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Depression and Reduced Neural Response to Emotional Images: Distinction From Anxiety, and Importance of Symptom Dimensions and Age of Onset

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Abnormal patterns of attention to threat and reward have been proposed as potential mechanisms of dysfunction in anxiety and unipolar depressive disorders. However, few studies have simultaneously examined whether these patterns of attention are shared among disorders or distinguish between them. In the present study, we recorded the Late Positive Potential (LPP), an event-related potential and putative index of motivated attention, from 145 patients with anxiety and unipolar depressive disorders and 32 controls, as they viewed blocks of rewarding and threatening images, respectively. We found that a current diagnosis of depression was associated with a reduced LPP to rewarding visual stimuli. This appeared to be specific to a subgroup of individuals with early onset depression; this subgroup was also characterized by a reduced LPP to threatening images. Anxiety diagnosis and age of onset of anxiety, whether comorbid with depression or not, was unrelated to the magnitude of the LPP. Finally, a transdiagnostic symptom dimension measuring current severity of suicidal ideation was related to a reduced LPP to both rewarding and threatening images. These data suggest that dysfunction in neural markers of attention to threat and reward can effectively distinguish features of depression from anxiety, particularly early onset depression, and may track suicidal ideation across disorders.

General Scientific Summary
Depression and Anxiety are two classes of psychiatric disorders that are notoriously difficult to disentangle: They often co-occur and the diagnoses encompass very heterogeneous groups of individuals. This study may help differentiate these diagnoses by identifying patterns of neural response to emotional content in depression that differ from anxiety, and also identifying a specific depressed subgroup driving these effects. These results also show that increased suicidality, regardless of diagnosis, was associated with a tendency to pay less attention to emotional images.

Keywords: late positive potential, anxiety, depression, threat, reward

Anxiety and unipolar depressive disorders (i.e., internalizing disorders) are among the most common (Demyttenaere et al., 2004; Kessler, Berglund, et al., 2005), and costly forms of disease worldwide (Mathers, Fat, & Boerma, 2008). However, despite the enormous public health burden they impose, treatments for these disorders remain only moderately efficacious, likely because of the limitations of psychiatric diagnoses as treatment targets (Atkinson et al., 2013; Insel et al., 2010; Sanislow et al., 2010). Disorders are highly comorbid (Kaufman & Charney, 2000; Kessler, Berglund, et al., 2005; Kessler, Chiu, Demler, & Walters, 2005; Moffitt et al., 2007), and diagnostic categories encompass heterogeneous groups of patients (Helzer, Kraemer, & Krueger, 2006; Klein, 2008). These issues pose challenges to research and treatment: heterogeneity can obscure effects that are specific to a subgroup of patients with the disorder, whereas comorbidity makes it difficult to determine which condition drives the observed effects.

To address these and other problems with categorical nomenclature, the National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) initiative. Rather than relying on categorical definitions of psychopathology, RDoC aims to characterize psychological dysfunction via disturbances in transdiagnostic functional *dimensions* (Cuthbert, 2014; Cuthbert & Insel, 2010; Sanislow et al., 2010). In particular, looking beyond diagnostic variables to dimensional measures of response to reward and threat may be helpful in addressing both heterogeneity and comorbidity within the internalizing dimension. Reward and threat represent two fundamental motivational imperatives that elicit approach and avoidance tendencies, respectively, and have evolved to promote individual and species survival (Bradley, Co-

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dispoti, Cuthbert, & Lang, 2001; Bradley, Sabatinelli, & Lang, 2014). Abnormal patterns of attention—a process that directs cognitive resources to motivationally salient stimuli and information—to reward and threat may be useful in untangling anxiety and depression and refining phenotypes within the internalizing spectrum (e.g., Shankman et al., 2013). For instance, though heightened negative affect is thought to be common to both anxiety and depression, there is evidence that blunted response to positive events is a unique factor in depression (Clark & Watson, 1991; Keller et al., 2000; Shankman & Klein, 2003; Shankman et al., 2013), and heightened response to threat is a unique factor in anxiety (Compton, Heller, Banich, Palmieri, & Miller, 2000; Shankman et al., 2013; Weinberg, Klein, & Hajcak, 2012).

However, reduced response to reward and heightened response to threat appear to explain only a part of the clinical heterogeneity in depression and anxiety, respectively. For example, some individuals with a diagnosis of depression are not reward-insensitive (e.g., Foti, Carlson, Sauder, & Proudfit, 2014; Shankman, Klein, Tenke, & Bruder, 2007; Weinberg & Shankman, 2015), whereas some anxious individuals are (Kessel et al., 2015). Moreover, there is conflicting evidence as to whether individuals with a diagnosis of depression may also be hyperresponsive to threat (Siegle, Carter, & Thase, 2006; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), or are instead better characterized by blunted emotional responses to all emotional stimuli (Bylsma, Morris, & Rottenberg, 2008; Proudfit et al., 2015; Rottenberg, Gross, & Gotlib, 2005). Consistent with the latter possibility, some data suggest that increased threat response observed in depression might be driven primarily by comorbid symptoms of anxiety (Beesdo et al., 2009; Engels et al., 2010).

Thus, to clarify how dysfunction in attentional circuits related to reward and threat map onto clinical manifestations of depression and anxiety, researchers will need to complement case-control studies with research that accounts for heterogeneity and comorbidity. In addition to measuring diagnostic comorbidity by recruiting representative clinical samples, it will also be important to consider transdiagnostic symptom dimensions that present across depression and anxiety disorders (Watson, 2009; Watson & Clark, 2006). Many symptom dimensions, such as lassitude, irritability, and suicidality, have been identified in factor analytic studies (Watson et al., 2012), and there is evidence that suicidality is associated with abnormal reward responding across diagnostic categories (Dombrovski, Szanto, Clark, Reynolds, & Siegle, 2013; Dombrovski et al., 2011; Elman, Borsook, & Volkow, 2013). Less is known about other such constructs, as few studies have used empirically derived dimensions, nor have they examined these dimensions across multiple internalizing disorders.

Age of onset of internalizing disorders may be another important source of heterogeneity, as juvenile- and adult-onset affective disorders appear to have distinct courses and etiologies (Jaffee et al., 2002; Klein & Allmann, 2014). Early onset (i.e., before the age of 18) affective disorders appear to be associated with higher rates of comorbidity, as well as increased use of long-term psychiatric services, and overall impaired functioning (Weissman et al., 1999). Early onset anxiety and depression also appear more heritable and familial (Goldstein et al., 1997; Levinson et al., 2003; Merikangas et al., 1999; Rosenbaum et al., 1992) than adult-onset affective disorders, implicating genetic risk factors. Consistent with this, neural and peripheral markers of reward and threat processing appear to reflect biological susceptibility factors, in that abnormalities are often present before disease onset (e.g., Gotlib et al., 2010; Grillon, Dierker, & Merikangas, 1997; Kujawa, Proudfit, & Klein, 2014). In particular, early onset depression appears to be more strongly associated with reward-processing deficits relative to later onset (Durbin, Klein, Hayden, Buckley, & Moerk, 2005; Shankman et al., 2007), though few studies have examined the influence of comorbid anxiety, or whether threat responding might also be impaired.

Our aims in the present study were to examine neural markers of attention to threatening and rewarding visual stimuli across internalizing disorders, as well as in relation to empirically derived phenotypes that cut across these disorders. We focused our analyses on the Late Positive Potential (LPP), a component of the event-related potential (ERP) that presents as a sustained positive-going deflection in the waveform beginning as early as 200 ms after stimulus onset (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Hajcak, Dunning, & Foti, 2009) and persisting for the duration of picture presentation (Hajcak & Olvet, 2008; Pastor et al., 2008). The LPP reflects attentional engagement with salient environmental stimuli, and is reliably enhanced by emotional relative to neutral images (Cuthbert et al., 2000; Foti, Hajcak, & Dien, 2009; Pastor et al., 2008; Schupp et al., 2000), and particularly those categories of emotional images most pertinent to survival, affiliation, and reproduction (Briggs & Martin, 2009; Weinberg & Hajcak, 2010).

The LPP appears to arise from the ongoing activation of, and communication between, multiple regions of the brain—including visual, parietal, and frontal cortices (Keil et al., 2002; Sabatinelli, Keil, Frank, & Lang, 2013; Sabatinelli, Lang, Keil, & Bradley, 2007), as well as subcortical structures like the ventral striatum and the amygdala (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; Sabatinelli et al., 2013). However, there is evidence that rewarding and threatening visual images engage distinct, albeit overlapping, neural networks (Sabatinelli, Bradley, Lang, Costa, & Versace, 2007), and moreover, that these distinct networks can contribute differentially to the magnitude of the LPP. In a recent study that combined electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI), Liu and colleagues (2012) demonstrated that activity in the ventral lateral prefrontal cortices, insula, precuneus, left middle temporal cortex, and left postcentral cortex was uniquely correlated with the LPP elicited by threatening images. Activity in the amygdala, nucleus accumbens (NAcc), and medial prefrontal cortex (MPFC), regions of the brain that have been implicated in reward processing (Knutson et al., 2003; Rogers et al., 2004) uniquely predicted the LPP elicited by rewarding images. This suggests that, despite the fact that the magnitude of the LPP is increased to both threat and reward, the respective underlying neural systems may differ, and further suggests that the magnitude of the LPP might be useful in tracking individual differences in neural networks implicated in processing reward and threat.

Indeed, variation in the LPP has been linked to both depression and anxiety. A blunted LPP to threatening content has been observed in current depression (Foti, Olvet, Klein, & Hajcak, 2010) and risk for depression (Kujawa, Hajcak, Torpey, Kim, & Klein, 2012; Nelson et al., 2015). Similarly, there is evidence for an enhanced LPP to unpredictable threatening images in individuals

with Generalized Anxiety Disorder (GAD; MacNamara & Hajcak, 2009, 2010), in specific-phobic individuals viewing phobic objects (e.g., Flykt & Caldara, 2006; Leutgeb, Schafer, & Schienle, 2009), and in socially phobic individuals viewing angry and fearful faces (Moser, Huppert, Duval, & Simons, 2008).

However, most of these studies focused on attention to threatening but not rewarding stimuli, and few studies have examined how depression and anxiety might independently or synergistically influence the response to rewarding and threatening affective content (see, however, MacNamara & Proudfit, 2014). Therefore, the present study sought to examine motivated attention to both rewarding and threatening images in a diverse sample of individuals with internalizing disorders. We hypothesized that anxiety disorders might be more strongly associated with an enhanced response to threatening images, whereas unipolar depressive disorders would exhibit a blunted response to both affective image types (Bylsma et al., 2008; Foti et al., 2010; Kujawa et al., 2012; Proudfit et al., 2015; Rottenberg et al., 2005), but that this effect would be strongest for rewarding images (e.g., Treadway & Zald, 2011). There is also evidence that reward-insensitivity may be particularly characteristic of some subgroups of depressed individuals (e.g., Foti et al., 2014; Shankman et al., 2007)—particularly individuals with an early onset of depression (e.g., Shankman et al., 2007). To that end, we also examined the magnitude of the LPP in early versus adult onset anxiety and depression. Finally, to address distortions posed by heterogeneity and to identify specific phenotypes linked to abnormal emotional processing, we also examined the association of the LPP with empirically derived symptom dimensions across all diagnostic categories. These analyses were necessarily more exploratory, and were guided by the results of the diagnostic-level analyses.

Method

Participants

Participants for this study were recruited in one of two ways: 318 patients were recruited from outpatient Psychology and Psychiatry clinics at Stony Brook University, local community mental health centers, and assisted-living facilities and community programs for the mentally ill, to gain a wide and representative range of internalizing psychopathology. An additional 26 participants were patients who presented at Stony Brook University Medical Center for treatment of chronic medical conditions (e.g., diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, or autoimmune disorders); thus, they were drawn from the same source population of Suffolk County, NY, residents as the psychiatric patients, using a similar recruitment strategy—and had no lifetime depressive or anxiety disorders. This control group was selected to approximate functional disability and demographics of the psychiatric group and isolate effects of psychopathology from those related to nonspecific impairment, as "super-healthy controls" may increase the rates of false positives in psychiatric research (e.g., Lewis & Pelosi, 1990). Many individuals in this control group reported limited social functioning as a result of their physical impairments, and 36% of this group was unemployed. None of the individuals in the control group reported depression or anxiety secondary to a general medical condition. All 344 participants were offered $125 for their participation in a 5-hr protocol.

Once in the lab, all participants were administered the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (SCID; First et al., 1995). The SCID is a well-validated semistructured interview for current and past *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (*DSM–IV*) Axis I diagnoses. The SCID was administered by five master's-level clinicians. Before the study, all diagnostic interviewers underwent an extensive training process, and regular meetings were held throughout the course of the study to ensure continued agreement and compliance. Interrater reliability was assessed based on 21 participants in this study. For each reliability SCID, a second clinician from the group was selected at random to rate video-recorded interviews blind to original ratings. For the diagnoses of interest in the present study, κs ranged from .70 (for current posttraumatic stress disorder [PTSD]) to 1.00. All diagnostic-level information reported here is based on the SCID. Age of onset data for each diagnosis was also collected during the course of the SCID. The interviewers also gathered participant-reported information on current psychotropic medication usage.

We were interested in individuals who met diagnostic criteria for a current *DSM–IV* anxiety disorder (agoraphobia, generalized anxiety disorder [GAD], obsessive compulsive disorder [OCD], PTSD, panic disorder, simple phobia, and social phobia), and/or a current unipolar depressive disorder (MDD or dysthymia), *or* no current or past Axis I diagnoses. Of the 344 participants, 42 were excluded because they did not complete the viewing task which was the target of this study, 48 did not have a current anxiety or depressive disorder but had a lifetime Axis I disorder and could not be assigned to study groups, and 69 had lifetime bipolar or psychotic disorder; the remaining 177 participants were retained in the current analyses.

In addition to the SCID, participants were administered the Interview for Mood and Anxiety Symptoms (IMAS; Kotov, Perlman, Gamez, & Watson, 2015; Ruggero et al., 2014). Like the SCID, the IMAS provides information on symptoms in the past month. However, every question is asked of every participant (i.e., there are no skip-out rules), permitting dimensional assessment of psychopathology. The IMAS was designed to cover all *DSM–IV* mood and anxiety disorder symptom criteria, and includes 29 subscales related to unipolar depression and anxiety: dysphoria (5 items; $\alpha = .79$), lassitude (5 items; $\alpha = .82$), anhedonia (6 items; $\alpha = .81$), insomnia (4 items; $\alpha = .73$), suicidality (4 items; $\alpha = .63$), appetite loss (3 items; $\alpha = .84$), agitation (5 items; $\alpha = .77$), psychomotor retardation (5 items; $\alpha = .72$), excessive worry (5 items; $\alpha = .84$), additional GAD symptoms (7 items; $\alpha = .81$), reexperiencing (4 items; $\alpha = .73$), avoidance (3 items; $\alpha = .74$), numbing (3 items; $\alpha = .74$), hyperarousal (6 items; $\alpha = .80$), dissociation (3 items; $\alpha = .56$), panic physiological (8 items; $\alpha = .76$), panic psychological (7 items; $\alpha = .72$), interactive anxiety (3 items; $\alpha = .71$), performance anxiety (6 items; $\alpha = .79$), fear of public places (6 items; $\alpha = .82$), fear of enclosed places (6 items; $\alpha = .79$), animal phobia (3 items; $\alpha = .70$), situational phobia (3 items; $\alpha = .63$), blood-injection-injury phobia (4 items; $\alpha = .61$), obsessions (6 items; $\alpha = .75$), cleaning (5 items; $\alpha = .79$), rituals (6 items; $\alpha = .81$), and checking (4 items; $\alpha = .83$). Extensively trained lay interviewers administered the IMAS. Individual items are scored on a 3-point rating scale (*absent*, *subthreshold*, or *above threshold*). All interviews were recorded; a second interviewer selected at random from the lay interviewers rescored 34 record-

ings. Interrater reliability was excellent, with ICCs ranging from .93 to .99 across the scales included here. All of the subscales included in analyses were screened to ensure approximately normal distribution, with the criteria that skewness and kurtosis not exceed 1.5.

Task and Materials

Two hundred-seventy images were selected from the International Affective Picture System (IAPS; Bradley, Lang, & Cuthbert, 2005). Rewarding images included erotic images of heterosexual couples, as well as affiliative images (e.g., smiling families, people embracing, and babies laughing). Threat images included images of mutilation, death, and animal and human threat. Neutral images included images of objects (e.g., a lamp, a mushroom), as well as images of neutral human faces. Normative ratings (Lang et al., 2007) indicated that the 90 threatening pictures were less pleasant (valence $M = 2.44$, $SD = .69$) than the 90 neutral pictures ($M = 5.15$, $SD = .65$) which were less pleasant than the 90 rewarding pictures ($M = 7.13$, $SD = .62$; higher numbers indicate more pleasant ratings). Threatening ($M = 6.10$, $SD = .74$) and rewarding ($M = 5.91$, $SD = .85$) images were more emotionally arousing than neutral images ($M = 3.32$, $SD = .72$; higher numbers indicate higher arousal). Specific images used in the study are listed in Appendix A.

All visual stimuli were presented on a Pentium D computer, using Presentation software (Neurobehavioral Systems, Inc.; Albany, CA). Before each trial, participants viewed a white fixation cross on a black background. Each picture was displayed in color at 48.26 cm, the full size of the monitor. Participants were seated approximately 60.96 cm from the screen and the images occupied about 40° of visual angle horizontally and vertically.

Procedure

Subsequent to verbal instructions indicating that they would be passively viewing pictures of varying emotional quality, participants were seated and electroencephalograph sensors were attached. All participants performed multiple tasks during the experiment; results from other tasks are reported elsewhere (e.g., MacNamara, Kotov, & Hajcak, 2015; Weinberg, Kotov, & Proudfit, 2015). The order of the tasks was counterbalanced across subjects. For the current study, participants viewed three blocks of images, with each block consisting of rewarding-only, threatening-only, or neutral-only images.[1] The order of the blocks was random across subjects, and between each block, participants were given a short break. Within each block, the order of picture presentation was random for each participant, and each image was presented twice; blocks lasted approximately 5 min each. Each image was presented for 1,500 ms, with fixed 2 s intervals between image presentations.

EEG Recording and Data Processing

Continuous EEG recordings were collected using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Thirty-four electrode sites were used, including FCz and Iz, based on the 10/20 system, as well as two electrodes on the right and left mastoids. Electrooculogram (EOG) generated from eye movements and eyeblinks was recorded using four facial electrodes: horizontal eye movements (HEM) were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Vertical eye movements (VEM) and blinks were measured via two electrodes placed approximately 1 cm above and below the right eye. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio and amplified with a gain of 1× by a BioSemi ActiveTwo system (BioSemi, Amsterdam). The data were digitized at 24-bit resolution with a LSB value of 31.25 nV and a sampling rate of 1,024 Hz, using a low-pass fifth order sinc filter with −3 dB cutoff point at 208 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode, located between PO3 and POz, producing a monopolar (nondifferential) channel. CMS forms a feedback loop with a paired driven right leg (DRL) electrode. Offline, all data were referenced to the average of the left and right mastoids, and band-pass filtered from 0.01 to 30 Hz. Eyeblink and ocular corrections were conducted using VEM and HEM channels per a modification of the original algorithm published in Gratton, Coles, and Donchin (1983).

A semiautomatic procedure was used to detect and reject artifacts. The criteria applied were a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of less than 0.50 μV within 100 ms intervals. These intervals were rejected from individual channels in each trial. Visual inspection of the data was then conducted to detect and reject any remaining artifacts (e.g., ocular artifacts that were not fully removed during ocular correction, or slow-wave activity which was not identified by the automatic parameters). Eight participants were excluded at this stage as a result of poor data quality (i.e., they had fewer than 12 usable trials per condition; Moran, Jendrusina, & Moser, 2013). For the remaining subjects, an average of 2% of the data was identified as artifactual using the automated criteria. An average of 6.7% was identified during the visual inspection process.

The EEG was segmented for each trial beginning 200 ms before picture onset and continuing for 1,700 ms (i.e., the entire duration of picture presentation). For each trial, a baseline of the average activity in a 200 ms window before picture onset was subtracted from every data point. ERPs were constructed by separately averaging epochs by picture content (rewarding, neutral, and threatening). Previous research has demonstrated that the LPP is maximal at centro-parietal sites (Foti & Hajcak, 2008; Foti et al., 2009; Hajcak et al., 2009), and visual inspection of grand averages confirmed that this was also the case in the current sample; therefore, the LPP was scored as the average activity at three centro-parietal sites (Pz, CP1, and CP2), between 400 and 1,000 ms (Hajcak, Dunning, & Foti, 2007; MacNamara, Ferri, & Hajcak,

[1] A blocked design was selected for this study for several reasons: First, the type of preceding image can influence the processing of a subsequent image (e.g., a very unpleasant image preceding a neutral image can interfere with attention—and attenuate the magnitude of the Late Positive Potential [LPP]—to the neutral image). In this study, we were primarily interested in the purer response to pleasant and unpleasant images uncomplicated by extraneous variables such as prior trial effects. In addition, random presentation creates the possibility that a picture type could be a local oddball (in terms of frequency), which can influence the LPP.

2011).[2] The LPPs elicited by rewarding and threatening images were significantly associated with one another, $r = .56$, $p < .001$, as were rewarding and neutral, $r = .60$, $p < .001$, and threatening and neutral, $r = .46$, $p < .001$.

Results

Participant Characteristics

Table 1 presents demographic and clinical variables for the sample. Overall, 52.5% ($n = 94$ of participants were diagnosed with a current unipolar depressive disorder (37.3% MDD, 15.8% dysthymic disorder, 3.9% both). Additionally, 68.4% ($n = 121$) met criteria for current *DSM–IV* anxiety disorders. Rates of anxiety disorders were as follows: specific phobia (32.7% of the sample), social phobia (25.0%), panic disorder (25.5%), GAD (29.6%), obsessive–compulsive disorder (OCD; 11.2%), agoraphobia (19.9%), and posttraumatic stress disorder (PTSD; 14.8%). Among individuals with an anxiety disorder diagnosis, 42% ($n = 54$) had only one anxiety diagnosis, 26% ($n = 33$) had two diagnoses, 18% ($n = 23$) had 3 diagnoses, and 14% ($n = 19$) had four or more anxiety disorder diagnoses. Because there were too few cases of individual anxiety disorder diagnoses without some comorbidity, we opted to collapse across all anxiety disorders for subsequent analyses. In grouping people this way, 39.5% ($n = 70$) met criteria for both anxiety and depression; 29% ($n = 51$) met criteria for an anxiety disorder but no depression, and 14% ($n = 24$) met criteria for depression but no anxiety. Finally, 18.1% ($n = 32$) had no current or past diagnoses.[3] Six of these participants were initially recruited as a part of the psychiatric group, and were receiving care at a mental health clinic for issues including marital therapy/couples counseling, distress related to unemployment, and loneliness; however, none met criteria for any current or past Axis I disorder.

Age of onset of the first depressive episode was available for 72 currently depressed participants ($M = 22.18$, $SD = 12.73$; range: 5 to 51); of these, 41 participants had their first depressive episode before the age of 18 (early onset), and 31 had their first depressive episode after the age of 18 (adult onset). Age of onset for first anxiety disorder was also available for 103 individuals with a current anxiety diagnosis ($M = 14.80$ $SD = 12.37$; range: 2 to 64). Seventy-nine first met criteria for an anxiety diagnosis before the age of 18 (early onset), and 24 first met criteria after the age of 18 (adult onset).

ERP Results

Association with diagnosis. Table 1 presents average LPP values by picture type, and Table 2 presents bivariate associations with psychological variables of interest across the whole sample. A diagnosis of current depression predicted a reduced LPP to rewarding images; depression was not associated with the LPP elicited by neutral or threatening images. However, the correlation between a diagnosis of depression and the LPP elicited by rewarding and threatening images did not differ in our sample ($Z = -.67$, $p = .51$). A diagnosis of anxiety did not relate to the LPP elicited by any picture type. Neither gender nor age was significantly related to the LPP elicited by any picture type.

Two simultaneous regressions were conducted to examine the unique effects of anxiety and depression on the LPP to rewarding and threatening images (Tables 3 and 4, respectively). In each instance, disorder status (i.e., current anxiety and depression) were entered in the first step, followed by their interaction in Step 2. The LPP to rewarding images was blunted in current depression $t(175) = 1.98$, $p = .02$, but not in relation to anxiety or the interaction of depression and anxiety (see Table 3). The associations with the LPP to threatening images were in a similar direction (see Table 4), but did not reach significance.

These effects are depicted in Figure 1, which presents grand average stimulus-locked ERP waveforms for the LPP. For presentation purposes, the LPP is depicted in individuals with no diagnosis, with a current anxiety disorder only, with a current depressive disorder only, and with both current anxiety and depressive disorder. Individuals with a diagnosis of depression, whether comorbid with anxiety or not, were characterized by a blunted LPP to rewarding images.

Association with age of onset. Table 2 presents bivariate associations between age-of-onset of depression and anxiety and the LPP elicited by each stimulus category. Earlier age of depression onset within currently depressed individuals was associated with increased blunting of the LPP elicited by both rewarding and threatening images. Age of onset for anxiety disorders was unrelated to the magnitude of the LPP elicited by any image type.

To further explore this effect, we subdivided the currently depressed group into early and adult-onset subgroups. Table 5 presents demographic and clinical information for these groups, as well as average LPP values by picture type. Grand average stimulus-locked ERP waveforms for the LPP among those with early- and adult-onset depression, as well as the control group, are presented in Figure 2.

Two one-way analysis of variances (ANOVAs) were conducted, examining group (HC, early onset, and adult onset) differences in the magnitude of the LPP to rewarding and threatening images; after each ANOVA, three Fisher's Least Significant Difference (LSD) *t* tests were conducted comparing the magnitude of the LPP between groups. As suggested by Figure 2, age of onset of depression significantly affected the magnitude of the LPP elicited by rewarding pictures $F(2, 99) = 5.20$, $p = .007$, such that early onset depression was associated with a significantly blunted LPP compared to both controls $D = 3.28$ $SE = 1.05$, $p = .002$ and the adult onset group $D = 2.25$, $SE = 1.08$, $p = .04$, but adult onset depression did not differ significantly from the controls $D = 1.03$, $SE = 1.13$, $p = .36$. This was also true for threatening pictures $F(2, 99) = 4.35$, $p = .02$; individuals with early onset depression

[2] In every instance, results for the 1,000 to 1,500 ms time-window were in a similar direction but weaker; data available from the authors upon request.

[3] Because posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) are no longer included in the anxiety disorders category of *Diagnostic and Statistical Manual for Mental Disorder-Fifth Edition* (*DSM–5*), we also conducted all of the subsequent analyses excluding these two diagnostic categories; the pattern of results was the same in every instance. Additionally, because specific phobias tend not to be as impairing or generally pervasive in their symptom presentation, we also ran all of the subsequent analyses excluding six individuals who met criteria for specific phobia only. In every instance, the pattern of results was the same.

Table 1
Demographic, Clinical, and Event-Related Potential (ERP) Data for the Sample

	No anxiety or depression (N = 32)	Anxiety only (N = 51)	Depression only (N = 24)	Both (N = 70)
Demographics				
Age	51.03 (13.88)	39.66 (14.51)	40.41 (11.31)	42.47 (12.58)
Sex (% female)	46%	74%	46%	75%
Ethnicity (% White)	82%	83%	82%	80%
% employed	64%	44%	32%	25%
% on disability	21%	37%	39%	29%
Lifetime diagnoses				
Anxiety disorder (% positive)	0 %	100%	50%	100%
MDD or Dysthymia (% positive)	0 %	80%	100%	100%
Age of first onset				
Depressive disorder	—	21.81 (12.73)	19.71 (8.69)	23.96 (14.08)
Anxiety disorder	—	13.60 (11.27)	20.50 (6.63)	15.73 (13.19)
IMAS scales				
Dysphoria	.75 (1.72)	2.58 (3.13)	6.71 (2.18)	6.44 (3.02)
Lassitude	.88 (1.76)	4.70 (3.70)	8.04 (2.76)	8.05 (2.65)
Anhedonia	1.13 (2.45)	5.11 (4.16)	7.75 (3.27)	8.72 (2.83)
Suicidality	.64 (.93)	1.11 (1.45)	2.71 (2.0)	2.36 (2.26)
Insomnia	1.56 (2.31)	3.40 (2.94)	4.64 (2.74)	5.49 (2.54)
Appetite Loss	.78 (1.68)	1.94 (2.33)	2.54 (2.44)	3.93 (2.24)
Agitation	.84 (2.0)	2.40 (2.60)	4.54 (3.75)	5.21 (3.52)
Retardation	.64 (1.35)	1.38 (2.36)	2.75 (3.05)	3.52 (3.12)
Excessive worry	.67 (1.55)	1.66 (2.02)	2.79 (2.10)	3.65 (2.13)
GAD symptoms	1.87 (3.0)	4.62 (3.62)	8.29 (3.15)	8.84 (2.80)
Re-experiencing	2.37 (2.68)	4.66 (3.09)	5.58 (2.10)	5.82 (2.27)
Avoidance	.77 (1.42)	2.30 (2.49)	2.81 (2.43)	3.49 (2.30)
Hyperarousal	1.64 (2.51)	4.04 (4.02)	5.36 (3.51)	6.12 (3.91)
Numbing	.49 (1.39)	1.55 (2.21)	2.93 (2.34)	3.12 (2.05)
Dissociation	.36 (.90)	.77 (1.53)	1.11 (1.57)	1.24 (1.53)
Panic physiological	2.76 (3.49)	7.49 (4.73)	6.14 (3.96)	9.89 (5.23)
Panic psychological	1.15 (2.01)	2.61 (3.66)	3.14 (3.15)	4.59 (3.38)
Interactive anxiety	.54 (1.10)	1.47 (1.82)	.96 (1.50)	2.99 (2.08)
Performance anxiety	1.77 (2.95)	4.42 (3.51)	3.82 (3.03)	6.91 (3.38)
Fear of public places	.38 (1.07)	2.45 (3.11)	1.46 (1.58)	4.72 (3.94)
Fear of enclosed places	1.03 (1.89)	3.92 (3.46)	2.54 (3.32)	5.79 (4.08)
Animal phobia	.51 (1.49)	1.00 (1.54)	1.14 (1.67)	2.19 (2.14)
Situational phobia	.95 (1.59)	2.60 (2.01)	1.39 (1.85)	3.29 (2.05)
Blood-injection-injury phobia	.87 (1.44)	1.57 (2.20)	.96 (1.97)	1.59 (2.0)
Cleaning	.23 (.78)	.49 (1.33)	.36 (.95)	.77 (1.86)
Rituals	.59 (1.86)	1.60 (2.76)	.96 (1.88)	1.60 (2.58)
Checking	.46 (1.37)	1.96 (2.65)	1.64 (2.66)	2.77 (3.0)
Obsessions	.82 (1.75)	2.60 (3.18)	3.54 (3.59)	3.68 (3.28)
LPP				
Reward	6.43 (4.50)	5.41 (4.95)	4.67 (3.55)	3.95 (4.58)
Neutral	1.41 (3.63)	.84 (4.02)	.50 (3.37)	.22 (3.76)
Threat	6.72 (6.17)	7.03 (4.34)	6.17 (4.74)	5.42 (5.79)

Note. GAD = generalized anxiety disorder.

exhibited a blunted LPP relative to those with no diagnosis D = 2.70, SE = 1.27, p = .04 and those with adult onset depression D = 3.59, SE = 1.30, p = .007, whereas those with adult onset depression did not differ from healthy controls D = .89, SE = 1.36, p = .51. As indicated in Table 5, the early and adult onset depression groups did not differ significantly from one another on any demographic or self-report variable (with the exception of symptoms of blood-injection phobia, which were higher in the adult-onset group).

Associations with transdiagnostic phenotypes. Because the forgoing results suggested that depression was significantly associated with the magnitude of the LPP, whereas anxiety disorders were not, bivariate associations between the LPP and eight IMAS subscales associated with depression were also examined across the whole sample and are presented in Table 2. As indicated in Table 2, several IMAS depression subscales were associated with a reduced LPP to both rewarding and threatening images. To identify unique associations, we conducted two multiple regressions, one predicting neural response to rewarding images (see Table 3) and a second predicting neural response to threatening images (see Table 4), with symptoms of depression entered as predictors in each case. As indicated in Tables 3 and 4, current levels of suicidal ideation remained significantly associated with the magnitude of the LPP elicited by both rewarding and threatening images even after controlling for other symptoms of depression. In both instances, increased suicidal ideation related to re-

Table 2
Pearson's Correlations Between Diagnostic Variables, Interview for Mood and Anxiety Symptoms (IMAS) Scales, and the Magnitude of the Late Positive Potential (LPP)

	LPP		
	Reward	Neutral	Threat
Diagnosis			
Current Depressive Disorder	−.19*	−.10	−.12
Current Anxiety Disorder	−.10	−.09	−.02
Age of onset for first depressive episode (n = 72)	.25*	.02	.26*
Age of onset for first anxiety episode (n = 103)	.01	−.07	−.11
Demographics			
Age	.06	−.01	.01
Gender (0 = male)	.02	.002	.09
IMAS Scale			
Dysphoria	−.13†	−.07	−.12†
Lassitude	−.13†	−.09	−.08
Anhedonia	−.15*	−.10	−.03
Suicidality	−.21**	−.10	−.22**
Insomnia	−.13†	−.09	−.07
Appetite loss	−.06	−.08	−.10
Agitation	−.14†	−.02	−.06
Retardation	−.04	−.08	.06

Note. GAD = generalized anxiety disorder.
† $p < .10$. * $p < .05$. ** $p < .01$.

duced processing of emotional content, across all groups. Scatter plots displaying the bivariate association with rewarding images as well as the partial correlations after controlling for the influence of the other relevant IMAS scales are depicted in Figure 3.

Discussion

The present study was the first to examine the magnitude of the LPP in a clinical sample that included multiple diagnoses within the internalizing spectrum, age of onset, and empirically derived symptom dimensions. This was also the first study to examine neural response to both rewarding and threatening visual stimuli across a broad spectrum of internalizing disorders. Consistent with our hypotheses, a diagnosis of depression was associated with a blunted LPP to rewarding visual stimuli, but a diagnosis of anxiety was not. Contrary to our hypotheses, anxiety was not associated with variation in the LPP to threatening stimuli; similarly, a comorbid diagnosis of anxiety in the context of depression appeared to have no additive or interactive effect on the LPP. Additionally, although a diagnosis of depression was not significantly associated with a reduced LPP to threatening stimuli, the association was in the same direction as the association with rewarding stimuli. These data are in keeping with evidence that depression may be characterized by decreased attentional engagement with motivationally salient content in general (Bylsma et al., 2008; Proudfit et al., 2015; Rottenberg et al., 2005).

We further demonstrated that the association between the LPP and a diagnosis of depression may be driven by a subset of individuals with early onset depression, who were characterized by a dramatically reduced LPP. Indeed, among individuals with adult-onset depression, the LPP elicited by rewarding and threatening images was comparable to that observed in never-depressed controls. Moreover, individuals with early onset depression exhibited reduced processing of rewarding and threatening information relative to individuals with adult onset depression, and this blunting was observed despite similar clinical presentation of symptoms at the time of the EEG assessment. This is consistent with previous studies indicating that early and adult onset depression often have similar clinical presentations during a depressive episode, though early onset depression tends to have a more malignant course and is associated with greater comorbidity (Klein et al., 1999a). These data suggest that the blunted LPP in early onset individuals did not reflect state-related differences in severity of depression at the time of the assessment. These findings extend previous evidence for impairments in reward functioning related to MDD, and link variability in the LPP to rewarding visual stimuli to the more specific phenotype of early onset depression (Shankman et al., 2007). Moreover, these data suggest that age of onset is an important source of heterogeneity in depression (Klein & Allmann, 2014; Klein et al., 1999a, 1999b), and demonstrate how diagnostic heterogeneity can obscure meaningful differences in neural response. Considering age of onset may be helpful in explaining the often-contradictory results of previous studies examining neural response to threat in depression. Notably, age of onset of anxiety disorders appeared to be unrelated to the LPP. However, anxiety disorders also tend to have an earlier average age of onset than unipolar mood disorders, and it is common to meet criteria for an anxiety disorder before adulthood (with the exception of GAD; Kessler, Berglund, et al., 2005); it may be this is a less meaningful source of heterogeneity within the anxiety disorders.

These data may also point toward etiological differences reflected in age of onset of depression. Early onset depression represents a strongly heritable subtype of depression (Levinson et al., 2003; Lyons et al., 1998; Weissman et al., 1984), and the

Table 3
Results of Two Separate Regressions Predicting the Late Positive Potential (LPP) to Rewarding pictures; First, (A) a Simultaneous Regression Was Conducted Examining the Association Between Diagnosis and the LPP; Next (B), a Simultaneous Regression Was Conducted Examining the Association Between the Interview for Mood and Anxiety Symptoms (IMAS) Subscales and the LPP

Predictor	b (SE)	β [95% CI]
A: Diagnosis		
Anxiety Disorder	−.71 (.75)	−.07 [−2.18, .77]
Depressive Disorder	−1.64 (.69)	−.18* [−3.00, −.27]
Anxiety × Depressive Disorder Interaction	−.04 (1.49)	−.002 [−2.97, 2.90]
	Total model R^2 = .04	
B: IMAS Scales		
Suicidality	−.46 (.21)	−.20* [−.88, −.04]
Dysphoria	−.05(.15)	−.04 [−.24, .35]
Lassitude	.002 (.15)	.002 [−.29, .29]
Anhedonia	−.13 (.13)	−.12 [−.39, .13]
Insomnia	−.11 (.14)	−.07 [−.38, .16]
Appetite loss	.13 (.18)	.07 [−.23, .48]
Agitation	−.09 (.13)	−.07 [−.34, .16]
Retardation	.12 (.15)	.07 [−.17, .41]
	Total model R^2 = .07	

* $p < .05$.

Table 4
Results of Two Separate Regressions Predicting the Late Positive Potential (LPP) to Threatening Pictures; First (A), a Simultaneous Regression Was Conducted Examining the Association Between Diagnosis and the LPP; Next (B), a Simultaneous Regression Was Conducted Examining the Association Between the Interview for Mood and Anxiety Symptoms (IMAS) Subscales and the LPP

Predictor	*b* (*SE*)	β [95% CI]
A. Diagnosis		
Anxiety Disorder	−.09 (.87)	−.008 [−1.80, 1.62]
Depressive Disorder	−1.29 (.80)	−.12 [−2.87, .30]
Anxiety × Depressive Disorder	−1.41 (1.73)	−.06 [−4.81, 2.00]
	Total model R^2 = .02	
B. IMAS Scales		
Suicidality	−.56 (.25)	−.21* [−1.05, −.07]
Dysphoria	−.04 (.17)	−.03 [−.24, .38]
Lassitude	−.09 (.17)	−.07 [−.43, .24]
Anhedonia	.10 (.15)	.08 [−.20, .41]
Insomnia	−.08 (.16)	−.05 [−.39, .23]
Appetite loss	−.13 (.21)	−.06 [−.53, .28]
Agitation	−.02 (.15)	−.01 [−.31, .27]
Retardation	.29 (.17)	.16 [−.05, .63]
	Total model R^2 = .07	

* $p < .05$.

magnitude of the LPP is subject to genetic influence (Weinberg, Venables, Proudfit, & Patrick, 2015). The blunted LPP may therefore represent a heritable biomarker of the distinct subtype of early onset depression. Because these analyses were conducted in adults who were already presenting with significant levels of pathology, it is also possible that the blunted LPP we observed in the early onset-depression group was the consequence of a longer duration of depressive illness, and not a vulnerability marker. As the majority of our sample could not reliably estimate the number of depressive episodes that they had experienced, we were not able to control for recurrence in our analyses (Klein & Allmann, 2014). More work will be necessary to parse the effects of age of onset and recurrence on processing of emotional material. However, there is other evidence that children at risk for depression, conferred by parental history of depression, exhibit a blunted LPP to emotional content (Kujawa et al., 2012; Nelson et al., 2015), suggesting that hyporeactivity to emotional stimuli may be a vulnerability marker that precedes the onset of mood disorders. Future studies should examine the LPP longitudinally, and among at-risk individuals.

Additionally, in the present study, age of onset was assessed retrospectively, and is therefore an approximation (Prusoff, Merikangas, & Weissman, 1988). However, it is worth noting that the effects we observed for early compared with adult onset depression were significant using both continuous measurements of age of onset, which rely on recall of specific ages (as in the correlations presented in Table 2), and dichotomous early and adult groups, which are less dependent on precise age estimates.

Critically, we also looked beyond disorders by considering transdiagnostic dimensions of internalizing psychopathology in relation to the LPP. We found evidence that higher past-month suicidal ideation predicted a blunted LPP to rewarding images across all diagnoses, even controlling for other symptoms of depression; these data are broadly consistent with prior evidence that suicidal ideation and attempts can be linked to perturbations in reward processing (Dombrovski et al., 2010; Dombrovski, Szanto, Clark, Reynolds, & Siegle, 2013; Dombrovski et al., 2011; Dougherty et al., 2009; Elman, Borsook, & Volkow, 2013; Mathias et al., 2011). However, as was the case for age of onset, current suicidal ideation also was associated significantly with a reduced LPP to threatening images. These data suggest that extant evidence for an association between anhedonia and suicidal ideation (Fawcett, 1988; Nock & Kazdin, 2002; Oei, Verhoeven, Westenberg, Zwart, & Van Ree, 1990; Robbins & Alessi, 1985) may reflect broad attentional disengagement with both rewarding and threatening material, and not just reward-related attentional deficits.

The observed effects in early onset depression were not evident in other internalizing disorders. We did not find the expected

Table 5
Demographic, Clinical, and Event-Related Potential (ERP) Data for Early and Adult Onset Depression Groups

	Early onset depression (n = 41)	Adult onset depression (n = 31)
Demographics		
Age (*SD*)	37.98 (12.72)	45.84 (10.23)
Sex (% female)	68%	65%
Ethnicity (% White)	85%	74%
% employed	22%	16%
% on disability	34%	32%
IMAS Scales		
Dysphoria	7.22 (2.55)	6.84 (2.33)
Lassitude	8.63 (2.22)	8.77 (2.11)
Anhedonia	8.59 (2.39)	9.16 (2.92)
Suicidality	2.88 (2.29)	2.58 (2.62)
Insomnia	5.46 (2.45)	5.65 (2.35)
Appetite loss	4.24 (2.12)	3.77 (2.25)
Agitation	5.24 (3.68)	5.90 (3.32)
Retardation	3.46 (3.08)	4.26 (3.35)
Excessive worry	3.49 (2.15)	4.19 (1.76)
GAD symptoms	9.46 (1.83)	9.39 (2.89)
Re-experiencing	6.08 (2.04)	5.80 (1.99)
Avoidance	3.65 (2.39)	3.77 (2.34)
Hyperarousal	6.46 (3.74)	6.94 (3.33)
Numbing	3.37 (2.02)	3.45 (2.17)
Dissociation	1.49 (1.94)	1.35 (1.31)
Panic physiological	9.88 (5.29)	8.84 (4.64)
Panic psychological	4.46 (3.54)	4.29 (3.01)
Interactive anxiety	2.51 (2.25)	2.68 (2.09)
Performance anxiety	6.27 (3.62)	6.65 (3.45)
Fear of public places	4.00 (3.59)	4.61 (4.06)
Fear of enclosed places	4.80 (4.43)	5.35 (3.83)
Animal phobia	1.83 (2.20)	2.16 (1.97)
Situational phobia	2.68 (2.15)	3.00 (2.05)
Blood-injection-injury phobia	.88 (1.66)	1.87 (2.08)*
Cleaning	1.12 (2.36)	.87 (2.08)
Rituals	1.15 (1.84)	1.77 (2.81)
Checking	2.46 (2.89)	2.77 (3.06)
Obsessions	4.44 (3.59)	3.81 (3.27)
LPP		
Reward	3.00 (4.03)	5.25 (4.98)*
Neutral	−.14 (3.40)	.28 (3.99)
Threat	3.79 (4.20)	7.38 (6.38)**

Note. GAD = generalized anxiety disorder; LPP = late positive potential.
* $p < .05$. ** $p < .01$.

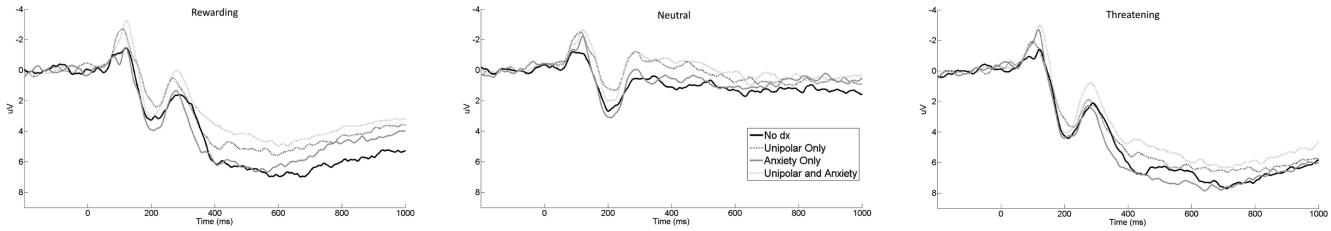

Figure 1. Picture-locked event-related potential (ERP) waveforms at a pooling of electrode sites Pz, Cz, CP1, and CP2 for individuals with no current or past diagnosis, a current diagnosis of anxiety only, a current diagnosis of a unipolar depressive disorder only, and a current diagnosis of both anxiety and a unipolar depressive disorder. Per ERP convention, negative voltages are plotted up. A current diagnosis of depression was associated with a blunted Late Positive Potential (LPP) to rewarding pictures.

connection between diagnosis of anxiety and an enhanced LPP to threatening images. In the current study, stimuli were presented in a blocked design (see also Weinberg & Hajcak, 2011). However, in tasks where threatening images were task-irrelevant and unpredictable, an enhanced LPP to threat has instead been observed in anxious individuals (e.g., MacNamara & Hajcak, 2010). This may reflect the fact that context and predictability can influence attention to emotion differentially in different anxiety diagnoses (Gorka, Nelson, Phan, & Shankman, 2014; Lang & McTeague, 2009; MacNamara & Hajcak, 2010; MacNamara & Proudfit, 2014; McTeague & Lang, 2012; Weinberg & Hajcak, 2011). Moreover, for some diagnoses, the influence of anxiety on the LPP has been shown to be content-specific or idiographic (e.g., spider-phobic individuals viewing images of spiders have an enhanced LPP; Norberg, Peira, & Wiens, 2010), and may not generalize to all visually threatening content. In the current study, comorbidity among anxiety disorder diagnoses was high, as is common in the population (Kessler, Berglund, et al., 2005), which may have obscured diagnosis-specific effects, as well as effects of age of onset for distinct disorders. And finally, we would note that rates of lifetime comorbidity with depression were even higher than current rates. Indeed, only 10 of the psychiatric subjects in the present study had never experienced a unipolar mood episode, suggesting the absence of a unique effect of anxiety might be the result of a limited number of pure anxiety cases. Future studies employing very large samples and targeted recruiting may be able to examine unique contributions of distinct diagnoses to the LPP.

A final limitation is that the control sample in this study was composed of individuals with chronic medical conditions, in an attempt to approximate the functional disability and demographics of the psychiatric group, and to decrease potential false-positive rates associated with the use of superhealthy controls (Lewis & Pelosi, 1990). We did not record use of nonpsychiatric medications in the study; however, many individuals in the psychiatric group were also receiving treatment for medical conditions. This renders it difficult to estimate the effects that pharmacological treatments for medical conditions might have had on the results. However, we would note here that the LPP in the control group here was very similar to the LPP of a medication-free control sample using the same paradigm (Weinberg & Hajcak, 2011).

The current results are broadly consistent with previous investigations of depression that have found blunted ERP measures of reward processing using monetary rewards (Foti, Carlson, Sauder, & Proudfit, 2014; Weinberg, Liu et al., 2015). The present study observed reduced reward processing in depression using pleasant pictures. There is evidence that pleasant images—including those depicting positive social interactions and erotic encounters—engage networks and structures associated with reward processing and appetitive motivation (e.g., NAcc and MPFC; Karama et al., 2002; Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; O'Doherty et al., 2003; Sabatinelli, Bradley, et al., 2007). Thus, the blunted LPP to pleasant images in depression may reflect a similar phenomenon as that seen in studies using monetary reward. Future studies might directly compare monetary reward and rewarding images in depression and anxiety to examine whether these deficits are general or specific to stimulus types.

The current study was intended to be consistent with the principles of the RDoC initiative, in that we examined neural response

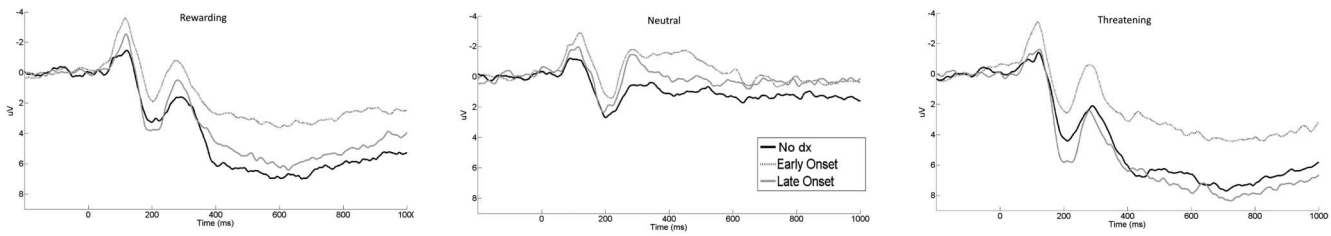

Figure 2. Picture-locked event-related potential (ERP) waveforms at a pooling of electrode sites Pz, Cz, CP1, and CP2 for individuals with no current or past diagnosis, early onset depression, and adult onset depression. Per ERP convention, negative voltages are plotted up. Participants with early onset depression displayed a blunted Late Positive Potential (LPP) to both rewarding and threatening images compared to individuals with no diagnosis and individuals with adult onset depression.

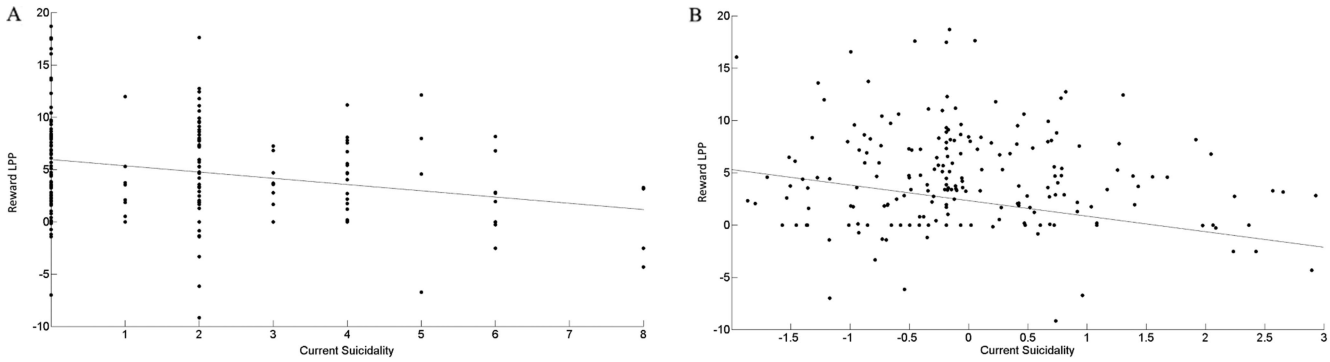

Figure 3. (A) Scatterplots depicting the zero-order correlations between the Late Positive Potential (LPP) elicited by rewarding pictures and current ratings of suicidality (B) Scatter plots depicting the partial correlation following the multiple regression between the LPP elicited by rewarding pictures and current ratings of suicidality, after controlling for dysphoria, lassitude, anhedonia, insomnia, appetite loss, agitation, and psychomotor retardation.

to reward and threat across multiple manifestations of internalizing psychopathology (Cuthbert, 2014; Cuthbert & Insel, 2010; Sanislow et al., 2010). However, studies like this one may also be useful in refining the RDoC matrix itself, which is explicitly a work in progress. At present, the RDoC matrix distinguishes between emotion/motivation-related domains (e.g., negative and positive valence systems) and cognitive systems (e.g., attention and visual perception). This conceptual dichotomy may not be reflected in the function of the brain (e.g., Mohanty, Egner, Monti, & Mesulam, 2009; Pessoa & Adolphs, 2010). Indeed, attention is a construct that seems to straddle both affective and cognitive domains, and the LPP reflects this; decades of work suggests that emotional content captures attention in a preferential fashion (e.g., motivated attention; Bradley et al., 2001), but also that attentional variables influence emotional response (e.g., Dunning & Hajcak, 2009). Likewise, the LPP is sensitive to both bottom-up properties of stimuli (e.g., Weinberg & Hajcak, 2010) and top-down manipulations of attention (e.g., MacNamara & Proudfit, 2014), making it difficult to say whether the reduced LPP observed in the present study is a function of attentional or motivational deficits—or both. This raises questions about the extent to which cognitive control and motivational variables can and should be considered distinct from one another, as well as questions about how and when variation in one domain may be causal of variation in another (Weinberg, Meyer, et al., 2015).

In conclusion, the present study found that early onset depression and suicidal ideation were associated with a blunted neural response to rewarding and threatening images. Profiles of reward- and threat-related neural response may represent important biological markers differentiating depression from anxiety, and differentiating subtypes of depression (Cuthbert, 2014; Insel et al., 2010). These results also raise the possibility that blunted neural response to emotional stimuli may be a vulnerability marker for a particularly pernicious form of depression (Klein et al., 1999a, 1999b). Incorporating biological markers of reward and threat sensitivity into self-report and clinical assessment batteries may facilitate accurate assessment and differential diagnosis (e.g., Carter & Barch, 2007). Future studies that use longitudinal design, at-risk individuals, and multimodal neuroimaging approaches will be necessary to further substantiate this. Ultimately, these approaches might provide state-independent biomarkers that will be useful in identifying individuals at future risk for unipolar depressive disorders and anxiety disorders, as well as biological targets for novel and more personalized treatment.

References

Atkinson, C., Lozano, R., Naghavi, M., Vos, T., Whiteford, H., & Murray, C. (2013). The burden of mental disorders in the USA: New tools for comparative analysis of health outcomes between countries. *Lancet, 381,* S10. http://dx.doi.org/10.1016/S0140-6736(13)61264-7

Beesdo, K., Lau, J. Y., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., . . . Pine, D. S. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry, 66,* 275–285. http://dx.doi.org/10.1001/archgenpsychiatry.2008.545

Bradley, M. M., Codispoti, M., Cuthbert, B. N., & Lang, P. J. (2001). Emotion and motivation I: Defensive and appetitive reactions in picture processing. *Emotion, 1,* 276–298. http://dx.doi.org/10.1037/1528-3542.1.3.276

Bradley, M. M., Lang, P. J., & Cuthbert, B. N. (2005). *International Affective Picture System (IAPS): Digitized photographs, instruction manual and affective ratings*. Gainesville, FL: University of Florida.

Bradley, M. M., Sabatinelli, D., & Lang, P. J. (2014). Emotion and motivation in the perceptual processing of natural scenes. In K. Kveraga & M. Bar (Eds.), *Scene vision: Making sense of what we see* (pp. 273). Cambridge, MA: MIT Press.

Briggs, K. E., & Martin, F. H. (2009). Affective picture processing and motivational relevance: Arousal and valence effects on ERPs in an oddball task. *International Journal of Psychophysiology, 72,* 299–306. http://dx.doi.org/10.1016/j.ijpsycho.2009.01.009

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clinical Psychology Review, 28,* 676–691. http://dx.doi.org/10.1016/j.cpr.2007.10.001

Carter, C. S., & Barch, D. M. (2007). Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: The CNTRICS initiative. *Schizophrenia Bulletin, 33,* 1131–1137. http://dx.doi.org/10.1093/schbul/sbm081

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal*

of Abnormal Psychology, 100, 316–336. http://dx.doi.org/10.1037/0021-843X.100.3.316

Compton, R. J., Heller, W., Banich, M. T., Palmieri, P. A., & Miller, G. A. (2000). Responding to threat: Hemispheric asymmetries and interhemispheric division of input. *Neuropsychology, 14,* 254–264. http://dx.doi.org/10.1037/0894-4105.14.2.254

Cuthbert, B. N. (2014). The RDoC framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry; Official Journal of the World Psychiatric Association (WPA), 13,* 28–35. http://dx.doi.org/10.1002/wps.20087

Cuthbert, B. N., & Insel, T. R. (2010). Toward new approaches to psychotic disorders: The NIMH Research Domain Criteria project. *Schizophrenia Bulletin, 36,* 1061–1062.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. *Biological Psychology, 52,* 95–111. http://dx.doi.org/10.1016/S0301-0511(99)00044-7

Demyttenaere, K., Bruffaerts, R., Posada-Villa, J., Gasquet, I., Kovess, V., Lepine, J., . . . Morosini, P. (2004). Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA, 291,* 2581–2590.

Dombrovski, A. Y., Clark, L., Siegle, G. J., Butters, M. A., Ichikawa, N., Sahakian, B. J., & Szanto, K. (2010). Reward/Punishment reversal learning in older suicide attempters. *The American Journal of Psychiatry, 167,* 699–707. http://dx.doi.org/10.1176/appi.ajp.2009.09030407

Dombrovski, A. Y., Szanto, K., Clark, L., Reynolds, C. F., & Siegle, G. J. (2013). Reward signals, attempted suicide, and impulsivity in late-life depression. *Journal of the American Medical Association Psychiatry, 70,* 1020–1030. http://dx.doi.org/10.1001/jamapsychiatry.2013.75

Dombrovski, A. Y., Szanto, K., Siegle, G. J., Wallace, M. L., Forman, S. D., Sahakian, B., . . . Clark, L. (2011). Lethal forethought: Delayed reward discounting differentiates high- and low-lethality suicide attempts in old age. *Biological Psychiatry, 70,* 138–144. http://dx.doi.org/10.1016/j.biopsych.2010.12.025

Dougherty, D. M., Mathias, C. W., Marsh-Richard, D. M., Prevette, K. N., Dawes, M. A., Hatzis, E. S., . . . Nouvion, S. O. (2009). Impulsivity and clinical symptoms among adolescents with non-suicidal self-injury with or without attempted suicide. *Psychiatry Research, 169,* 22–27. http://dx.doi.org/10.1016/j.psychres.2008.06.011

Dunning, J. P., & Hajcak, G. (2009). See no evil: Directing visual attention within unpleasant images modulates the electrocortical response. *Psychophysiology, 46,* 28–33. http://dx.doi.org/10.1111/j.1469-8986.2008.00723.x

Durbin, C. E., Klein, D. N., Hayden, E. P., Buckley, M. E., & Moerk, K. C. (2005). Temperamental emotionality in preschoolers and parental mood disorders. *Journal of Abnormal Psychology, 114,* 28–37.

Elman, I., Borsook, D., & Volkow, N. D. (2013). Pain and suicidality: Insights from reward and addiction neuroscience. *Progress in Neurobiology, 109,* 1–27. http://dx.doi.org/10.1016/j.pneurobio.2013.06.003

Engels, A. S., Heller, W., Spielberg, J. M., Warren, S. L., Sutton, B. P., Banich, M. T., & Miller, G. A. (2010). Co-occurring anxiety influences patterns of brain activity in depression. *Cognitive, Affective & Behavioral Neuroscience, 10,* 141–156. http://dx.doi.org/10.3758/CABN.10.1.141

Fawcett, J. (1988). Predictors of early suicide: Identification and appropriate intervention. *The Journal of Clinical Psychiatry, 49* (Suppl.), 7–8.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1995). *Structured clinical interview for DSM-IV Axis I disorders (SCID).* New York: New York State Psychiatric Institute, Biometrics Research.

Flykt, A., & Caldara, R. (2006). Tracking fear in snake and spider fearful participants during visual search: A multi-response domain study. *Cognition and Emotion, 20,* 1075–1091. http://dx.doi.org/10.1080/02699930500381405

Foti, D., Carlson, J. M., Sauder, C. L., & Proudfit, G. H. (2014). Reward dysfunction in major depression: Multimodal neuroimaging evidence for refining the melancholic phenotype. *NeuroImage, 101,* 50–58. http://dx.doi.org/10.1016/j.neuroimage.2014.06.058

Foti, D., & Hajcak, G. (2008). Deconstructing reappraisal: Descriptions preceding arousing pictures modulate the subsequent neural response. *Journal of Cognitive Neuroscience, 20,* 977–988.

Foti, D., Hajcak, G., & Dien, J. (2009). Differentiating neural responses to emotional pictures: Evidence from temporal-spatial PCA. *Psychophysiology, 46,* 521–530. http://dx.doi.org/10.1111/j.1469-8986.2009.00796.x

Foti, D., Olvet, D. M., Klein, D. N., & Hajcak, G. (2010). Reduced electrocortical response to threatening faces in major depressive disorder. *Depression and Anxiety, 27,* 813–820. http://dx.doi.org/10.1002/da.20712

Goldstein, R. B., Wickramaratne, P. J., Horwath, E., & Weissman, M. M. (1997). Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years): Panic disorder. *Archives of General Psychiatry, 54,* 271–278.

Gorka, S., Nelson, B., Phan, K., & Shankman, S. (2014). Insula response to unpredictable and predictable aversiveness in individuals with panic disorder and comorbid depression. *Biology of Mood & Anxiety Disorders, 4,* 9.

Gotlib, I. H., Hamilton, J. P., Cooney, R. E., Singh, M. K., Henry, M. L., & Joormann, J. (2010). Neural processing of reward and loss in girls at risk for major depression. *Archives of General Psychiatry, 67,* 380–387. http://dx.doi.org/10.1001/archgenpsychiatry.2010.13

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55,* 468–484.

Grillon, C., Dierker, L., & Merikangas, K. R. (1997). Startle modulation in children at risk for anxiety disorders and/or alcoholism. *Journal of the American Academy of Child & Adolescent Psychiatry, 36,* 925–932. http://dx.doi.org/10.1097/00004583-199707000-00014

Hajcak, G., Dunning, J. P., & Foti, D. (2007). Neural response to emotional pictures is unaffected by concurrent task difficulty: An event-related potential study. *Behavioral Neuroscience, 121,* 1156–1162. http://dx.doi.org/10.1037/0735-7044.121.6.1156

Hajcak, G., Dunning, J. P., & Foti, D. (2009). Motivated and controlled attention to emotion: Time-course of the late positive potential. *Clinical Neurophysiology, 120,* 505–510. http://dx.doi.org/10.1016/j.clinph.2008.11.028

Hajcak, G., & Olvet, D. M. (2008). The persistence of attention to emotion: Brain potentials during and after picture presentation. *Emotion, 8,* 250–255. http://dx.doi.org/10.1037/1528-3542.8.2.250

Helzer, J. E., Kraemer, H. C., & Krueger, R. F. (2006). The feasibility and need for dimensional psychiatric diagnoses. *Psychological Medicine, 36,* 1671–1680. http://dx.doi.org/10.1017/S003329170600821X

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., . . . Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry, 167,* 748–751. http://dx.doi.org/10.1176/appi.ajp.2010.09091379

Jaffee, S. R., Moffitt, T. E., Caspi, A., Fombonne, E., Poulton, R., & Martin, J. (2002). Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of General Psychiatry, 59,* 215–222.

Karama, S., Lecours, A. R., Leroux, J. M., Bourgouin, P., Beaudoin, G., Joubert, S., & Beauregard, M. (2002). Areas of brain activation in males and females during viewing of erotic film excerpts. *Human Brain Mapping, 16,* 1–13. http://dx.doi.org/10.1002/hbm.10014

Kaufman, J., & Charney, D. (2000). Comorbidity of mood and anxiety disorders. *Depression and Anxiety, 12* (Suppl. 1), 69–76. http://dx.doi.org/10.1002/1520-6394(2000)12:1+<69::AID-DA9>3.0.CO;2-K

Keil, A., Bradley, M. M., Hauk, O., Rockstroh, B., Elbert, T., & Lang, P. J. (2002). Large-scale neural correlates of affective picture processing. *Psychophysiology, 39,* 641–649. http://dx.doi.org/10.1111/1469-8986.3950641

Keller, J., Nitschke, J. B., Bhargava, T., Deldin, P. J., Gergen, J. A., Miller, G. A., & Heller, W. (2000). Neuropsychological differentiation of depression and anxiety. *Journal of Abnormal Psychology, 109,* 3–10. http://dx.doi.org/10.1037/0021-843X.109.1.3

Kessel, E. M., Kujawa, A., Hajcak Proudfit, G., & Klein, D. N. (2015). Neural reactivity to monetary rewards and losses differentiates social from generalized anxiety in children. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 56,* 792–800.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of *DSM–IV* disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62,* 593–602. http://dx.doi.org/10.1001/archpsyc.62.6.593

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month *DSM–IV* disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62,* 617–627. http://dx.doi.org/10.1001/archpsyc.62.6.617

Klein, D. N. (2008). Classification of depressive disorders in the DSM-V: Proposal for a two-dimension system. *Journal of Abnormal Psychology, 117,* 552–560. http://dx.doi.org/10.1037/0021-843X.117.3.552

Klein, D. N., & Allmann, A. E. S. (2014). Course of depression: Persistence and recurrence. In I. H. Gotlib & C. L. Hammen (Eds.), *Handbook of depression and its treatment* (3rd ed., pp. 64–83). New York, NY: Guilford Press.

Klein, D. N., Schatzberg, A. F., McCullough, J. P., Dowling, F., Goodman, D., Howland, R. H., . . . Keller, M. B. (1999a). Age of onset in chronic major depression: Relation to demographic and clinical variables, family history, and treatment response. *Journal of Affective Disorders, 55,* 149–157. http://dx.doi.org/10.1016/S0165-0327(99)00020-8

Klein, D. N., Schatzberg, A. F., McCullough, J. P., Keller, M. B., Dowling, F., Goodman, D., . . . Harrison, W. M. (1999b). Early- versus late-onset dythymic disorder: Comparison in out-patients with superimposed major depressive episodes. *Journal of Affective Disorders, 52,* 187–196. http://dx.doi.org/10.1016/S0165-0327(98)00079-2

Knutson, B., Fong, G. W., Bennett, S. M., Adams, C. M., & Hommer, D. (2003). A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: Characterization with rapid event-related fMRI. *Neuroimage, 18,* 263–272.

Kotov, R., Perlman, G., Gámez, W., & Watson, D. (2015). The structure and short-term stability of the emotional disorders: A dimensional approach. *Psychological Medicine, 45,* 1687–1698. http://dx.doi.org/10.1017/S0033291714002815

Kujawa, A., Hajcak, G., Torpey, D., Kim, J., & Klein, D. N. (2012). Electrocortical reactivity to emotional faces in young children and associations with maternal and paternal depression. *Journal of Child Psychology and Psychiatry, 53,* 207–215. http://dx.doi.org/10.1111/j.1469-7610.2011.02461.x

Kujawa, A., Proudfit, G. H., & Klein, D. N. (2014). Neural reactivity to rewards and losses in offspring of mothers and fathers with histories of depressive and anxiety disorders. *Journal of Abnormal Psychology, 123,* 287–297. http://dx.doi.org/10.1037/a0036285

Lang, P., & Bradley, M. M. (2007). The International Affective Picture System (IAPS) in the study of emotion and attention. In J. A. Coan & J. J. B. Allen (Eds.) *Handbook of emotion elicitation and assessment* (pp. 29–46). New York, NY: Oxford Press.

Lang, P. J., & McTeague, L. M. (2009). The anxiety disorder spectrum: Fear imagery, physiological reactivity, and differential diagnosis. *Anxiety, Stress & Coping: An International Journal, 22,* 5–25. http://dx.doi.org/10.1080/10615800802478247

Leutgeb, V., Schäfer, A., & Schienle, A. (2009). An event-related potential study on exposure therapy for patients suffering from spider phobia. *Biological Psychology, 82,* 293–300. http://dx.doi.org/10.1016/j.biopsycho.2009.09.003

Levinson, D. F., Zubenko, G. S., Crowe, R. R., DePaulo, R. J., Scheftner, W. S., Weissman, M. M., . . . Chellis, J. (2003). Genetics of recurrent early-onset depression (GenRED): Design and preliminary clinical characteristics of a repository sample for genetic linkage studies. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 119B,* 118–130. http://dx.doi.org/10.1002/ajmg.b.20009

Lewis, G. L. Y. N., & Pelosi, A. J. (1990). The case-control study in psychiatry. *The British Journal of Psychiatry, 157,* 197–207.

Liu, Y., Huang, H., McGinnis-Deweese, M., Keil, A., & Ding, M. (2012). Neural substrate of the late positive potential in emotional processing. *The Journal of Neuroscience, 32,* 14563–14572. http://dx.doi.org/10.1523/JNEUROSCI.3109-12.2012

Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Lin, N., Meyer, J. M., . . . Tsuang, M. T. (1998). A registry-based twin study of depression in men. *Archives of General Psychiatry, 55,* 468–472. http://dx.doi.org/10.1001/archpsyc.55.5.468

MacNamara, A., Ferri, J., & Hajcak, G. (2011). Working memory load reduces the late positive potential and this effect is attenuated with increasing anxiety. *Cognitive, Affective & Behavioral Neuroscience, 11,* 321–331. http://dx.doi.org/10.3758/s13415-011-0036-z

MacNamara, A., & Hajcak, G. (2009). Anxiety and spatial attention moderate the electrocortical response to aversive pictures. *Neuropsychologia, 47,* 2975–2980. http://dx.doi.org/10.1016/j.neuropsychologia.2009.06.026

MacNamara, A., & Hajcak, G. (2010). Distinct electrocortical and behavioral evidence for increased attention to threat in generalized anxiety disorder. *Depression and Anxiety, 27,* 234–243. http://dx.doi.org/10.1002/da.20679

MacNamara, A., Kotov, R., & Hajcak, G. (2015). Diagnostic and symptom-based predictors of emotional processing in generalized anxiety disorder and major depressive disorder: An event-related potential study. *Article under review*.

MacNamara, A., & Proudfit, G. H. (2014). Cognitive load and emotional processing in generalized anxiety disorder: Electrocortical evidence for increased distractibility. *Journal of Abnormal Psychology, 123,* 557–565. http://dx.doi.org/10.1037/a0036997

Mathers, C. D., Fat, D. M., & Boerma, J. (2008). *The global burden of disease: 2004 update*. Geneva, Switzerland: World Health Organization. http://dx.doi.org/10.1016/B978-012373960-5.00335-X

Mathias, C. W., Dougherty, D. M., James, L. M., Richard, D. M., Dawes, M. A., Acheson, A., & Hill-Kapturczak, N. (2011). Intolerance to delayed reward in girls with multiple suicide attempts. *Suicide and Life-Threatening Behavior, 41,* 277–286. http://dx.doi.org/10.1111/j.1943-278X.2011.00027.x

McTeague, L. M., & Lang, P. J. (2012). The anxiety spectrum and the reflex physiology of defense: From circumscribed fear to broad distress. *Depression and Anxiety, 29,* 264–281. http://dx.doi.org/10.1002/da.21891

Merikangas, K. R., Avenevoli, S., Dierker, L., & Grillon, C. (1999). Vulnerability factors among children at risk for anxiety disorders. *Biological Psychiatry, 46,* 1523–1535.

Moffitt, T. E., Harrington, H., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M., & Poulton, R. (2007). Depression and generalized anxiety disorder: Cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry, 64,* 651–660. http://dx.doi.org/10.1001/archpsyc.64.6.651

Mohanty, A., Egner, T., Monti, J. M., & Mesulam, M. M. (2009). Search for a threatening target triggers limbic guidance of spatial attention. *The Journal of Neuroscience, 29,* 10563–10572. http://dx.doi.org/10.1523/JNEUROSCI.1170-09.2009

Moran, T. P., Jendrusina, A. A., & Moser, J. S. (2013). The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Research, 1516,* 66–75. http://dx.doi.org/10.1016/j.brainres.2013.04.018

Moser, J. S., Huppert, J. D., Duval, E., & Simons, R. F. (2008). Face processing biases in social anxiety: An electrophysiological study. *Biological Psychology, 78,* 93–103.

Nelson, B. D., Perlman, G., Hajcak, G., Klein, D. N., & Kotov, R. (2015). Familial risk for distress and fear disorders and emotional reactivity in adolescence: An event-related potential investigation. *Psychological Medicine, 45,* 2545–2556. http://dx.doi.org/10.1017/S0033291715000471

Nock, M. K., & Kazdin, A. E. (2002). Examination of affective, cognitive, and behavioral factors and suicide-related outcomes in children and young adolescents. *Journal of Clinical Child and Adolescent Psychology, 31,* 48–58. http://dx.doi.org/10.1207/S15374424JCCP3101_07

Norberg, J., Peira, N., & Wiens, S. (2010). Never mind the spider: Late positive potentials to phobic threat at fixation are unaffected by perceptual load. *Psychophysiology, 47,* 1151–1158.

O'Doherty, J., Winston, J., Critchley, H., Perrett, D., Burt, D. M., & Dolan, R. J. (2003). Beauty in a smile: The role of medial orbitofrontal cortex in facial attractiveness. *Neuropsychologia, 41,* 147–155. http://dx.doi.org/10.1016/S0028-3932(02)00145-8

Oei, T. I., Verhoeven, W. M., Westenberg, H. G., Zwart, F. M., & van Ree, J. M. (1990). Anhedonia, suicide ideation and dexamethasone nonsuppression in depressed patients. *Journal of Psychiatric Research, 24,* 25–35. http://dx.doi.org/10.1016/0022-3956(90)90022-I

Pastor, M. C., Bradley, M. M., Löw, A., Versace, F., Moltó, J., & Lang, P. J. (2008). Affective picture perception: Emotion, context, and the late positive potential. *Brain Research, 1189,* 145–151. http://dx.doi.org/10.1016/j.brainres.2007.10.072

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: From a 'low road' to 'many roads' of evaluating biological significance. *Nature Reviews Neuroscience, 11,* 773–783. http://dx.doi.org/10.1038/nrn2920

Proudfit, G. H., Bress, J. N., Foti, D., Kujawa, A., & Klein, D. N. (2015). Depression and event-related potentials: Emotional disengagement and reward insensitivity. *Current Opinion in Psychology, 4,* 110–113.

Prusoff, B. A., Merikangas, K. R., & Weissman, M. M. (1988). Lifetime prevalence and age of onset of psychiatric disorders: Recall 4 years later. *Journal of Psychiatric Research, 22,* 107–117. http://dx.doi.org/10.1016/0022-3956(88)90075-1

Robbins, D. R., & Alessi, N. E. (1985). Depressive symptoms and suicidal behavior in adolescents. *The American Journal of Psychiatry, 142,* 588–592. http://dx.doi.org/10.1176/ajp.142.5.588

Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Hirshfeld, D. R., Faraone, S. V., & Kagan, J. (1992). Comorbidity of parental anxiety disorders as risk for childhood-onset anxiety in inhibited children. *American Journal of Psychiatry, 149,* 475–481.

Rogers, R. D., Ramnani, N., Mackay, C., Wilson, J. L., Jezzard, P., Carter, C. S., & Smith, S. M. (2004). Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biological Psychiatry, 55,* 594–602.

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology, 114,* 627–639. http://dx.doi.org/10.1037/0021-843X.114.4.627

Ruggero, C. J., Kotov, R., Watson, D., Kilmer, J. N., Perlman, G., & Liu, K. (2014). Beyond a single index of mania symptoms: Structure and validity of subdimensions. *Journal of Affective Disorders, 161,* 8–15. http://dx.doi.org/10.1016/j.jad.2014.02.044

Sabatinelli, D., Bradley, M. M., Lang, P. J., Costa, V. D., & Versace, F. (2007). Pleasure rather than salience activates human nucleus accumbens and medial prefrontal cortex. *Journal of Neurophysiology, 98,* 1374–1379. http://dx.doi.org/10.1152/jn.00230.2007

Sabatinelli, D., Keil, A., Frank, D. W., & Lang, P. J. (2013). Emotional perception: Correspondence of early and late event-related potentials with cortical and subcortical functional MRI. *Biological Psychology, 92,* 513–519. http://dx.doi.org/10.1016/j.biopsycho.2012.04.005

Sabatinelli, D., Lang, P. J., Keil, A., & Bradley, M. M. (2007). Emotional perception: Correlation of functional MRI and event-related potentials. *Cerebral Cortex, 17,* 1085–1091. http://dx.doi.org/10.1093/cercor/bhl017

Sanislow, C. A., Pine, D. S., Quinn, K. J., Kozak, M. J., Garvey, M. A., Heinssen, R. K., . . . Cuthbert, B. N. (2010). Developing constructs for psychopathology research: Research domain criteria. *Journal of Abnormal Psychology, 119,* 631–639. http://dx.doi.org/10.1037/a0020909

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology, 37,* 257–261. http://dx.doi.org/10.1111/1469-8986.3720257

Shankman, S. A., & Klein, D. N. (2003). The relation between depression and anxiety: An evaluation of the tripartite, approach-withdrawal and valence-arousal models. *Clinical Psychology Review, 23,* 605–637. http://dx.doi.org/10.1016/S0272-7358(03)00038-2

Shankman, S. A., Klein, D. N., Tenke, C. E., & Bruder, G. E. (2007). Reward sensitivity in depression: A biobehavioral study. *Journal of Abnormal Psychology, 116,* 95–104. http://dx.doi.org/10.1037/0021-843X.116.1.95

Shankman, S. A., Nelson, B. D., Sarapas, C., Robison-Andrew, E. J., Campbell, M. L., Altman, S. E., . . . Gorka, S. M. (2013). A psychophysiological investigation of threat and reward sensitivity in individuals with panic disorder and/or major depressive disorder. *Journal of Abnormal Psychology, 122,* 322–338. http://dx.doi.org/10.1037/a0030747

Siegle, G. J., Carter, C. S., & Thase, M. E. (2006). Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. *The American Journal of Psychiatry, 163,* 735–738. http://dx.doi.org/10.1176/ajp.2006.163.4.735

Siegle, G. J., Steinhauer, S. R., Thase, M. E., Stenger, V. A., & Carter, C. S. (2002). Can't shake that feeling: Event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry, 51,* 693–707. http://dx.doi.org/10.1016/S0006-3223(02)01314-8

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent features. *Biological Psychiatry, 61,* 198–209. http://dx.doi.org/10.1016/j.biopsych.2006.05.048

Treadway, M. T., & Zald, D. H. (2011). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience and Biobehavioral Reviews, 35,* 537–555. http://dx.doi.org/10.1016/j.neubiorev.2010.06.006

Watson, D. (2009). Differentiating the mood and anxiety disorders: A quadripartite model. *Annual Review of Clinical Psychology, 5,* 221–247. http://dx.doi.org/10.1146/annurev.clinpsy.032408.153510

Watson, D., & Clark, L. (2006). Clinical diagnosis at the crossroads. *Clinical Psychology: Science and Practice, 13,* 210–215. http://dx.doi.org/10.1111/j.1468-2850.2006.00026.x

Watson, D., O'Hara, M. W., Naragon-Gainey, K., Koffel, E., Chmielewski, M., Kotov, R., . . . Ruggero, C. J. (2012). Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment, 19,* 399–420. http://dx.doi.org/10.1177/1073191112449857

Weinberg, A., & Hajcak, G. (2010). Beyond good and evil: The time-course of neural activity elicited by specific picture content. *Emotion, 10,* 767–782. http://dx.doi.org/10.1037/a0020242

Weinberg, A., & Hajcak, G. (2011). Electrocortical evidence for vigilance-avoidance in Generalized Anxiety Disorder. *Psychophysiology, 48,* 842–851. http://dx.doi.org/10.1111/j.1469-8986.2010.01149.x

Weinberg, A., Klein, D. N., & Hajcak, G. (2012). Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *Journal of Abnormal Psychology, 121,* 885–896.

Weinberg, A., Kotov, R., & Proudfit, G. H. (2015). Neural indicators of error processing in generalized anxiety disorder, obsessive-compulsive disorder, and major depressive disorder. *Journal of Abnormal Psychology, 124,* 172–185. http://dx.doi.org/10.1037/abn0000019

Weinberg, A., Liu, H., Hajcak, G., & Shankman, S. A. (2015). Blunted neural response to rewards as a vulnerability factor for depression: results from a family study. *Journal of Abnormal Psychology*. [Advance online publication.] http://dx.doi.org/10.1037/abn0000081

Weinberg, A., Meyer, A., Hale-Rude, E., Perlman, G., Kotov, R., Klein, D., & Hajcak, G. (2015). Error-related negativity and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology*. Manuscript in press.

Weinberg, A., Shankman, S. (2015). *Blunted reward processing in remitted melancholic depression. under review*.

Weinberg, A., Venables, N. C., Proudfit, G. H., & Patrick, C. J. (2015). Heritability of the neural response to emotional pictures: Evidence from ERPs in an adult twin sample. *Social Cognitive and Affective Neuroscience, 10,* 424–434. http://dx.doi.org/10.1093/scan/nsu059

Weissman, M. M., Wickramaratne, P., Merikangas, K. R., Leckman, J. F., Prusoff, B. A., Caruso, K. A., . . . Gammon, G. D. (1984). Onset of major depression in early adulthood. Increased familial loading and specificity. *Archives of General Psychiatry, 41,* 1136–1143. http://dx.doi.org/10.1001/archpsyc.1984.01790230022003

Weissman, M. M., Wolk, S., Wickramaratne, P., Goldstein, R. B., Adams, P., Greenwald, S., . . . Steinberg, D. (1999). Children with prepubertal-onset major depressive disorder and anxiety grown up. *Archives of General Psychiatry, 56,* 794–801.

Appendix

Images Used in the Study

Rewarding Images

5621, 8030, 8034, 8080, 8158, 8161, 8163, 8170, 8179, 8180, 8185, 8186, 8190, 8191, 8193, 8200, 8206, 8210, 8251, 8280, 8300, 8341, 8370, 8380, 8400, 8470, 8490, 8492, 8496, 8499, 1440, 1441, 1463, 1601, 1710, 1722, 1750, 1920, 2040, 2045, 2058, 2070, 2071, 2080, 2091, 2150, 2155, 2160, 2165, 2208, 2209, 2224, 2303, 2332, 2340, 2344, 2345, 2346, 2347, 2550, 4604, 4608, 4611, 4643, 4647, 4650, 4651, 4652, 4656, 4658, 4659, 4660, 4664, 4666, 4668, 4670, 4672, 4676, 4680, 4683, 4687, 4689, 4690, 4693, 4694, 4695, 4697, 4698, 4800, 4810

Neutral Images

7000, 7002, 7004, 7006, 7010, 7025, 7034, 7035, 7040, 7041, 7050, 7053, 7055, 7056, 7061, 7062, 7077, 7078, 7081, 7090, 7095, 7096, 7100, 7136, 7150, 7161, 7165, 7170, 7175, 7185, 2102, 2104, 2190, 2191, 2200, 2210, 2211, 2214, 2215, 2221, 2235, 2240, 2270, 2271, 2272, 2273, 2279, 2280, 2302, 2305, 2308, 2357, 2370, 2381, 2383, 2385, 2393, 2512, 2570, 7550, 5390, 5471, 5510, 5520, 5530, 5531, 5500, 5726, 5731, 5740, 5750, 7489, 7490, 7491, 7495, 7500, 7504, 7510, 7521, 7545, 7546, 7547, 7560, 7590, 7595, 7640, 7700, 7710, 9360, 9468

Threatening Images

1280, 2730, 2981, 7380, 9008, 9040, 9043, 9140, 9181, 9182, 9183, 9185, 9186, 9187, 9295, 9300, 9301, 9302, 9320, 9321, 9322, 9325, 9326, 9331, 9340, 9342, 9373, 9561, 9570, 9571, 9830, 1050, 1114, 1120, 1300, 1301, 1304, 1310, 1525, 1930, 2811, 3530, 6212, 6230, 6231, 6231, 6242, 6244, 6250, 6250, 6312, 6313, 6315, 6370, 6550, 6560, 6561, 6563, 6571, 6825, 9425, 3001, 3010, 3015, 3016, 3019, 3030, 3051, 3061, 3062, 3064, 3069, 3101, 3102, 3103, 3110, 3120, 3131, 3140, 3150, 3168, 3170, 3181, 3185, 3190, 3195, 3213, 3215, 3261, 3266, 3400

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