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Divergent Relationship of Depression Severity to Social Reward Responses Among Patients with Bipolar Versus Unipolar Depression

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Abstract

Neuroimaging studies of mood disorders demonstrate abnormalities in brain regions implicated in reward processing. However, there is a paucity of research investigating how social rewards affect reward circuit activity in these disorders. Here, we evaluated the relationship of both diagnostic category and dimensional depression severity to reward system function in bipolar and unipolar depression. In total, 86 adults were included, including 24 patients with bipolar depression, 24 patients with unipolar depression, and 38 healthy comparison subjects. Participants completed a social reward task during 3T BOLD fMRI. On average, diagnostic groups did not differ in activation to social reward. However, greater depression severity significantly correlated with reduced bilateral ventral striatum activation to social reward in the bipolar depressed group, but not the unipolar depressed group. In addition, decreased left orbitofrontal cortical activation correlated with more severe symptoms in bipolar depression, but not unipolar depression. These differential dimensional effects resulted in a significant voxelwise group by depression severity interaction. Taken together, these results provide initial evidence that deficits in social reward processing are differentially related to depression severity in the two disorders.

Keywords

neuroimaging; mood disorders; magnetic resonance imaging

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1. Introduction

A major depressive episode is the most common clinical phenotype in both major depressive disorder (MDD) and bipolar disorder (BD). In fact, symptoms of mania are present only 9% of the time while symptoms of depression are present 32% of the time during the course of bipolar I illness (Judd et al., 2002). Furthermore, depressive symptoms overwhelmingly contribute to the high rates of morbidity and mortality in both disorders (Ferrari et al. 2010; Forte et al., 2015; Post, 2005). Despite this phenotypic overlap, treatment response differs between bipolar and unipolar depression (Connolly and Thase, 2011; Ghaemi et al., 2004). Thus, greater understanding of differences in the pathophysiology of depressive symptoms in these disorders is necessary (Phillips and Schwartz, 2014). Dimensional approaches are increasingly applied to identify both common and dissociable features of psychiatric disorders. However, relatively few studies have utilized these approaches to compare unipolar and bipolar depression (Almeida and Phillips, 2013; Whitton et al., 2015).

Recent work examining the pathogenesis of mood disorders has consistently implicated the brain's reward system. Significant lines of evidence from both animal studies and human neuroimaging link reward processing to a network of regions centered on the ventral striatum (VS), as well as cortical regions such as orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (vmPFC) (Kable and Glimcher, 2009; Knutson et al., 2001; Satterthwaite et al., 2007). This core reward network was confirmed by a comprehensive meta-analysis (Bartra et al., 2013).

Growing evidence from human neuroimaging similarly implicates reward system dysfunction in mood disorders. To date, studies investigating reward system abnormalities in mood disorders have predominantly utilized monetary reward paradigms. In bipolar disorder, studies in both manic and euthymic bipolar patients demonstrate reward hyper-responsivity in the VS and OFC compared to normal controls (Abler et al., 2008; Caseras et al., 2013; Nusslock et al., 2012). In contrast, studies in unipolar depression report hypo-responsivity in the VS during reward-related tasks (Pizzagalli et al., 2005; Pizzagalli et al., 2008; Pizzagalli et al., 2009; Smoski et al., 2009; Steele et al., 2007; Stoy et al., 2012). A similar blunting of reward responses is associated with a diverse group of psychiatric disorders and symptoms (Hägele et al., 2015; Simon et al., 2010; Wolf et al., 2014). Very few studies have compared reward-related activity between bipolar depression and unipolar depression (Chase et al., 2013; Redlich et al., 2015). Recently, we reported on common and dissociable dysfunction of the reward system in bipolar and unipolar depression (Satterthwaite et al., 2015). Across disorders, depression severity was significantly associated with reduced activation to monetary rewards and diminished resting-state connectivity within the reward network.

While neuroimaging studies have predominantly evaluated monetary rewards, there has been increasing interest in understanding how social rewards impact reward network recruitment and decision-making behaviors (Ruff and Fehr, 2014). Social valuation drives many aspects of decision-making and interpersonal interaction, playing a critical and pervasive role in human behavior (Gunaydin and Deisseroth, 2015). Furthermore, social impairment is present in multiple psychiatric disorders, implicating dysfunction in social reward

processing across diagnostic categories (Kohls et al., 2013; Miklowitz and Johnson, 2009). Existing studies implicate common reward network regions such as the VS, OFC, and vmPFC in the processing of both social and monetary rewards (Ruff and Fehr, 2014). However, prior research also points to unique aspects of social reward processing. For example, imaging and single-unit recording studies have identified distinct neurons in the striatum, OFC and ACC that selectively encode social aspects of rewards (Izuma et al., 2008; Sescousse et al., 2010; Smith et al., 2010).

Currently, there is a paucity of data investigating social reward processing in mood disorders, and to our knowledge no prior neuroimaging studies have compared social reward processing in bipolar and unipolar depression. Clinical studies suggest a dissociable relationship between depressive symptoms and reactivity to social stimuli between the two disorders (Ng and Johnson, 2013). While interpersonal sensitivity has been correlated with greater depressive symptoms in both disorders (Boyce et al., 1992; Ayduk et al., 2001; Posternak and Zimmerman, 2001; Johnson and Kizer, 2002; Cohen et al., 2004), bipolar depression is associated with higher rejection sensitivity than unipolar depression, suggesting dissociable differences in social valuation between the two depressive disorders (Ehnavall et al., 2014). Furthermore, the reward hypersensitivity model of bipolar disorder predicts increased sensitivity to approach stimuli such as anger in relation to bipolar depression severity (Carver et al., 2009; Johnson et al., 2012), suggesting that sensitivity towards social stimuli may be in accordance with a disorder-specific model.

Using a facial affective reward paradigm, we examined reward system responses to social affective feedback in patients with bipolar depression (n=24), unipolar depression (n=24) and healthy controls (n=38). Based on the limited prior work outlined above, we hypothesized that both categorical and dimensional impairment in social reward activation would be present in depressed subjects, and that these abnormalities would be more prominent in bipolar than unipolar depression. As described below, we did not find categorical group differences in social reward activation. Rather, we found evidence for a dimensional reduction in social reward activation that correlated with depressive symptoms in bipolar depression, but not in unipolar depression.

2. Methods

2.1. Study design

The study included two half-day visits (mean interval between visits: 11.3 days). After providing a complete description of the study, written informed consent was obtained. The University of Pennsylvania Institutional Review Board approved all study procedures. On the first study visit, subjects were assessed using the Structured Clinical Interview for DSM-IV, and enrolled in the study if they met criteria for a current depressive episode in the context of either major depressive disorder or bipolar disorder (type I or II). On the second visit, depression was assessed using the Beck Depression Inventory (BDI) (Beck et al., 1996) and neuroimaging was performed. Functional imaging data were acquired from 93 subjects. Following quality assurance, the final sample included in the analysis of the social reward task comprised 86 subjects (Table 1). For a list of medications by class, see Supplementary Table 1.

2.2 Subject inclusion and exclusion criteria

Mood disorder subjects were eligible for inclusion if they met criteria for a current depressive episode in the context of either major depressive disorder or bipolar disorder (type I or II). Subjects could not be enrolled if they had a history of substance abuse of dependence (excluding nicotine) in the past six months by history or a positive urine drug screen on the day of the study. Control subjects were excluded if they met criteria for any Axis I psychiatric disorder.

Functional imaging data were acquired on 93 subjects. Of these subjects, 90 had complete data from the social reward task. However, 7 subjects (4 bipolar, 1 unipolar, 2 healthy controls) were excluded from the final analysis of the social reward task due to failure to perform the task at a basic level (>4 nonresponses per run or invariant choices in the task; $n=5$) or poor image coverage of the brain ($n=2$). No additional subjects were excluded for excessive in-scanner motion (mean relative displacement $> 0.5\text{mm}$). Thus, following quality assurance, 86 subjects were included in the final analysis of the task fMRI data, including 48 subjects with depression (24 subjects with bipolar depression [21 bipolar type 1, 3 bipolar type 2], 24 subjects with unipolar depression) and 38 healthy controls.

2.3 Image acquisition and fMRI paradigm

All imaging data were acquired on a 3T Siemens TIM TRIO scanner with a 32-channel head coil (Supplementary Table 2). Sequences acquired include a T1-weighted structural image, a B0 field map for distortion correction and two runs of the social reward task using single shot gradient-echo echoplanar fMRI BOLD. The social reward task used here (Figure 1A) is an adaptation of a monetary reward procedure originally developed by Delgado et al. (Delgado et al., 2000) and subsequently modified (Wolf et al., 2014). The approach of using facial affective feedback to study social reward responses has previously been applied in psychiatric disorders (Groppe et al., 2013; Cremers et al., 2014; Flores et al., 2015). In each trial, a gender-neutral and affect-neutral facial mask was presented to the subjects in the guessing phase. Following a variable inter-stimulus interval, facial affective feedback was provided in the outcome phase and consisted of clearly male or female faces expressing either happy or angry expressions depending on whether subjects guessed correctly or not. Happy and angry faces were drawn from a previously validated set of intensely emotional human faces that have been used extensively in other studies (Gur et al., 2002; Kohler et al., 2003). Subjects were instructed that outcomes depended on their guesses, but in fact outcome order was pseudorandomized with an equal number of happy and angry outcomes. Each individual trial contained two parts, a guessing phase (2 seconds) and an outcome phase (2 seconds), separated by a jittered intra-trial delay (2-12 s, mean 5 s). Inter-trial intervals were jittered the same way. Each task run comprised 336s of analyzed data including 24 trials (12 happy, 12 angry).

2.4 Structural image processing and functional image registration

In order to maximize sensitivity to detect effects in small subcortical structures like the ventral striatum, advanced structural image processing and registration procedures were employed. The T1 image was skull stripped using a multi-atlas skull strip procedure (Doshi et al., 2013) and multiplicative intrinsic component optimization was used for bias

correction (Li et al., 2014). Images were registered to the Montreal Neurological Institute template using a highly-accurate deformable registration with attribute matching and mutual-salience weighting (Ou et al., 2011). After distortion correction using the B0 image, functional images were co-registered to the structural image with boundary-based registration (Greve et al., 2009) and normalized to template space by concatenating the co-registration and deformation so that only one interpolation was performed.

2.5 Image analysis: social reward task

Social reward task image preprocessing and time-series analyses were performed using FEAT (fMRI Expert Analysis Tool) in FSL (Jenkinson et al., 2012). Images were distortion corrected, slice-timing corrected, motion-corrected using a tri-linear interpolation with 6 degrees of freedom, high-pass filtered (100s), spatially smoothed using a Gaussian kernel of 6mm FWHM, and grand mean scaled. Subject-level time-series analysis was carried out using FSL's improved linear model (Woolrich et al., 2001); task regressors (event duration 2s) were convolved with a canonical double-gamma hemodynamic response function. Happy and Angry trials were modeled as separate regressors during the outcome phase of the task. The guessing phases, outcome phases for non-response trials, rare extraneous button presses, and 6 motion parameters were all included in the model as nuisance regressors. In our previous reports using a monetary reward version of this task (Wolf et al., 2014, Satterthwaite et al., 2015) robust and selective activation of VS was noted for monetary rewards compared to monetary losses. Therefore, for the social reward task, our *a priori* contrast of interest was happy>angry outcomes.

Three group level analyses were conducted. The first examined categorical group differences using a voxelwise one-way ANOVA with three groups. Second, group differences in the dimensional effect of depression severity (i.e., total BDI) were examined using a BDI $\times$ group interaction model. Finally, dimensional effects of BDI were examined across both mood groups and within each mood group separately. All models included age, sex and in-scanner motion as nuisance covariates. Significant effects were defined in whole-brain voxelwise task fMRI data as clusters with a voxel height threshold $Z > 2.33$ (uncorrected $p < 0.01$) and spatial extent probability threshold $p < 0.05$ (131 voxels), as calculated by 10,000 Monte Carlo simulations using AFNI 3dClustSim, Version 16.0.

2.6 Evaluation of potentially confounding variables

Given prior studies reporting reward system changes in association with medication usage (Abler et al., 2007) and smoking status (Peters et al., 2011), we evaluated the influence of these potentially confounding variables. Specifically, we re-evaluated significant results on a cluster-wise basis with addition of either smoking status, task processing speed (response time), number of depressive episodes, illness duration or composite medication load as additional model covariates. Here, heterogeneity of medication class (antipsychotics, mood stabilizers, antidepressants, benzodiazepines) and medication dose was standardized into a composite medication variable, based on a previously described method (Hassel et al., 2008).

3. Results

3.1 Social reward fMRI task recruits bilateral ventral striatum

The contrast of happy>angry outcomes in the social reward paradigm produced strong and selective bilateral VS activation across groups (Figure 1B, left). Activation was also present in the bilateral orbitofrontal cortex (Figure 1B, right) as well as other cortical regions such as ventromedial prefrontal cortex (Supplementary Table 3). A voxel-wise, one-way ANOVA with three groups, testing group differences of the happy>angry contrast did not reveal any significant clusters surviving whole-brain correction for multiple comparisons.

3.2 Bipolar depression severity is associated with blunted response to social rewards

The group $\times$ BDI interaction model demonstrated a significantly stronger inverse relationship between depression severity and social reward activation in bipolar depression than in unipolar depression, localized to bilateral ventral striatum and left orbitofrontal cortex (Figure 2; Supplementary Table 4). Results were essentially unchanged when these clusters were re-evaluated with smoking status, task processing speed (response time), number of depressive episodes, illness duration or composite medication dose included as model covariates. Analyses of unipolar and bipolar groups separately showed that this interaction was driven by significant inverse correlations in bipolar disorder that were not present in unipolar disorder. In bipolar disorder, greater depression severity was associated with diminished activation of key regions within the reward system including the bilateral ventral striatum (Figure 3A) and left orbitofrontal cortex (Figure 3B). These effects in bipolar disorder were significant within the same clusters showing the group $\times$ BDI interaction, and were robust enough to survive whole brain correction. Analysis of happy and angry contrasts showed that observed associations with BDI in bipolar disorder were related to both reduced responses to happy faces and increased responses to angry faces (Supplementary Figure 1). In unipolar disorder, depression severity did not significantly correlate with reward system activation (Figure 3C-D; Supplementary Table 5). Dimensional BDI analysis across all depressed subjects in both mood groups did not identify significant effects within core reward regions (Supplementary Table 5).

4. Discussion

To our knowledge, this is the first study to evaluate both categorical and dimensional reward system dysfunction during the processing of social rewards in mood disorders. Contrary to our categorical hypothesis, we did not find any average differences between groups, nor did we find dimensional effects of depression severity within the core reward system that were shared across unipolar and bipolar disorders. Consistent with the differential dimensional hypothesis that depression-associated social reward abnormalities would be more prominent in bipolar disorder, depression severity was associated with blunting of reward system response to social affective feedback in bipolar but not unipolar depression. These results highlight the value of distinct reward paradigms, and provide novel evidence for dissociable neural correlates of depression severity in mood disorders.

Prior studies evaluating dimensional reward system dysfunction in mood disorders have largely relied on monetary reward paradigms. Thus, there is limited data examining how these disorders might impact the processing of different types of reward including social rewards. This is surprising given that impaired social functioning affects a number of psychiatric disorders (Bosc, 2000; De Silva et al., 2013; Foulkes et al., 2015). A few neuroimaging studies have utilized social reward paradigms to identify reward system abnormalities in autism spectrum disorders (ASD) (Kohls et al., 2013; Delmonte et al., 2012; Dichter et al., 2012). Similar to our study, these studies used facial affective fMRI tasks for social reward evaluation.

We found evidence for a dimensional reduction in reward activation for the happy compared to angry contrast that correlated with depressive severity in bipolar depression, but not in unipolar depression. This effect was driven by both blunted activation to happy faces and increased activation to angry faces, suggesting both reduced sensitivity to social reward and enhanced sensitivity to rejection with increasing severity of depression in bipolar disorder. The increased activation to angry faces is consistent with prior studies demonstrating state rejection sensitivity in bipolar disorder (Ehnvall et al., 2014). With greater depression severity, individuals with bipolar depression may perceive increased salience following rejection than individuals with unipolar depression. Alternatively, since anger can also be considered an approach emotion, and bipolar disorder is associated with elevated approach responses including anger (Carver et al., 2009; Johnson et al., 2012), this might contribute to the observed relationship between depression severity in bipolar disorder and anger-evoked activation in brain regions linked to approach responses. The effects were present in brain regions critical for reward processing including bilateral VS and left OFC. Notably, these reward regions have also been found to be overactive in both euthymic and manic bipolar patients (Bermphohl et al., 2010; Nusslock et al., 2012). Together, these results suggest that changes in activity in bilateral VS and left OFC may be associated with dysregulated sensitivity to rewards across mood states in bipolar disorder.

In our recent study utilizing a monetary reward task, depression severity was associated with blunted VS responses for win>loss in both bipolar and unipolar depression (Satterthwaite et al., 2015). Using the social reward task, we see blunted responses in VS with depression severity in bipolar, but not unipolar depression. These findings suggest that distinct reward tasks identify unique features of reward system dysfunction in these disorders. For example, bipolar depressed subjects may demonstrate higher symptom sensitivity to social rewards than unipolar depressed patients, but similar symptom sensitivity to monetary rewards. Here, processing of social feedback could be a distinguishing brain phenotype between the depressive states. Additionally, it is possible that the bipolar depressed group has a particular pattern of depressive phenomenology that relates more strongly to social reward system function than the pattern in unipolar depression. However, supplementary analyses of BDI sub-domains do not support this interpretation (see Supplementary Table 6). Together, these findings highlight the importance of examining social and monetary rewards in mood disorders. Future development of conceptual models of reward processing abnormalities in affective disorders will benefit from incorporating data from different types of reward stimuli to identify common and dissociable aspects of reward deficits in these disorders.

These results add to an emerging literature identifying both common and dissociable aspects of reward system dysfunction in the pathophysiology of mood disorders. Prior work has aimed to identify categorical differences in reward system activity between diagnostic groups and healthy control groups (Berpohl et al., 2010; Linke et al., 2012; Nusslock et al., 2012). One study showed increased activation during anticipation of monetary reward in left ventrolateral prefrontal cortex in a bipolar depression group compared with both unipolar depression and healthy control groups (Chase et al., 2013). Recently, we found higher ventral striatum activation and resting connectivity in bipolar depression than in unipolar depression (Satterthwaite et al., 2015). The current study did not identify diagnostic differences in reward system activation to social stimuli. Here, the dimensional reduction in reward activation in bipolar depression may have precluded identification of significant categorical differences. Subsequent studies that select for depressed populations with social deficits may offer additional sensitivity in identifying categorical differences between depressed groups.

It is important to distinguish the current study from prior neuroimaging studies using facial images to evaluate emotion-processing abnormalities in mood disorders (Bertocci et al., 2012; Fournier et al., 2013; Grotegerd et al., 2014; Henderson et al., 2014). Explicit emotion-processing tasks typically present faces and ask participants to identify the emotion presented or judge the degree of elicited emotion. A meta-analysis comparing correlates of emotional processing in bipolar and major depressive disorders highlight common and distinct engagement of limbic, thalamic and cortical regions (Delvecchio et al., 2012). In bipolar disorder, emotion-processing studies report abnormally elevated amygdala activity (Phillips and Swartz, 2014; Almeida et al., 2009). This is distinct from our findings assessing social reward, which identifies abnormalities in reward regions including ventral striatum and orbitofrontal cortex, but not in emotion-processing regions such as the amygdala. These results highlight that paradigms presenting faces in the context of social reward processing are sensitive to abnormalities in distinct neural circuits than those presenting faces in emotion-processing or non-reward contexts.

This study had the following limitations. First, the association between depression severity and reward system hypo-responsivity in this cross-sectional study does not establish causation in either direction. Second, we did not include euthymic or manic bipolar subjects. Future longitudinal neuroimaging studies are needed to evaluate the temporal dynamics of reward system abnormalities in mood disorders, comparing different mood states to distinguish state and trait abnormalities. Third, our findings suggest no significant impact of composite medication load upon neural activity for the subjects present in this study. However, future studies should also examine effects in un-medicated depressed individuals. Fourth, we used a facial affective feedback task to assess responses to social rewards. More interactive and complex social reward paradigms that utilize faces with verbal praise or even live interactions via hyperscanning can be applied in future studies to develop and evaluate models of social reward processing (Scott-Van Zeeland et al. 2010; Bilek et al., 2015; Cox et al., 2015). Finally, we did not assess real-world social function, and future work would benefit from the inclusion of social and other functional outcome measures.

Despite these limitations, our results suggest that reward system dysfunction following the processing of social rewards distinguishes dimensional effects of depression severity in bipolar and unipolar depression. Additional efforts to understand the relationship between depression severity and social motivation will broaden our understanding of the pathogenesis of bipolar depression. Finally, continued investigation in this area may foster the development of novel interventions for bipolar depression that directly target impairments in social motivation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Abler B, Erk S, Walter H. Human reward system activation is modulated by a single dose of olanzapine in healthy subjects in an event-related, double-blind, placebo-controlled fmri study. *Psychopharmacology*. 2007; 191:823–833. [PubMed: 17265148]
- Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. *Neuropsychopharmacology*. 2008; 33:2217–2227. [PubMed: 17987058]
- Almeida JR, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ, Phillips ML. Abnormal amygdala-prefrontal effective connectivity to happy faces differentiates bipolar from major depression. *Biological Psychiatry*. 2009; 66:451–459. [PubMed: 19450794]
- Almeida JR, Phillips ML. Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychological Medicine*. 2012; 42:1417–1428. [PubMed: 22099606]
- Almeida JR, Phillips ML. Distinguishing between unipolar depression and bipolar depression: Current and future clinical and neuroimaging perspectives. *Biological Psychiatry*. 2013; 73:111–118. [PubMed: 22784485]
- Ayduk O, Downey G, Kim M. Rejection sensitivity and depressive symptoms in women. *Personality and Social Psychology Bulletin*. 2001; 27:868–877.
- Bartra O, McGuire JT, Kable JW. The valuation system: A coordinate-based meta-analysis of BOLD fmri experiments examining neural correlates of subjective value. *NeuroImage*. 2013; 76:412–427. [PubMed: 23507394]
- Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996; 67:588–597. [PubMed: 8991972]
- Berpohl F, Kahnt T, Dalanay U, Hägele C, Sajonz B, Wegner T, Stoy M, Adli M, Kruger S, Wrase J, Strohle A, Bauer M, Heinz A. Altered representation of expected value in the orbitofrontal cortex in mania. *Hum Brain Mapp*. 2010; 31:958–969. [PubMed: 19950195]
- Bertocci MA, Bebko GM, Mullin BC, Langenecker SA, Ladouceur CD, Almeida JR, Phillips ML. Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychological Medicine*. 2012; 42:1417–1428. [PubMed: 22099606]

- Bosc M. Assessment of social functioning in depression. *Compr Psychiatry*. 2000; 41:63–69. [PubMed: 10646621]
- Bilek E, Ruf M, Schäfer A, Akdeniz C, Calhoun VD, Schmahl C, Demanuele C, Tost H, Kirsch P, Meyer-Lindenberg A. Information flow between interacting human brains: Identification, validation, and relationship to social expertise. *Proc Natl Acad Sci*. 2015; 112:5207–12. [PubMed: 25848050]
- Boyce P, Hickie I, Parker G, Mitchell P, Wilhelm K, Brodaty H. Interpersonal sensitivity and the one-year outcome of a depressive episode. *Aust N Z J Psychiatry*. 1992; 26:156–161. [PubMed: 1642605]
- Carver CS, Harmon-Jones E. Anger is an approach-related affect: evidence and implications. *Psychological Bulletin*. 2009; 135:183. [PubMed: 19254075]
- Caseras X, Lawrence NS, Murphy K, Wise RG, Phillips ML. Ventral striatum activity in response to reward: Differences between bipolar I and II disorders. *The American Journal of Psychiatry*. 2013; 170:533–541. [PubMed: 23558337]
- Chase HW, Nusslock R, Almeida JRC, Forbes EE, LaBarbara EJ, Phillips ML. Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. *Bipolar Disord*. 2013; 15:839–854. [PubMed: 24148027]
- Cohen AN, Hammen C, Henry RM, Daley SE. Effects of stress and social support on recurrence in bipolar disorder. *J Affect Disord*. 2004; 82:143–147. [PubMed: 15465589]
- Connolly KR, Thase ME. The clinical management of bipolar disorder: A review of evidence-based guidelines. *Prim Care Companion CNS Disord*. 2011; 13
- Cox A, Kohls G, Naples AJ, Mukerji CE, Coffman MC, Rutherford HJV, Mayes LC, McPartland JC. Diminished social reward anticipation in the broad autism phenotype as revealed by event-related brain potentials. *Soc Cogn Affect Neurosci*. 2015; doi: 10.1093/scan/nsv024
- Cremers HR, Veer IM, Spinhoven P, Rombouts SA, Roelofs K. Neural sensitivity to social reward and punishment anticipation in social anxiety disorder. *Front Behav Neurosci*. 2015; 8doi: 10.3389/fnbeh.2014.00439
- Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA. Tracking the hemodynamic responses to reward and punishment in the striatum. *J Neurophysiol*. 2000; 84:3072–3077. [PubMed: 11110834]
- Delmonte S, Balsters JH, McGrath J, Fitzgerald J, Brennan S, Fagan AJ, Gallagher L. Social and monetary reward processing in autism spectrum disorders. *Mol Autism*. 2012; doi: 10.1186/2040-2392-3-7
- Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, Hietala J, Lawrie SM, Martinot JL, McIntosh AM, Meisenzahl E, Frangou S. Common and distinct neural correlates of emotional processing in bipolar disorder and major depressive disorder: A voxel-based meta-analysis of functional magnetic resonance imaging studies. *Eur Neuropsychopharmacol*. 2012; 22:100–113. [PubMed: 21820878]
- De Silva MJ, Cooper S, Li HL, Lund C, Patel V. Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. *Br J Psychiatry*. 2013; 202:253–260. [PubMed: 23549941]
- Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. *Journal of Autism and Developmental Disorders*. 2012; 42:147–160. [PubMed: 22187105]
- Doshi J, Erus G, Ou Y, Gaonkar B, Davatzikos C. Multi-atlas skull-stripping. *Acad Radiol*. 2013; 20:1566–1576. [PubMed: 24200484]
- Ehnvall A, Mitchell PB, Hadzi-Pavlovic D, Parker G, Frankland A, Loo C, Breakspear M, Wright A, Roberts G, Lau P, Perich T. Rejection sensitivity and pain in bipolar versus unipolar depression. *Bipolar Disord*. 2014; 16:190–198. [PubMed: 24636342]
- Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Medicine*. 2013; 10:e1001547. [PubMed: 24223526]
- Flores A, Münte TF, Doñamayor N. Event-related EEG responses to anticipation and delivery of monetary and social reward. *Biol Psychol*. 2015; doi: 10.1016/j.biopsycho.2015.04.005

- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med*. 1995; 33:636–647. [PubMed: 7596267]
- Forte A, Baldessarini RJ, Tondo L, Vázquez GH, Pompili M, Girardi P. Long-term morbidity in bipolar-i, bipolar-ii, and unipolar major depressive disorders. *J Affect Disord*. 2015; 178:71–78. [PubMed: 25797049]
- Foulkes L, Bird G, Gökçen E, McCrory E, Viding E. Common and distinct impacts of autistic traits and alexithymia on social reward. *PloS one*. 2015; 10:e0121018. [PubMed: 25853670]
- Fournier JC, Keener MT, Almeida J, Kronhaus DM, Phillips ML. Amygdala and whole-brain activity to emotional faces distinguishes major depressive disorder and bipolar disorder. *Bipolar Disord*. 2013; 15:741–752. [PubMed: 2391154]
- Ghaemi SN, Rosenquist KJ, Ko JY, Baldassano CF, Kontos NJ, Baldessarini RJ. Antidepressant treatment in bipolar versus unipolar depression. *The American Journal of Psychiatry*. 2004; 161:163–165. [PubMed: 14702267]
- Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*. 2009; 48:63–72. [PubMed: 19573611]
- Groppe SE, Gossen A, Rademacher L, Hahn A, Westphal L, Gründer G, Spreckelmeyer KN. Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. *Biol Psychiatry*. 2013; 74:172–179. [PubMed: 23419544]
- Grotegerd D, Stuhmann A, Kugel H, Schmidt S, Redlich R, Zwanzger P, Rauch AV, Heindel W, Zwitterlood P, Arolt V, Suslow T, Dannlowski U. Amygdala excitability to subliminally presented emotional faces distinguishes unipolar and bipolar depression: An fmri and pattern classification study. *Hum Brain Mapp*. 2014; 35:2995–3007. [PubMed: 24038516]
- Gunaydin, LA.; Deisseroth, K. Cold Spring Harbor symposia on quantitative biology. Cold Spring Harbor Laboratory Press; 2015. Dopaminergic Dynamics Contributing to Social Behavior.
- Gur RC, Sara R, Hagendoorn M, Marom O, Hughett P, Macy L, Turner T, Bajcsy R, Posner A, Gur RE. A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *J Neurosci Methods*. 2002; 115:137–143. [PubMed: 11992665]
- Hafeman DM, Chang KD, Garrett AS, Sanders EM, Phillips ML. Effects of medication on neuroimaging findings in bipolar disorder: An updated review. *Bipolar Disord*. 2012; 14:375–410. [PubMed: 22631621]
- Hägele C, Schlagenhauf F, Rapp M, Sterzer P, Beck A, Bermpohl F, Stoy M, Strohle A, Wittchen HU, Dolan RJ, Heinz A. Dimensional psychiatry: Reward dysfunction and depressive mood across psychiatric disorders. *Psychopharmacology (Berl)*. 2015; 232:331–341. [PubMed: 24973896]
- Hassel S, Almeida JR, Kerr N, Nau S, Ladouceur CD, Fissell K, Kuper DJ, Phillips ML. Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. *Bipolar disorders*. 2008; 10:916–927. [PubMed: 19594507]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British journal of addiction*. 1991; 86:1119–1127. [PubMed: 1932883]
- Henderson SE, Vallejo AI, Ely BA, Kang G, Krain Roy A, Pine DS, Stern ER, Gabbay V. The neural correlates of emotional face-processing in adolescent depression: A dimensional approach focusing on anhedonia and illness severity. *Psychiatry Res*. 2014; 224:234–241. [PubMed: 25448398]
- Izuma K, Saito DN, Sadato N. Processing of social and monetary rewards in the human striatum. *Neuron*. 2008; 58:284–294. [PubMed: 18439412]
- Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. *NeuroImage*. 2012; 62, 782–790.
- Johnson, SL.; Kizer, A. Bipolar and unipolar depression: A comparison of clinical phenomenology and psychosocial predictors. In: Gotlib, IH.; Hammen, CL., editors. *Handbook of depression*. New York: Guilford Press; 2002. p. 141-165.
- Johnson SL, Edge MD, Holmes MK, Carver CS. The behavioral activation system and mania. *Annual Review of Clinical Psychology*. 2012; 8:243.

- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry*. 2002; 59:530–537. [PubMed: 12044195]
- Kable JW, Glimcher PW. The neurobiology of decision: Consensus and controversy. *Neuron*. 2009; 63:733–745. [PubMed: 19778504]
- Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *The Journal of Neuroscience*. 2001; 21:RC159. [PubMed: 11459880]
- Kohler CG, Turner TH, Bilker WB, Brensinger CM, Siegel SJ, Kanes SJ, Gur RE, Gur RC. Facial emotion recognition in schizophrenia: Intensity effects and error pattern. *The American Journal of Psychiatry*. 2003; 160:1768–1774. [PubMed: 14514489]
- Kohls G, Schulte-Rüther M, Nehr Korn B, Müller K, Fink GR, Kamp-Becker I, Herpertz-Dahlmann B, Schultz RT, Konrad K. Reward system dysfunction in autism spectrum disorders. *Soc Cogn Affect Neurosci*. 2013; 8:565–572. [PubMed: 22419119]
- Li C, Gore JC, Davatzikos C. Multiplicative intrinsic component optimization (MICO) for MRI bias field estimation and tissue segmentation. *Magn Reson Imaging*. 2014; 32:913–923. [PubMed: 24928302]
- Linke J, King AV, Rietschel M, Strohmaier J, Hennerici M, Gass A, Meyer-Lindenberg A, Wessa M. Increased medial orbitofrontal and amygdala activation: Evidence for a systems-level endophenotype of bipolar I disorder. *The American Journal of Psychiatry*. 2012; 169:316–325. [PubMed: 22267184]
- Miklowitz DJ, Johnson SL. Social and familial factors in the course of bipolar disorder: Basic processes and relevant interventions. *Clin Psychol*. 2009; 16:281–296.
- Ng TH, Johnson SL. Rejection sensitivity is associated with quality of life, psychosocial outcome, and the course of depression in euthymic patients with bipolar I disorder. *Cognitive Therapy and Research*. 2013; 37:1169–1178.
- Nusslock R, Almeida JR, Forbes EE, Versace A, Frank E, Labarbara EJ, Klein CR, Phillips ML. Waiting to win: Elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disord*. 2012; 14:249–260. [PubMed: 22548898]
- Ou Y, Sotiras A, Paragios N, Davatzikos C. DRAMMS: Deformable registration via attribute matching and mutual-saliency weighting. *Med Image Anal*. 2011; 15:622–639. [PubMed: 20688559]
- Peters J, Bromberg U, Schneider S, Brassen S, Menz M, Banaschewski T, Conrod PJ, Flor H, Gallinat J, Garavan H, Heinz A, Itterman B, Lathrop M, Martinot JL, Paus T, Poline JB, Robbins TW, Rietschel M, Smolka M, Ströhle A, Struve M, Loth E, Schumann G, Büchel C. IMAGEN Consortium. Lower ventral striatal activation during reward anticipation in adolescent smokers. *The American Journal of Psychiatry*. 2011; 168:540–549. [PubMed: 21362742]
- Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: Toward a new conceptualization of underlying neural circuitry and a road map for future research. *The American Journal of Psychiatry*. 2014; 171:829–843. [PubMed: 24626773]
- Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry*. 2005; 57:319–327. [PubMed: 15705346]
- Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research*. 2008; 43:76–87. [PubMed: 18433774]
- Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *The American Journal of Psychiatry*. 2009; 166:702–710. [PubMed: 19411368]
- Post RM. The impact of bipolar depression. *J Clin Psychiatry*. 2005; 66:5–10. [PubMed: 16038596]
- Posternak MA, Zimmerman M. Symptoms of atypical depression. *Psychiatry Res*. 2001; 104:175–181. [PubMed: 11711170]
- Redlich R, Dohm K, Grotegerd D, Opel N, Zwieterlood P, Heindel W, Arolt V, Kugel A, Dannlowski U. Reward processing in unipolar and bipolar depression: a functional MRI study. *Neuropsychopharmacology*. 2015; 40:2623–2631. [PubMed: 25881114]

- Ruff CC, Fehr E. The neurobiology of rewards and values in social decision making. *Nature Reviews Neuroscience*. 2014; 15:549–562. [PubMed: 24986556]
- Satterthwaite TD, Green L, Myerson J, Parker J, Ramaratnam M, Buckner RL. Dissociable but inter-related systems of cognitive control and reward during decision making: Evidence from pupillometry and event-related fmri. *NeuroImage*. 2007; 37:1017–1031. [PubMed: 17632014]
- Satterthwaite TD, Kable JW, Vandekar L, Katchmar N, Bassett DS, Baldassano CF, Ruparel K, Elliott MA, Sheline YI, Gur RC, Gur RE, Davatzikos C, Leibenluft E, Thase ME, Wolf DH. Common and dissociable dysfunction of the reward system in bipolar and unipolar depression. *Neuropsychopharmacology*. 2015; 40:2258–2268. [PubMed: 25767910]
- Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY. Reward processing in autism. *Autism Res*. 2010; 3:53–67. [PubMed: 20437601]
- Sescousse G, Redouté J, Dreher JC. The architecture of reward value coding in the human orbitofrontal cortex. *The Journal of Neuroscience*. 2010; 30:13095–13104. [PubMed: 20881127]
- Simon JJ, Biller A, Walther S, Roesch-Ely D, Stippich C, Weisbrod M, Kaiser S. Neural correlates of reward processing in schizophrenia--relationship to apathy and depression. *Schizophr Res*. 2010; 118:154–161. [PubMed: 20005675]
- Smith DV, Hayden BY, Truong TK, Song AW, Platt ML, Huettel SA. Distinct value signals in anterior and posterior ventromedial prefrontal cortex. *The Journal of Neuroscience*. 2010; 30:2490–2495. [PubMed: 20164333]
- Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, Dichter GS. FMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *J Affect Disord*. 2009; 118:69–78. [PubMed: 19261334]
- Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. *Brain*. 2007; 130:2367–2374. [PubMed: 17586866]
- Stoy M, Schlagenhauf F, Sterzer P, Birmpohl F, Hägele C, Suchotzki K, Schmack K, Wrase J, Ricken R, Knutson B, Adli M, Bauer M, Heinz A, Ströhle A. Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *J Psychopharmacol*. 2012; 26:677–688. [PubMed: 21926423]
- Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry*. 2015; 28:7–12. [PubMed: 25415499]
- Wolf DH, Satterthwaite TD, Kantrowitz JJ, Katchmar N, Vandekar L, Elliott MA, Ruparel K. Amotivation in schizophrenia: Integrated assessment with behavioral, clinical, and imaging measures. *Schizophrenia Bulletin*. 2014; 40:1328–1337. [PubMed: 24657876]
- Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*. 2001; 14:1370–1386. [PubMed: 11707093]

Figure 1. Task paradigm and activation

A) Schematic of the fMRI social reward paradigm. Facial feedback was probabilistically 50% happy and 50% angry. B) Across the whole brain, the bilateral ventral striatum was the most strongly activated region for the happy versus angry contrast, while other regions such as the orbitofrontal cortex were also robustly activated (unmasked image, analysis included all subjects retained in fMRI analysis).

Group by Depression Severity Interaction

Figure 2.

Group by depression severity interaction demonstrates a significant ($z > 2.33$, whole-brain corrected $P < 0.05$) stronger inverse relationship between depression severity and social reward activation in bipolar depression than in unipolar depression in bilateral VS (A) and left OFC (B). Descriptive scatterplots show the relationship between depression severity (BDI) and activation to happy > angry social feedback from bilateral VS clusters (C) and L OFC cluster (D).

Figure 3.

Bipolar depression severity is associated with diminished response to social rewards. Activation in the happy > angry contrast is dimensionally reduced in association with depression severity for bipolar depressed (A-B) but not unipolar depressed groups (C-D). Reward system regions showing a significant reduction in activation in the bipolar group included bilateral ventral striatum and left orbitofrontal cortex ($z > 2.33$, whole-brain corrected $P < 0.05$).

Table 1
Sample characteristics

Variable	Bipolar depressed (n=24)	Unipolar depressed (n=24)	Controls (n=38)	p-value
	Percentage	Percentage	Percentage	
Gender (% Female)	58%	42%	55%	ns ^{a,1}
Handedness (% Right)	92%	83%	89%	ns ^{a,2}
Race (% Caucasian)	66%	50%	47%	ns ^{a,3}
Smoke (% Y)	29%	25%	34%	ns ^{a,4}
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (yrs)	38.0 (11.7)	38.4 (12.9)	39.4 (11.8)	ns ^{b,5}
Education (yrs)	15.4 (2.2)	14.6 (2.6)	14.7 (2.2)	ns ^{b,6}
Maternal education (yrs)	14.8 (2.9)	13.6 (2.5)	14.1 (2.9)	ns ^{b,7}
BDI (total) ^d	22.4 (7.9)	25.0 (8.7)	2.4 (4.8)	ns ^{b,8}
Illness duration (yrs)	15.3 (10.2)	14.0 (10.6)	n/a	ns ^{c,9}
Depressive episodes (total)	12.0 (12.2)	7.3 (10.9)	n/a	ns ^{c,10}
Antipsychotic dose (mg) ^e	404.9 (261.2)	375.8 (413.3)	n/a	ns ^{c,11}
In-Scanner motion ^f	0.11 (0.07)	0.11 (0.06)	0.10 (0.04)	ns ^{b,12}

^a Pearson's Chi-squared test with simulated p-value used to compare proportions for categorical variables between three groups.

^b One-Way Analysis of Variance Model (ANOVA) used for comparing group means between three groups.

^c Welch Two Sample t-test comparing unipolar and bipolar depressed groups.

^d Beck Depression Inventory (BDI - IA) total score.

^e Mean calculated among subjects taking antipsychotics, CPZ equivalents (mg).

^f Mean relative scan-to-scan displacement in mm, in sample retained for fMRI analysis.

¹ $\chi^2(2, N=86) = 1.57, p = 0.46$.

² $\chi^2(2, N=86) = 0.89, p = 0.74$.

³ $\chi^2(2, N=86) = 2.36, p = 0.31$.

⁴ $\chi^2(2, N=86) = 0.61, p = 0.77$.

⁵ $F(2, 83) = 0.11, p = 0.90$.

⁶ $F(2, 83) = 0.89, p = 0.42$.

⁷ $F(2, 83) = 1.12, p = 0.33$.

⁸ Tukey HSD non-significant for comparison of bipolar depressed and unipolar depressed groups ($p = 0.43$). (comparisons between normal controls and depressed groups are significant).

⁹ $t(46) = 0.48, p = 0.64$.

$$^{10}t_{(28)} = 0.48, p = 0.28.$$

$$^{11}t_{(1.17)} = 0.10, p = 0.94.$$

$$^{12}F_{(2, 83)} = 0.78, p = 0.46.$$

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