Psychiatry Research: Neuroimaging 254 (2016) 18–25

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Divergent relationship of depression severity to social reward responses among patients with bipolar versus unipolar depression

Anup Sharma [a,1,*], Theodore D. Satterthwaite [a,1], Lillie Vandekar [a], Natalie Katchmar [a], Aylin Daldal [a], Kosha Ruparel [a], Mark A. Elliott [b], Claudia Baldassano [a], Michael E. Thase [a], Raquel E. Gur [a,b], Joseph W. Kable [c], Daniel H. Wolf [a]

[a] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104, USA
[b] Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104, USA
[c] Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104, USA

ARTICLE INFO

Article history:
Received 26 April 2016
Received in revised form
28 May 2016
Accepted 5 June 2016
Available online 7 June 2016

Keywords:
Neuroimaging
Mood disorders
Magnetic resonance imaging

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.

Published by Elsevier Ireland Ltd.

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.,

* Correspondence to: University of Pennsylvania School of Medicine, 10th Floor Gates Building, 3400 Spruce Street, Philadelphia, PA 19104, USA.
E-mail address: anup@mail.med.upenn.edu (A. Sharma).
[1] Contributed equally as co-first authors

http://dx.doi.org/10.1016/j.pscychresns.2016.06.003
0925-4927/Published by Elsevier Ireland Ltd.

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).