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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.

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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., 2013; 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 Swartz, 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.,

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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 (Ehnvall 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.

Table 1.
Sample characteristics.

Variable	Bipolar depressed ($n=24$) Percentage	Unipolar depressed ($n=24$) Percentage	Controls ($n=38$) Percentage	p-value
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]

[1] χ^2 (2, $N=86$)=1.57, $p=0.46$.
[2] χ^2 (2, $N=86$)=0.89, $p=0.74$.
[3] χ^2 (2, $N=86$)=2.36, $p=0.31$.
[4] χ^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, $p=0.46$.

[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.

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 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 (Fig. 1(A)) 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., 2015; 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 s) and an outcome phase (2 s), 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.,

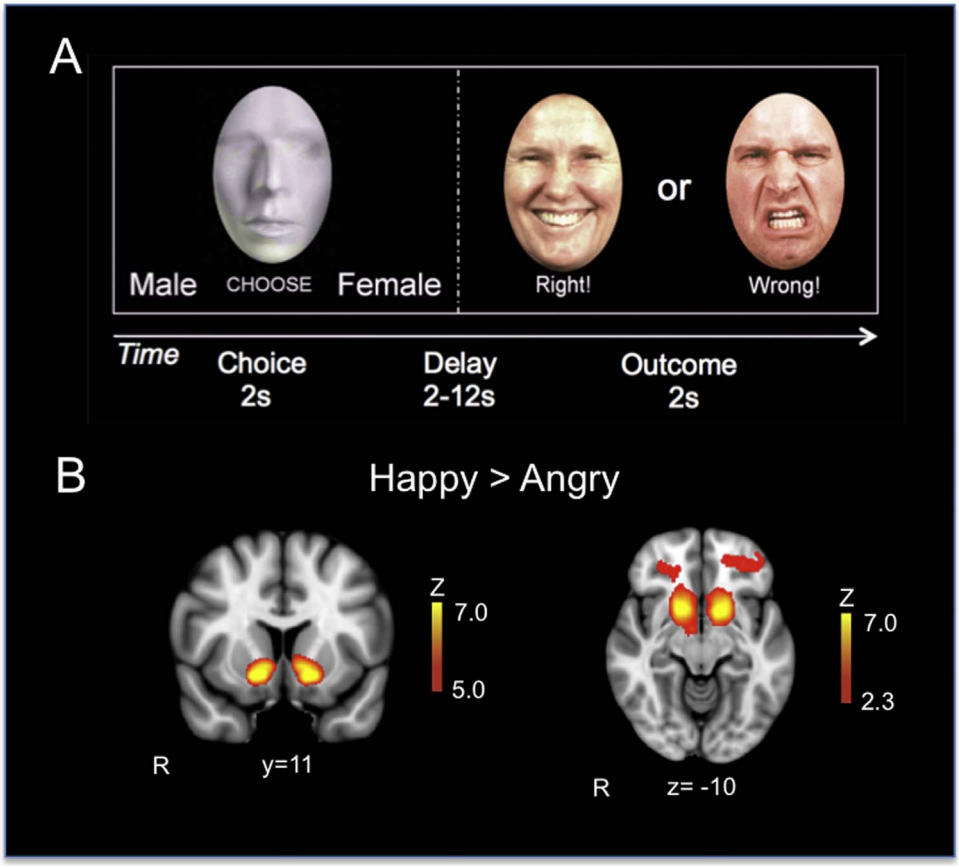

Fig. 1. Task paradigm and activation. A) Schematic of the fMRI social reward paradigm. Facial feedback was probabilistically 50% happy and 50% angry. B) Across the whole brain, the bilateral ventral striatum was the most strongly activated region for the happy versus angry contrast, while other regions such as the orbitofrontal cortex were also robustly activated (unmasked image, analysis included all subjects retained in fMRI analysis).

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 (100 s), 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 2 s) 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 × 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 (Fig. 1(B), left). Activation was also present in the bilateral orbitofrontal cortex (Fig. 1(B), 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 × 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 (Fig. 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 (Fig. 3(A)) and left orbitofrontal cortex (Fig. 3(B)). These effects in bipolar disorder were significant within the same clusters showing the group × 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 Fig. 1). In unipolar disorder, depression severity did not significantly correlate with reward system activation (Fig. 3(C)-(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

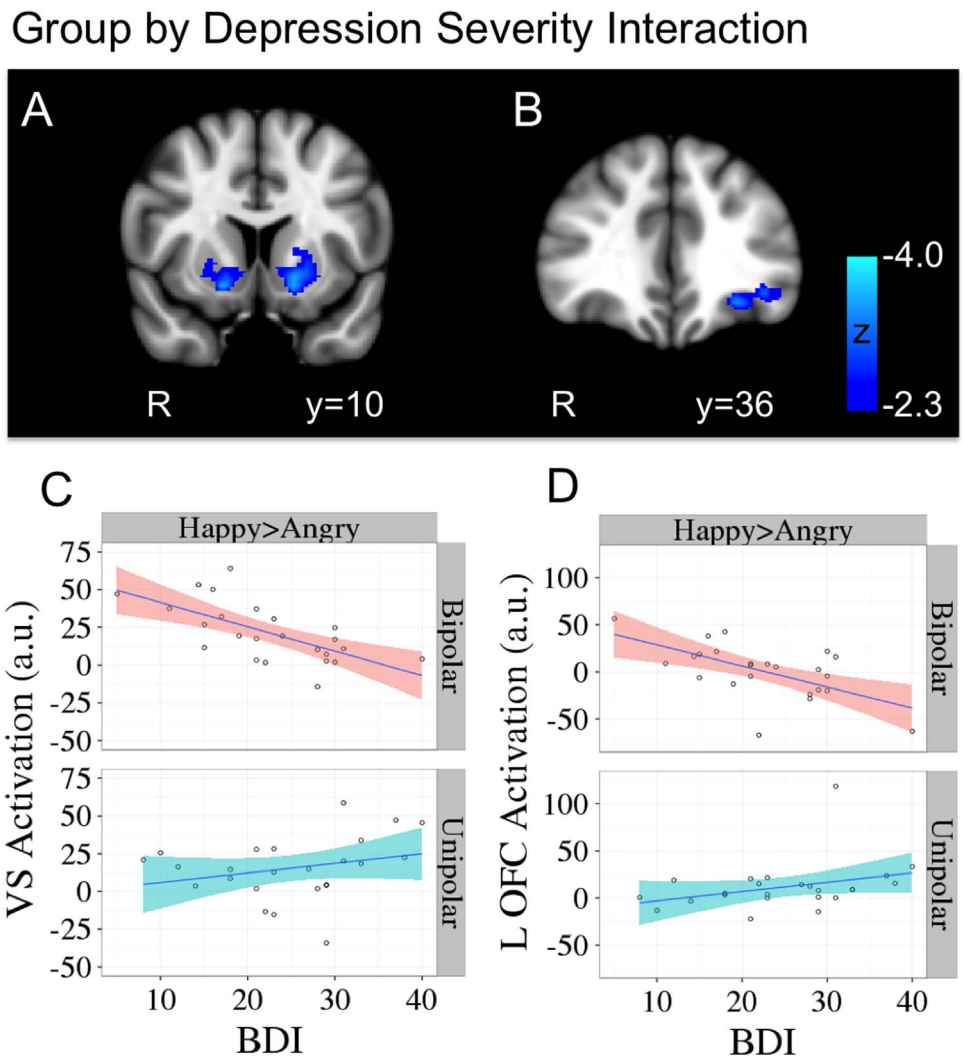

Fig. 2. Group by depression severity interaction demonstrates a significant ($z > 2.33$, whole-brain corrected $P < 0.05$) stronger inverse relationship between depression severity and social reward activation in bipolar depression than in unipolar depression in bilateral VS (A) and left OFC (B). Descriptive 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).

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 (Bermpohl 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 subdomains 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

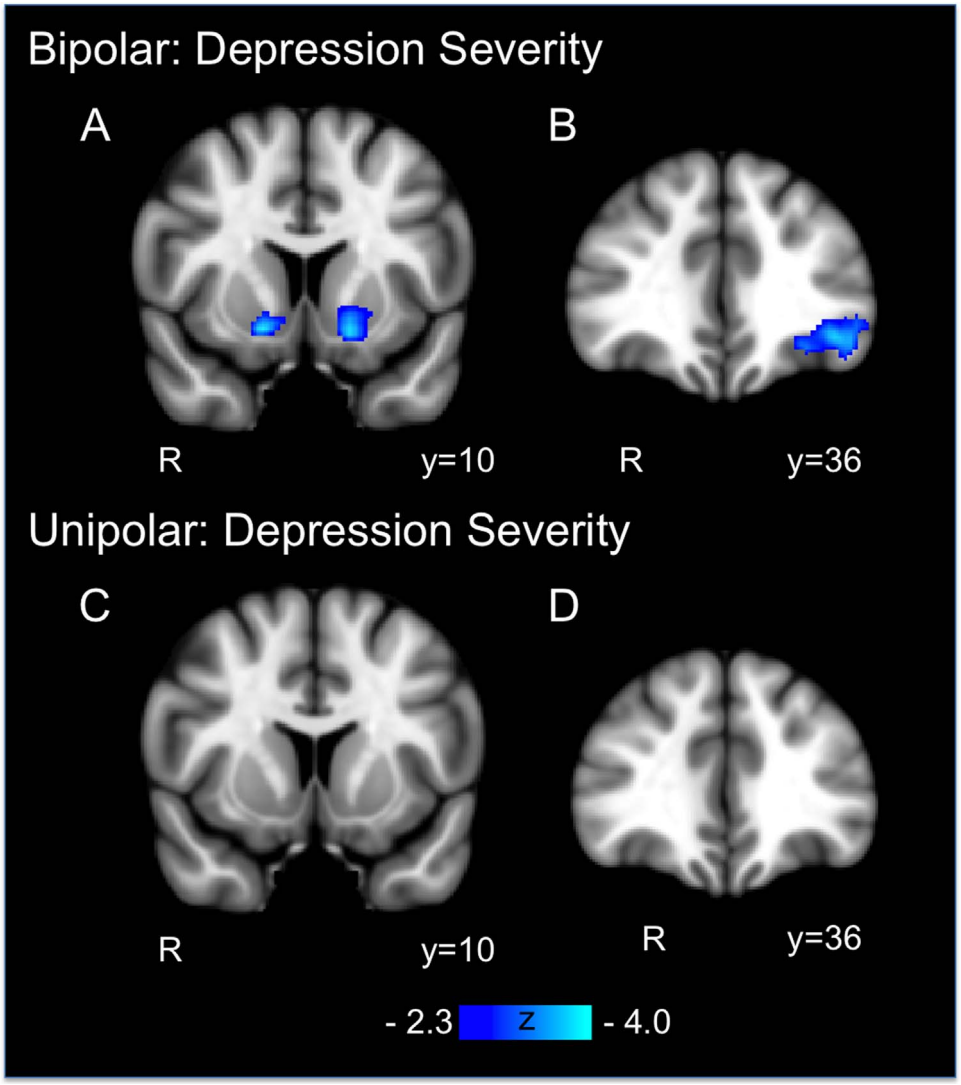

Fig. 3. Bipolar depression severity is associated with diminished response to social rewards. Activation in the happy > angry contrast is dimensionally reduced in association with depression severity for bipolar depressed (A-B) but not unipolar depressed groups (C-D). Reward system regions showing a significant reduction in activation in the bipolar group included bilateral ventral striatum and left orbitofrontal cortex ($z > 2.33$, whole-brain corrected $P < 0.05$).

the pathophysiology of mood disorders. Prior work has aimed to identify categorical differences in reward system activity between diagnostic groups and healthy control groups (Bermpohl 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.

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Contributors

AS, TDS, MAE, CB, MET, REG, JWK and DHW designed research. AS, TDS, LV, NK, AD, KR and DHW collected data and performed research. AS, TDS, LV, NK, AD and DHW analyzed data. AS, TDS, MAE, CB, MET, REG, JWK, DHW wrote the paper.

Conflict of Interest

The authors declare no conflict of interest. Dr. Thase reports no conflicts directly pertaining to this research. Over the past 36 months, he reports the following relationships: Alkermes, AstraZeneca, Bristol-Myers Squibb, Cerecor, Eli Lilly, Dey Pharma, Forest Laboratories, Gerson Lehman Group, Guidepoint Global, H. Lundbeck A/S, MedAvante, Merck, Neuronetics, Otsuka, Ortho-McNeil, Pamlab, Pfizer, PGx, Shire, Sunovion, Super-nus, Takeda, and Transcept Pharmaceuticals.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2016.06.003.

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