Published in final edited form as:

J Affect Disord. 2013 September 25; 150(3): 1192–1196. doi:10.1016/j.jad.2013.05.019.

Altered affective processing in bipolar disorder: an fMRI study

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Abstract

Background—Previous studies have reported that patients with bipolar disorder (BPD) exhibit altered emotional processing and regulation. However, results remain largely inconsistent across studies. The aim of the current study was to further examine affective processing in patients with bipolar disorder.

Methods—Twenty-three patients diagnosed with BPD (Type I) and 18 healthy matched controls completed a backward-masked affect paradigm while undergoing functional magnetic resonance imaging. Participants also completed a computerized, overt task of facial emotional discrimination after scanning.

Results—Results demonstrated altered affective processing of happy and fearful stimuli in bipolar participants in the amygdala, anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) relative to controls. BPD participants also displayed significant deficits in identifying fearful facial affect.

Limitations—This study has a moderate sample size, and the patients with BPD were significantly older than the healthy control participants; this did not appear to impact results, and although statistically significant, it is not likely biologically significant.

Conclusions—These findings may have implications for patients with BPD, as altered affective processing could result in deficits in reading social cues.

Keywords

Bipolar disorder; fMRI; emotion; affective processing; cingulate; amygdale

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Conflict of Interest

All authors declare no conflicts of interest.

Contributors

K.S. prepared the first draft of the manuscript and assisted M.K.D. in the recruitment, screening, and implementing study procedures including fMRI paradigms. A.G. was responsible for fMRI data processing and analysis. S.G. is the Principal Investigator of the current research study and was responsible for all aspects of the study, including the diagnostic and clinical assessment of all subjects and overseeing all scan acquisition.

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Introduction

Bipolar disorder (BPD) affects approximately 2.3 million individuals in the United States alone (National Institute of Public Health, 2008). Considered one of the most debilitating of the mood disorders, BPD can be a significant source of distress, disability, and burden not only on patients, but on relatives and caregivers as well. In fact, BPD has been listed among the top ten leading causes of disability in the world (Woods et al., 2000). Research has consistently shown that patients with BPD exhibit abnormalities in affective processes, specifically in identifying facial emotional expressions (Bozikas et al., 2006; Keener et al., 2012; Venn et al., 2004;). In addition, functional neuroimaging studies designed to investigate the neurobiological bases of BPD have reported dysfunction in emotional processing and regulation, predominantly in subcortical limbic regions (Almeida et al., 2009; Killgore et al., 2008; Malhi et al., 2007a, b; Yurgelun-Todd et al., 2000); however, results have been largely inconsistent across studies. In the current study, we examined affective processing in patients with BPD, hypothesizing that they would demonstrate altered patterns of brain activation relative to healthy control participants when viewing affective faces presented below the level of conscious awareness. We also expected differences between the groups on an overt task of affect discrimination.

Methods

Participants

As part of a larger, ongoing neuroimaging study, twenty-three patients diagnosed with Bipolar Disorder (BPD) Type 1 and 18 healthy control participants (HC) aged 18–50 participated in the current investigation. All participants received the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P; First, Spitzer, Gibbon, & Williams, 1994) to ensure that no Axis I pathology was present other than BPD in the patient group. BPD participants were also required to be primarily euthymic at the time of study, and pharmacotherapeutic regimens must have been stable for at least 12 weeks prior to enrollment in the study.

Study Design

Prior to participation, study procedures were explained, and participants were required to read and sign an informed consent form approved by the McLean Hospital Institutional Review Board, which described the procedures and voluntary nature of the study. All participants completed a backward-masked affect paradigm while undergoing functional magnetic resonance imaging (fMRI) as done previously (Gruber, Rogowska, and Yurgelun-Todd, 2009). FMRI stimuli were comprised of black and white photographs of male and female faces with different expressions obtained from the Neuropsychiatry Section of the University of Pennsylvania. The task was comprised of five alternating blocks of 10 trials during each of 2 affective conditions (happy or fearful). Trials were separated by a 1 second interstimulus interval. Blocks 1, 3 and 5 consisted of neutral targets and neutral masks while blocks 2 and 4 were comprised of emotional targets and neutral masks. No commingling of emotional stimuli type occurred within a scanning epoch – only one emotional target type per scan was presented. The emotional (happy, fearful) or neutral target face was presented for 30 msec, followed immediately by a neutral masking face for 170 msec. Scanning epochs consisted of a total of 150 sec with an additional 6 sec initially for calibration, during which time no data was acquired, yielding an acquisition time of 2 min 36 sec for each of the two affective conditions. Stimuli were presented this way to facilitate contrast analyses between the emotional masked stimuli and the neutral condition of neutral targets followed by neutral masks. In order to ensure that participants were attending to the task, they were instructed to indicate whether each stimulus was male or female via a button press.

After scanning, all participants completed the Facial Expression of Emotion Stimuli and Test (FEEST), a computerized task designed to assess the ability to recognize overt facial expression. In this task, sixty faces are each presented for 5 sec, and participants are instructed to choose which emotion each stimulus most closely resembles from a multiple choice list (anger, disgust, fear, happiness, sadness, and surprise).

Imaging Methods

All imaging was performed on a Siemens Trio whole body 3T MRI scanner (Siemens Corporation, Erlangen, Germany) using a quadrature RF head coil; 40 contiguous coronal slices were acquired from each participant, ensuring whole brain coverage (5 mm thick). Images were collected with TR = 3000, using a single shot, gradient pulse echo sequence (TE = 30 msec, flip angle = 90, 50 images per slice).

Data Processing and Analysis

fMRI images were analyzed using SPM8 (version 4290, Wellcome Department of Imaging Neuroscience, University College, London, UK) software package running in Matlab (version R2010b, MathWorks, Natick, MA, USA). First, fMRI data were corrected for motion in SPM8 using a 2-step intra-run realignment algorithm. A criterion of 3 mm of head motion in any direction was considered exclusionary. Realigned images were then normalized to an EPI template in Montreal Neurological Institute (MNI) stereotactic space and re-sampled into 2 mm cubic voxels and then spatially smoothed using an isotropic Gaussian kernel with 8 mm full width at half maximum (FWHM). Global scaling was not used, high-pass temporal filtering with a cut-off of 128 sec was applied, and serial autocorrelations were modeled with an AR(1) model in SPM8. Statistical parametric images were calculated individually for each participant during the presentation of masked happy and fearful facial affect, using a general linear model. These images were subsequently entered into second level model, subjected to a voxel-wise contrast and t-test to assess statistical significance. We then made direct comparisons between the patients with BPD and controls, both with and without including the movement parameters as regressors in the design. Region of interest (ROI) masks were created using the Wake Forest University Pickatlas utility and included the cingulate gyrus, dorsolateral prefrontal cortex and amygdala. The amygdala mask was dilated in 3D (dilation=1) to cover the entire amygdala. Contrast analyses were conducted for each facial expression, which consisted of the subtraction of one group map from the other; for example, the cingulate activity of the participants with BPD during the happy face condition was subtracted from cingulate activity of the healthy control to determine which areas showed increased activity in controls relative to BPD patients. The statistical threshold was set at 0.05 uncorrected and a minimum cluster extent (k) of 10 contiguous voxels.

Results

Demographics

Eighteen healthy controls and 23 patients diagnosed with BPD Type I were enrolled in the current investigation. Healthy controls and BPD participants had an average age of 23.11 ± 3.15 and 26.65 ± 6.65 years old, respectively, which reached statistical significance ($p=.05$). However, participants were well-matched for years of education ($HC=15.53 \pm 1.22$; $BPD=14.57 \pm 1.68$), and this difference is likely not biologically significant. In the HC group, 17 of 18 participants were right-handed, and in the BPD group, 17 of 24 participants were right-handed. Average BPD onset was determined to be 16.53 ± 3.65 years old. Of the 23 BPD participants, 17 took a primarily mood stabilizer, 4 were on antidepressants, 11 on antipsychotics, and 4 took benzodiazepines daily. An additional 4 participants were

unmedicated at the time of the study, but were primarily euthymic as assessed via the SCID-P.

Masked Affect Results

Single sample analyses revealed that during the fear condition, BPD participants demonstrated increased activation in frontal regions, including the anterior cingulate (ACC) and dorsolateral prefrontal cortex (DLPFC), as well as altered activation in the amygdala relative to controls. Contrast analyses of the two groups revealed that patients with BPD demonstrated increased activation within the anterior cingulate cortex (ACC), bilateral amygdala and dorsolateral prefrontal cortex (DLPFC) relative to the HC group. Similarly, during the happy condition, BPD participants exhibited more diffuse patterns of activation relative to the HC group within the ACC, DLPFC, and amygdala. Contrast analyses of the groups for the happy condition demonstrated that patients with BPD had higher activation in subgenual anterior cingulate, right DLPFC, and left amygdala relative to the HC group, who had higher activation in midcingulate and the left DLPFC. See Figure 1.

FEEST Results

Interestingly, results from the FEEST paradigm revealed significantly lower accuracy for the patients with BPD for the identification of fearful faces relative to the HC group; HCs achieved an average of 80% (SD = 14.14) accuracy for identifying fearful faces, while BPD participants only achieved an average of 68.91 (SD = 21.74). However, no significant between-group difference was detected between groups for the identification of happy faces (HC = 98.89 ± 3.23 ; BPD = 97.39 ± 7.51).

Discussion

Results from the current study suggest that individuals with BPD process affective stimuli differently from healthy control participants. This is true despite the fact that the stimuli used were administered below the level of conscious awareness, suggesting a disruption early in the neural circuit responsible for affective processing. In addition, relative to HC participants, patients with BPD also had more difficulty with the overt identification of fearful affect despite an ability to accurately identify happy facial affect. These findings are consistent with a recent meta-analysis that found evidence of emotional processing deficits in BPD patients (Sanamé et al. 2012), as well as a recent study which reported that BPD participants display significant impairment in recognizing facial emotions (Lahera et al., 2012). Given the behavioral alterations and difficulty in inhibiting inappropriate responses often seen in patients with BPD, these findings may have implications for reading cues in social situations, which may result in negative consequences. In fact, studies of BPD patients have demonstrated that relative to controls, BPD participants experience impairments discriminating social cues that aid in interpersonal judgments (Cusi, MacQueen, and McKinnon, 2012), and that these impairments can have a negative impact on social activities and the ability to take initiative (Aydemir et al., 2013).

Limitations

While intriguing, data from the current study should be interpreted in light of several limitations. First, the current study includes a moderate number of participants, and it will be important for future investigations to recruit larger sample sizes. Further, the BPD group was significantly older than the control group; however, activation patterns remained the same after regressing for age, suggesting that age could not account for the between-group differences detected. Additionally, although all patients with BPD were required to have been on a fixed pharmacotherapeutic regimen for a minimum of 12 weeks, it is unclear whether medication status may have impacted the results. Given the fact that patients with

BPD had significantly lower accuracy relative to controls on the FEEST for fearful but not the happy affect condition, it is unlikely that medications were solely responsible for the study findings. Further, mood stabilizers, benzodiazepines, and selective serotonin reuptake inhibitors (SSRIs) have generally been shown to attenuate activation (Arce et al., 2008; Bell et al., 2005; Del-Ben et al. 2005, Murphy et al. 2009, Paulus et al., 2005), and in this study, BPD participants overall showed increased activation (number of voxels) relative to controls.

Conclusions

Taken together, these findings suggest that patients diagnosed with BPD have alterations in the underlying neural processing of affective or emotional information relative to control participants and have difficulties with the identification of certain emotional expressions. This may result in an inability to appropriately read social cues, which often leads to miscommunication, misinterpretation, and compromised interpersonal relationships. Given the importance of processing affective information appropriately, further research is needed to more clearly examine the impact of affective processing and discrimination deficits on social interactions in those diagnosed with BPD, which may have implications for treatment.

Acknowledgments

Role of Funding Source

This study was supported by NIDA grant R21 DA21241-2 awarded to Dr. Gruber and by generous funds donated by the Jim and Pat Poitras Foundation.

The authors thank Megan Racine for her assistance in recruiting and screening subjects.

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Figure 1.

Contrast analyses demonstrate that BPD participants generally displayed increases in ACC, DLPFC, and amygdala activation during the processing of affective stimuli presented below the level of conscious awareness, relative to the controls.

Table 1

Masked Affect fMRI Results

Local maxima for group comparisons with anterior cingulate, dorsolateral prefrontal cortex, and amygdala regions of interest (ROI).

<i>CONDITION</i> Region of Interest Contrast	Region	Cluster Size (voxels)	x	y	z	SPM (t)
<i>FEAR</i>						
ACC						
Control>Bipolar	No activation	-	-	-	-	-
Bipolar>Control						
	Right medial Frontal Gyrus, BA10	30	12	52	12	3.69
	Right Cingulate Gyrus, BA31	150	14	-40	40	3.37
	Left medial Frontal Gyrus, BA32	29	-10	10	44	2.93
	Right Cingulate Gyrus, BA24	65	8	4	40	2.52
	Left Anterior Cingulate, BA32	22	-8	26	24	2.20
	Right Anterior Cingulate, BA32	11	6	38	-6	1.98
DLPFC						
Control>Bipolar						
	Right Middle Frontal Gyrus, BA9	38	42	44	26	2.37
	Left Middle Frontal Gyrus, BA6	24	-30	6	48	2.14
	Left Middle Frontal Gyrus, BA6	20	-20	20	54	2.01
Bipolar>Control						
	Right Superior Frontal Gyrus, BA10	242	22	54	8	5.01
	Right Superior Frontal Gyrus, BA6	85	18	8	64	2.86
	Left Superior Frontal Gyrus, BA8	41	-10	52	38	2.79
	Left medial Frontal Gyrus, BA6	12	-12	6	52	2.70
	Left Middle Frontal Gyrus, BA6	24	-20	4	62	2.65
	Left Middle Frontal Gyrus, BA10	18	-34	36	14	2.62
	Right Middle Frontal Gyrus, BA8	55	44	16	40	2.54
	Left Superior Frontal Gyrus, BA10	20	-12	54	16	2.42
	Left Superior Frontal Gyrus, BA10	12	-28	60	6	2.36

<i>CONDITION</i> Region of Interest Contrast	Region	Cluster Size (voxels)	x	y	z	SPM (t)
	Left Superior Frontal Gyrus, BA8	22	-24	44	42	2.23
	Left Inferior Frontal Gyrus, BA47	29	-52	30	0	2.27
	Right Inferior Frontal Gyrus, BA47	31	44	32	0	2.12
	Left insula, BA13	22	-40	18	6	2.10
	Left Middle Frontal Gyrus, BA10	12	-30	48	8	2.02
Amygdala						
Control>Bipolar						
	Left Uncus, BA28	14	-32	2	-22	2.20
Bipolar>Control						
	Right Parahippocampal Gyrus, BA34	36	18	0	-12	2.44
	Left Parahippocampal Gyrus, BA34	26	-24	2	-12	2.13
HAPPY						
ACC						
Control>Bipolar						
	Left Cingulate Gyrus, BA31	25	-12	-42	32	1.69
	Right precuneus, BA31	22	16	-44	36	2.43
	Left Cingulate Gyrus, BA24	41	-4	6	30	2.24
Bipolar>Control						
	Left Anterior Cingulate, BA24	22	0	30	-2	2.30
	Right Anterior Cingulate, BA32	17	12	34	14	2.17
DLPFC						
Control>Bipolar						
	Left Superior Frontal Gyrus, BA8	133	-20	16	44	2.88
	Right Middle Frontal Gyrus, BA8	30	48	26	44	2.32
	Left Superior Frontal Gyrus, BA6	35	-10	20	56	2.29
	Right Middle Frontal Gyrus, BA6	42	32	0	54	2.19
Bipolar>Control						
	Right Superior Frontal Gyrus, BA8	36	16	48	42	2.13

<i>CONDITION</i> Region of Interest Contrast	Region	Cluster Size (voxels)	x	y	z	SPM (t)
	Right Inferior Frontal Gyrus, BA45	149	52	18	18	3.15
	Left Superior Frontal Gyrus, BA6	52	-28	-6	64	2.85
	Right Middle Frontal Gyrus, BA6	145	36	54	10	2.63
	Right Inferior Frontal Gyrus, BA10	12	54	40	-2	2.30
	Left Middle Frontal Gyrus, BA10	43	-34	38	16	2.28
Amygdala						
Control>Bipolar						
	No activation	-	-	-	-	-
Bipolar>Control						
	Left Uncus, BA28	125	-22	2	-28	3.86