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Original Article

fMRI during affect discrimination in bipolar affective disorder

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Objective: It has been hypothesized that disturbances in affect may represent distinct etiologic factors for bipolar affective disorder. The neural mechanisms mediating affective processes and their relationship to brain development and the pathophysiology of bipolar affective disorder remain to be clarified. Recent advances in neuroimaging techniques have made possible the non-invasive examination of specific brain regions during cortical challenge paradigms. This study reports findings based on fMRI data acquired during fearful and happy affect recognition paradigms in patients with bipolar affective disorder and in healthy adult subjects.

Methods: Prior to the scan, subjects were instructed to view the stimuli and to identify the type of facial expression presented. Echo planar scanning was performed on a 1.5 Tesla scanner which had been retrofitted with a whole body echo planar coil, using a head coil.

Results: The data indicate that in adult subjects with bipolar affective disorder, there is a reduction in dorsolateral prefrontal cortex activation and an increase in amygdalar activation in response to fearful facial affect. In a healthy comparison group, signal intensity changes were not found in these regions. In addition, although the patients with bipolar affective disorder completed the task demands, they demonstrated an impaired ability to correctly identify fearful facial affect but not the happy facial affect displayed.

Conclusion: These findings are consistent with the hypothesis that in some patients with bipolar affective disorder, there may be a reduction of frontal cortical function which may be associated with affective as well as attentional processing deficits.

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Abnormalities in the control of affective and cognitive processes are well-documented symptoms of bipolar affective disorder (1, 2). It has been hypothesized that disturbances in the ability to modulate behavior and affect may represent distinct etiologic factors for this illness (3). However, the neural mechanisms mediating affective processing and their relationship to the pathophysiology of bipolar affective disorder remain to be clarified. Recent advances in neuroscience have further clarified the individual components which comprise affective behavior, allowing a more focused investigation of the systems which underlie emotion (4). The application of neuroimaging techniques have made possible the non-invasive examination of specific brain regions during cortical challenge paradigms in healthy adults as well as in patients with psychiatric disorders. This study reports findings based on fMRI data acquired during fearful and happy affect recognition paradigms in patients with bipolar affective disorder and in healthy adults.

Clinical descriptions and empirical studies have indicated that individuals with bipolar affective disorder exhibit exaggerated affective responses and poor insight and judgement when compared with healthy subjects (5, 6). Difficulty with affective modulation has been identified even during

euthymic states, suggesting that disturbances in emotional processing capacity may be a factor in the development of bipolar illness. For example, individuals with bipolar affective disorder demonstrate difficulty with emotional discrimination and labeling, as well as inappropriate and incongruent affective responses (7–9). It has also been reported that offspring of patients with bipolar affective disorder demonstrate early disturbances in behavioral modulation, which may be reflective of an underlying predisposing factor for the illness (10–12).

Despite the significance of affective processing to the healthy adjustment of the individual, the investigation into the neurobiology of emotional processing in bipolar disorder has been limited. One reason for this may be the complexity in the definition of emotional states and the difficulty in specifying the behavioral unit to be studied. For example, affective processing encompasses a number of interdependent functions, including the perception, experience, expression, and modulation of affect (13). In addition, emotional processing occurs at multiple physiologic levels, each of which is mediated by an array of corresponding, interconnected brain regions (14). One heuristic applied to the neurobiological study of emotional processing has been the identification of multiple neurocognitive stages including orienting, event encoding, response choice and sustained context. The first and last of these stages are of particular interest to this study, as they are thought to place demands on the dorsolateral prefrontal cortex (15). We hypothesized, therefore, that if individuals with bipolar affective disorder have functional deficits associated with the dorsolateral prefrontal cortex, they would demonstrate altered responsivity to emotional stimuli.

Several lines of investigation suggest that the integrity of the prefrontal cortex may be particularly salient for understanding the pathophysiology of bipolar affective disorder. Specifically, the frontal executive system has been shown to play a major role in the assimilation and integration of information and in the ability to plan, inhibit, and initiate emotional and behavioral responses (16, 17). Recent studies have highlighted the association between anomalous frontal lobe function and neuropathological behavior (18), citing earlier studies of non-psychiatric patients who have documented affective changes as a consequence of frontal lobe injury. Comparisons with bipolar illness have been made on the basis of neurologic patients who demonstrate emotional lability, grandiosity, irritability and aggression secondary to stroke, trauma, or frontal lobe damage (18, 19). In adult subjects with right frontal lesions, behavioral symptoms such as impulsivity, confabulation, and verbosity have been reported, underscoring the similarities in clinical presentation between patients with bipolar affective disorder and neurologic patients with frontal damage (20, 21).

Studies applying structural and functional brain imaging methods have also produced results consistent with frontal or prefrontal lobe abnormalities in bipolar affective disorder (22). A recent review of magnetic resonance imaging (MRI) studies in these patients reported an increase in focal white matter abnormalities (or signal hyperintensities) generally localized to the frontal lobes and basal ganglia, and further suggested that frontal lobe atrophy may be present in some cases of affective illness (23). These structural changes have also been associated with behavioral effects, as one investigation found that frontal hyperintensities were correlated with performance on frontal-executive tasks (24), while another investigator reported that reductions in frontal volume were associated with diffuse cognitive deficits on neuropsychological testing in patients with bipolar affective disorder (25). Furthermore, studies applying functional neuroimaging techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) to patients with bipolar disorder have also found evidence for abnormal frontal lobe activity (26, 27, 22). One recent study found a reduction in blood flow and glucose metabolism in the left subgenual prefrontal cortex in both unipolar and bipolar depressive patients (28), a brain region which was found to be demonstrably smaller among affective disorder patients with positive family history of affective illness (29). These findings suggest an alteration in the neurodevelopment of the prefrontal cortex in bipolar illness that may be due in part to familial or genetic factors.

As noted above, it has been hypothesized that during affective processing, the orienting stage places demands on the dorsolateral prefrontal cortex (15). One type of investigation that has the potential to evaluate the orienting response in affective processing is the study of facial affect recognition. The application of this stimulus condition is generally aimed at describing the ability to discriminate between affective categories (30–35). Recent investigations have demonstrated that recognition of facial affect, particularly fearful affect, induces demonstrable changes in brain activation (36–39). Furthermore, neuroimaging studies of affective reactivity have reported altered lateral prefrontal activation in addition to changes in medial prefrontal activation (40–43). We therefore selected the pre-

sentation of fearful facial affect, a task likely to generate a strong orienting response, to examine the dorsolateral prefrontal cortical activation in patients with bipolar affective disorder. While emotional experience requires the interplay between a widely distributed neuronal network, two regions, the prefrontal cortex and the amygdala, have been identified as playing a prominent role in both affective processing and bipolar affective disorder. Both human and animal studies have produced converging results implicating the prefrontal cortex and amygdala in facial affect recognition (4, 17), while neuroimaging and neurocognitive studies of bipolar patients have demonstrated dorsolateral prefrontal cortex and amygdalar abnormalities (44, 45). This study is aimed at investigating signal activation in two regions, the prefrontal cortex and the amygdala during fearful affect recognition. We utilized this task to ascertain the extent to which externally presented affective stimuli would differentially activate the dorsolateral prefrontal cortex and the amygdala.

As reviewed above, behavioral changes demonstrated in patients with bipolar affective disorder may be associated with neurobiological deficits in affective processing ability. Given the interconnectivity within the frontal cortex and the reciprocity between the prefrontal cortex and the amygdala, we would expect that patients with bipolar affective disorder would demonstrate greater limbic reactivity due to a reduction of prefrontal inhibition. The present study attempts to clarify this issue by evaluating patterns of cortical activation in patients with bipolar affective disorder and healthy adult subjects. We applied functional magnetic resonance imaging (fMRI) techniques to measure changes in the dorsolateral prefrontal cortex and the amygdala in response to fearful and happy facial affect recognition tasks in these two subject groups. As previous studies of mood induction and discrimination have identified gender based differences in regional cerebral activation (46, 47), we divided our subject groups by gender. We hypothesized that compared to normal control subjects, patients with bipolar affective disorder would demonstrate an increase in amygdalar activation and a decrease in prefrontal activation in response to a fearful affect recognition task.

Methods

We studied 24 right-handed subjects: 14 patients with a stable DSM-IV diagnosis of bipolar affective disorder and ten non-psychiatric adult control subjects. All subjects received a structured clinical interview (SCID-P) to ensure proper psychiatric diagnosis, and in the case of the control subjects, to ensure that none had an Axis I disorder. All diagnoses were made according to DSM-IV criteria without prior information regarding psychiatric history or knowledge of subject group. All structured clinical interviews were performed by a trained clinical diagnostician (SG) with 8 years of experience in diagnostic interviewing and with established reliability for all Axis I diagnoses (kappa ≥ 0.90). Information obtained through clinical interviews was verified by chart and record review. Subjects with a history of organic brain syndrome, head injury, or current substance abuse were excluded. Subjects who wore any type of corrective lenses were also excluded. No comorbid psychiatric diagnoses were present in any of the study subjects. With regard to substance abuse, four of the fourteen (28.5%) patients with bipolar affective disorder did meet the diagnostic criteria for a past history of substance abuse, however, all of these were in remission for at least six months prior to the study. Each subject was given information regarding the fMRI procedure and all signed an informed consent form.

As seen in Table 1, the patient group included 7 men and 5 women, with a mean educational level of 14.7 ($\pm$ 1.9) years. All patients with bipolar affective disorder were right handed, and were administered the Young Mania Rating Scale (YMRS); (range = 2–29) and the Hamilton Depression Scale (Ham-D); (range = 4–24). All were stable outpatients maintained with a fixed pharmacologic regimen for at least 6 months. All but two of the patients with bipolar affective disorder were taking a mood stabilizer (85.7%) and all but one patient with bipolar affective disorder were taking antipsychotic medications (92.8%). The distribution for medication type is as follows: lithium (58.3%), valproic acid (41.6%); atypical antipsychotic (67%), conventional neuroleptic (16.7%).

Non-psychiatric control subjects, recruited from the staff and local community, included 5 men and 5 women, with a mean educational level of 16.1 ($\pm$ 1.5) years. All control subjects were right handed, none were taking any psychotropic medications, and none had a history of substance abuse or dependence.

Subjects were instructed to view the stimuli and to silently identify the facial expression presented. Scanning was performed on a 1.5 Tesla scanner retrofitted with a whole body echo planar coil, using a quadrature head coil. The term 'retrofitted' refers to a modification, enabling a standard GE Signa Scanner system to be equipped with an instascan echo planar option. This option provides a higher strength gradient coil, improved gradient

power, data acquisition and computing. A T1 weighted sagittal image was used to localize a plane perpendicular to the AC-PC line. Twelve to 14 high resolution coronal images were acquired for each subject, which covered an area from the anterior portion of the frontal pole to just posterior to the central sulcus. These coronal images were taken in the same plane as the echo planar images to allow for anatomic correlation with the functional imaging data. Functional images were collected every three seconds using a gradient echo pulse sequence (TE = 40 ms, flip angle = 75°). An image matrix of 64×128 was used with a 3×3 mm in-plane resolution and a 6 mm slice thickness. Each stimulus sequence resulted in a total study length of 150 s. During each cognitive task condition, a series of 50 sequential images were obtained.

Stimuli were generated by a Macintosh computer and were projected with a magnetically shielded LCD video projector onto a translucent screen placed at the subjects' feet. The subject was able to see the screen by the use of a mirror placed above their head in the scanner. Once inside the scanner but prior to the experiment, a member of the research staff ensured that the study subject could easily view the screen, and that the subject was comfortable. Each scan sequence or epoch was divided into five alternating 30-s segments which lasted for a total of 150 s. The segments consisted of a 30-s baseline period, followed by a 30-s stimulus ('on'), a 30-s period without any stimulus, ('off' or recovery) a second 30-s stimulus period ('on'), and finally a 30-s ('off' or recovery) period. During baseline and 'off' periods, subjects were asked to visually fixate on a white fixation point located in the center of the screen. In one condition, each of the two 'on' periods was comprised of three faces, each displayed for 9.5 s. Subjects were asked to attempt to silently discriminate and label the expression on each of the faces (36). All six faces presented in this condition were individuals displaying expressions of fear (Ekman faces # 12, 13, 15, 14, 16, 17). In the second condition, during each of the two 'on' periods, subjects viewed three faces, each displayed for 9.5 s. Subjects were asked to attempt to silently discriminate and label the expression on each of the faces. All 6 faces presented in this condition were individuals displaying expressions of happiness (Ekman faces # 4, 2, 1, 8, 7, 9). The faces used were grayscale black and white photographs taken from Ekman (30, 48). In order to measure subject performance, all subjects were asked to report the affect displayed immediately after each scanning epoch, while still inside the magnet. Fearful expressions were chosen based on previous work which showed an amygdala related response to fearful faces (49, 50). Faces displaying happy affect were included as a comparison condition.

Cortical activation was measured using neuroanatomically defined regions of interest (ROI) based on both high resolution magnetic resonance (MR) and echo planar magnetic resonance (EPMR) images. All conventional MR images were interpreted by a neuroradiologist, and no clinical abnormalities were detected for any study subject. Measures of signal intensity were derived by averaging the signal measured in all pixels in each ROI for each time point during the task activation period. This included the 30-s baseline condition, the two activation segments of 30 s

Table 1. Clinical and demographic data for bipolar patient sample

Patient	Age	Education	YMRS	HAM-D	Age at onset	LOI	Race	CPZ equiv.	Anti-psychotic	Mood stabilizer
1	32	16	17	15	16	192	W	150	Thioridazine	Valproic acid
2	39	13	2	10	25	168	W	300	Olanzapine	LiCO3
3	36	14	5	24	32	48	W	200	Olanzapine	LiCO3
4	35	16	24	10	19	192	W	308	Risperidone	Valproic acid
5	54	18	10	12	28	312	W	231	Risperidone	Valproic acid
6	35	16	5	4	21	156	W	75	Clozapine	None
7	39	16	16	10	18	264	W	0	N/A	LiCO3
8	25	16	6	8	22	43	W	80	Haloperidol	LiCO3
9	24	15	29	8	21	36	W	80	Haloperidol	Valproic acid
10	21	16	12	8	15	72	C	500	Clozapine	LiCO3
11	19	11	20	5	17	23	W	200	Clozapine	LiCO3
12	23	14	6	8	23	6	W	200	Olanzapine	None
13	19	11	8	12	19	6	W	450	Olanzapine	Valproic acid
14	41	14	15	4	31	132	W	460	Olanzapine/ Perphenazine	Valproic acid

Note: YMRS = Young Mania Rating Scale; HAM-D = Hamilton Rating Scale for Depression; LOI = Length of illness in months; CPZ equiv. = Chlorpromazine equivalent per day.

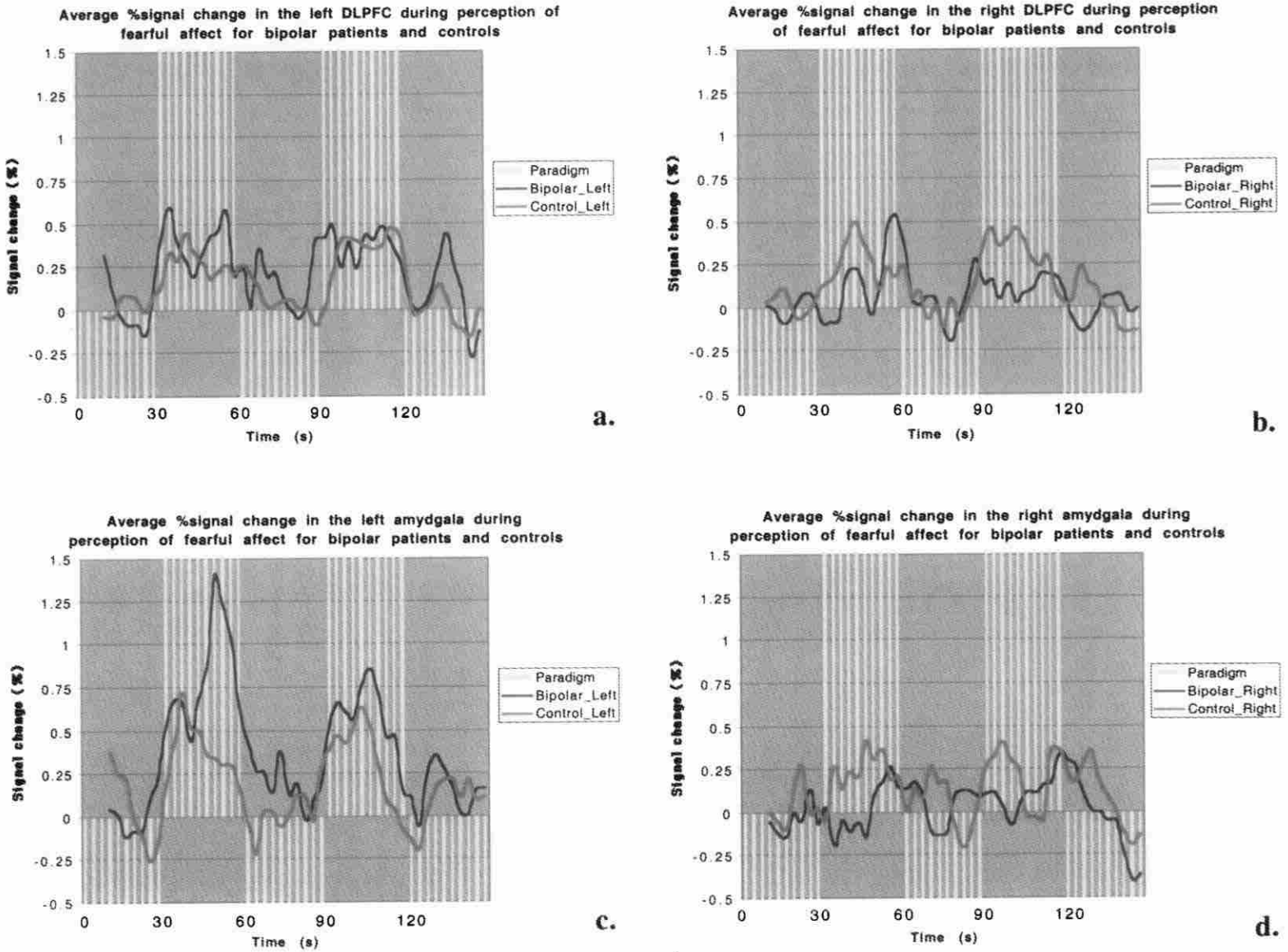

Fig. 1. (a) Average percent signal change in the left DLPFC during perception of fearful affect for bipolar patients and controls. (b) Average percent signal change in the right DLPFC during perception of fearful affect for bipolar patients and controls. (c) Average percent signal change in the left amygdala during perception of fearful affect for bipolar patients and controls. (d) Average percent signal change in the right amygdala during perception of fearful affect for bipolar patients and controls.

duration, and the two 30-s recovery segments in each scanning epoch. Normalization of signal at baseline was completed for each study epoch for every individual. Signal responses were averaged for each condition and between group comparisons in mean signal intensity were made.

Regions of interest were selected with reference to an anatomic atlas (51) and placements were made based on gyral boundaries and structural landmarks visible on MR images (52). Inter-rater reliability for the selection of the ROIs was completed, and a kappa value of 0.94 was achieved. Each ROI was comprised of four pixels, 3×3 mm sampled from one coronal slice. The first ROI included the amygdala, localized in the coronal plane immediately posterior to the interhemispheric connection of the anterior commissure (Fig. 2). The second ROI included the left dorsolateral prefrontal cortex (Brodmann's areas 46 and 9), which was localized in the coronal plane immediately anterior to the genu of the corpus collosum through the rostral aspect of the anterior cingulate, an example of which is seen in Fig. 3. All images were corrected for in-plane as well as translational motion using the DART program (53). Data for which motion exceeded 1 mm in any direction or 1° of rotation were not included in analyses.

Results

The percent signal intensity change that occurred during subjects' viewing of fearful faces as compared to baseline was considered the dependent variable in a 2 (sex) $\times$ 2 (diagnosis) $\times$ 2 (region) repeated measures analysis of variance. Sex and diagnostic category served as between subject variables while region of interest (left amygdala versus right dorsolateral prefrontal cortex) was considered a within subject variable. Average percent signal change for the patients with bipolar affective disorder and the control subjects is illustrated in Fig. 1a–d. This analysis yielded a significant three-way interaction between diagnosis, sex, and region, $F[1, 20] = 5.96$, $p = 0.024$, suggesting that the moderating effect of sex on regional activation operated differently for patients and controls. These effects were further decomposed by conducting separate analyses for patients and controls.

A significant sex by region interaction emerged for the patients with bipolar affective disorder $F[1, 12] = 9.57$, $p = 0.009$. Male patients showed negligible difference between the percent of signal change in the left amygdala and that of the dorsolateral prefrontal cortex, $t[8] = 0.69$, n.s., however, female patients demonstrated a nearly significant difference between the activation of these two regions, $t[4] = 2.56$, $p = 0.06$. When female patients were compared to female controls, they differed significantly in terms of the left amygdala activation, $t[9] = -2.79$, $p = 0.02$, but not for right dorsolateral prefrontal activation, $t[9] = 1.10$, n.s.

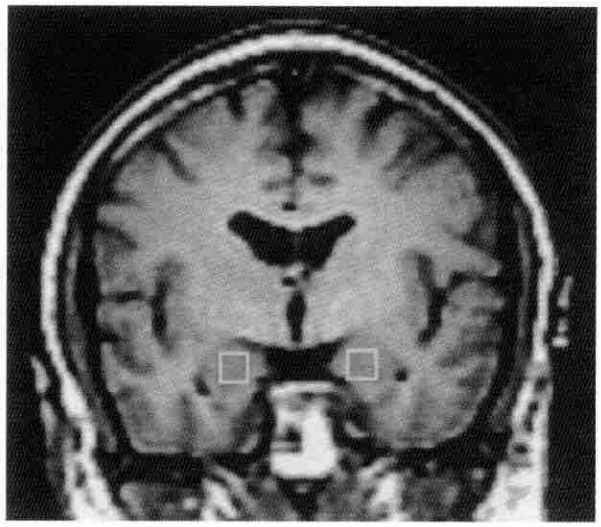

Fig. 2. Coronal slice of bipolar patient showing relative changes in signal intensity in the amygdala during the viewing of fearful facial affect.

In contrast, no interaction between sex and regional activation was detected for the healthy control subjects $F[1, 8] = 0.06$, n.s. Male and female control subjects did not differ with regard to overall percent activation change when viewing fearful faces, $F[1, 8] = 3.18$, n.s., and there was no difference in the percent signal change between the left amygdala and right dorsolateral prefrontal cortex, $F[1, 8] = 0.30$, n.s.

To evaluate whether the same interaction effect occurred for viewing happy faces, we conducted an

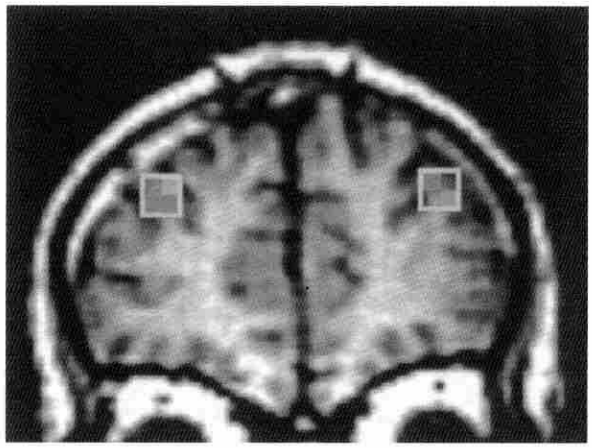

Fig. 3. Coronal slice of bipolar patient showing relative changes in signal intensity in the DLPFC during the viewing of fearful facial affect.

identical 2 (sex) × 2 (diagnosis) × 2 (region) repeated measures analysis of variance on the percent of signal intensity change for the happy face condition. The ANOVA revealed no interactions or main effects across regions when subjects viewed happy faces, regardless of sex or diagnostic category $F[1, 18] = 1.24$, n.s., suggesting that regional activation did not differ significantly between the left amygdala and the right prefrontal cortex for either of the subject groups.

To better understand the influence of demographic and clinical variables on changes in signal intensity, we derived correlation coefficients for all variables with regard to signal intensity changes during the discrimination of fearful affect in each region of interest. When considered as a group, no significant correlations were detected for age, age at onset, or length of illness and signal intensity change for any region of interest for the patients with bipolar affective disorder. In order to examine any gender specific relationships, the patient sample was then split by sex. While no significant correlations between these demographic variables emerged for the male patients, female patients had a significantly inverse correlation for age at onset and signal intensity change in the left dorsolateral prefrontal region ($r = -0.907$; $p = 0.034$). No other correlations for the demographic variables were significant for the female patients in any other region of interest.

With regard to clinical variables, no significant correlations emerged for either the YMRS or the HAM-D scores and signal intensity change in any region of interest when the patients were examined as a group. Once split by sex, the pattern for male patients was the same. However, female patients demonstrated a significant positive correlation between YMRS score and signal intensity change in the left dorsolateral prefrontal region ($r = 0.867$; $p = 0.057$).

In order to examine the relationship between pharmacotherapy and changes in signal intensity, correlations were completed for chlorpromazine (CPZ) equivalents and individual regions of interest. No significant correlations were detected for any region of interest and CPZ equivalents when the patients with bipolar affective disorder were considered as a group; however, significant correlations emerged when the patient sample was split by sex. For male patients, a significant inverse relationship was found for CPZ equivalent and left amygdalar signal change ($r = -0.674$; $p = 0.046$) while for female patients this relationship was not significant ($r = 0.230$; $p = 0.709$). No other correlations were statistically significant for either gender.

Performance or total percent correct for the affect recognition paradigm was calculated for each of the study groups. While all ten of the healthy control subjects correctly identified the facial affect presented in both conditions, only ten of the fourteen patients with bipolar affective disorder (71.4%) were able to correctly identify the fearful affective stimuli. The four patients who could not successfully identify the affect presented were evenly distributed with regard to gender (two males, two females).

Discussion

Findings from this preliminary study indicate differential patterns of activation in response to fearful facial affect recognition paradigms in patients with bipolar affective disorder relative to normal control subjects. The reduced activation in the right prefrontal area and increased activation in the left amygdalar region in patients with bipolar affective disorder suggests changes in fronto-limbic circuitry underlying fearful affect recognition, an observation which is in agreement with previous investigations which have hypothesized disruptions of the frontal network in bipolar affective disorder (28, 22, 29). The differences in regional activation occurred despite the fact that patients appeared to be engaged and attempting to complete the task demands. However, as the patients produced fewer correct responses during the identification task, we cannot rule out that the altered activation in the regions of interest was related to the patients' performance. These results were particularly striking in female patients with bipolar affective disorder, where notable decreases in activation were present in the right dorsolateral prefrontal cortex and increases in the left amygdala were evident during the process of affect recognition. These findings are consistent with previous reports that have identified these regions as part of the circuitry underlying emotional processing (54, 17, 55).

At this time, we do not have a measure of the relative importance of any single brain region or any individual cognitive function for the accurate completion of affective labeling tasks. The complexity of the demands inherent in the affective labeling task has been highlighted in a recent study which examined the relationship between affective processing and neuropsychological function. The authors reported that for patients with bipolar affective disorder, poor performance on a task requiring the discrimination of facial affect was associated with a reduction of attentional capacity during early visual processing (7).

Despite the apparent consistency of our study findings with previous investigations, it is evident that the interpretation of our study findings is not uncomplicated. As noted above, this is due in part to the fact that our challenge task requires the integration of a number of cognitive and emotional processes. For example, the identification of facial affect requires the ability to extract visuospatial and figural information, as well as the ability to concentrate, attend, recall affective categories and label the affect presented (56). Thus, the challenge paradigms incorporated elements of both emotional and cognitive processing, making it impossible to isolate a single component function which may be responsible for the observed disruption in affective processing using the current study design. However, the use of a compound task is also a strength of the study, as it places demands on diffuse cortical and subcortical networks which must be coordinated and integrated, a function usually associated with the prefrontal cortex. The demands placed on executive brain systems have been related to the process of self-regulation (57, 58). It is in these complex multi-modal processing tasks that deficit performance is revealed in patients with bipolar affective disorder.

For example, although overall intellectual functioning appears relatively unaffected in patients with bipolar affective disorder (25), many individuals show poorer performance on tests involving attention, concentration, and psychomotor speed (59, 60), neuropsychological processes which are known to be reduced as a consequence of dysfunction within the frontal executive system. Patients with bipolar affective disorder have also demonstrated deficits on higher-order tasks such as tests of abstract reasoning and executive control known to be more directly subserved by frontal and prefrontal cortical regions (25, 61, 60, 24, 62). One interpretation of our findings is that the observed alterations in facial affect recognition demonstrated by the female patients in our study may be related to orienting or attentional mechanisms, mediated by the dorsolateral prefrontal cortex.

The neuroimaging findings from the current study also complement studies of neurobiologic correlates of social behavior, which have identified frontal system dysfunction in association with disturbed affective and social capacity. In healthy adult subjects, selective prefrontal damage has been shown to disturb previously intact social knowledge which results in inappropriate behavioral responses although no impairment in cognitive functioning is evident (16). One recent investigation of two subjects with documented lesions in the prefrontal cortex prior to the age of 16 months found that in adulthood, these patients demonstrated intact cognitive abilities, however, they were impaired in the ability to acquire and implement social reasoning (63). The results of this study led the authors to speculate that early lesions in the prefrontal cortex may have altered the ability to acquire the array of social knowledge necessary for intact social development. These results may be particularly relevant to the development of psychiatric disorders as it has been previously hypothesized, based on the association between obstetrical complications and neuropsychological performance, that executive control processes, such as higher cortical functions subserved by the frontal network, may be particularly vulnerable to injury (64, 65). Furthermore, studies of patients with bipolar affective disorder have demonstrated that perinatal obstetrical complications are elevated in these patients suggesting that perinatal injury to specific neural circuits may represent a risk factor for the development of major mood disorders (66, 67).

The importance of the frontal cortex in affective processing has been emphasized in numerous recent studies. Although many previous investigations have highlighted the anterior portion of the limbic system as responsible for mediating affective, and motivational functions, the lateral areas of the prefrontal cortex have been hypothesized to be more closely associated with attention and higher order functions (68). Our finding of reduced dorsolateral prefrontal cortex activation in response to fearful facial affect in a subgroup of patients with bipolar affective disorder is consistent with the hypothesis that executive functions play a role in affective processing and may be altered in some individuals with affective disorders.

Several studies of healthy emotional response have reported an increase in activation of the medial prefrontal cortex, regardless of the emotional valence experienced (69, 70). For example, a study that experimentally induced either depressed or elated mood produced an increased activation of the lateral orbitofrontal cortex for both conditions (40).

It has been suggested that the medial prefrontal cortex may play an important role in the conscious aspects of emotional experience and may be important for monitoring ongoing emotions and inhibiting or modulating affective experiences (70, 71). Furthermore, neuroimaging studies have suggested that the medial and lateral regions of the orbitofrontal cortices may serve different affective functions (40, 43, 72). The dorsolateral prefrontal cortex has also received attention in models of affective processing. In addition to its initial role in

orienting to external stimuli, the dorsolateral prefrontal cortex has been implicated in the regulation of mood (13, 42).

Animal and human brain imaging studies indicate that the dorsolateral prefrontal cortex has reciprocal connections with the cingulate cortex, as well as other frontal brain regions, suggesting that the dorsolateral prefrontal cortex may influence the amygdala through its effects on the cingulate (4, 42). In one investigation which administered procaine hydrochloride, researchers found increased rCBF in limbic areas and a relative decrease in frontal rCBF, suggesting that these regions are highly interdependent (54). More recently, reciprocal rCBF changes involving subgenual cingulate and right dorsolateral prefrontal areas during a mood manipulation paradigm were reported. The study results were consistent with the ability of the dorsolateral prefrontal cortex to mediate both mood and attention (42).

There are several limitations to the current study. In this investigation, only a limited range of facial affect was examined (fearful and happy). Fearful facial affect was included as there is evidence from both animal and human studies that the amygdala, a region implicated in the pathophysiology of bipolar affective disorder, produces a robust response to fearful stimuli. Furthermore, since recent neuroimaging studies have reported detectable amygdalar activation in response to fearful facial affect (36), we hypothesized that a dysfunction in fearful affective processing in patients with bipolar affective disorder may be associated with a reduction in frontal activation when compared with normal controls. Although happy faces served as a comparison task in this study to demonstrate specific rather than general brain changes, a recent investigation has reported a dissociation between brain regions underlying different affective categories (73). As individual affective categories are therefore likely to involve different neural systems, future investigations should include the presentation of neutral faces as well as additional categories of emotional expression.

A second limitation of the current study is the relative inability to monitor subjects' performance during the challenge paradigms. While we assume that all subjects are in fact completing the task to the best of their ability while inside the scanner, no absolute measure of compliance during the scanning sequence was administered. This lack of monitoring does not allow us to conclude that changes in activation were specifically associated with changes in performance, as we can not rule out the effects of effort. Additional studies are therefore needed to measure responses to individual stimuli during each scanning epoch.

An additional limitation of the current study concerns the potential confounds of pharmacologic treatment and clinical state. While all patients with bipolar affective disorder were determined to be clinically stable at the time of scanning, there were notable differences between patients in mood and energy level. The small size of our patient sample likely contributed to our limited findings of a relationship between clinical variables and regional signal intensity change. It is of note, however, that despite the small sample sizes, a significant relationship between YMRS score and signal intensity change in the dorsolateral prefrontal cortex was demonstrated for female bipolar affective disorder patients. Also of note is the fact that we identified a significant inverse relationship between amygdalar signal intensity change and total CPZ equivalent for the male patients with bipolar affective disorder. Given the known effects of antipsychotics on the limbic system, it is possible that our male patients demonstrated a differential response to treatment which blunted their amygdalar response. Due to the small sample size in this study, it is premature to draw any conclusions. However, our finding of altered cerebral activation in female patients is consistent with previous reports on gender differences in emotional processing (46, 47). Additional studies based on larger sample sizes are needed to clarify the relationship between gender, clinical state and pharmacotherapy on regional signal intensity changes.

With regard to medication status, all but one of the patients included in the study were taking mood stabilizing medications (lithium or valproate), which is considered a standard treatment for bipolar affective disorder. It is not known, however, what effect these agents may have on signal intensity changes during affective and cognitive tasks. Additionally, all but two patients were taking an antipsychotic, another common pharmacologic intervention for this disorder. Previous investigations have reported that typical antipsychotics result in significant clinical improvement, although cognitive deficits have been shown to remain the same or worsen with standard neuroleptic treatment (74, 75). In contrast, studies of treatment with atypical antipsychotics, including clozapine, risperidone, and olanzapine, have shown an improvement in performance on tasks requiring executive function, like the maze learning task (76). It is therefore likely that medication effects are associated with changes in affective response. While all of the patients in the current study had been on a fixed pharmacologic regimen for at least six months, it is unclear how the patients who were taking lithium may have dif-

fered from those taking valproic acid, and how patients receiving an atypical antipsychotic may have differed from those who were receiving conventional neuroleptics with regard to changes in signal intensity. Future studies with larger sample sizes are needed to examine the acute and long-term cortical effects of different pharmacotherapies on gender differences and emotional processing.

In order to more clearly determine the significance of the signal intensity changes demonstrated in the patients with bipolar affective disorder, morphometric measures, which include the measurement of the relative volume of gray and white matter, should be completed on all study subjects. This is especially important given the finding of altered amygdalar volume in patients with bipolar affective disorder (45, 77). Future investigations which include these measurements would allow correlational analyses to be completed which may help clarify the relationship between neuroanatomical and neurophysiological function.

The interpretation of the study findings is also limited by a number of technical considerations. The temporal resolution of our data acquisition and the use of a block design restrict the detection of signal responses that may occur early in processing. This is likely to have particular significance in the study of attentional functions, where brief early responses may be undetected. Furthermore, our use of a priori defined regions of interest increased the statistical power of the study by allowing us to test a specific hypothesis, however, it constrained the analyses of brain regions examined. Moreover, each ROI was drawn from only a single coronal slice, which may not have included a representative activation sample for the region.

In summary, this preliminary study reports fMRI data suggestive of a differential pattern of signal intensity change in female patients with bipolar affective disorder compared to healthy control subjects during a task requiring the discrimination of facial affect. These findings are consistent with previous neuroimaging studies that have implicated the dorsolateral prefrontal region in affective processing. The reduction in cortical activation in the right prefrontal region appears coincident with an increase in left amygdalar activation, suggesting a disruption of higher-order processes within the fronto-limbic system in bipolar affective disorder. Additional studies with larger study samples are needed to examine the effects of clinical state, medication, gender, and cognitive processing ability as they relate to affective discrimination.

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