following picture onset and can be sustained for at least several seconds during the entire picture viewing period (e.g., Cuthbert et al., 2000).

This affective LPP is thought to reflect motivated attention resulting from activation in basic motivational systems that mediate appropriate survival (e.g., approach and avoidance) behaviors (e.g., Lang et al., 1997). As such, it is thought to be sensitive to the intensity or activation level of the current motivational state (i.e., motivational significance) rather than its direction or valence (i.e., appetitive or defensive). Although previous data suggest that the magnitude of the LPP response is primarily modulated by arousal, there is some evidence that the specific topography of the LPP at frontal sites may reflect valence. For example, Cunningham, Espinet, DeYoung and Zelazo (2005) found that the LPP over right frontal sites started earlier and had a larger amplitude when elicited by negative stimuli (in this case, words), whereas the LPP over left frontal sites started earlier and had a larger amplitude when elicited by positive stimuli. LPP effects occurred for both evaluative and non-evaluative judgments, but the magnitude of the LPP response was stronger in the evaluative conditions. These results suggest that while the magnitude of the LPP primarily reflects arousal, the specific topography of the LPP response may reveal information about evaluative processing that may reflect valence.

Importantly, the affective response of the LPP to emotionally relevant stimuli (high arousing emotional stimuli versus neutral stimuli) has been demonstrated repeatedly in a variety of paradigms, suggesting it is a relatively robust and stable phenomenon. Specifically, affective discrimination of this late ERP component occurs with a variety of stimulus and context manipulations. For example, Cuthbert et al. (1995) found similar affective ERP modulation when either passively viewing pictures, or making explicit evaluative ratings and Cardinale, Ferrari, De Cesarei, Biondi and Codispoti (2005) demonstrated affective modulation of the LPP in the context of making non-affective categorizations of emotional stimuli. Further, emotion modulation of the LPP is found regardless of stimulus size (De Cesarei and Codispoti, 2006), duration (Codispoti et al., 2007), or complexity (Bradley et al., 2007). Emotional modulation of the LPP also occurs after stimulus repetitions, although the effect may attenuate at repeated presentations of identical stimuli (e.g., Codispoti, Ferrari, De Cesarei, and Cardinale, 2006, Codispoti et al., 2007) Taken together, these findings suggest that affective modulation of the LPP is a robust phenomenon that is not strongly influenced by perceptual factors or task requirements.

The LPP in affective studies differs from the non-affective P300 (i.e., another positive potential occurring in response to rare stimuli in non-affective oddball tasks) in that it usually occurs later, is more sustained (beginning around 300ms and occurring well beyond 1000ms) and appears to be partially lateralized, with larger LPP amplitudes over the right than left parietal region (Hajcack, MacNamara and Olvet, 2010; Pastor et al., 2008; Schupp et al., 2000). However, there appears to be some overlap between the two components, particularly in the 300-500ms range. A principal components analysis

(PCA) that attempted to differentiated emotional modulation of the P300 and LPP found that emotional modulation of the P300 is evident primarily in occipital-parietal sites around 350ms following picture onset, while emotional modulation of the LPP appears most evident at occipital to central recording sites with peaks around 850 and 1600ms following picture onset (Foti, Hajcak and Dien, 2009).

Validity of the LPP as a measure of emotional responding. One way to validate the LPP and other ERP components as reflective of emotional responding is to examine their correspondence with other psychophysiological and self-report measures of emotional reactivity, particularly for measures sensitive to changes in arousal (e.g., Cuthbert, Schupp, Bradley, Birbaumer and Lang, 2000). Specifically, Cuthbert et al. (2000) obtained measures of EEG activity (400-700ms and 700-1000ms time windows) in combination with mean affective self-report ratings, EMG corrugator responses, heart rate and skin conductance. A principal components analysis of the data revealed a two-factor solution including an arousal factor that included both EEG measures of the LPP, skin conductive and arousal judgments and a valence factor that included heart rate, corrugator and valence self-report ratings (Cuthbert et al., 2000). The EEG measures also loaded on the valence factor, though not as strongly as their loading on the arousal factor. Cuthbert et al. (2000) reported that the LPP (in the 700-1000ms time window) was highly correlated with picture arousal ratings (r=.73). Further, Codispoti et al., (2007) demonstrated that the LPP (in the 300-600ms time window) has very high temporal stability (r=.98 for group average magnitudes in each block across the two days; the mean correlation within individuals was r=.55) in its responses to positive and negative stimuli when individuals were tested a week apart, even when the specific

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affective pictures used were changed (but with valence and arousal consistent).

Although earlier components thought to be involved in basic perceptual processing

(150-300 ms) also showed affective modulation to arousal, these components were not

stable over time and were not correlated with the LPP response (r=.03), suggesting that

the LPP is particularly relevant for emotional responding (Codispoti et al., 2007).

Further, in a study that combined fMRI with ERP, the LPP (400-900 ms) was found to

be correlated with neural activity in the lateral occipital, inferotemporal and parietal

visual areas, supporting the idea that the LPP reflects facilitated perceptual processing of

motivationally relevant, emotional stimuli (Sabatinelli, Lang, Keil and Bradley, 2007).

Emotion modulated ERPs in mood-disordered individuals. Despite its

advantages, few studies have examined emotion-modulated ERP processes in mood-

disordered individuals. More commonly, studies have used ERPs to examine more basic

perceptual processes in mood disorders. For example, individuals high on dysthymia

exhibit reduced ERP component amplitudes associated with initial perceptual processing

of stimuli such as auditory tones (i.e., N100, P100, P200), while normal perceptual

processing was found on individuals high on anhedonia (Yee, Deldin and Miller, 1992).

Individuals high on dysthymia and anhedonia have also been found to exhibit reduced

P300 amplitudes to memory tasks and fail to respond appropriately to changing task

demands, suggesting that these individuals used less optimal resource allocation

strategies relative to controls (Yee and Miller, 1994). Similarly, individuals diagnosed

with MDD have demonstrated reduced P3 (Roschke and Wagner, 2003) and N2

amplitudes (Ogura et al., 1993) in auditory oddball paradigms, indicating specific

deficits in resource allocation and mismatch detection. Although these studies did not

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explicitly address affective processing, they do demonstrate that ERPs are sensitive to depression.

There is also a small body of work that concerns the relationship between depression and earlier ERP components involved in the cognitive processing of less intense emotional stimuli such as positively or negatively valenced words or facial expressions. These studies are relevant to understanding emotional reactivity in depression, because differences in how individuals with mood disorders may attend to or perceive emotional stimuli may influence how emotional responses are subsequently generated. For example, in depressed individuals, the P300 (which reflects resource allocation) has been repeatedly found to be reduced in depressed relative to nondepressed individuals in studies of emotional face processing and emotional word recognition (e.g., Blackburn, Roxborough, Muir, Glabus, and Blackwood, 1990; Dietrich et al., 2000; Cavanagh and Geisler, 2006), comparable to the P300 findings for nonaffective stimuli (e.g., Roschke and Wagner, 2003). Similarly, the N2 amplitude is also reduced in MDD individuals when viewing happy faces (Deldin, Keller, Gergen and Miller, 2000). Depressed individuals have also demonstrated enhanced negativity biases, such that individuals with MDD experience a larger P300 response to negatively valenced words (in comparison to neutral words) relative to healthy controls and previously depressed individuals, suggesting that differences in the processing of negative stimuli are mood state dependent (Ilardi, Atchley, Enloe, Kwasney and Garratt, 2007). Further, Shestyuk, Deldin, Brand and Deveney (2005) examined sustained processing of emotional words in MDD and healthy individuals, demonstrating reduced slow wave components (900-4500 ms) in response to positive words relative to neutral

or negative words in MDD individuals. Yee and colleagues (1988) examined emotional responses to to fearful stimuli in dysthymics using ERPs, as indexed by the N200, a component the authors interpret as reflecting processes involved in orienting to a stimulus, and found that dysthymic individuals showed normal or heightened initial orientation reactions, but withdrew and ceased affective processing as the actual emotional stimulus approached, suggesting a dysfunctional orientation response in dysthymics. In sum, previous research suggests that early attention and orientation processes as well as sustained encoding processes may be impaired in mood-disordered individuals in their processing of emotionally valenced stimuli. However, ERP components more directly relevant to later stages of emotional reactivity, such as the LPP, have not been examined in diagnosed MDD or RMD samples.

The LPP and psychopathology

Although the LPP response to emotional pictures has not been examined in depressed individuals per se, one study of the LPP response (Ding, Ding, and Jinhong, 2007) examined the effect of high levels of neuroticism, a trait related to MDD vulnerability (e.g., Kendler, Gatz, Gardner and Pederson, 2006),. Ding and colleagues (2007) demonstrated a group by task interaction, such that individuals high on the trait neuroticism exhibited a smaller LPP magnitude in response to negative pictures, but no differences in response to positive pictures. These results raise the possibility that MDD individuals may also exhibit a diminished LPP response to negatively valenced emotional pictures. Complicating this prediction, however, individuals high on trait

anxiety, another characteristic of persons with MDD, have shown increased LPP magnitudes to negative emotional pictures (Mocaiber et al., 2009).

Although the LPP has not yet been examined in MDD, recent clinical studies have begun to use the LPP to examine emotional responses to specific types of stimuli predicted to have particular emotional significance for those disorders. For example, individuals with obesity are shown to exhibit larger LPP's to food relative cues compared to healthy controls (Nijs, Franken and Murisa, 2008) and studies of individuals with substance abuse, including abuse of alcohol (Namkoong, Lee, Lee, Lee and An, 2004), heroin (Franken et al., 2003), cocaine (Dunning et al., 2011) and nicotine (Versace, et al., 2011) have found that individuals with substance abuse disorders (but not healthy controls) exhibit larger LPP's for substance related cues compared to neutral cues and may also exhibit deficits in their LPP response (reduced LPP magnitude) for non-drug related affective pictures (Dunning et al., 2011).

Influence of emotion regulation processes on emotional responding

The ongoing emotional state also represents an interaction between the innate strength of a reaction (emotional reactivity) and efforts to control or alter the reaction (emotion regulation). Thus, explicit study of emotion regulation should improve our understanding of affective style and the time course of emotional responding. Gross and Thompson (2007) proposed that emotion processing can be altered by specific emotion regulation strategies at four basic stages of the emotion generation process, including confrontation with the emotion eliciting event (i.e., situation selection), deployment of attention to the event, appraisal processes to evaluate the event and the engagement of

response tendencies towards the event (e.g., physiological and behavioral responses). Although emotion regulation can refer to non-conscious processes, most of the extant work has largely focused on understanding conscious cognitive strategies for regulating emotions which include both antecedent-focused (e.g., reappraisal) and response-focused (e.g., suppression) strategies (Gross and Thompson 2007).

Cognitive reappraisal emotion regulation strategies have received attention, in part, because they can be plausibly linked to psychopathology and psychotherapy. Cognitive reappraisal generally refers to a set of strategies intentionally used to increase or decrease one's emotions, typically by changing the way one thinks about the significance of an emotion-evoking event (Gross and Thompson, 2007). Psychopathology, such as mood and anxiety disorders, is theorized to involve deficits in cognitive reappraisal and cognitive-behavioral therapy emphasizes using cognitive restructuring techniques to develop more adaptive reappraisals of automatic negative thoughts and beliefs (e.g., Campbell-Sills and Barlow, 2007). Thus, cognitive reappraisal is a reasonable emotion regulation strategy critical for understanding emotional responding and deficits in emotional responding found in mood disorders.

Reappraisal strategies have been shown to have an impact on emotional reactivity in healthy individuals across several emotion response systems (behavioral, cognitive, physiological, neural and self-report measures). For example, the use of cognitive reappraisal strategies has been associated with reductions in the behavioral expressions of and self-reported emotion in response to disgusting films (e.g., Gross, 1998), in memory recall of unpleasant pictures (e.g., Dillon, Ritchey, Johnson and LaBar, 2007), in physiological reactivity to negative stimuli (i.e., EMG and startle

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eyeblink; Jackson, Malmstadt, Larson and Davidson, 2000) and in fMRI studies of brain activity elicited by unpleasant pictures (i.e., amygdala and prefrontal cortex, respectively; e.g., Ochsner et al., 2004). Reappraisal, in contrast to suppression, has been associated with increased positive affective and decreased negative affect, as well as better interpersonal functioning and well-being (Gross and John, 2003). For example, Gross (1998) examined differences in physiological and behavioral emotional reactivity following cognitive reappraisal and behavioral suppression strategies employed in response to emotional film stimuli and demonstrated that reappraisal was associated with decreases in negative emotional experience. The empirical evidence thus far suggests that reappraisal strategies may have particularly adaptive benefits; however, little attention has been paid to investigating the use of reappraisal strategies in depression.

Although experimental laboratory studies have not yet been conducted, the use of specific emotion regulation strategies in daily life, such as reappraisal or suppression, has also been examined in depressed individuals and healthy controls. In self-report studies by Gross, Richards and John (2008) of emotion regulation in daily life in healthy individuals, participants reported regulating their emotions on average 6.6 times per week, with cognitive reappraisal and response suppression being the most commonly reported strategies. Further, Gross et al. (2008) found that the frequency of use of specific emotion regulation strategies was related to their self-reported ability to use those strategies effectively in the lab. These results suggest the use of emotion regulation strategies in daily life is related to an individual's ability to effectively use adaptive regulation strategies, (such as reappraisal) which may have implications for

understanding the emotion regulation deficits observed in depression. Also along these lines, Mauss, Cook, Cheng and Gross (2007) demonstrated that individuals who were high on their reported use of reappraisal strategies responded with less self-reported anger, less negative affect and more positive affect after an anger-inducing laboratory manipulation. Physiological measures also showed evidence that individuals high on reappraisal were more successful at down-regulating their emotional responses (Mauss et al., 2007). Indeed, individuals with major depression have been found to use positive reappraisal strategies less frequently relative to healthy controls (instead using avoidance or other less effective coping strategies), even when the stressfulness of the events are controlled for (Kuyken and Brewin, 1994). Fortunately, evidence from cognitive-behavioral therapy treatment studies suggests that competency with use of reappraisal strategies is not fixed and that the more an individual practices regulation skills in daily life, the more effective they become (e.g., Beck, Rush, Shaw $ Emery, 1979).

Does reappraisal influence the affective LPP response? Laboratory studies with healthy individuals have found that ERP components related to affective responding may be modified by emotion regulation instructions to reappraise the emotional stimulus. For example, Moser, Hajcak, Bukay and Simons (2006) demonstrated that instructions to decrease emotional responding resulted in reductions of the LPP response to negatively valenced affective pictures relative to a passive viewing condition. This finding was replicated and extended by Hajcak and Nieuwenhuis (2006) and by Moser, et al. (2009) using instructions to reappraise negative stimuli as less negative. Specifically, instructions to reappraise unpleasant stimuli have been shown to decrease the magnitude of the LPP response, with modulation of the LPP beginning to occur just

after 300ms after stimulus onset, which has been interpreted as reflecting a diminished emotional response following emotional regulation instructions (e.g., Hajcak and Niewenhuis, 2006). This interpretation is consistent with findings that the magnitude of the LPP is positively correlated with subjective ratings of emotion intensity (e.g., Cuthbert et al., 2000). Krompinger, Moser and Simons (2008) found that cognitive reappraisal of positive pictures also resulted in an attenuated LPP response to positive emotional pictures, comparable to the findings of the impact of reappraisal on response to negative pictures.

To rule out whether the reduction in the LPP response might be due to a shift in how the pictures were appraised or due to an increase in task difficulty associated with reappraisal (that it may increase cognitive load), Foti and Hajcak (2008) followed-up on these findings with a paradigm in which participants were given audio recorded narratives that reappraised the negative images, rather than having participants generate their own reappraisals. They found that changes in narrative were sufficient to modulate the LPP response to emotional pictures, such that the LPP was reduced for negative emotional pictures after hearing a reappraisal narrative. Self-report arousal ratings were also reduced. In sum, these findings suggest that the reduction in the LPP response magnitude during reappraisal cannot be explained by reappraisal being a more difficult task than passing viewing. One important extension of this work would be to examine whether reappraisal has a diminished impact on the LPP among mood-disorders individuals who might be theorized to be impaired at this emotion regulation strategy.

The Current Study

Research examining emotional reactivity in mood-disordered individuals has consistently found dysfunctions in emotional responding in mood-disordered relative to healthy individuals; but effects are heterogeneous. Unfortunately, prior research has done little to isolate two critical sources of heterogeneity represented by the time course of emotional responding and the impact of emotion regulation strategies on emotional reactivity. Further, it remains unclear whether emotion deficits apparent in MDD are specific to the current negative mood state or may reflect a trait-like vulnerability to developing the disorder. In light of these limitations in previous research, this study utilized event-related potentials to examine emotional responses (as reflected by the LPP) to affective pictures in a sample of currently depressed (MDD), fully remitted depressed (RMD) and healthy individuals with no history of psychopathology. The emotion regulation strategy of reappraisal were used in this study, because (1) it is reported as commonly used in daily life, (2) extensive research has examined the effects of this strategy in healthy samples and (3) clinical research suggests that depression may be characterized by difficulties in cognitive reappraisal of negative events.

Specific Aims

Specific aim 1a. To replicate previous research demonstrating an LPP response to emotional pictures in healthy individuals and extend findings to MDD individuals. Given previous findings of blunted emotional reactivity in other emotional response systems, it was hypothesized that MDD individuals would show less-arousal related change in the LPP to emotional pictures relative to healthy controls.

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Specific aim 1b. To examine whether any group differences found are specific to the current negative mood state by comparing responses in the MDD and RMD groups. If group differences between the MDD and controls in the magnitude of the emotion-modulated LPP response are driven by prevalent negative mood, the RMD group should more closely resemble the healthy individuals. However, if group differences are driven by a more trait like characteristic related to vulnerability to developing depression or a residual effect of previous depressive episodes, the RMD group should more closely resemble currently depressed individuals. Based on recent previous findings in a similar sample (Rottenberg et al., 2005) it was hypothesized that LPP effects would depend on current mood state and the RMD group would more closely resemble the healthy controls. However, as other previous studies of emotional reactivity have also found the opposite pattern (e.g., Sigmon and Nelson-Gray, 1992), this was a low confidence prediction. To our knowledge, no prior studies have made this comparison using event-related potentials.

Specific aim 2a. To replicate previous findings demonstrating modulation of the LPP response to positive and negative emotional images in healthy individuals with reappraisal instructions and to extend these findings to MDD individuals to examine impairments in the implementation of cognitive reappraisal on emotional reactivity in mood-disordered individuals. Based on previous findings, it was expected that emotion regulation instructions to reappraise emotional stimuli would result in a reduction in the LPP amplitude in healthy individuals for both positive and negative stimuli. Given the emotional deficits observed in depression, it was hypothesized that MDD individuals would show a reduced effect of reappraisal on modulation of the LPP response

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amplitude in response to emotional pictures, particularly for the negatively valenced stimuli.

Specific aim 2b (exploratory). If group difference are observed, another aim is to examine whether group differences found in the modulation of the LPP response with reappraisal are specific to the current negative mood state or a more trait-like characteristic that may confer vulnerability to developing MDD (or a residual effect of previous depressive episodes). If group differences between the MDD and control group are driven by the presence of a negative mood state, the RMD group should more closely resemble the healthy individuals. However, if group differences are driven by a more trait-like characteristic related to vulnerability to developing depression or a residual effect of past depressive episodes, the RMD group should more closely resemble the MDD individuals. Given that the reappraisal effect on the LPP has not yet been examined in MDD, we did not make specific predictions about the RMD group.

METHOD

Participants

See Appendix 1 for a general outline of the method. Participants included 25 unipolar depressed persons, 26 recovered depressed persons and 25 healthy nonpsychiatric controls recruited from the greater Tampa Bay area through fliers and online postings. Participants in this project were part of a larger ongoing study in the Mood and Emotion Lab. Groups were matched on age, self-reported ethnic identity, gender composition and socio-economic status. Inclusion criteria were: English fluency, between the ages of 18 and 60, with current Major Depressive Disorder (MDD), fully remitted Major Depression (RMD), or no history of psychopathology (healthy controls). Diagnoses were made according to DSM-IV criteria. All subjects were required to meet the following additional criteria: English fluency, right handed, age between 18 and 60, no reported history of brain injury, no lifetime history of primary psychotic ideation, no lifetime diagnoses of bipolar disorder, no behavioral indications of possible impaired mental status and no reported substance abuse within the past six months. Since this was a naturalistic study of depressive symptoms, data concerning treatment was collected, but patients' treatments were not altered in any way. Participants provided written informed consent at the time of the diagnostic interview session and were compensated $15/hour for their time.

The present study monitored medication use but did not require that participants be unmedicated. Few studies have examined the impact of antidepressant medications

on the LPP or other ERP components involved in affective processing. One study

(Labuschagne, Croft, Phan and Nathan, 2008) examining the effects of a selective

serotonin reuptake inhibitor (citalopram) in healthy individuals on the affective LPP

response (to emotional facial expressions) demonstrated that the use of citalopram

(versus placebo) resulted in an enhanced LPP response to sad faces, independent of

behavioral measures of mood change. However, another investigation (Kerestes et al.,

2009) found no effect of citalopram or reboxetine (a norepinephrine reuptake inhibitor)

on the LPP response to emotional faces in healthy individuals, but demonstrated a

potentiated N250 response (associated with processing happy versus neutral faces),

suggesting that antidepressant use may shift perceptual biases in emotional processing

towards more positive stimuli. Some modest evidence indicates that antidepressants

may impact ERP components in response to emotional pictures. With this caveat, we

retained medicated participants in the sample to increase study feasibility and the real-

world generalizability of the study sample to persons with mood disorders.

The proposed sample size was selected to achieve a power of at least .80 with a

two-tailed alpha level of .05, using methods suggested by Cohen (1988). No meta-

analyses have reported an averaged effect size of the emotion-modulated LPP response,

but studies with healthy individuals have consistently found very large effects ($f > .9$) in

the change in LPP magnitude for high arousing positive or negative pictures versus low-

arousing neutral pictures. The effect size for the impact of reappraisal strategies on the

emotion modulated LPP response has also been large ($f > .4$). No studies have

examined a group by task interaction with MDD or RMD individuals in examinations of

the emotion-modulated LPP response, so it remains unclear what the effect size would

be. However, in other ERP studies of MDD individuals examining group by task interactions in studies of cognitive processing, typically large size group by condition effects (f > .4) are observed (e.g., Shestyuk et al., 2005; Ilardi et al., 2007). Assuming a large effect size (f > .4) for the group by condition interactions, a total sample size of 75 individuals would have an observed power of .87.

Diagnostic procedure

Participants who contacted the lab to participate in the study were first screened with a brief phone screening based on key diagnostic questions from the SCID-I/P. Participants deemed likely to qualify were invited to the lab to complete a SCID-I/P interview for a conclusive determination of depression status, administered by clinical psychology doctoral students. As part of the larger study, a total of 820 potential participants were initially screened by telephone. Of those individuals, 271 were scheduled to complete the Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/P W/ PSY SCREEN; First, Spitzer, Gibbon and Williams, 2002). A total of 240 participants completed the initial SCID diagnostic interview and 143 were determined to be eligible following the SCID interview.

Participants who meet criteria for one of the three diagnostic groups (MDD, RMD, or Control) based on the outcome of the diagnostic interview were invited to return to the lab to participate in the ERP protocol within three weeks. Of 143 participants determined eligible by the SCID for the larger study, 76 completed the ERP

session. Participants from the parent study participated in the ERP session depending on

their interest and the feasibility of scheduling. A total of 17 participants returned later

than three weeks; these cases were re-administered the mood modules of the SCID-I/P

interview to confirm their diagnostic status (and all were still eligible). Some

participants were also recruited after their 6-month follow-up SCID in the larger study

(14 participants). Most participants also completed additional psychophysiological

laboratory sessions on separate dates as part of the parent study. Other laboratory

sessions involved collection of respiratory sinus arrhythmia and other cardiovascular

data in response to emotional films and stressful tasks, none of which overlapped with

the present protocol.

Measures

Demographics questionnaire. Participants completed a questionnaire targeting

age, ethnicity, education, marital status and socioeconomic status information.

Handedness measure. Initially, handedness was assessed by asking participants

verbally whether they identified as right or left handed at one of the diagnostic interview

or other study sessions. In order to assess handedness more thoroughly, given that there

is evidence that emotional responding may be lateralized in the brain, the short version

of the Edinburgh Handedness Inventory (Oldfield, 1971) was used to assess type and

degree of laterality. This 10-item self-report measure assesses hand preferences, which

has been shown to reflect a more accurate representation of degree and type of laterality

(Williams, 1991). Scores on the EHI range from -100 (more left-handed) to +100 (more

right-handed). Established cut-offs suggest that scores of 40 or more on these measure

reflect primarily right-handedness, scores between -40 to +40 reflect ambidexterity and scores <-40 reflect primarily left-handedness (Oldfield, 1971).

Diagnostic interviews. Diagnostic evaluations were based on DSM-IV (APA, 2000) criteria using the Structured Clinical Interview for DSM-IV Axis I (SCID-I/P; First et al., 2002). Inter-rater reliabilities with the SCID-I are higher than those typically reported for diagnostic reliability (i.e., r>.82 for major Axis I diagnostic categories; Skre, Onstad, Torgersen and Kringlen, 1991). Formerly depressed participants met SCID-I/P criteria for a past episode of MDD. To ensure the formerly depressed individuals are not currently symptomatic, we implemented guidelines from the NIMH Collaborative Program on the Psychobiology of Depression to screen out individuals who had current symptoms of depression (e.g., Keller, Lavori, Mueller and Endicott, 1992). According to these guidelines, participants must report virtually no signs of depressive illness (i.e., no more than two symptoms and those symptoms experienced only to a mild degree) when questioned week-by-week using a modified version of the SCID-I about the presence of all nine DSM-IV depression symptoms during the eight weeks prior to the interview. Healthy control participants were required to be free of any lifetime diagnoses of an Axis-I disorder when assessed with the SCID-I/P.

As a part of ongoing efforts to monitor diagnostic reliability in the parent study, there was a reliability analysis of 15 cases that were selected and contained both eligible and ineligible participants. Diagnostic agreement with the original decisions was assessed with a second rater who was blind to the diagnostic decisions of the first rater and who independently assessed the SCID-I solely on the basis of the audiotape records. For the classification of current major depression (MDD) and healthy control subjects,

the decisions of the first and second rater agreed in all 15 cases, $k =1.00$. For the classification of recovered major depression (RMD) the decision of the first and second rater agreed in 14 of 15 cases, $k =.81$.

Symptom severity measures. At the time of the SCID interview, participants were also administered the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), which is a well-validated clinician-rated measure designed to assess the presence and severity of depression symptomatology. Each item is scored on a 0-2 or 0-4 scale during a structured interview with the patient and the sum of these ratings is used as a score of global severity of depressive symptoms. For the Hamilton Rating Scale for Depression (HAM-D), we obtained very high levels of interrater reliability, $\alpha=.98$. The Beck Depression Inventory (BDI-II; Beck, Steer and Brown, 1996) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown and Steer, 1988) were also administered at the ERP session. The BDI-II and the BAI are both 21-item well-validated self-report measures of depression and anxiety symptom severity.

To measure dispositional positive and negative affect, the trait version of the Positive and Negative Affect Scale (PANAS; Watson, Clark and Tellegen, 1998) was administered at the ERP session. The PANAS is a 20-item inventory measuring several discrete emotions as well as positive and negative affect dimensions. Each mood item is rated on a 9-point scale, ranging from 0=not at all to 8=extremely. The PANAS is a well-validated measure that has successfully differentiated depression and anxiety in clinical samples (e.g., Jolly, Dyck, Kramer and Wherry, 1994).

Self-report measures of emotion regulation tendencies. The Emotion Regulation Questionnaire (ERQ; Gross and John, 2003), also administered at the ERP session, was

used to assess individual differences in the use of the emotion regulation strategies. This measure was selected due to its focus on reappraisal and suppression strategies and the ERQ has demonstrated adequate internal consistency on its two scales (α=.79 reappraisal, α =.73 suppression) and test-retest reliability (r=.69; Gross and John, 2003). See appendix for a copy of the measure.

Post-task questionnaires. A post-task questionnaire was completed after each of two sets of trial blocks as a manipulation check to obtain information about emotion regulation strategies used by participants. The questionnaire also asked participants about their ability to use the reappraisal instructions effectively. See Appendices 3 and 4 for a copy of the post-task questionnaires.

Affective ratings. Participants provided self-report ratings of the arousal and valence of individual pictures with a modified version of the self-assessment manikin (SAM; Bradley and Lang, 1994). The SAM is a picture-based rating scale, in which participants provided ratings based on a range of pictures from a smiling figure to a frowning figure (for valence) and from an excited figure to a sleepy figure (for arousal) on a keyboard using a 9-point scale where higher numbers indicated higher arousal or more positive valence. The SAM is reliable with split-half correlations of r = .94 for valence and r = .93 for arousal (Lang, 1995) and high correlations with other widely used measures, such as the, Semantic Differential Scale (Bradley and Lang, 1994).

Materials

ERP Apparatus. All stimuli and instructions were presented using a DELL Genuine Intel x86 Family 6 model 8 computer and a 21-inch Sony Multiscan 220GS

monitor. The computer software E-prime (version 1.2; Schneider, Eschman and

Zuccolotto, 2002) was used to present all stimuli and collect responses and participants'

responses were recorded via a standard keyboard. Collection of ERP data was carried

out through the use of the Electrical Geodesics Incorporated System 200 (EGI, Eugene,

OR). Brain electrophysiology was recorded with a 128-channel Electrical Geodesics

Incorporated sensor net in conjunction with NETSTATION 4.2 acquisition software

powered by a Macintosh G4. Electroencephalographic data were sampled at 1000Hz.

Affective Stimuli. Pictures included 120 low-arousal neutral, 120 high-arousal

pleasant and 120 high-arousal unpleasant affective pictures from the International

Affective Picture System (IAPS) designed to elicit positive (e.g., smiling families,

sporting events, nudes), negative (e.g., human threat, animal threat, mutilation), or

neutral affect (e.g., household objects, leaves, neutral faces)[1]. Pleasant and unpleasant

pictures were matched on reported levels of arousal using published norms (Lang,

Bradley, and Cuthbert, 2005). Only high arousing pictures were used because ERP

studies of affective processing using the IAPS stimuli have demonstrated less consistent

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[1] The numbers of the IAPS pictures used were the following: unpleasant (1019, 1030, 1040, 1070, 1110, 1202, 1271, 1274, 1301, 1302, 1304, 2345.1, 2661, 2688, 2692, 2717, 2811, 2981, 3001, 3005.1, 3010, 3010, 3015, 3016, 3017, 3022, 3059, 3062, 3064, 3100, 3101, 3102, 3103, 3110, 3120, 3131, 3140, 3168, 3191, 3195, 3210, 3211, 3213, 3216, 3220, 3225, 3230, 3250, 3530, 3550.1, 4664.2, 5961, 5972, 5973, 6021, 6022, 6200, 6210, 6212, 6213, 6220, 6231, 6244, 6250, 6260, 6370, 6410, 6510, 6520, 6530, 6560, 6570, 6570.1, 6821, 6830, 6832, 6836, 6838, 6840, 6940, 7135, 8230, 8480, 8485, 9042, 9050, 9120, 9140, 9160, 9181, 9183, 9185, 9187, 9230, 9250, 9253, 9302, 9322, 9325, 9332, 9400, 9405, 9413, 9423, 9425, 9427, 9429, 9480, 9490, 9491, 9570, 9571, 9590, 9620, 9900, 9901, 9905, 9910, 9921, 9925), pleasant (1310, 1560, 1650, 1720, 1726, 2045, 2155, 2208, 2209, 2216, 2345, 2389, 2704, 4002, 4008, 4090, 4142, 4180, 4210, 4220, 4225, 4232, 4300, 4302, 4310, 4490, 4505, 4530, 4597, 4598, 4599, 4604, 4608, 4609, 4611, 4623, 4626, 4640, 4645, 4651, 4652, 4658, 4659, 4664, 4664.1, 4668, 4669, 4670, 4672, 4676, 4677, 4680, 4681, 4683, 4687, 4690, 4692, 4694, 4697, 4698, 4770, 4800, 5215, 5260, 5450, 5470, 5480, 5621, 5622, 5626, 5628, 5700, 5825, 5910, 5950, 6900, 6910, 7220, 7230, 7270, 7405, 7499, 7570, 7640, 7650, 7660, 8001, 8021, 8031, 8034, 8060, 8090, 8160, 8161, 8163, 8178, 8179, 8180, 8185, 8185, 8190, 8191, 8193, 8200, 8206, 8210, 8341, 8370, 8380, 8400, 8420, 8470, 8492, 8496, 8499, 8500, 8531, 9150, 9156, 9411) and neutral (2026, 2102, 2190, 2210, 2221, 2320, 2377, 2381, 2383, 2411, 2440, 2480, 2495, 2499, 2514, 2516, 2570, 2720, 2745.1, 2850, 2870, 2880, 2890, 5020, 5120, 5390, 5471, 5510, 5520, 5530, 553, 5720, 5726, 5731, 5740, 6150, 7001, 7002, 7004, 7006, 7009, 7012, 7019, 7020, 7025, 7026, 7030, 7032, 7038, 7040, 7045, 7052, 7055, 7059, 7060, 7100, 7150, 7170, 7179, 7185, 7187, 7217, 7224, 7233, 7234, 7235, 7255, 7490, 7491, 7493, 7500, 7700, 7705, 7710, 7950, 8312, 9210, 9260, 9360, 9700).

effects (increasing in the LPP magnitude) for pictures low on arousal (for review, see Oloffson et al., 2008). Pictures were selected to be comparable in valence, arousal and category to those used by prior studies of the LPP response to affective pictures (e.g., Keil et al., 2002; Cuthbert et al., 2000; Schupp et al., 2000).

ERP data collection procedure

Overview. At the time of the ERP session, participants first completed the BDI-II, BAI, PANAS, ERQ and the handedness self-report measures. During this time, the experimenter prepared an electrolyte solution composed of 1 liter distilled H2O, 1.5 teaspoons of NaCl and .75 teaspoons of baby shampoo and submersed the appropriately sized net for absorption of said solution. Upon completion of all questionnaires, the participant's head was measured and the 128-channel net was fitted on the participant's head and adjusted as needed for proper fit and to insure channel impedances were less than 50kΩ. Prior to each of the experimental blocks, participants performed several practice trials to familiarize themselves with the task and instructions. Once the participants were seated in the experiment room alone in front of the monitor the preprogrammed instructions led them through the remainder of the experiment. Brief periodic breaks were given every 5-10 minutes.

Experimental blocks. Two sets of trial blocks were administered, corresponding to the passive viewing and emotion regulation conditions. Blocks were divided into approximately 5-minute segments (approximately 8 in each set of trial blocks) where brief breaks were provided to the participants. Participants were asked to provide affective ratings of valence and arousal after a subset of trials. Due to time constraints,

these valence and arousal ratings were obtained only for the last trial of each block, for a total of 8 ratings (2 positive-passive, 2 positive-reappraise, 2 negative-passive, 2 negative-neutral). A Post-Task Questionnaire was completed after each set of trial blocks as a manipulation check to obtain information about emotion regulation strategies used by the participants. The first set of trial blocks consisted of passive viewing of 40 positive, 40 negative and 40 neutral pictures in a paradigm similar to that used in previous LPP research (e.g., Schupp et al., 2000; Cuthbert et al., 2000). Picture order was randomized, with the condition that no more than 3 trials of the same type appeared successively.

The second set of trial blocks consisted of passive viewing and reappraisal of positive and negative pictures and passive view of neutral pictures. This design was comparable to the paradigm used by Krompinger and colleagues (2008). Different pictures were used in the second set of trial blocks, but the pictures were matched on arousal and valence to pictures used in the first set of trial blocks. Specifically, this set of trial blocks included 80 passive-neutral, 40 passive-positive, 40 reappraise-positive, 40 passive-negative and 40 reappraise-negative trials, presented in random order. Different pictures were used for passive viewing and reappraisal trials that were matched on valence and arousal. The assignment of positive and negative pictures to the passive viewing and reappraisal was counterbalanced across participants. Because previous research has found carry over effects with regulation instructions of this type (Deveney and Pizzagalli, 2008), we protected against carry over by presenting the emotion regulation instructions prior to the second set of trial blocks, after the first set of trial blocks was completed, comparable to the procedure used by Hajcak and Nieuwenhuis

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(2006). This prevented the emotion regulation instructions from influencing the passive viewing set of trial blocks so that we could first establish the basic effect of emotional salience on the LPP in the three groups. In this way, an effect of the emotion-modulated LPP during passive picture viewing could be obtained before introducing a reappraisal condition, easing the interpretation of any group differences.

Trial sequences. For the passive viewing trialsblocks, a fixation cross appeared 1 second in the center of the screen in order to focus participants' attention to the upcoming pictures. This was followed by a blank screen presented for 500ms. IAPS pictures were then displayed for 6 seconds. For a subset of pictures, 500ms after picture offset, participants were asked to provide valence and arousal ratings of each picture, using the Self Assessment Manikin (SAM). Following the ratings, the next trial would begin after a variable inter-trial interval of 1-2 seconds (i.e., to reduce anticipation effects) in which participants were instructed to relax.

For the reappraisal trial blocks, a cue word indicating the task instructions ("LOOK" or "REAPPRAISE") appeared in the center of the screen for 1 second, followed by a blank screen for 500ms. IAPS pictures were again displayed for 6 seconds. For a subset of pictures, 500ms after picture offset, participants were asked to provide valence and arousal ratings of each picture, using SAM. See Appendix 2 for a visual diagram of the trial sequences.

Emotion regulation instructions. The instructions for passive viewing paralleled those used by Moser et al. (2009) and others. As in previous studies examining the modulation of the affective LPP with emotion regulation instructions (e.g., Moser et al., 2009), participants were not asked to attempt to reappraise neutral images, to avoid

confusion about how to regulate processes to pictures that elicit little or no emotion. For the emotion regulation condition, the reappraisal instructions closely followed those used by Hajcak and Nieuwenhuis (2006), in which the reappraisal instructions were effective at modulating the LPP response for negative images. To adapt the instructions for use with positive images, additions were made, comparable to those used by Krompinger et al. (2008). For ''Look'' trials, participants were asked to view the pictures and respond naturally without trying to alter their natural response while continuing to focus on the image. To "Reappraise," participants were instructed on how to reinterpret an unpleasant or pleasant picture so that it no longer elicits an emotional response.[2]

During the instructional portion, several examples (2 positive and 2 negative) were given by the experimenter in which it was described how to generate a less negative (or less positive) interpretation of the picture content (e.g., for a negative image, a bloody crime scene could be seen as the place where a murder investigation was finally solved. A positive erotic image could be seen as individuals engaging in risky behavior). Following this, the participant was given the opportunity to practice 2 positive and 2 negative reappraisals aloud, with feedback given by the experimenter, with additional assistance as needed. After the instructions and examples were given, participants completed five emotion regulation practice trials (2 positive, 2 negative and

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[2] Instructions given to participants for the regulation portion of the study prior to examples and practice trials were as follows: "In this part of the experiment, you will also be viewing a sequence of pictures and providing ratings of how you felt while viewing some of the pictures. Unlike before, you will also see a cue word appear about a second before each picture indicating instructions to follow while viewing the picture. These cue words will either be 'Look' or 'Reappraise.' For 'Look' trials, as before, please attend to the pictures and respond naturally. For 'Reappraise' trials, you will be asked to change your thoughts about negative images so that they become less negative. Similarly, for positive images, you will be asked to change your thoughts so they are experienced as less positive. We will do some examples in a minute. However, you do not want to change an emotion into the opposite emotion, for example, changing a positive picture into something negative. Rather, the idea is to change your thoughts about the pictures so that they become less emotional."

1 neutral). Examples and practice trials used pictures not included in the stimulus set. Following the instructions and practice trials, participants were given the opportunity to ask questions and work on more examples until the participants felt comfortable with the emotion regulation instructions and were able to generate appropriate reinterpretations.

Data Processing and Analysis

EEG Data Preprocessing. ERPs were digitally filtered with a 40hz low-pass filter and segmented into epochs around the stimuli presented (200ms before trial onset/2000ms after the onset of each affective stimuli). Epochs were screened for noncephalic artifact and marked as bad (i.e., excluded from further analysis) if they contain more than 15 bad channels using an automated artifact detection program. All participants had at least 20 good trials per condition and were included in the analyses. The artifact-free epochs were then averaged separately for each experimental condition within each individual. The epochs were then baseline corrected by 200ms and transformed using an average reference montage. Individual participant ERPs were combined to create grand average waveforms, which were first visually inspected.

As reviewed earlier, the LPP typically begins around 400ms, peaks around 850ms and extends for several seconds. We were guided by previous findings for defining the most logical LPP windows to use in this experiment (see Hajcak, MacNamara and Olvet, 2010 for review). Specifically, the dependent measure for the passive viewing block was defined as the mean amplitude of the an early LPP at 700-900ms following stimulus onset averaged over a parietal cluster that included the electrodes closest to CZ, PZ, CPZ, CP1 and CP2 (similar to Hajcak, Dunning and Foti,

2009) in the Geodesic Sensor Net (GSN). For the emotion regulation block, the dependent measure was defined as the defined as the mean amplitude of a late LPP at 1500-1700ms following stimulus onset averaged over the same parietal cluster. This window was chosen as the most likely to exhibit a regulation effect based on prior work finding peak effects in this window (MacNamara, Foti and Hajcak, 2009), though others have found reappraisal effects beginning around 700ms (Hajcak and Niewenhuis, 2006). Data were then transferred to SPSS 18 statistical software for further analysis. Prior to hypothesis testing, data were initially screened for any extreme outliers (>3SD's) in the extracted means for each condition within each individual.

Hypothesis Testing. To test hypotheses for specific aims 1a and 1b, a 3x3 repeated measures ANOVA was planned to examine group and picture condition main effects and group by condition interactions. Group (Control, MDD, RMD) and picture condition (negative, neutral, positive) were the independent variables and the average magnitude of the LPP for passive picture viewing in the first set of trial blocks was the dependent variable. Follow-up ANOVA and t-tests were planned to examine the specific nature of any group and condition differences. As mentioned earlier, the LPP time window selected was 700-900ms based on previous findings that the LPP in response to emotional images should be maximal in this window.

To test hypotheses for specific aims 2a and 2b, a 3x5 repeated measures ANOVA was planned to examine group and picture condition main effects and group by condition interactions. Group (Control, MDD, RMD) and picture condition (positive passive, positive regulation, negative passive, negative regulation, neutral) were the independent variables and the average magnitude of the LPP response in the emotion

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regulation trial blocks was the dependent variable. Follow-up ANOVA and t-tests were

planned to examine the specific nature of group and condition differences. We planned

to use the mean amplitude of the LPP in the 1500-1700ms time window, based on

previous findings that the largest impact of reappraisal on the LPP typically occurs in

this period. However, if the effects were not found in this time window, we planned

exploratory analyses in adjacent time windows. This would allow us to locate the

window in which the regulation effect was most apparent in the healthy controls to use

in examination of group effects.

RESULTS

Demographics and Clinical Characteristics of the Sample

A total of 25 Control, 25 MDD and 27 RMD eligible participants completed the ERP portion of the study. One RMD participant was later excluded from analyses after she revealed a previously undisclosed neurological condition (traumatic brain injury) during the ERP session. All remaining participants had valid data and were included in the analyses. This included one RMD participant who was missing data for the first passive viewing block due to a technical failure.

Because groups did not differ on age, ethnicity, gender, education level, income and marital status (all $ps > .05$ for Cramer V tests), these variables were not considered further. Table 1 contains demographic information of the sample according to diagnostic group. Final participants were primarily females (73.7%) and all were fluent in English and between the ages of 18 and 59 (mean age = 30.72). The final sample approximated the ethnic distribution of the Tampa Bay area: 68.4% Caucasian, 6.6% African American, 3.9% Asian, 19.7% Hispanic and 2.6% Mixed/Other.

Analyses of symptom severity scores were in line with the diagnostic categorizations. A one-way ANOVA confirmed that MDD individuals had significantly higher BDI, BAI and HRSD scores relative to healthy controls ($p<.001$). Further, the RMD and healthy controls groups did not significantly differ on depression severity measures ($p>.1$). For anxiety severity, the RMD group had marginally higher BAI scores relative to controls ($p=.06$). On the PANAS, the MDD group reported more PA

and less NA relative to both the RMD and control groups (p<.001), but the RMD and healthy controls did not differ (p>1.). As we did not include any healthy controls who were taking psychoactive medications or receiving psychotherapy or with a co-morbid anxiety diagnosis, we only examined whether the MDD and RMD groups differed on these variables. Cramer's V tests were not significant for psychotherapy for depression or antidepressant/anxiolytic use, with approximately one in four mood disorders participants reporting use of these medications. The MDD group did have a significantly higher rate of current co-morbid anxiety relative to the RMD group (Cramer's V, p<.01).

Although we initially excluded participants who verbally reported that they were left-handed during an earlier session in the study, according to the EHI, 5 participants scored in the ambidextrous range and 2 in the left-handed range, using the cut-offs established by the EHI (Oldfield, 1971.). Further, handedness differed by group (Cramer's V, p<.05), with the RMD group including both of the left-handed individuals. Therefore, analyses were run first with all participants included, then with the left-handed and ambidextrous individuals (EHI scores <40) excluded to see whether the patterns of results was effected by inclusion of these participants.

Table 1. Demographic and Treatment Characteristics of the Sample

	Group		
	MDD	RMD	Control
Variable	*(n = 25)*	*(n = 26)*	*(n = 25)*
Age, M (SD)	33.68 (12.29)	30.04 (11.95)	28.48 (12.41)
% Caucasian	62.9%	69.2%	72.0%
% Female	84.0%	65.4%	72.0%
% College Graduate	40.0%	46.1%	52.0%
Median Income	$20,000-$24,999	$20,000-$24,999	$25,000-34,999
% Single	36.0%	73.1%	72.0%
# Children (SD)	.80 (1.04)	.31 (.62)	.36 (.91)
% Antidepressants	20.0%	23.1%	0%
% Anxiolytics	8.0%	0%	0%
% Psychotherapy	28.0%	7.7%	0%
% Comorbid Anxiety	60.0%	19.2%	0%
Handedness (EHI)*	82.28 (21.97)	52.81 (49.89)	79.68 (18.28)

*Note. *Scores on the EHI range from -100 (more left-handed) to +100 (more right-handed). Established cut-offs suggest that scores of 40 or more on these measure reflect primarily right-handedness, scores between -40 to +40 reflect ambidexterity and scores <-40 reflect primarily left-handedness (Oldfield, 1971).*

Table 2: Means and Standard Deviations of Symptom and Self-Report Measures

	MDD	RMD	Control
HRSD	17.12 (4.01)	2.04 (2.25)	1.76 (2.74)
BDI	28.08 (8.51)	4.96 (5.05)	2.16 (1.11)
BAI	14.48 (8.80)	6.69 (6.45)	3.04 (3.96)
PA	2.30 (.71)	3.85 (1.06)	3.08 (1.19)
NA	2.24 (1.09)	1.45 (.72)	1.29 (.57)
ERQ-Reappraisal	4.53 (1.09)	5.03 (.86)	5.09 (.91)
ERQ-Suppression	3.86 (1.37)	2.77 (1.12)	2.83 (1.11)

Note. HRSD=Hamilton Rating Scale for Depression, BDI=Beck Depression Inventory, BAI=Beck Anxiety Inventory, PA=Positive Affect, NA=Negative Affect, ERQ=Emotion Regulation Questionnaire.

Emotion Regulation Questionnaire

On the emotion regulation questionnaire, MDD individuals reported significantly less use of reappraisal strategies in daily life relative to healthy controls (p<.05) and marginally less relative to RMD individuals (p=.07). For suppression, MDD individuals

reported significantly more use of suppression regulation strategies relative to both

RMD individuals and healthy controls (p<.01).

Valence and Arousal Ratings

As a manipulation check, paired t-tests were conducted to examine whether

positive and negative images differed from neutral on valence and arousal ratings and

whether valence and arousal ratings were reduced for reappraisal trials relative to

passive viewing trials. Collapsing across groups, all paired t-tests were significant in the

expected directions (all *ps*<.05). Therefore, overall, effects of valence, arousal and the

reappraisal manipulation were all apparent in the self-report valence and arousal ratings.

See Table 3 for means and standard deviations by group of self-reported valence and

arousal ratings.

To examine whether there were any group effects for valence and arousal ratings

during the passive viewing block, a one-way ANOVA was conducted with group status

as a predictor and the positive and negative valence and arousal ratings as the dependent

variables. Group was not a significant predictor of any of the positive and negative

valence and arousal ratings (all ps>.1). Follow-up tests showed one significant

difference that emerged, where RMD individuals rated the neutral images during the

emotion regulation block as more positive than the MDD individuals (t=2.6, p=.04), but

this difference was not observed for the neutral image ratings during the passive viewing

block (p>.1), and the overall group effect was not significant, so this finding should be

interpreted with caution.

To examine whether groups differed on valence and arousal change associated with reappraisal effects, change scores were first computed where the valence and arousal ratings for the reappraisal trials were subtracted from the corresponding passive viewing trials. One-way ANOVA with group as a predictor were then conducted with these change scores as the dependent variables. The only group effect that emerged was for the negative valence change score (F=3.20, p=.047). Follow-up t-tests revealed that for negative pictures the RMD group significantly differed from controls (t=2.5, p=.02) and marginally different from the MDD group (t=1.9, p=.07), such that the RMD group showed less benefit of the reappraisal instructions relative to the other groups (less improvement in valence ratings for reappraised versus passively viewed negative pictures). The MDD and control groups did not significantly differ from one another.

Table 3. Means and Standard Deviations of Valence and Arousal Ratings

	MDD		RMD		Control	
	Valence	Arousal	Valence	Arousal	Valence	Arousal
Passive Viewing Block						
Positive	5.68(.98)	4.56(1.67)	5.91(.87)	4.97(1.59)	5.52(.93)	4.71(1.42)
Negative	2.91(.94)	4.50(2.14)	3.58(1.21)	5.01(1.54)	3.13(1.07)	4.73(1.74)
Neutral	4.76(.59)	2.56(1.19)	4.99(.49)	3.04(1.51)	4.90(.76)	2.72(1.34)
Regulation Block						
Positive - Passive	5.08(.90)	4.13(2.10)	6.04(.87)	4.46(6.75)	5.72(.88)	4.62(1.90)
Positive - Regulation	3.69(.92)	3.92(1.92)	5.45(.86)	4.30(5.75)	5.16(1.06)	4.21(1.87)
Negative - Passive	2.98(.82)	4.13(2.10)	3.51(1.20)	4.36(1.73)	3.21(1.13)	4.47(2.10)
Negative - Regulation	3.69(.92)	3.92(1.92)	3.77(1.16)	4.36(1.73)	4.10(1.17)	4.14(2.01)
Neutral - Passive	4.65(.42)	2.52(1.45)	4.99(.49)	3.04(1.51)	4.83(.75)	3.09(1.61)

Note: Ratings were provided on a keyboard using a 9-point scale ranging from 1-9, with higher numbers indicating higher arousal or more positive valence.

Post-Task Questionnaire

For the passive viewing block, on the post-task questionnaire, there were marginally significant group effects for attempts to use suppression for positive (F=2.9,

p=.06) images. Specifically, follow-up tests revealed that MDD individuals reported more attempts to suppress emotions for positive images relative to healthy controls (p=.02) and marginally more relative to RMD individuals (p=.09). This pattern is consistent with what was reported on the ERQ, where healthy controls reported less use of suppression strategies in general.

For the emotion regulation block, surprisingly, all groups reported similar ability to utilize the reappraisal instructions to regulate their emotions, with no significant group effects apparent (all ps>.1). In general, all groups reported a good ability to reappraise the pictures as instructed (mean=5.6 for positive pictures and 5.12 for negative pictures on a scale from 1=strongly disagree to 7=strongly agree) and little difficulty with the task (mean=3.89 for positive and 4.20 for negative pictures).

LPP Results for Passive Viewing Blocks

Waveforms were first visually inspected and mean amplitudes for each individual and condition were inspected for extreme outliers (see Figure 1). No extreme outliers (<3 SD's) were present. As expected, it was confirmed that the LPP appeared to be maximal in the time window 700-900ms post-stimulus and statistics for this time window were extracted for further analysis. Initial analyses concerned whether the results were impacted by medication status. Two 1 x 3 (negative, neutral, positive) repeated-measures ANOVAS were conducted within the MDD and RMD groups together (none of the Controls were taking psychoactive medications) with antidepressant use and anxiolytic use within the past month as covariates. Neither

medication covariates were significant predictors of the LPP magnitude. Therefore, we subsequently collapsed across medication status in subsequent analyses.

To test hypotheses for specific aims 1a and 1b, a 3 (Group: MDD, RMD, Control) x 3 (Condition: negative, neutral, positive) repeated measures ANOVA was conducted with the mean LPP amplitude in the selected cluster as the dependent variable. As expected, there was a significant quadratic effect of condition (positive, negative, neutral pictures) on the LPP magnitude (F=90.31, p<.001). Follow-up t-tests revealed that the effects were in the expected direction, with negative and positive high-arousing pictures having significantly higher LPP mean magnitudes relative to neutral pictures (t=8.83, p<.001 for negative vs. neutral; t=6.59, p<.001 for positive vs. neutral). The LPP mean magnitude was nominally higher for negative vs. positive pictures; however, follow-up t-tests revealed this difference was not significant (p>.1). See Figure 2 for LPP means by condition and group for the passive viewing block.

In examining the impact of group status, a marginally significant group x condition interaction was observed (F=2.08, p=.09). To examine whether the quadratic effect was apparent in each group, the three groups were then analyzed separately with a 1 x 3 (Negative, Neutral, Positive) repeated-measures ANOVA.   For all 3 groups taken individually, there was a significant quadratic effect of condition (p<.01). Follow-up t-tests also demonstrated a greater LPP magnitude, as expected, for both positive and negative pictures relative to neutral (p<.01). The marginal group-level interaction appears to be driven by the RMD group who uniquely exhibited a trend towards a larger LPP for negative relative to positive (p=.08), while for the other two groups there was

no difference between the LPP elicited for positive versus negative pictures. Contrary to hypotheses, the MDD group did not exhibit less emotional modulation of the LPP.

Because more ambidextrous and left-handed individuals were in the RMD group, to ensure that these effects were not driven by handedness the analyses were re-run excluding these 8 individuals (6 RMD's and 2 MDD's dropped from the analysis). The pattern of results remained similar, with a significant quadratic effect of condition (F=66.71, p<.001), and a trend group by condition interaction (F=2.19, p=.12). There was also still a trend apparent with the RMD group exhibiting slightly higher LPP magnitudes for negative versus positive pictures (t=1.5, p=.15). Therefore, inclusion of the ambidextrous and left-handed individuals did not appear to change the pattern of results.
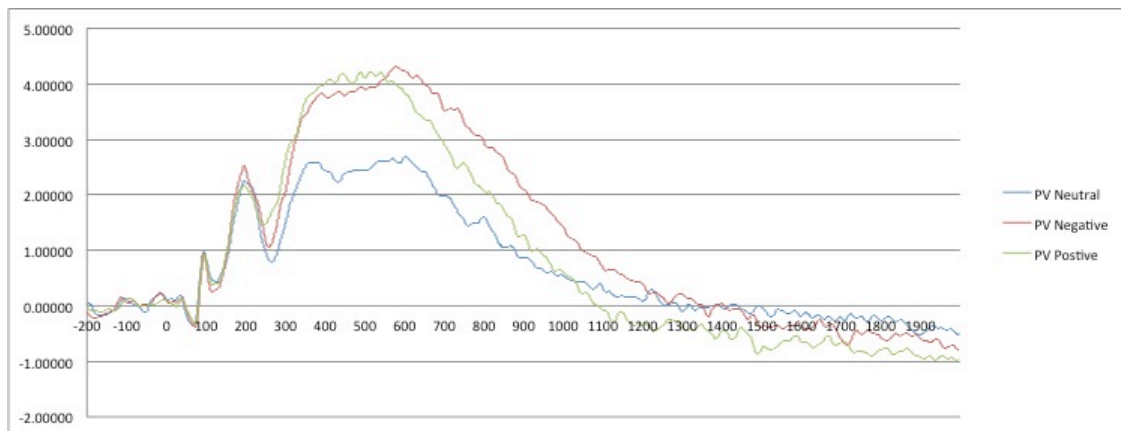
Figure 1. Grand average ERP waveforms plotted for each condition in the passive viewing block.

Note. Waveforms were averaged over a parietal cluster that included the electrodes closest to CZ, PZ, CPZ, CP1 and CP2. Stimuli were presented at Time=0 and the previous 200ms were used as baseline.

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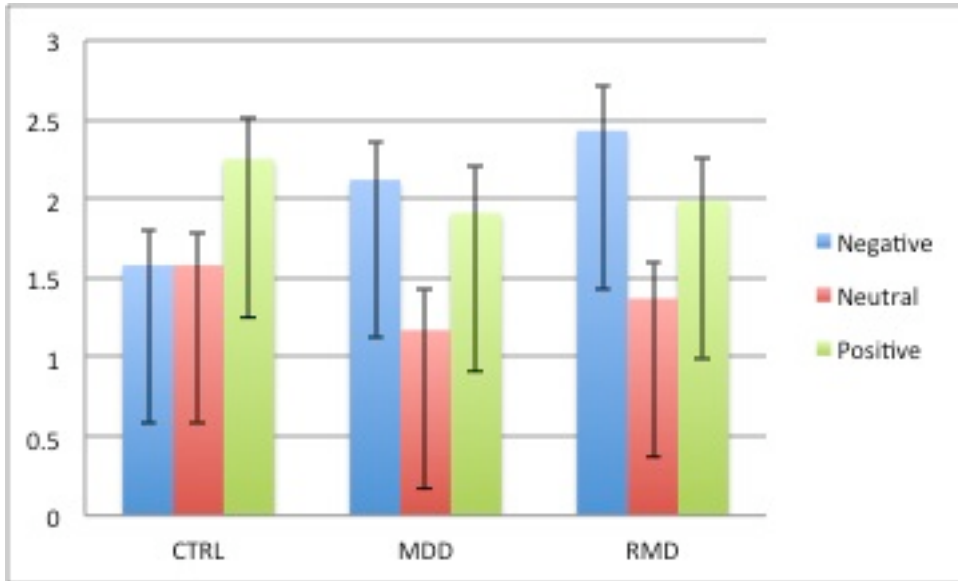
Figure 2. Mean LPP amplitudes for the passive viewing block by group and condition. Note. Waveforms were averaged over a parietal cluster in the 700-900ms time window.

LPP Results for Emotion Regulation Blocks

Waveforms were first visually inspected and mean amplitudes for each individual and condition were inspected for extreme outliers. See Figure 3 for a plot of the waveforms by group and condition for the emotion regulation block. Initial inspection of the LPP means for the emotion regulation blocks revealed 3 participants (2 Controls and 1 RMD) with multiple extreme outliers in an emotion regulation condition (>3 SD's). These participants were removed from subsequent analyses of emotion regulation.

Next, we examined whether we replicated previous findings in the 1500-1700ms window, specifically, whether we observed a decreased LPP response in healthy individuals with cognitive reappraisal instructions. To accomplish this we conducted a 1x5 (Condition: Negative Passive, Positive Passive, Negative Regulation Positive Regulation, Neutral) repeated-measures ANOVA within the healthy control group.

There was a trend for a linear effect of condition (F=2.55, p=.1). Follow-up t-tests

revealed that, there was a positive reappraisal effect with the LPP magnitude for positive

reappraisal being significantly lower relative to positive passive viewing (t=2.13, p=.05).

However, unexpectedly, the LPP for positive passive viewing versus neutral was only a

trend (t=1.63, p=.1), and the LPP for negative passive viewing viewing versus neutral

was not significant (t=1.07, p>.1). Given the lack of an LPP effect for negative passive

viewing versus neutral, it is not surprising that there was also no negative regulation

effect apparent, with negative passive viewing and negative regulation not significantly

differing (t=.13, p>.1). While other studies typically find that the LPP lasts for several

seconds (Hajcak et al., 2011), it is possible that given the extended length of the protocol

used here the duration of the LPP component may be reduced, as evidence by the lack of

a significant emotional (positive or negative) versus neutral LPP in this time window.

Although there was a small positive regulation effect present in this window, given the

weak positive passive versus neutral effect, it appeared that this may also not be the best

window to examine As a result, exploratory analyses were conducted in the three earlier

time windows, 1300-1500, 1100-1300 and 900-1100ms to see if a negative regulation

effect, or a stronger positive regulation effect, would be apparent earlier in the time

course.

In the 1300-1500ms time window, a significant linear effect of condition was

apparent (F=5.21, p=.03). Follow-up t-tests revealed that positive passive viewing

elicited a larger LPP magnitude relative to neutral (t=2.50, p<.05) and a smaller LPP for

positive regulation versus positive passive viewing (t=2.15, p<.05). However, neither

the LPP difference between negative passive viewing versus neutral, nor the effect of

negative regulation versus negative passive viewing was apparent. In the 1100-1300ms time window, again, there was a significant linear effect of condition (F=7.10, p=.01), with a trend regulation effect for positive regulation versus positive passive viewing (t=1.49, p=.15), but no negative regulation effects. The LPP effects for positive passive viewing versus neutral were only a trend (positive: t=1.50, p=.11), while the effect for negative passive viewing versus neutral was significant (t=2.41, p=.03). For the 900-1100ms time window, a significant linear effect of condition was again found (F=13.33, p=.001). Finally, a significant regulation effect for negative pictures was observed (t=2.15, p=.04), but the regulation effect for positive pictures was no longer significant (t=.68, p=.51). Here also the LPP effect was apparent for negative versus neutral pictures (t=4.04, p<.001), and the LPP was marginally greater for positive pictures versus neutral (t=1.88, p=.07).

In sum, although significant effects were not in the expected time windows, results demonstrated a regulation effect for the healthy controls in the expected direction, with the positive regulation effect of a reduced LPP being strongest in the 1300-1500ms time window (significant effects for both positive regulation versus passive and positive versus neutral) and the negative regulation effect of a reduced LPP being strongest in the 900-1100ms time window (significant effects for both negative regulation versus passive and negative versus neutral). Therefore, repeated measures ANOVA to examine the impact of group status on these effects were targeted to these specific time windows, with separate analyses for positive and negative regulation to test hypotheses for specific aims 2a and 2b.

To examine the impact of group status on the positive regulation effect observed in the healthy controls in the 1300-1500ms time window, a 3 (Group) x 3(Condition: Positive Passive, Positive Regulation, Neutral) repeated measures ANOVA was conducted with the mean LPP amplitude in the selected cluster as the dependent variable. While there was an overall linear effect of condition (F=7.40, p<.01), there were no group or group by condition interaction effects. All groups exhibited lower LPP mean magnitudes for the positive regulation versus positive passive viewing conditions; however, this effect was only significant for the control group (t=2.60, p=.02). See Figure 4 for mean LPP magnitudes by group and condition for the positive regulation effect.

Similarly, to examine the impact of group status on the negative regulation effect observed in healthy controls in the 900-1100ms time window, a 3(Group) x 3 (Condition: Negative Passive, Negative Regulation, Neutral) repeated measures ANOVA was conducted with the mean LPP amplitude in the selected cluster as the dependent variable. There was an overall linear (F=24.94, p<.001) and quadratic effect of condition (F=6.82, p<.05). Importantly these effects were qualified by marginally significant group by condition quadratic effect (F=2.87, p=.06). To decompose this negative regulation effect, follow-up t-tests comparing conditions for each group separately revealed that the MDD group did not show a regulation effect (negative regulation not significantly different from negative passive viewing); and both negative passive and negative regulation pictures elicited a larger LPP relative to neutral (ps<.01). For RMD participants, the opposite regulation effect was observed, with larger LPPs for the negative regulation versus the negative passive viewing condition (p<.01). For the

RMD group, the negative regulation and negative passive viewing also both elicited larger LPP magnitudes relative to neutral (ps<.001). This pattern was opposite to the regulation effect observed in healthy controls described earlier, where instructions to reappraise negative pictures resulted in a reduced LPP magnitude. The lack of a regulation effect observed in the MDD group supports our hypothesis that the MDD group would show deficits in their ability to use reappraisal to reduce the magnitude of the LPP. For the MDD group, reappraisal had no effect on the emotional response to negative pictures, as indexed by neural activity. Surprisingly, the RMD group differed from both the MDD group and the controls, demonstrating a larger LPP for the regulation condition, paradoxically suggesting that reappraisal actually intensified the emotional response to negative pictures, as indexed by neural activity. In other words, for the negative pictures neither the MDD nor the RMD groups exhibited the expected benefits of reappraisal (a reduced LPP in reappraisal versus passive viewing). See Figure 5 for LPP magnitudes by group and condition for the negative regulation effect.

Similar to the analyses conducted for the passive viewing blocks, because more ambidextrous and left-handed individuals were in the RMD group, to ensure that these effects were not driven by handedness the above analyses were re-run excluding these 8 individuals (6 RMD's and 2 MDD's dropped from the analysis). The pattern of results remained similar for the positive regulation findings in the 1300-1500ms time window, with a significant linear effect of condition still apparent (F=5.88, p=.02), with no significant group by condition interaction. All groups means remained in the expected directions, with positive regulation LPP means lower relative to positive passive viewing means, but again with only the control group demonstrating a significantly greater LPP

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magnitude for positive passive viewing versus positive regulation (t=2.6, p=.02). The

pattern of results also remained similar for the negative regulation findings in the 900-

1100ms time window, with a significant linear effect of condition still apparent

(F=22.77, p<.001), although the group by condition interaction was reduced to trend

level (F=2.28, p=.11). Follow-up t-tests also revealed comparable findings, with the

control group still demonstrating a reduced LPP for the negative regulation relative to

negative passive viewing (t=2.15, p=.04), and the RMD group showing the opposite

effect with a marginally larger LPP for the negative regulation relative to negative

passive viewing (t=1.89, p=.07). Again, the MDD group did not exhibit a negative

regulation effect in either direction (t=.56, p=.58). In sum, inclusion of the

ambidextrous and left-handed individuals did not appear to have an impact on the

overall pattern of findings.
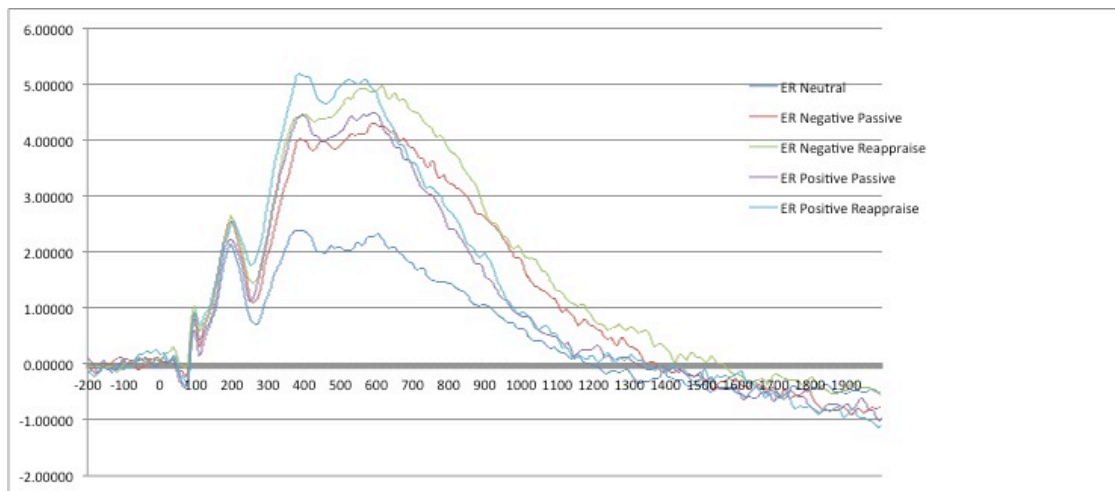
Figure 3. Grand average ERP waveforms plotted for each condition in the emotion
regulation block.

Note. Waveforms were averaged over a parietal cluster that included the electrodes
closest to CZ, PZ, CPZ, CP1 and CP2. Stimuli were presented at Time=0 and the
previous 200ms were used as baseline.
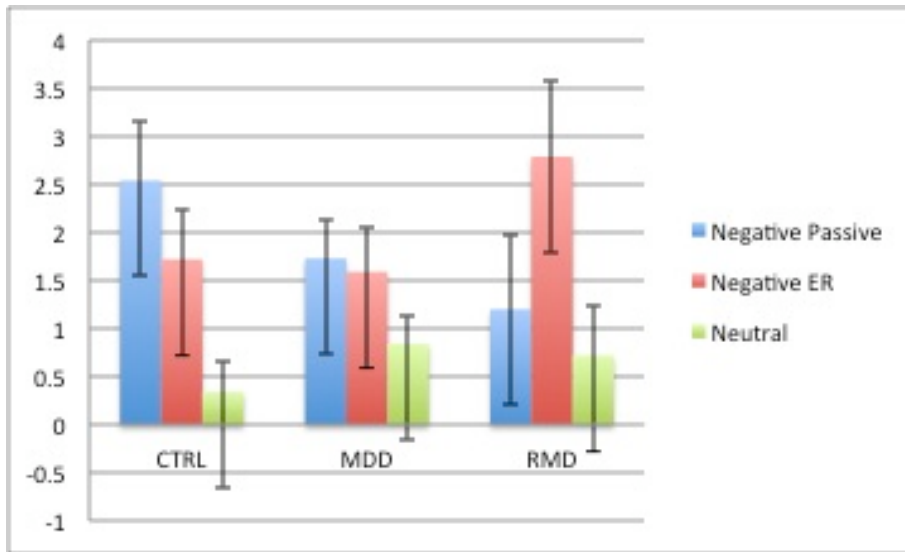
Figure 4. Mean LPP amplitudes for the negative passive viewing, negative regulation, and neutral conditions in the emotion regulation block by group and condition.

Note. Waveforms were averaged for the selected parietal cluster in the 900-1100ms time window.   Error bars represent standard errors.
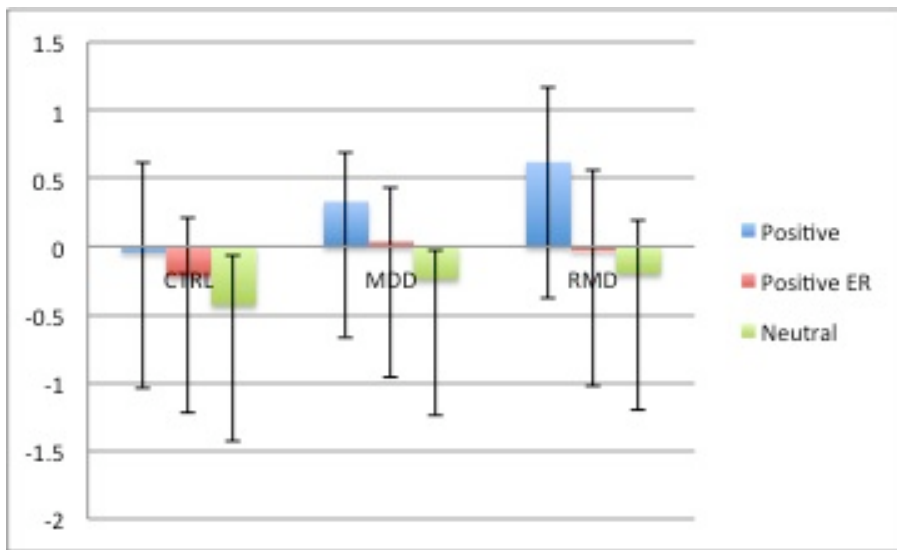
Figure 5. Mean LPP amplitudes for the positive passive viewing, positive regulation, and neutral conditions in the emotion regulation block by group and condition.

Note. Waveforms were averaged for the selected parietal cluster in the 1300-1500ms time window.   Error bars represent standard errors.

DISCUSSION

Previous research examining emotional reactivity in mood-disordered individuals has consistently found dysfunctions in emotional responding in mood-disordered individuals, though the effects are heterogeneous (Bylsma et al, 2008). Prior research has done little to isolate potential sources of heterogeneity, as represented by the time course of emotional responding and the impact of emotion regulation strategies. Further, little is known about whether individuals with remitted depression show trait-like emotional deficits comparable to individuals with MDD, or whether the effects are mood state dependent.

The aim of the current study was to examine depression-related differences in emotional responding and the impact of reappraisal emotion regulation strategies in the context of high-arousing positive and negative emotional pictures. A secondary aim was to examine whether individuals with remitted depression more closely resembled those with current depression or healthy never-depressed controls. This study utilized ERPs to examine the magnitude of the Late Positive Potential (LPP), a component demonstrated to be sensitive to motivationally relevant emotional stimuli and regulation instructions (Hajcak et al., 2010). In a regulation condition, participants were asked to reappraise positive and negative emotional pictures as less emotional, using instructions comparable to other studies (e.g., Hajcak and Nieuwenhuis, 2006).

LPP Results for Passive Viewing Blocks

The expected pattern of LPP responding was observed for healthy controls, with both positive and negative high arousing pictures eliciting a stronger LPP relative to neutral pictures. This is consistent with a growing body of other studies demonstrating the importance of the LPP as an index of emotional salience (for review, see Hajcak, 2010). Further, the mood-disordered group also exhibited higher LPP's for emotional pictures than for neutral pictures. A marginally significant group by condition quadratic interaction was also observed. Because follow-up tests did not reach statistical significance, interpretative caution is warranted. For the RMD group, negative pictures elicited a marginally larger LPP for negative relative to positive stimuli, with no differences observed for positive versus negative pictures in the other two groups, suggesting that for the RMD individuals negative pictures may be slightly more motivationally salient relative to positive pictures. Although the comparisons in the other two groups were weaker and did not reach trend level significance, it is notable that the MDD group also exhibited the same pattern as the RMD group with the LPP mean for negative pictures being slightly higher relative to positive pictures, while for the healthy controls the LPP mean for positive pictures was slightly higher relative to negative pictures. Again, these findings did not reach significance and limited conclusions can be drawn, but given the closer similarity between the MDD and RMD group, the pattern of results may be more consistent with a trait like effect.

In sum, in the passive viewing conditions, contrary to our hypothesis, there was no evidence of less emotion modulation of the LPP relative to controls among currently depressed persons or persons with remitted depression. This is in contrast to previous

studies of emotional reactivity in MDD utilizing other physiological measures (see Bylsma, et al., 2008, for review). One possibility for the discrepancy may be the relatively brief duration of the stimuli and measured emotional responses. For example, in studies using the emotion-modulate startle paradigms, startle probes are typically presented 3-5 seconds post-picture onset (e.g., Lang, Bradley and Cuthbert, 1990). Results suggest that initial emotional reactions may be comparable in mood disordered and healthy individuals, with deficits in emotional responding perhaps appearing later. Analyses later in the time course of the LPP may help to elucidate whether this may be the case.

LPP Results for Emotion Regulation Blocks

In the emotion regulation block, the LPP did not appear to last as long as anticipated in healthy participants (prior studies demonstrating an LPP effect for at least several seconds), particularly for negative pictures, which may have reduced our ability to find regulation effects. Although other studies have reported a longer LPP, with reappraisal instructions showing a peak effect around 1600ms (MacNamara, et al., 2009), the extended protocol used here with the passive viewing block occurring first, may have reduced the intensity of the LPP response for the second block, as evidenced by the lack of an emotional LPP effect (emotional versus neutral) in the later time windows for the emotion regulation block. Hajcak and Nieuwenhuis (2006) also used a similar extended protocol with a passive viewing block followed by a regulation block without a similar reduction in the LPP intensity, though their regulation block was somewhat shorter and did not include a positive regulation condition.

Therefore, rather than using the 1500-1700ms time window as the exclusive window for examining regulation effects, we examined several earlier time windows where the LPP effect of emotional versus neutral pictures was more apparent in healthy participants. For both positive and negative pictures, we observed an effect of reappraisal on the LPP, such that regulation instructions reduced the magnitude of the LPP for emotional pictures relative to passive viewing. This effect was most apparent in the 1300-1500ms time window for positive pictures and the 900-1100 time window for negative pictures, suggesting a differential time course for reappraisal of positive versus negative events. Therefore, these identified time windows were used to test for group effects. We are cautious in interpreting the reasons why positive and negative emotion regulation effects were apparent in different time windows because of the paucity of studies that have positive and negative reappraisal conditions in the same paradigm.

For positive picture conditions, all groups showed a similar impact reduction of the LPP response to positive pictures in the 1300-1500ms time window, with no group by condition interaction, suggesting that all groups were able to utilize reappraisal effectively to reduce reactivity to positive material, as indexed by ERP. This converged with group differences on self-report ratings of valence and arousal. However, in examining the groups individually, only the control group showed a significant effect of positive regulation versus positive passive viewing, suggesting that this effect is more robust in healthy controls. For negative pictures, a significant group by condition interaction was observed. Specifically, consistent with predictions, the MDD group failed to show a negative regulation effect (differences between in LPP magnitude for reappraisal versus passive viewing were not significant). For the RMD group, the

opposite regulation effect was observed, with a larger LPP elicited for negative

regulation versus the negative passive viewing.

In sum, results suggest that both the MDD and RMD groups show intact ability

to reduce the emotional salience of positive stimuli using reappraisal strategies, as

indexed by the LPP, although the effect may be weaker in the MDD and RMD groups.

However, both the MDD and RMD groups demonstrate deficits in their ability to

reappraise negative emotional pictures, with no reductions in the LPP observed in the

MDD group and enhanced LPP during reappraisal observed in the RMD group, also

consistent with reappraisal deficits in mood disorders. The lack of an effect of

reappraisal for negative pictures in the MDD group was consistent with predictions that

MDD individuals would demonstrate deficits in their ability to utilize regulation

strategies effectively. Further, the lack of an appropriate regulation effect of reappraisal

in the RMD group was consistent with the regulation difficulties observed in MDD,

suggesting this may be representative of a trait-like effect that may confer vulnerability

to depression. Reappraisal strategies are thought to act through evaluative processes that

compute the affective significance of emotional stimuli (McCrae et al., 2010). It may be

that a deficit in this evaluative process contributes to the etiology of depression, or may

be a residual of a prior depressive episode.

Self-report Findings

On the emotion regulation questionnaire MDD individuals reported generally

less use of reappraisal and more use of suppression relative to RMD individuals and

healthy controls in daily life, consistent with previous literature suggesting that MDD is

characterized by deficits in cognitive reappraisal (e.g., Campbell-Sills and Barlow, 2007). It may be that lack of practice utilizing reappraisal strategies leads to deficits in their effectiveness. Further, the RMD group and controls more closely resembled each other, suggesting that the choice of regulation strategies may be impacted by current mood state, rather than reflecting an underlying vulnerability to developing depression.

On valence and arousal ratings provided for a subset of emotional pictures during the passive viewing block, all groups looked generally comparable in terms of their valence ratings of positive, negative and neutral emotional pictures, with valence and arousal ratings for emotional pictures differing from neutral in the expected directions. For the emotion regulation block, when all groups were collapsed together regulation effects were apparent, with arousal and valence ratings shifting in the expected directions for regulated versus passively viewed pictures. However, a group effect was observed where the RMD group showed less benefit of the reappraisal instructions relative to the other groups, in terms of changes in valence for the negative reappraised pictures relative to negative passively viewed pictures, while the MDD and control groups did not differ from one another. These findings are consistent with the LPP findings that RMD individuals failed to show an appropriate reduction in the LPP for the reappraisal condition to negative pictures. However, in contrast, on a post-task questionnaire, all groups reported similar ability to utilize the reappraisal instructions to regulate their emotions for both positive and negative pictures. Given some of the discrepancies observed in the self-report and LPP responses, data from other response systems, such as facial EMG data, would be useful to help clarify what these findings mean for the ability of mood-disordered individuals to successfully utilize reappraisal.

The LPP findings showing abnormal negative reappraisal effects for the MDD group are consistent with previous research suggesting mood-disordered individuals have difficulty regulating negative emotions (e.g., Gross and Munoz, 1995). Further, the presence of deficits in the RMD group may reflect an underlying vulnerability for developing a major depressive episode, or a residual effect from a past episode, although the effect is in the opposite direction for those in a current episode. Both the MDD and RMD groups failed to benefit from reappraisal of the negative images, as indicated by the lack of reduction in the LPP response for reappraised versus passively viewed negative images. As this is the first study to demonstrate this effect, replication of this finding would be useful to determine whether or not it can be substantiated.

Conclusions, Limitations and Future Directions

This study was the first to assess the LPP response to emotional pictures and the impact of reappraisal on the LPP response in a clinical MDD and RMD sample. Results suggest that MDD and RMD individuals show generally comparable patterns of responding to positive versus negative stimuli, as reflected by the LPP, although with the RMD group showing a marginally larger LPP response to negative versus positive images. No group effects were observed for positive regulation effects in the LPP or self-report valence and arousal ratings. However, the MDD and RMD groups demonstrated deficits in their responses to reappraisal for the negative images, as reflected by a lack of a reduction in the LPP for reappraisal relative to passive viewing. Also consistent with these findings, the RMD group demonstrated a reduced ability to shift negative valence ratings in the negative reappraisal condition. Self-report findings

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from the ERQ that MDD individuals utilize reappraisal strategies less frequently in daily life are also consistent with these findings. Findings are mixed as to whether observed deficits are more reflective of a negative mood state or a trait characteristic, with the RMD group more closely resembling the MDD group in regards to the LPP findings, while more closely resembling the healthy controls in the ERQ findings.

Given that findings did not occur in the expected time windows and some paradoxical findings were observed in the RMD group, planned follow-up analyses of these data include further examination of the time course of the LPP response to emotional salience and impact of reappraisal strategies to examine group difference in the latency and duration of effects, in order to provide a better understanding of the current findings. Further, examination of other relevant ERP components may help to shed light on other emotionally relevant processes, such as attention. Principal components analysis (PCA) may also be useful to better differentiate the affective LPP from other overlapping components, such as the P300.

One limitation of this study is that, since we did not regulate treatment of the MDD and RMD groups, many participants were taking antidepressants and anxiolytics, which may impact the results. We did not observe any impact of antidepressant or anxiolytic use on the LPP response in co-variate analyses; however, it is still possible that use of these medications may impact the findings in some way. Further, as depression and anxiety are highly co-morbid, it was not possible to recruit a pure depressed sample with no co-morbid anxiety diagnoses. Therefore, co-morbid anxiety may be driving some of the findings. However, again, exploratory co-variate analyses did not show a significant impact of anxiety severity or presence of a co-morbid anxiety

diagnosis on the LPP response. Further, while we attempted to initially exclude non-right handed individuals, some left-handed and/or ambidextrous individuals were included in the final sample. However, follow-up analyses removing these individuals from the primary analyses did not show any substantial change in the pattern of results, suggesting that, at least for the particular effects examined here, laterality effects did not appear to be an issue. Key strengths of this study include use of a clinical sample of individuals with MDD, inclusion of a remitted group, and utilization of the ERP method, which affords high temporal precision.

In future studies, more detailed examinations of the time course of the LPP response in mood-disordered individuals would also be useful to further examine which particular processes may be dysfunctional in depression. Along these lines, examination of other regulation strategies besides reappraisal would be informative, such as distraction, which has been shown to impact the LPP at an earlier stage in the time course (around 300ms post-stimulus) and is thought to be more reflective of basic attentional processes (e.g., Thiruchselvam, Blechert, Sheppes, Rydstrom and Gross, 2011). Future studies should also further examine the impact of medication use or co-morbid anxiety in mood-disordered samples. Treatment studies may benefit from examining emotional responding and ability to use specific regulation strategies and how emotional responding and use of adaptive regulation strategies, such as reappraisal, may change following cognitive-behavioral therapy. Utilization of the LPP and a reappraisal paradigm could potentially be used as a biological outcome measure for clinical interventions focusing on skills training in reappraisal process.

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APPENDICES

Appendix 1: Method Outline

Table A1. Method Outline.

Recruitment and Screening
1. Participants were recruited through a larger project being conducted in the Mood and Emotion Lab through fliers and online postings in the community.   2. Participants first screened by phone.   3. Participants deemed eligible invited to come to the lab for a SCID interview.
Diagnostic Interviews
1. Participants completed the SCID interview with a clinical psychology graduate student, including the Hamilton Rating Scales for Depression. Demographics information also collected at this time.   2. Individuals meeting criteria for current MDD, RMD, or healthy controls based on the SCID who reported being right-handed were invited to participant in the ERP portion of the study within 3 weeks of the initial SCID interview (or in some cases, the follow-up SCID interview 6 months later).   **3.** Most participants also complete other laboratory sessions as part of the larger study in the Mood and Emotion Lab. Those sessions involved measuring respiratory sinus arrhythmia and other cardiovascular variables in response to emotional films and stressful tasks. Clinical and physiological assessments for the larger study occurred at two time points 6 months part.
ERP Session
1. Consent (specific for ERP portion of the study)   2. Self report questionnaires administered (EHI, BDI-II, BAI, PANAS, ERQ)   3. Participants fitted with the ERP net   4. Instructions for Part I   5. Administration of Part I – Passive Viewing Trial Blocks   6. Post-Task Questionnaire Part I   7. Instructions for Part II   8. Administration of Part II – Emotion Regulation Trial Blocks   9. Post-Task Questionnaire Part II   10. Debriefing and payment

Passive Viewing Trial Blocks

+		Positive, Negative, or Neutral Picture		Valence and Arousal Ratings (subset of trials)	Variable iti
1000 ms	500 ms	6 s	500 ms		1-2 s

Emotion Regulation Trial Blocks

Cue		Positive, Negative, or Neutral Picture		Valence and Arousal Ratings (subset of trials)	Variable iti
1000 ms	500 ms	6 s	500 ms		1-2 s

Figure A1. Diagram of trial sequences for passive viewing and emotion regulation trial blocks.

Appendix 3: Post-Task Questionnaire Part 1

We would like to ask you some questions about your emotional responses to the pictures in the last task. For each item, please answer using the following scale.

1---------------2---------------3---------------4---------------5---------------6---------------7
strongly disagree   neutral   strongly agree

<u>When viewing the **positive** pictures:</u>

1. _____ I did not try to change my emotional experience.

2. _____ I changed the way I was thinking about the pictures to increase my emotion.

3. _____ I changed the way I was thinking about the pictures to decrease my emotion.

4. _____ I tried to distract myself from the pictures by thinking about something else.

5. _____ I looked away from the pictures to avoid experiencing emotion.

6. _____ I tried to detach myself from the situation in the picture.

7. _____ I tried to view the picture in a way that was personally relevant.

8. _____ I tried to suppress my emotions.

9. _____ I felt in-control of my emotions.

10. _____ I used another strategy to alter my emotions.

   <u>Please describe:</u>

<u>When viewing the **negative** pictures:</u>

1. _____ I did not try to change my emotional experience.

2. _____ I changed the way I was thinking about the pictures to increase my emotion.

3. _____ I changed the way I was thinking about the pictures to decrease my emotion.

4. _____ I tried to distract myself from the pictures by thinking about something else.

5. _____ I looked away from the pictures to avoid experiencing emotion.

6. _____ I tried to detach myself from the situation in the picture.

7. _____ I tried to view the picture in a way that was personally relevant.

8. _____ I tried to suppress my emotions.

9. _____ I felt in-control of my emotions.

10. _____ I used another strategy to alter my emotions.

   <u>Please describe:</u>

Appendix 4: Post-Task Questionnaire Part 2

We would like to ask you some questions about your emotional responses to the pictures in the last task. For each item, please answer using the following scale.

1--------------2--------------3--------------4--------------5--------------6--------------7
strongly disagree   neutral   strongly agree

<u>When instructed to "Reappraise" the pictures:</u>

Positive Pictures

1. _____ I was successfully able to reappraise the pictures according to the directions.

2. _____ It was difficult for me to reappraise the pictures.

3. _____ I did not try to reappraise the pictures.

4. _____ I used another strategy to change my emotion when viewing the pictures.

     Please describe:

Negative Pictures

1. _____ I was successfully able to reappraise the pictures according to the directions.

2. _____ It was difficult for me to reappraise the pictures.

3. _____ I did not try to reappraise the pictures.

4. _____ I used another strategy to change my emotion when viewing the pictures.

     Please describe:

<u>When instructed to "Look" at the pictures:</u>

Positive Pictures

1. _____ I did not try to change my emotional experience.

2. _____ I tried to reappraise the pictures.

3. _____ I used another strategy to change my emotion when viewing the pictures.

     Please describe:

Negative Pictures

4. _____ I did not try to change my emotional experience.

5. _____ I tried to reappraise the pictures.

6. _____ I used another strategy to change my emotion when viewing the pictures.

     Please describe: