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Abnormal Cortico-Striatal Activity During Fear Perception in Bipolar Disorder

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Abstract

The time-course of responses to repeated presentations of affective stimuli is well characterized in healthy individuals but remains to be characterized in patients with bipolar disorder. Using functional magnetic resonance imaging (fMRI), we compared early- and late-stage brain activation during a two-block fearful face perception task in 14 adult bipolar patients to that of 13 healthy controls. Whereas control subjects showed increased orbitofrontal, anterior cingulate, and striatum activity during the late (versus early) stage of the task, bipolar patients failed to show normal task-related activity in these regions. Results suggest that bipolar disorder may involve cortico-striatal dysfunction.

Keywords

FMRI; Neuroimaging; Bipolar Disorder; Mania; Mood; Prefrontal Cortex; Limbic System; Striatum; Basal Ganglia

Bipolar Disorder is a severe psychiatric illness characterized by affective instability, extreme mood fluctuations [1], and neurocognitive deficits that implicate dysfunction of frontal, striatal, and limbic networks [2-4]. Bipolar patients may also have deficits in affective perception and emotional labeling [5,6], which may be present early in the course of the illness [7]. Functional neuroimaging studies have shown that during the perception of facial affect, patients with bipolar disorder have reduced prefrontal activity and elevated amygdala responses relative to healthy controls [6,8], suggesting prefrontal disinhibition of limbic circuits during the processing of facial affect.

Affective processing is not a static phenomenon, as healthy individuals show changes in activity within specific neural structures during repeated presentations of emotional stimuli [9]. In healthy volunteers, there is habituation of the amygdala and prefrontal cortex during very rapid and repetitive presentation of affective faces [10]. Interestingly, repetition of such stimuli also leads to response-facilitation in the ability to make gender discriminations of previously seen faces, which correlates with increased activation of the caudate nucleus in healthy individuals. Thus, striatal activity in response to repeated stimuli may reflect normal response learning [11]. Although well delineated in healthy subjects, the effects of repeated affective stimulation have not been examined in patients with bipolar disorder. In the present study, we attempted to characterize how these patients process emotional stimuli over time. We directly compared early versus late-stage functional activity during an emotional face perception task in a sample of bipolar patients during their first hospitalization to an age matched healthy control sample. It was hypothesized that patients would show differences in

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early versus late stage blood oxygen level dependent (BOLD) signal changes within the prefrontal cortex, amygdala, and striatum relative to controls during affect perception.

Methods

Subjects

Fourteen patients ($\underline{M}_{age}$ = 28.1; $\underline{SD}$ = 11.2) meeting criteria for bipolar disorder (11 male; 3 female) during their first inpatient psychiatric admission underwent scanning very early in their hospitalization (average of 9 days following admission). Diagnoses were based on the Structured Clinical Interview for DSM-III-R — Patient Version (SCID-P) [12]. Patients were clinically stable on the day of scanning, with 85.7% of the sample taking an atypical antipsychotic agent (olanzapine or risperidone); 35.7% taking a mood stabilizer (lithium or depakote); 28.6% taking a benzodiazepine (ativan or klonopin); 7.1% taking an antidepressant (sertraline); and 7.1% taking a beta blocker (atenolol). The mean score of patients on the Hamilton Rating Scale for Depression was 15.6 (SD = 9.9) and was 14.3 (SD = 8.9) on the Young Mania Rating Scale. Patients had a mean of 14.3 years of education. Patients were excluded if they had previous psychiatric hospitalizations, duration of illness exceeding one year, or treatment with mood stabilizers or antipsychotics exceeding a total of 3 months. Thirteen healthy ($\underline{M}_{age}$ = 25.5; $\underline{SD}$ = 4.7) age-matched control participants (12 male, 1 female) with no psychiatric history and a mean of 15.6 years of education were recruited. Participants provided written consent after a thorough explanation of the procedures. A nominal financial compensation was provided for participation.

FMRI Stimulation Paradigms

Participants completed a fearful face perception task while undergoing fMRI. These tasks and procedures have been described in detail elsewhere [13-15]. Briefly, the task involved passive viewing of a series of black and white photographs of faces expressing fear [16]. The study followed an alternating block design, beginning with 30 seconds of resting fixation that alternated with subsequent 30-second blocks of faces and fixation rest conditions. Each face was presented for 9.5 seconds, separated by a 0.5 second inter-stimulus interval. Blocks alternated five times for a total of 150 seconds. Participants were reminded that they would be asked questions about the photographs at the end of the scan. Face stimuli were projected by LCD video and viewed on a translucent screen at the end of the scanning bed via a mirror mounted on the head coil.

Neuroimaging Methods

Subjects were scanned on a 1.5 Tesla GE LX MRI scanner equipped with a quadrature RF head coil (TR = 3 sec, TE = 40 msec, flip angle = 90 degrees). Fifty echoplanar functional images were acquired for each subject across 21 coronal slices (7mm, 1mm gap), with a 20 cm field of view and an acquisition matrix of 64 × 64. This provided an in-plane resolution of 3.125 × 7 × 3.125 mm. Matched T1-weighted high-resolution images were also acquired for each subject.

Image Processing

Using standard realignment algorithms implemented in SPM99 [17], the images were motion corrected, convolved into the three-dimensional space of the Montreal Neurological Institute (MNI), spatially smoothed using a non-isotropic Gaussian kernel (full width half maximum [FWHM] = 9 mm), and resliced to 2×2×2 mm using sinc interpolation.

Statistical Analysis

Initially, fixed effects statistical contrasts were created between the baseline resting conditions and the active face perception conditions. These contrast images served as the input data for a series of second level random effects analyses to compare activity within the first and second active blocks within each diagnostic group separately (paired t-tests) and between diagnostic groups for each block separately (between groups t-tests). For whole brain analyses, activation was evaluated at $p < .001$ (uncorrected), k (extent) = 20 contiguous voxels. The resulting SPM99 [18] maps were displayed as maximum intensity projections in three dimensions. To reduce Type I error, the data were also examined at a whole brain False Discovery Rate correction of $p < .05$, as shown in Table 1. Additionally, mean fMRI activity during the entire task was extracted from two regions of interest (ROIs) and plotted separately for each group. The first ROI comprised the averaged activation across the basal gangila (i.e., caudate, putamen, pallidum), while the second included both amygdala, as defined by a published neuroanatomical atlas [19]. The mean parameter estimates representing signal covariation with Block A (controlling for Block B) and Block B (controlling for Block A) were extracted for each subject's anatomical ROI and compared using mixed model analysis of variance and Bonferroni protected post-hoc comparisons ($p < .05$).

Results

Within Group Block Contrasts

For healthy control subjects viewing fearful faces, Table 1 shows that there were no regions that were more active during the first block of fearful faces (Block A) relative to the second block (Block B). In contrast, there was significantly greater activation within Block B relative to Block A. This activation included medially located regions such as the caudate, pallidum, posterior cingulate gyrus, and parahippocampal gyrus as well as a region of the lateral orbitofrontal cortex, (see Figure 1). For bipolar patients, there also were no regions that were more active during Block A than Block B (see Table 1 and Figure 1). In the patient group, however, Block B was associated with significantly greater activation distributed across a broad range of generally non-medial extra-striatal regions, including the hippocampus, parahippocampal gyrus, and cerebellum, as well as a several cortical regions including prefrontal, insular, parietal, and occipital lobes (see Table 1).

Between Group Contrasts

Activation was contrasted between bipolar patients and healthy control subjects for each block separately. At Block A, there were no regions where bipolar patients showed greater activation than controls. Conversely, controls showed a small region of greater activation than the patients, which was localized in the left calcarine cortex (see Figure 1). For Block B, bipolar patients showed significantly greater activation than controls in one small region of the right superior temporal pole. In contrast, controls showed significantly greater activation than patients within a large region of left striatal regions including the left putamen and caudate nucleus, as well as cortical regions including the left anterior cingulate gyrus, medial orbital frontal gyrus and the right middle frontal gyrus, superior temporal pole, and inferior orbital frontal gyrus. None of these differences survived whole brain correction for multiple comparisons, however.

Regions of Interest—Figure 1 displays the extracted fMRI signal time course (percent signal change) across all conditions of the scan for the basal ganglia and amygdala separately in each group. Whereas a clear task-related "on-off" pattern can be observed in the time-courses of the healthy controls, bipolar patients showed premature onset of activation in both regions prior to Block A and delayed offset following discontinuation of the stimuli. Mixed model analysis of variance for the extracted signal from the basal ganglia showed a main effect of

Block, $F(1,25) = 8.43$, $p = .008$, with greater activation during Block B, and a main effect of diagnosis, $F(1,25) = 4.48$, $p = .045$, with greater activation in the healthy controls relative to the patients. There was no significant interaction between Block and Diagnosis. For the amygdala, there was a main effect of Block, $F(1,25) = 4.61$, $p = .042$, a main effect of diagnosis, $F(1,25) = 4.90$, $p = .036$, and a significant Block × Diagnosis interaction, $F(1,25) = 4.26$, $p = .049$. Post-hoc comparisons showed no significant amygdala activation or change between Block A and B in patients, whereas controls showed a significant increase in amygdala activation from Block A to B ($p = .007$). Amygdala activation during Block B was greater in controls relative to patients ($p = .006$).

Discussion

During a fearful face perception task, patients with bipolar disorder showed a significantly different pattern of early-versus late-stage changes in BOLD signal relative to healthy controls. These differences suggest that in the early stage of the task, there were minimal group differences in whole brain activation, but over the course of the task, normal control subjects showed significant late-stage increases within the orbitofrontal cortex and striatum. Bipolar patients did not show this pattern. Instead they showed greater late-stage activation across a distributed network of posterior cortical and subcortical brain regions typically associated with perceptual and memory processes. Statistical comparison between the groups at this latter stage of the task suggest that bipolar patients showed significantly less task-related activation than controls within the putamen, caudate, anterior cingulate gyrus, orbitofrontal cortex, and superior temporal pole, regions that have been implicated in affective processing and its modulation [20,21], although these were not evident at a more stringent corrected threshold. Together, these findings suggest that during multiple presentations of faces expressing fear, healthy subjects show progressive activation of striatal regions involved in emotion-based learning and motivational control [22], possibly reflecting a process of affective-motivational-behavioral adaptation whereby affective information is learned and integrated with ongoing motivational routines to prepare the individual for appropriate action [11]. Conversely, bipolar patients failed to show this pattern, instead activating diffuse cortical areas involved in visual perception, memory encoding and recall, facial perception, and visceral sensation. Thus, these findings provide further evidence for a dysfunction within the fronto-striatal circuitry in patients with bipolar disorder [2,4,23].

Inspection of the ROI time-course plots clearly shows abnormal BOLD signal responses in the basal ganglia and amygdala in the bipolar group relative to the healthy controls. Whereas controls showed notable changes in signal intensity in both ROIs that coincided with the onset and offset of the stimuli, particularly during the second block, bipolar patients failed to show these task related increases in either ROI. The interaction between diagnostic group and stimulus Block was significant for the amygdala, suggesting that bipolar patients failed to show the increase in responsiveness upon later exposure to the emotional stimuli exhibited by the controls. Other possible differences between diagnostic groups, such as anticipatory activation and delayed offset of initial responses in the patient group were visually apparent, but these will require further research to substantiate. It remains unknown whether such response patterns are correlated with behavioral and cognitive features of bipolar disorder.

As with any study of actively medicated patients, these data are limited by potential differences in medication type, dosage, and current clinical state among the patients. Attempts were made to control for these factors at intake and by selecting only patients during their first psychiatric admission. Furthermore, due to the selection of only first admission patients, it is possible that there was some diagnostic heterogeneity in the sample that will only be evident longitudinally. It is also important to note that these findings should be considered as preliminary, as the whole brain activation was evaluated at an uncorrected height threshold of $p < .001$ and none of the

whole brain imaging comparisons between diagnostic groups survived correction for multiple comparisons. Finally, this sample was small and will require replication. With due consideration given to these limitations, however, the present findings provide compelling preliminary evidence that first episode bipolar patients differ from healthy controls in the time-course of responsiveness of key affect processing regions to facial expressions of fear.

Conclusion

Compared to healthy controls, patients with bipolar disorder showed impaired late stage responsiveness of cortico-striatal regions to repeated visual presentations of fearful faces. Findings are consistent with previous evidence suggesting that bipolar disorder may involve cortico-striatal dysfunction and further suggest a potential neurobiological mechanism whereby patients may show anticipatory affective responses with slow habituation.

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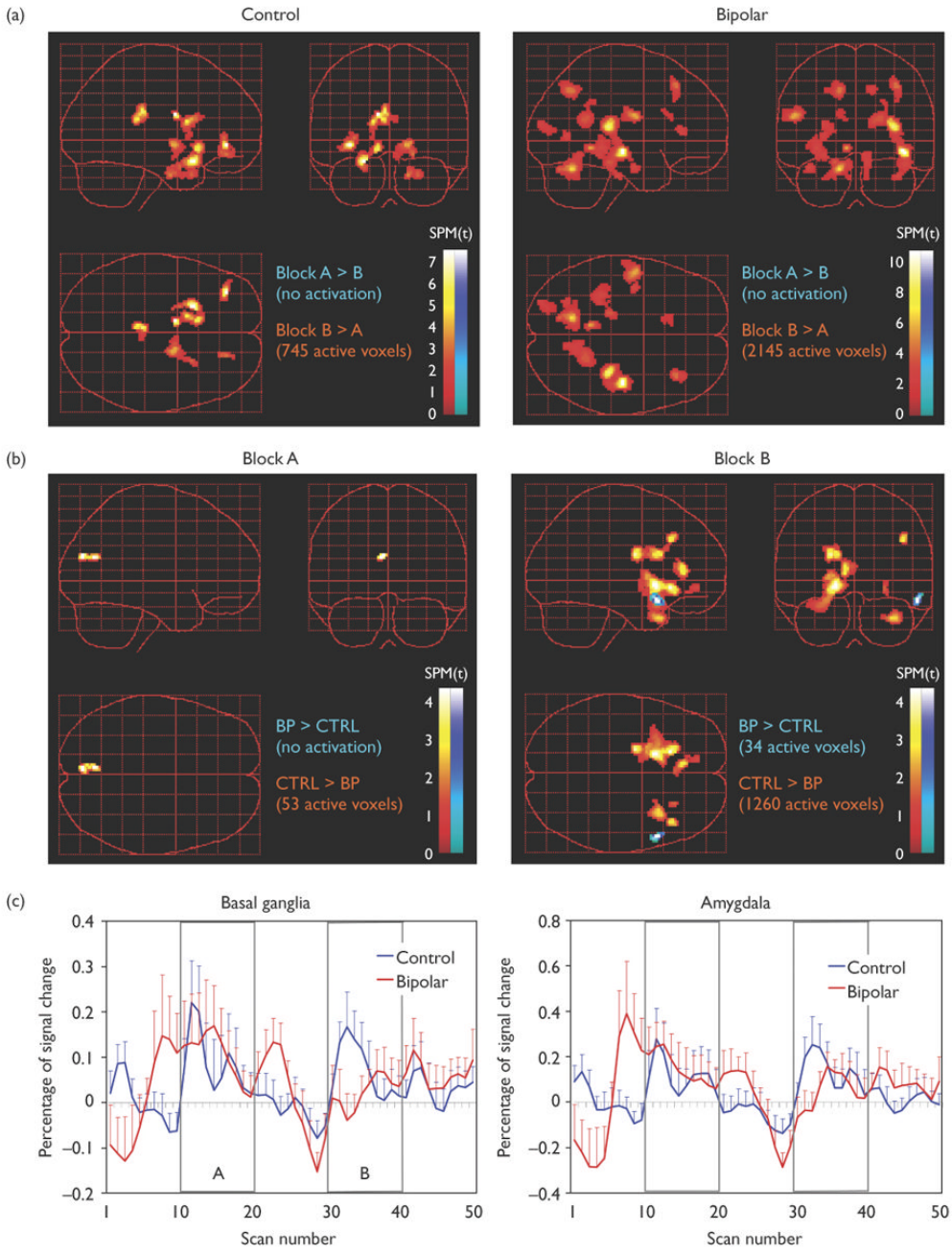

Figure 1.

Bipolar patients differed significantly in the pattern of early-versus late-stage activation in response to fearful faces. a) Control: B > A = basal ganglia, orbitofrontal cortex, and posterior cingulate; Bipolar: B > A = widespread posterior cortical regions. b) Block A: Controls > Bipolar Patients = left calcarine cortex; Block B: Control > Bipolar = striatum, anterior cingulate gyrus, and orbitofrontal cortex. Bipolar > Control = superior anterior temporal pole during Block B. c) Time-course plots showing the mean activation within the basal ganglia and amygdala during the task show clear and reliable task-related activation in healthy control subjects, whereas bipolar patients tended to show premature onset and delayed offset during the early block (block A) and minimal task-related activity during the late block (Block B).

Table 1

Local Maxima for Contrasts Between Block A and B in 13 Healthy Controls and 14 1st Episode Bipolar Patients.

Analysis Condition Region	Number of Voxels	x	y	z	SPM {t}
Early vs Late Block Comparisons					
Control: A > B					
No Active Voxels	--	--	--	--	--
Control: B > A					
L Inferior Orbital Frontal Gyrus	182	-22	14	-18	6.18
L Caudate	146	-10	-2	22	6.12
L Inferior Orbital Frontal Gyrus	86	-34	42	-4	6.04
L Posterior Cingulate Gyrus	115	-4	-30	24	5.65
R Pallidum	122	16	-4	-4	5.00
R Parahippocampal Gyrus	65	16	-6	-30	4.79
R Superior Orbital Frontal Gyrus	29	20	42	-12	4.71
Bipolar: A > B					
No Active Voxels	--	--	--	--	--
Bipolar: B > A					
R Hippocampus	579	40	-18	-8	9.93*
L Cerebellum	240	-14	-62	-24	7.17*
L Postcentral Gyrus	208	-52	-8	22	6.69*
L Cerebellum	42	-8	-46	-6	6.56*
L Superior Parietal Lobe	170	-14	-64	44	6.06*
R Middle Frontal Gyrus	81	34	28	46	5.97*
R Precu neus	211	20	-52	18	5.62*
L Parahippocampal Gyrus	36	-18	-30	-18	5.53*
L Fusiform Gyrus	36	-40	-8	-22	5.31*
L Hippocampus	186	-34	-36	-6	5.29*
R Insula	34	36	32	8	5.22
R Cerebellum	147	10	-60	-18	5.12
L Calcarine Cortex	28	-28	-66	4	5.07
L Middle Occipital Gyrus	85	-28	-88	14	5.05

Analysis Condition Region	Number of Voxels	x	y	z	SPM {t}
R Precuneus	40	14	-58	44	4.87
L Anterior Cingulate Gyrus	22	-14	22	22	4.26
Diagnostic Group Comparisons					
Block A: Bipolar > Control					
No Active Voxels	--	--	--	--	--
Block A: Control > Bipolar					
L Calcarine Cortex	53	-6	-70	20	3.81
Bloc k B: Bipolar > Control					
R Superior Temporal Pole	34	54	14	-18	3.87
Block B: Control > Bipolar					
L Putamen	693	-16	12	-4	4.82
L Caudate	242	-20	-6	22	4.60
L Anterior Cingulate Gyrus	106	-8	34	12	4.35
R Middle Frontal Gyrus	40	42	24	36	4.33
R Superior Temporal Pole	133	34	14	-32	4.21
R Inferior Orbital Frontal Gyrus	21	26	28	-6	3.86
L Medial Orbital Frontal Gyrus	25	-12	48	-6	3.76

Note. L = left hemisphere; R = right hemisphere. Atlas coordinates are from the MNI standard atlas, such that x reflects the distance (mm) to the right or left of midline, y reflects the distance anterior or posterior to the anterior commissure, and z reflects the distance superior or inferior to the horizontal plane through the AC-PC line. All activated voxels are significant at $p < .001$ (uncorrected), with a spatial extent of 20 contiguous voxels.

* Survives False Discovery Rate (FDR) correction for whole brain volume at $p < .05$, with a spatial extent of at least 20 contiguous voxels.