A Functional Magnetic Resonance Imaging Study of Bipolar Disorder

State- and Trait-Related Dysfunction in Ventral Prefrontal Cortices

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Background: Abnormalities in prefrontal and anterior cingulate cortices are implicated in disturbances of attention, cognition, and impulse regulation in bipolar disorder. Acute episodes have been associated with dysfunction in these brain regions, and more enduring trait-related dysfunction has been implicated by volumetric and cellular abnormalities in these regions. The relative contributions of prefrontal regions to state and trait disturbances in bipolar disorder, however, have not been defined. We sought to characterize state- and trait-related functional impairment in frontal systems in bipolar disorder.

Methods: Thirty-six individuals with bipolar disorder I (11 with elevated, 10 with depressed, and 15 with euthymic mood states) and 20 healthy control subjects matched for handedness and sex participated in an event-related functional magnetic resonance imaging study of the color-word Stroop to determine mean percentage of regional task-related signal change.

Results: Signal increased during the Stroop task similarly across diagnostic groups in a distribution that included dorsal anterior cingulate and prefrontal cortices, consistent with previously reported activations in this task. Signal changes associated with specific mood states in bipolar disorder were detected in ventral prefrontal cortex, with a blunted increase in signal on the right side in the elevated mood group (P=.005) and an exaggerated increase in signal on the left side in the depressed group (P=.02) compared with the euthymic group. Patients (vs healthy controls) demonstrated blunted activation in a spatially distinct, rostral region of left ventral prefrontal cortex that was independent of mood state (P<.005).

Conclusions: Bipolar disorder is associated with a trait abnormality in left ventral prefrontal cortex. Additional ventral prefrontal abnormalities may be associated with specific acute mood states. The hemispheric laterality of the abnormality and the directions of signal change may relate to the valence of the mood episode.

Arch Gen Psychiatry. 2003;60:601-609

CONVERGING EVIDENCE from neuroimaging, postmortem, and neuropsychological studies implicates state- and trait-related abnormalities in prefrontal cortices (PFCs) in bipolar disorder (BD). Secondary changes in emotional, attentional, and behavioral regulation, similar to the symptoms of BD, have been described in association with ventral and medial prefrontal lesions for more than a century.1,4 The hemispheric laterality of lesions, moreover, is thought to affect the valence of mood disturbances, with left hemisphere abnormalities associated with depressive symptoms and right hemisphere abnormalities associated with manic symptoms.6,7

Functional imaging studies of individuals at rest demonstrate regional abnormalities in primary mood disorders that are generally consistent with those predicted by the lesion studies. Findings in depression and mania converge on PFC and anterior cingulate cortex (ACC), although their directions of difference from normal resting levels and their ventral or dorsal locations vary according to the valence of the mood disturbance. In depression, for example, findings consist largely of increased ventral and decreased dorsal activity in PFC and ACC.8-12 In contrast, mania has been associated with decreased ventral and increased dorsal activity in PFC and ACC.13,14 The hemispheric lateralization of abnormalities has consisted primarily of relative reductions in left hemisphere activity in depression8,11,12 and right hemisphere activity in mania.13,14 However, other studies15,16 have differed in the direction or lateralization of their findings.

The variability in regional findings across studies may relate to the heteroge-
neity in patient characteristics and differing imaging methods. Participant samples have varied in the proportions of patients with unipolar or bipolar depression included or in clinical features, for example, treatment responsiveness, that may represent salient biological subtypes. Functional imaging data have differed in their spatial resolution and signal-to-noise characteristics, and significant variability in findings may have been introduced by the differing mental states of patients scanned “at rest.”

Activation tasks can provide improved control of, and therefore reduced variability in, the mental activity of patients during the scanning session. Furthermore, these tasks provide information concerning the capacity for specific brain regions to become engaged during a particular task. However, few functional imaging studies of mood disorders have been performed using task activation designs. Anterior cingulate cortex and dorsolateral PFC activation abnormalities in depressed individuals, compared with healthy controls, were reported in association with Stroop interference, Tower of London, verbal fluency, and spatial tasks; “emotional Stroop” and Wisconsin Card Sorting tasks, however, have not revealed frontal abnormalities. A relative failure of right ventral PFC (VPFC) activation in mania has been demonstrated during word generation and decision making. We are unaware of previous functional imaging studies of the 3 mood states of BD during cognitive or behavioral activation.

Recent structural neuroimaging, histopathological, and neuropsychological studies suggest the presence of trait abnormalities in frontal cortices of individuals with BD. Decreases in gray matter volume, glial cell density, and nonpyramidal cell density in layer II in frontal cortices, for example, implicate stable anatomical abnormalities in BD. Neuropsychological disturbances on tests of attention, memory, and executive functions, including the Stroop, have been reported in acute episodes of BD. Results of recent studies suggest that performance deficits on such cognitive tasks endure between acute BD episodes, further supporting the possible presence of enduring phenotypic abnormalities in prefrontal functioning.

We report a study of brain activity in patients with BD and healthy controls as they performed a color-naming Stroop task. A central feature of the Stroop task, long used clinically as a test of prefrontal function, is the requirement to inhibit the prepotent response to read words to name correctly the ink colors in which the words are presented. This requires the recruitment of ACC- and PFC-related functions to focus attention, inhibit automatic impulses, and respond appropriately during the task. The Stroop paradigm has been shown repeatedly in functional imaging studies to activate a distributed network of structures that include dorsal ACC and PFC. Thus, we used this task to engage the cognitive and behavioral processes, and their associated neural systems, that have long been implicated in BD.

Individuals experiencing elevated, depressed, and euthymic episodes of BD, as well as a healthy comparison group, were studied to examine state- and trait-related features of the disorder. We hypothesized that right VPFC dysfunction in BD would be associated with elevated mood states and that left lateralized VPFC abnormalities would be associated with depressed mood states, as reported previously. Exploratory analyses examined activity in other brain regions that were associated with state- and trait-related mood disturbances in these individuals.

Methods

Participants

Thirty-six individuals with BD (18 women and 18 men) and 20 healthy control subjects without a personal history of psychiatric disorder or a first-degree relative with a major mood or psychotic disorder (10 women and 10 men) were studied. Structured clinical interviews performed within 24 hours of scanning confirmed the presence or absence of DSM-IV Axis I disorders. Patients with BD were divided into 3 groups: the elevated mood group (5 women and 6 men aged 20–55 years; 7 were unmedicated), which met the criteria for current manic (n=7), hypomanic (n=3), or mixed (n=1) episodes; the depressed group (5 women and 5 men aged 21–50 years; 3 were unmedicated), which met the criteria for current major depressive episodes; and the euthymic group (8 women and 7 men aged 26–53 years; 3 were unmedicated).

All participants were right handed and without neurological illness, sustained loss of consciousness, or significant medical illness, other than treated hypothyroidism in 2 individuals with euthymic BD. Healthy controls were nonsmokers (information was not available on 1 subject); 13 patients with BD (36%) were smokers. All patients had a score of 28 or greater on the Folstein Mini-Mental State Examination, which was used to screen for gross cognitive dysfunction.

A history of psychosis was reported in 1 patient in the elevated mood group, 3 in the euthymic group, and 4 in the depressed group, and only the manic individual was psychotic at the time of scanning. The 3 patient groups had similar numbers of hospitalizations, with an average of approximately 2 hospitalizations per patient. Seventeen patients with BD had a history of alcohol or substance dependence. One depressed patient met the criteria for dependence 3 months before the study; the remainder of the patients had not met the criteria for at least 1 year. No patients drank alcohol or used street drugs for a minimum of 24 hours before scanning. No other comorbid Axis I disorders were diagnosed.

Thirteen patients were unmedicated for at least 1 month before scanning. Medications used by the other patients with BD included lithium (1 in the elevated mood group, 8 in the euthymic group, and 2 in the depressed group); anticonvulsants (2 in the elevated mood group, 5 in the euthymic group, and 4 in the depressed group); antidepressants (1 in the elevated mood group, 6 in the euthymic group, and 6 in the depressed group); olanzapine (1 in the elevated mood group and 2 in the euthymic group); typical antipsychotics (1 in the elevated mood group and 1 in the euthymic group); benzodiazepines (1 in the elevated mood group, 2 in the euthymic group, and 1 in the depressed group); benzotropine mesylate (1 in the euthymic group); and estrogen (1 in the euthymic group).

Rating scales for mood symptoms were administered on the day of scanning. The Clinician-Administered Rating Scale for Mania quantified manic symptoms, and the 29-item Hamilton Depression Rating Scale quantified depressive symptoms. After complete description of the study, all participants provided written informed consent in accordance with the requirements of the Department of Veterans Affairs and Yale University School of Medicine institutional review boards.
The Stroop task was performed during the scanning session according to previously published methods. Congruent stimuli (the words red, green, blue, and yellow in letters of the same color ink, eg, the word blue in blue letters) and incongruent stimuli (the same words in letters of a different color ink, eg, the word blue in green letters) were presented using PsyScope software and were viewed in a mirror mounted in the scanner head coil.

Each trial consisted of a 1300-millisecond stimulus presentation, followed by a 350-millisecond interstimulus interval, for a total of 1.65 seconds per trial. The incongruent trials constituted the infrequent events and were spaced 21.43 to 26.40 seconds apart to allow for the dissipation of the hemodynamic response before the collection of data for the next infrequent event. The spacing between incongruent stimuli varied pseudorandomly, once in every 13 to 16 congruent stimuli, to decrease the ability of the participant to predict the timing of the infrequent events. No word or color of an incongruent stimulus was the same as the preceding congruent color word to avoid priming effects. Each run consisted of 102 trials and was 2 minutes 48 seconds in duration. Nine runs were obtained for each participant.

Participants were instructed to name silently the color of the ink in which the words were presented. Participants performed the task outside of the scanning environment before scanning to ensure that they could understand the task and to help minimize anxiety during scanning. Participants also performed the task outside of the scanning environment after scanning to provide estimates of performance during the scanning session.

FUNCTIONAL MAGNETIC RESONANCE IMAGING
IMAGE ACQUISITION AND PROCESSING

The functional magnetic resonance imaging (fMRI) images were acquired using a 1.5-T scanner (General Electric Signa, Milwaukee, Wis) equipped with a quadrature head coil and echoplanar capability. Head positioning was standardized using the canthomeatal line and was secured with foam pillows and a band across the forehead. Conventional sagittal T1-weighted spin echo image series were acquired to prescribe the anterior commissure–posterior commissure plane. Ten axial-oblique anatomical images were acquired parallel to the anterior commissure–posterior commissure plane. The between-slice skip was 1 to 2 mm, so that the top of the ninth slice above the anterior commissure–posterior commissure plane was placed at the vertex. This slice prescription allowed us to better register individual brains to the standard Talairach transaxial slices.

The echoplanar images were acquired in these same anatomical locations using 102 images per slice. A digital interface enabled the computer to synchronize the stimulus presentation with the acquisition of images to an accuracy of 20 milliseconds. This time series used a T2*-sensitive gradient-recalled single-shot echoplanar pulse sequence (repetition time, 1650 milliseconds; echo time, 60 milliseconds; flip angle, 60°; acquisition matrix, 64 × 64; field of view, 20 × 20 cm; and voxel resolution, 3.12 × 3.12 mm in plane by 7-mm thickness).

The echoplanar images were coregistered with the anatomical images and then visually inspected for artifacts such as ghosting. The images were then motion corrected using SPM’99 software, with 12-parameter realignment to the middle image of the middle run. Spatial smoothing was performed with a gaussian filter of 6.3-mm full-width-at-half-maximum. Anatomical images were transformed into standard stereotactic space, and the transformation parameters were then applied to the echoplanar images.

The fMRI signal associated with presentation of the incongruent stimuli was calculated at the peak of the hemodynamic response after presentation of the incongruent stimuli, that is, from the third through sixth images after each incongruent stimulus. The fMRI signal associated with presentation of the congruent stimuli was calculated from the 6 images preceding the occurrence of the incongruent stimuli. A mean incongruent signal response and a mean congruent signal response were calculated at each pixel for each participant. The mean pixelwise signal change for the Stroop response was then calculated by subtracting the mean congruent signal response from the mean incongruent signal response at each pixel for each participant.

A region of interest (ROI) analysis was performed to test the hypothesis that the elevated mood BD group would demonstrate less right caudal VPFC (cVPFC) activation than the euthymic BD group in the cVPFC region shown to be associated with primary mania in a previous positron emission tomography study of BD. This same region was used to test the hypothesis that abnormalities in cVPFC would be lateralized to the left hemisphere in depressed patients with BD. This cVPFC ROI from the positron emission tomography study was defined within a proportional grid system of Talairach and Tournoux, using software developed by one of us (P.S.), in the transaxial slice positioned so that the central plane of the slice was approximately 14 mm ventral to the anterior commissure–posterior commissure plane. We did not investigate the most ventral extent of the region detected in the positron emission tomography study, as data collected in that portion of the region on our echoplanar images were degraded by susceptibility artifacts.

Group composite activation maps were constructed to explore whether other regions would demonstrate mood state-related differences in brain activity during performance of the Stroop task. The elevated mood and depressed groups were each compared with the euthymic group. Group composite maps were also generated to explore possible differences in brain activity of the pooled BD groups compared with the control group. Additional group composite maps were constructed to assess for possible medication effects and for the potential effect of smoking status in the BD group.

Maps of between-group comparisons in mean signal change were generated by calculating t statistics at each pixel of the image. These values were thresholded at P < .005, and a cluster filter was applied that required a minimum spatial extent of 20 adjacent activated pixels. This combined application of a statistical threshold and cluster filter has previously been shown to reduce substantially the false-positive identification of activated pixels at any given threshold. Its use was intended to balance adjustment for the multiple comparisons while maintaining sufficient sensitivity to detect task-related signal changes.

STATISTICAL ANALYSIS

Patients with BD and healthy control subjects were compared on age and performance variables (percentage of errors and reaction time) using 2-sample t tests when the normality assumption was satisfied and Wilcoxon rank sum tests otherwise. Comparisons among the 3 BD groups on the same variables were performed using 1-way analysis of variance or Kruskal-Wallis tests.

The ROI analysis was performed using a mixed model approach in a statistical software program (PROC MIXED, SAS, version 8.1; SAS Institute Inc, Cary, NC). The dependent variable was the mean percentage signal change for the Stroop response in the cVPFC ROI for each participant. The
model included fixed effects for hemisphere (left and right), BD group (elevated mood, depressed, and euthymic), a hemisphere × group interaction, and a random subject effect. The group × hemisphere interaction was tested first and was considered significant at $\alpha=.05$. Individual comparisons of right cVPFC in elevated mood vs euthymia and of left cVPFC in depression vs euthymia were performed at Bonferroni-corrected significance levels of $P=.025$. Age, sex, and performance variables (percentage of errors and reaction time) were considered as covariates in the model. The data were checked for normality before analysis using the Kolmogorov-Smirnov test.

Regions identified on group composite comparison maps were further investigated by comparing the groups on mean response using $t$ tests and analysis of variance. The normality and equality of variance assumptions were checked before analysis using Kolmogorov-Smirnov and Levene tests, respectively. The potential confounding effects of age, sex, and performance variables were investigated by including these covariates in the analysis of variance models. Data are given as mean ± SD.

### RESULTS

#### PARTICIPANT CHARACTERISTICS

The patients with BD were significantly older than the healthy controls ($39.1±10.0$ vs $31.7±11.0$ years; $t_{54}=2.6$, equal variances; $P=.01$). The 3 BD groups did not differ significantly in age from each other (elevated mood group: $40.5±10.8$ years; depressed group: $35.8±11.3$ years; and euthymic group: $40.4±8.4$ years; $F_{2,33}=0.77$; $P=.47$).

The mean mania score (Clinician-Administered Rating Scale for Mania) for the elevated mood group was $19.0±7.3$; the depressed group, $1.9±1.9$; and the euthymic group, $4.1±5.0$ (possible total score of 60 on 10 mania items). The mean depression score (Hamilton Depression Rating Scale) for the depressed group was $28.2±7.3$; the elevated mood group, $6.8±5.0$; and the euthymic group, $7.3±7.1$.

All participants seemed to perform the task easily. Groups did not differ significantly in their accuracy of responding. The mean percentage of errors on the incongruent stimuli was $7.0%±10.1%$ for the control group and $7.4%±12.9%$ for the BD group (Wilcoxon rank sum test, $Z=0.26; P=.80$). The BD groups did not differ significantly in the percentage of errors (elevated mood group: $7.6%±15.6%$; depressed group: $3.3%±7.0%$; euthymic group: $10.0%±13.8%$; Kruskall-Wallis test, $\chi^2_{2}=1.5; P=.47$). The Stroop response time (congruent response time subtracted from incongruent response time) was nonsignificantly increased in the BD group vs the control group ($267.0±129.0$ vs $203.8±83.0$ milliseconds; $t_{54}=1.50; P=.13$). The BD groups did not differ significantly in response time (elevated mood group: $286.3±128.7$ milliseconds; depressed group: $234.2±143.8$ milliseconds; euthymic group: $279.8±124.0$ milliseconds; $F_{2,33}=0.42; P=.66$).

Head movement did not differ significantly across the patient and control groups in either displacement (maximum across trials in the $x$, $y$, or $z$ planes: control group, $0.67±0.38$ mm; BD group, $0.83±0.37$ mm; $t_{54}=1.44$, unequal variances; $P=.16$) or rotation (mean pitch, roll, or yaw: control group, $0.90°±0.79°$; BD group, $0.89°±0.50°$; $t_{27.8}=−0.04$, equal variances; $P=.97$). The 3 BD groups also did not differ significantly from each other in displacement (elevated mood group: $0.94±0.41$ mm; depressed group: $0.84±0.38$ mm; euthymic group: $0.74±0.33$ mm; Welch $F_{2,33}=2.5; P=.10$) or rotation (elevated mood group: $1.13°±0.49°$; depressed group: $0.91°±0.61°$; euthymic group: $0.70°±0.37°$; $F_{2,33}=0.93; P=.41$).

#### MOOD STATE ANALYSES

In the ROI analysis, the hypothesized group × hemisphere effect was significant ($F_{1,47}=6.88; P=.003$). Increased signal associated with the Stroop response in this ROI was detected in the euthymic group in the right hemisphere. Signal was not increased in this region in the elevated mood group, and, thus, they showed a relative decrease in signal in the right hemisphere compared with the euthymic group ($F_{1,47}=8.54; P=.005$). Signal was increased bilaterally in this region in the depressed group, and, thus, they showed a relative increase in signal in the left hemisphere compared with the euthymic group ($F_{1,47}=6.41; P=.02$) (Figure 1 and Figure 2). Age, sex, and performance variables were explored as possible confounding variables in post hoc covariate analyses; they were not significantly associated with the degree of cVPFC activation and did not alter the effects of group and hemisphere. Post hoc correlations between the magnitude of the decreased right hemisphere activity and Clinician-Administered Rating Scale for Mania scores and between the magnitude of increased left hemisphere and Hamilton Depression Rating Scale scores were computed to examine whether the degree of abnormality was correlated with the severity of symptoms, but these did not reveal any significant associations. Results remained significant in the right cVPFC in an analogous analysis comparing the subgroup of patients with mania only ($n=7$) with the depressed and euthymic patients ($F_{1,42}=4.32; P=.04$), suggesting that inclusion of patients in hypomanic and mixed states did not affect the results substantially. Results also remained significant in a comparison between the unmedicated elevated mood subgroup ($n=7$) and the subgroup of unmedicated depressed and euthymic patients ($n=6$) ($t_{11}=−2.36$, unequal variances; $P=.04$), suggesting that medication use did not affect the results substantially. Additional analyses performed to compare the relative signal in the cVPFC ROI in the elevated mood, depressed, and euthymic subgroups each with the control group revealed a significant finding only in the comparison of the depressed group and the control group of an increase in the left hemisphere ($F_{1,32}=5.79; P=.02$). Group composite activation maps thresholded at $P<.005$ were performed to compare the elevated mood group and the depressed group each with the euthymic group. These did not demonstrate any additional regional group differences.

#### TRAIT ANALYSES

Group composite maps compared the BD and control groups. Regions of significant signal change associated with the Stroop task were similar across groups and included premotor cortex, dorsal ACC, dorsolateral and in...
ferior PFCs, sensory association cortices, and the basal ganglia. The one region in which signal change differed significantly between the patient and control groups was in a rostral region of the VPFC (rVPFC) in the left hemisphere. This was in the region of the confluence of the left middle and superior frontal gyri, bordering the superior frontal sulcus laterally and the orbitofrontal cortex ventrally (Figure 3). This rVPFC region includes components of Brodmann areas 10 and 47. The center of mass of the group differences in signal change was at Talairach coordinates $x = -18$ mm, $y = 41$ mm, and $z = -5$ mm. Its volume was approximately 684 mm$^3$.

This left rVPFC region was defined stereotactically on a proportional Talairach grid system to contain the pixels where significant group differences were detected on the group composite map comparing patients with BD and healthy controls. A significant difference in mean signal change in this region between the BD and control groups was detected, as expected from the group composite map ($t_{52.6} = -2.99$, unequal variances; $P = .004$). No significant differences in this rVPFC region were observed among the 3 BD groups ($F_{2,18.44} = 0.70$; $P = .51$) or between medicated and unmedicated individuals (2-sample equal variance $t$ test, $t_{34} = 1.26$; $P = .22$). Sex, age, and performance variables were not associated significantly with the degree of rVPFC activation.

A voxelwise comparison in a group composite map explored possible differences in brain activation associated with medication use. The only region in which the medicated and unmedicated groups differed was in a small region of temporal association cortex (Brodmann area 37). Smokers and nonsmokers in the BD group also differed only in a small area of temporal association cortex (Brodmann area 22/39).

**COMMENT**

Bipolar disorder is associated with state- and trait-related abnormalities in VPFC activation during an event-related color-naming Stroop interference task. Acute mood states of BD were associated with differing activity in cVPFC regions during this task. Blunted cVPFC activation in the right hemisphere was associated with elevated mood states, replicating a previous finding. Depression, in contrast, was associated with increased cVPFC activation in the left hemisphere. The BD and control groups demonstrated a broadly distributed pattern of regional brain activity during Stroop task performance that included dorsal ACC and dorsolateral PFC activation, consistent with previous functional imaging studies of healthy individuals performing this task. The BD group, however, differed significantly from the control group in activation of a left rVPFC region that was spatially distinct from, and located more dorsal and anterior to, the state-related regional abnormality. This left rVPFC dysfunction did not differ significantly among the 3 BD groups, suggesting that it may reflect a trait abnormality in these patients with BD.

Successful performance of the Stroop task requires recruitment of multiple attentional and cognitive processes, including the accurate detection of conflict between color and word signals, inhibition of automatic im-

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**Figure 1.** Bipolar disorder state-related differences in caudal ventral prefrontal cortex (cVPFC) activation. The mean percentage signal change associated with the Stroop response in the cVPFC region of interest is shown for each bipolar disorder group. A, In the left cVPFC, relatively higher signal is seen in the depressed group. B, In the right cVPFC, relatively lower signal is seen in the elevated mood group. Error bars represent SE.
Abnormalities in VPFC activation, however, suggest that the cognitive processes subserved by this region were differentially engaged in the BD group. The VPFC is thought to be central to the capacity to alter a prepotent, previously predominant or reinforced behavior. For example, individuals with VPFC lesions often perseverate with "go" responses in go/no-go tasks. The response to incongruent Stroop stimuli in this study required the inhibition of a prepotent response (to read the colored words) and the change from a previous predominant response type (congruent stimuli). The inhibition of prepotent verbal responses has been attributed to left VPFC in lesion and activation studies. The inhibition of verbal responses likely contributed to the robust activation of the left VPFC in healthy controls. Disturbances in neural processing in the left VPFC may have contributed to the nonsignificant trend toward higher Stroop response times and the putative trait-related impairments of VPFC activation in patients with BD.

Difficulty with reversals in response to changes in task contingencies after VPFC lesions has been associated with socially maladaptive or disinhibited behavior and with subjective reports of emotional changes. Abnormal processing of changes in stimulus-reward associations is thought to mediate the effects of VPFC lesions in producing abnormal response reversals, emotional disturbances, and behavioral dysregulation. We speculate that VPFC abnormalities in BD may similarly relate to disturbances in stimulus-reward associations and that these disturbed stimulus-reward associations may underlie the emotional, cognitive, and behavioral disturbances of BD, including the emotional lability, thought disorder, and pursuit of hedonic activities despite painful consequences that are characteristic of this disorder.

In VPFC, regions associated with the trait and state abnormalities of BD differed in their location and in the direction of their signal changes. The more dorsal and anterior regions of the rVPFC associated with the BD trait abnormality are more intimately interconnected with isocortical structures (such as dorsolateral PFC and lateral temporoparietal cortex) than are the more ventral VPFC regions, and they are thought to subserve higher-order cognitive and associative sensory functions. The more ventral cVPFC region, in which the state-related abnormalities were detected, is a site of convergent limbic input to PFC. It has dense connections with the amygdala, hippocampus, and hypothalamus and is therefore more associated with emotional and related viscerosensory processes. These considerations suggest that the BD trait may be associated with abnormalities in rVPFC-

Figure 2. Composite images of caudal ventral prefrontal cortex (cVPFC) activation (arrows) showing differences between mood states in bipolar disorder. A, Increased left cVPFC activation is seen in the depressed group (n=10) compared with the euthymic group (n=15). B, Reduced right cVPFC activation is seen in the elevated mood group (n=11) compared with the euthymic group (n=15) (P<.05, cluster filter of 20 pixels).

Figure 3. Composite image of rostral ventral prefrontal cortex (rVPFC) activation showing differences between the bipolar disorder and control groups. The axial-oblique image demonstrates the relatively attenuated signal increase in the left rVPFC in the bipolar disorder group (n=36) compared with the control group (n=20) (P<.05, cluster filter of 20 pixels).
related higher-order cognitive processes, whereas the additional involvement of the more ventral cVPFC regions may relate to the emotional and neurovegetative disturbances commonly observed in acute mood episodes.

The right hemisphere lateralization of signal abnormalities associated with elevated mood states, in contrast to the left hemisphere lateralization of signal abnormalities associated with depression, is consistent with findings from previous studies\(^6\) of hemispheric lateralization underlying differing mood states. The replication of a right cVPFC functional abnormality in association with 2 different, although related, activation paradigms\(^1\) suggests that individuals with pathologically elevated mood states have difficulty with the production of appropriate verbal responses that require the inhibition of inappropriate ones. Although increased dorsal ACC blood flow at rest has been reported in mania,\(^14\) activation differences were not detected in this region in mania, suggesting that the resting abnormalities may not reflect the capacity of this region to engage in goal-directed behavior.

Depression-related abnormalities also differed from those in mania in the direction of their signal changes. Increases in ventral and medial PFC activity, especially in the left hemisphere, have been reported in resting studies of depression,\(^10-12\) during emotional processing in depressed individuals,\(^6\) and during transient sad states in healthy individuals.\(^68,69\) Anterior paralimbic hyperactivity is thought to be a state-related correlate of depression and has been shown to lessen in response to various kinds of antidepressant and mood-stabilizing treatments.\(^17,20,70,71\) We did not observe dorsal ACC activation abnormalities associated with a depressed mood state, although decreased dorsal ACC resting activity\(^6\) and activation during cognitive tasks\(^22\) have been reported in depressed individuals. This discrepancy may relate to the older age, greater degree of cognitive impairment, and unipolar diagnoses of individuals in those studies. Participants in one study\(^23\) were similar in age to those we studied, but that sample consisted primarily of individuals with either unipolar depression or BD II. Future studies to clarify whether depressive subtypes differ in their recruitment of dorsal structures would be of interest.

The left hemisphere laterality of the trait-related region is consistent with the decreased left VPFC volume and glial density observed in BD.\(^15,27,72\) The presence of left rVPFC abnormalities across mood states suggests that dysfunction of this region may represent a diathesis to developing BD, but the presence of additional functional abnormalities during acute episodes suggests that this putative trait-related dysfunction alone may not suffice to produce acute episodes. The VPFC regions associated with the putative trait and state functional disturbances are highly interconnected.\(^69,73\) Understanding their relationship may improve our understanding of the neural abnormalities that underlie the switching process into manic or depressive states.

These findings and interpretations should be considered in light of the limitations of this study. First, medication use could have affected our findings. However, group comparisons remained significant when controlling for medication status, and comparisons of medicated and unmedicated patients with BD revealed differences in posterior association cortices only. Second, the generalizability of our findings may be limited, as the BD sample was confined to individuals who were suitable for scanning and who were largely free of psychotic symptoms. Third, confounding participant characteristics could have contributed to group differences. Age and a history of substance dependence were examined and were not significantly associated with VPFC activity. Fourth, we discussed the cross-sectional findings of this study as likely representing trait and state features of the disorder. A prospective longitudinal study that follows patients across mood states is necessary to more conclusively identify trait and state disturbances in function of the VPFC.\(^73\) Furthermore, the smaller subgroups in the analysis of mood states provided less statistical power to detect group differences than did the BD group as a whole. Fifth, the specificity of our findings to the diagnosis of BD is unclear, although findings from a previous study\(^74\) of schizophrenia differed from those reported herein. Sixth, group comparisons of signal change did not control for underlying regional brain volumes, and group differences in regional volumes could have contributed to the differences in regional activity reported herein. Seventh, it is unclear whether the regional abnormalities in brain function identified in this study represent the primary pathophysiological abnormalities of BD or whether they are a consequence of functional abnormalities in other brain regions, for example, subcortical nuclei, that project to VPFC.

An additional limitation of this study was the use of a subvocal response to the Stroop stimuli. We elected to use a subvocal response because overt speech can cause significant MRI signal artifacts.\(^7\) A subvocal response, however, precluded the online measurement of task performance during the scans, and, thus, we cannot be certain that participants were on task consistently or that performances remained similar across groups during the scanning session. Comparability in performance across groups in the scanning environment is supported by the similar performance measures for each group outside of the scanner and by the similarity of their activation maps to each other and to maps previously reported for healthy individuals.\(^60,56\) Stroop studies that used overt or covert verbal responses have demonstrated comparable measures of cognitive load and similar patterns of MRI activation\(^79,50\) and anterior event-related potential responses\(^76\) when they have been compared directly with one another. Furthermore, behavioral measures of Stroop interference outside the scanner correlated strongly with online, button-response measures of interference in the same participants during performance of a spatial variant of the Stroop task in the same event-related format inside the scanner \((r=0.83)\).\(^6\) Thus, despite its limitations, this study adds to converging evidence implicating VPFC abnormalities in the pathophysiological origin of acute mood episodes and enduring trait vulnerabilities in BD.

Submitted for publication January 11, 2002; final revision received August 12, 2002; accepted November 8, 2002.

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This study was supported by research grants from the Stanley Foundation (Muscatine, Iowa) (Dr Blumberg), the National Alliance for Research in Affective Disorders and Schizophrenia (Great Neck, NY) (Dr Blumberg), the Charles A. Dana Foundation (New York, NY) (Dr Peterson), the Suzanne Crosby Murphy Endowment at Columbia University College of Physicians and Surgeons (New York) (Dr Peterson), the Department of Veterans Affairs (Washington, DC) Research Career Development Award (Dr Blumberg), the Merit Review Entry Program Award (Dr Blumberg), the Research Enrichment Award Program Award (Drs Blumberg, Leung, and Krystal), the Alcohol Research Center (Dr Krystal), and the Clinical Neurosciences Division of the National Center for PTSD (West Haven) (Dr Krystal); grants MH01232 (Dr Peterson) and MH59139 (Dr Peterson) from the National Institute of Mental Health (Bethesda, Md); and grant KO2AA 00261-01 from the National Institute on Alcohol Abuse and Alcoholism (Bethesda) (Dr Krystal).

This study was presented in part at the 40th Annual Meeting of the American College of Neuropsychopharmacology; December 10, 2001; Waikoloa, Hawaii; and the 56th Annual Meeting of the Society of Biological Psychiatry; May 3, 2001; New Orleans, La.

We thank Kathleen Colonese, BA, for coordinating the research; Ralitza Gueorguieva, PhD, for statistical consultation; Hedy Sarofim, RTRMR, and Terry Hickey, RTRMRN, for their technical expertise; and the research subjects for their participation.

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