State and Trait Influences on Mood Regulation in Bipolar Disorder: Blood Flow Differences with an Acute Mood Challenge

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Background: *Even in remission, patients with bipolar disorder (BD) remain sensitive to external stressors that can trigger new episodes. Imitating such stressors by the controlled transient exposure to an emotional stimulus may help to identify brain regions modulating this sensitivity.*

Methods: *Transient sadness was induced in 9 euthymic and in 11 depressed subjects with BD. Regional blood flow (rCBF) changes were measured using ^{15}O-water positron emission tomography.*

Results: *Common changes in both groups were increased rCBF in anterior insula and cerebellum and decreased rCBF in dorsal-ventral-medial frontal cortex, posterior cingulate, inferior parietal, and temporal cortices. Decreases in dorsal ventral medial frontal cortices occurred in both groups, but subjects in remission showed a greater magnitude of change. Unique to remitted subjects with BD were rCBF increases in dorsal anterior cingulate and in premotor cortex. Lateral prefrontal rCBF decreases were unique to depressed subjects with BD. At baseline, remitted subjects showed a unique increase in dorsal anterior cingulate and orbitofrontal cortex.*

Conclusions: *Common rCBF changes in remitted and depressed subjects identifies potential sites of disease vulnerability. Unique cingulate and orbitofrontal changes both at baseline and with induced sadness seen in the absence of prefrontal rCBF decreases may identify regional interactions important to the euthymic state in this population.* Biol Psychiatry 2003;54:1274–1283 © *2003 Society of Biological Psychiatry*

Key Words: Bipolar disorder, remission, depression, mood challenge, PET

Introduction

Bipolar disorder (BD) is characterized by episodes of fluctuating moods of opposite polarity separated by periods of remission (American Psychiatric Association 1994). Clinical remission from an acute episode is generally seen as a "symptom-free period," but there is growing evidence that this state is frequently accompanied by an increased emotional reactivity as well as frank mood lability (Fukuda et al 1983; Keller et al 1986; Tsuang et al 1979), in addition to other measurable abnormalities in cognitive functioning (Ebert et al 1994; Loeber et al 1999; Videbech 2000). These impairments are reported to be more prominent in the bipolar population than in patients who have recovered from major depressive disorder (MDD; Bowden 2001). Although often undetected clinically, these phenomena suggest that despite remission of the acute episode, patients remain in an unstable affective state. This state is thought to contribute significantly to the vulnerability of patients with BD to external stressors such as life events or biological factors (medical illness, lack of sleep, exposure to emotional situations, etc.), which may trigger new episodes (Lauer et al 1998). Mood dysregulation in this context may be the clinical manifestation of an underlying functional brain diathesis that predisposes these patients to relapse and new episodes.

Using functional imaging, orbitofrontal resting state abnormalities have been identified during both acute depression and acute mania, but these studies provide few clues as to mechanisms mediating specific mood symptoms per se (Blumberg et al 2000a, 2000b; Drevets 2000).

Mood provocation strategies and functional imaging, on the other hand, have identified regionally specific differences between healthy control subjects and patients with MDD with acute shifts in negative mood state involving more widespread changes in medial frontal cortex and anterior and subgenual cingulate regions (Liotti et al 2000; Mayberg et al 1999). The study of patients with remitted BD thus provides an important approach to identify disease-specific biological markers of this well-known

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phenomenon. In addition, the identification of those regions that are most sensitive to provocation by external stressors may help to clarify mechanisms mediating clinical relapse in BD. Neural correlates of these clinical trait or disease diathesis markers are as yet uncharacterized.

To address these issues, an acute memory-evoked sad mood provocation with rCBF-positron emission tomography (PET) was used to study euthymic and depressed patients with BD. This approach examines neural correlates of the increased sensitivity to negative cognitions and negative behavioral stimuli commonly described in depressed patients (Segal et al 1996) as well as mechanisms mediating potential sites of vulnerability underlying the more rapid mood shifts that characterize bipolar illness. It is hypothesized that this controlled emotional induction paradigm provides a potential model of stressors experienced in everyday life known to exaggerate these abnormalities in mood regulation in remitted patients. Thus, exposure to such transient emotional stress would temporally unmask brain regions at greatest risk. It is further hypothesized that changes deviating from those seen previously in MDD or healthy control subjects will identify BD trait abnormalities with unique changes in remitted patients relative to depressed BD patients marking potential targets underlying relapse vulnerability.

Methods and Materials

Subjects

Twenty subjects with DSM-IV bipolar I disorder (9 remitted, 11 acutely depressed) in treatment at the Center for Addiction and Mental Health, Mood and Anxiety Division, University of Toronto, were included in the study. The diagnosis was made using the Structured Clinical Interview for DSM-IV (Spitzer et al 1990). Exclusion criteria included other Axis I or II diagnoses, history of head trauma or of substance abuse, medical and neurologic comorbidity, and medications other than mood stabilizers. Written informed consent was obtained from all subjects, and the study was approved by the Center for Addiction and Mental Health Ethics Committee.

Remitted Subjects

Remission (euthymia) was defined as absence of symptoms (recovery) of depression, mania, hypomania, and mixed mania for a minimum of 6 months without recurrence (American Psychiatric Association 1994). This was verified via review of clinic records as all subjects were in treatment at the Mood and Anxiety Division of the Center for Addiction and Mental Health of the University of Toronto. We used the documentation (rating scale assessment and clinical impression) provided by experienced and research-trained clinicians to select euthymic patients with BD. All potential subjects were seen by the first author for a clinical interview to assess their mood state over the previous 6 months. During this evaluation, the Hamilton Depression Rating Scale was administered to quantify current depressive symptoms.

Table 1. Demographics and Clinical Characteristics of Subjects with Bipolar Disorder

	Remitted	Depressed
n	9	11
Gender (female/male)	3/6	7/4
Age (years)	38 ± 12	43 ± 9
Age of Onset of BD	23 ± 6	21 ± 6
HAM-D Score	3 ± 2	26 ± 7
Months in Remission from any Mood Episode	6 ± 1	NA
Duration of Acute Depressive Episode (months)	NA	3 ± 2
Number of Previous Manias	3 ± 2	4 ± 3
Number of Previous Depressions	8 ± 5	8 ± 3
Mood Stabilizers (type, *n*)	9 VPA	9 VPA, 2 Li

BD, bipolar disorder; HAM-D, Hamilton Depression Rating Scale; Li, lithium; VPA, valproic acid.

Only patients with a HAM-D score of ≤ 6 were enrolled. The remitted group consisted of three women and six men, mean age 38 ± 12 years, with a mean HAM-D score of 3 ± 2, a mean age of onset of the bipolar illness of 23 ± 6 years, a mean number of previous manic episodes of 3 ± 2, and a mean number of previous depressive episodes of 8 ± 5. Subjects had recovered from a previous episode (depression in all subjects) for a mean of 6 ± 1 months (Table 1). None of the patients had a significant psychiatric, medical, or neurologic comorbidity, and all were on stable doses of mood stabilizers but no other medications.

Depressed Subjects

The 11 depressed subjects fulfilled DSM-IV criteria for a current depressive episode. The group consisted of seven women and four men, mean age was 42 ± 9 years, age of onset of the bipolar illness was 21 ± 6 years, the mean number of previous depressive episodes was 8 ± 3, the mean number of manias was 4 ± 3. The mean duration of the depressive episode was 12 ± 8 weeks and the mean HAM-D score was 26 ± 7. All patients received a mood stabilizer (nine valproic acid, two lithium), and none were taking antidepressants. Of the 11 depressed subjects, four had been treated with selective serotonin reuptake inhibitors (SSRIs; two paroxetine, two citalopram) without change in symptoms that were discontinued 2 weeks before the experiment.

Mood Induction

Induction of transient intense sadness was performed using a previously validated mood induction paradigm (Liotti et al 2000, 2002; Mayberg et al 1999). In brief, subjects were requested to draft an individualized autobiographical script describing a sad life event. Sad scenarios most commonly centered on loss of friends, relatives, or significant relationships. Each script was tested in advance to ensure reliability and reproducibility in inducing a sad mood.

During the PET experiment, the script was projected onto a computer screen, to facilitate recall of the event while the subject lay in the scanner. Scripts were presented for approximately 5 min ending 30 sec before the start of the actual scan. Scans were acquired at peak emotion, with eyes closed, script off, while

subjects were encouraged to focus on their sadness without active rumination on script details. This instruction served to reduce the activation of brain regions mediating such cognitive ruminations as demonstrated in previous experiments (Liotti et al 2000).

Mood was rated every 2 min following script presentation up to the time of the scan and immediately thereafter to document compliance with instructions. Intensity of sadness was quantified using a self-rating Likert scale (range: 0 = not sad to 7 = very sad). For all subjects, scans were not taken unless the mood state reached a minimum of 6 on the rating scale. Anxiety was similarly rated before and after each scan because this emotion is known to confound the brain changes associated with sadness (Liotti et al 2000).

Scan Acquisition and Image Reconstruction

Regional cerebral blood flow (rCBF) was measured using [^{15}O]-water and PET in two behavioral states: baseline euthymia and provoked sadness. Two trials of each condition were acquired using an alternating design, with neutral mood always preceding sad mood (i.e., the scanning sequence was rest 1, sad 1, rest 2, sad 2). Scans were acquired at the Center for Addiction and Mental Health on a GEMS/Scanditronix 2048b camera (15 parallel slices; 6.5-mm center-to-center interslice distance) using measured attenuation correction (68Ge/68Ga transmission scans). rCBF was measured using the bolus [^{15}O]-water technique (45 mCi ^{15}O-water dose/scan; scan initiated with bolus entry into the brain; scan duration = 60 sec). Subjects were fitted with a customized thermoplastic facemask to minimize head movement across acquisitions. Scans were spaced a minimum of 11 min apart to accommodate radioactive decay to background levels as well as to allow return to behavioral baseline.

Data Analysis

Statistical analyses were performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (version 5.3, Mathworks, Sherborn, Massachusetts). The data were first screened for distributional properties, outliers, and missing values. This process rejected no scans. All scans were then normalized to the Montreal Neurologic Institute's ICBM 152′ stereotactic template within SPM99, which references brain locations in three-dimensional space relative to the anterior commissure (Brett et al 2002; Collins et al 1994). The images were then corrected for differences in the whole-brain global mean and smoothed using a Gaussian kernel to a final in-plane resolution of 10 mm at full width at half maximum.

Final inclusion in group analyses required further evidence of a stable baseline scan in both neutral trials. No scans were excluded for artifacts; two trials were excluded because of an incomplete return to baseline behavioral levels in two remitted subjects.

Differences within (sad vs. neutral) and between groups (remitted vs. depressed) were the primary focus of this study and are reflected by the following series of statistical analyses: Significant regional changes in the sad relative to the resting state were assessed by the use of the general linear model and Gaussian random field theory to analyze spatially extended data through statistical parametric maps (Friston et al 1994, 1995). Cluster significance thresholds were set at the default 50 voxels (voxel = 8 mm^3). Based on previous results of sad mood induction in healthy control subjects and unipolar depressed subjects (Liotti et al 2002; Mayberg et al 1999), peak voxel value significance thresholds were set at $p < .01$ for five hypothesized regions (ventral subgenual cingulate, Brodmann Area [BA] 25, medial frontal cortex BA 9/10/11, dorsal anterior cingulate BA 24, dorsolateral prefrontal cortex BA 9/46, anterior insula) and at $p < .001$ (uncorrected) level for unhypothesized regions. Brain locations are reported as x, y, z coordinates in MNI space with approximate Brodmann areas identified by mathematical transformation of SPM99 coordinates into Talairach space (http://www.mrc-cbu.cam.ac.uk/Imaging/; Talairach and Tournoux 1988).

Primary analyses addressed the change patterns specific for each group (rest vs. sad for remitted (Rem) and depressed (Dep) subjects analyzed separately) and specific differences between the two groups ([rest vs. sad Rem] vs. [rest vs. sad Dep]). Secondary analyses assessed baseline differences between the two groups to interpret group change pattern similarities and differences. In addition, the influence of gender on the mood induction change pattern as well as stability of the change pattern between the two trials were examined. To further interpret potential disease-specific findings, a post hoc analysis compared the change patterns in the BD group to a previously published group of eight healthy women (aged 36 ± 6) without personal or family history of an affective disorder, scanned with the same mood induction protocol under identical experimental conditions on a like-generation PET camera (GE-Scanditronix 4095, 15-slice, 10 cm field of vision, 6.5-mm interslice distance, measured attenuation correction; Liotti et al 2000; Mayberg et al 1999). These data were reprocessed and reanalyzed in SPM99 to match the BD analyses directly.

Results

Mood Induction—Behavioral Effects

The mood provocation protocol produced robust behavioral effects in both groups, comparable to that previously reported in healthy control and MDD subjects. All but one BD patient had visible tears. Similar magnitude of change was seen in both trials in both groups (Table 2).

In remitted subjects, a maximal sad state was provoked within 30 sec to 1 min after exposure to the sad script. Return to baseline levels was generally equally rapid, although two patients had difficulty achieving a complete return to baseline following the first sadness provocation. No significant anxiety was reported during any of the scans.

The acutely depressed group reported a slightly elevated baseline sadness rating (3.1 ± .9); however, they still achieved a maximal sad state after provocation, although it took approximately 3 minutes to reach this state. All depressed patients easily returned to their preprovocation baseline mood state. The level of baseline anxiety was also

Table 2. Behavioral Effects of Mood Induction

	Remitted (n = 9)		Depressed (n = 11)	
Trials	Sadness	Anxiety	Sadness	Anxiety
Rest 1	.0 ± .0	1.1 ± .5	3.2 ± .9	1.6 ± 1.0
Rest 2	.0 ± 1.0	1.0 ± .5	3.0 ± 1.2	1.8 ± 1.2
Sad 1	7.0 ± .5	1.1 ± 1.0	7.0 ± .5	2.2 ± 1.5
Sad 2	6.9 ± .5	1.3 ± .5	7.0 ± .8	2.0 ± 1.3
Crying	9		10	

slightly higher than that of the remitted group. There were no statistically significant differences in scores across the two groups, however.

All subjects in both groups remained at peak sadness throughout the scan acquisition, verified by postscan self-report and debriefing. All participants confirmed that they were successful in avoiding active ruminations after the script was turned off. Anecdotally, all remitted subjects, reported feeling somewhat overwhelmed by the emotional experience. Remitted subjects also requested a slightly longer debriefing time after completion of the full session, describing a subjective feeling of emotional instability. None of these patients met clinical criteria for relapse. All remained clinically stable in remission at follow-up 2–3 days later.

rCBF Changes with Sadness

REMITTED PATIENTS. Acute sadness resulted in significant rCBF changes relative to baseline: increases in premotor cortex (BA 4/6), dorsal anterior cingulate (BA 24a), anterior insula, and cerebellum, and decreases in dorsal and ventral medial frontal cortex (BA 8/9/10), orbitofrontal cortex (BA 11), posterior cingulate (BA 23/31), inferior parietal (BA 40), and inferior temporal (BA 21) cortices (Table 3, Figure 1 top).

Table 3. Changes with Sadness in Remitted and Depressed Subjects with Bipolar Disorder

			BP Rem			BP Dep			Z Score[a]		
Zone and Region	Side	BA	x	y	z	x	y	z	Rem/Dep	Specificity	Interaction[b]
rCBF Increases											
Dorsal anterior insula	R		44	16	4	52	22	−8	4.3/4.6	Rem/Dep	
	R		56	18	−16	54	42	−12	4.9/4.0	Rem/Dep	
Cerebellum	L		−18	−56	22	−30	−54	20	3.7/4.2	Rem/Dep	
	R		18	−64	−22				3.6	Rem/Dep	
	R		24	−72	−34				3.9	Rem	
Dorsal anterior cingulate	R	24a	10	20	24				5.3	Rem	
Motor/premotor	R	4/6	66	−4	18				4.4	Rem	
	R	4/6	64	−8	24				4.2	Rem	
	L	4/6	−60	−4	16				5.1	Rem	
rCBF Decreases											
Orbital medial frontal	R	10/11	6	42	−10	8	56	−6	3.4/3.8	Rem/Dep	
	R	11	14	46	−20				3.5	Rem	I
Ventral medial frontal	R	10	20	62	−4	4	58	9	4.0/<3	Rem/Dep	
	L	10	−18	54	10				3.7	Rem	
	L	10	−14	64	0				3.9	Rem	
Frontal pole	L	8	−28	30	48	−28	28	44	4.5/3.8	Rem/Dep	
	L	8	−16	38	38				4.7	Rem	
Dorsolateral frontal	R	9				52	36	20	4.8	Dep/C	I
Ventral lateral	L	47				−42	10	−34	5.0	Dep	
Inferior parietal	R	40	46	−56	46	46	−62	36	3.8/3.6	Rem/Dep/C	
	R	40	42	−66	38	28	−72	30	3.7/3.6	Rem/Dep/C	
	R	40	58	−32	34				4.86	Rem/C	
	L	40				−36	−2	40	4.40	Dep	
Lateral inferior temporal	L	21/22/39	−58	−50	−24	−54	−52	−18	4.3/6.7	Rem/Dep/C	
	R	21/22/39				62	−40	−6	3.9/3.8	Dep/C	
	R	21/22/39				62	−10	−4	4.4/3.4	Dep/C	
	L	21	−58	−6	−30				4.7	Rem	
Posterior cingulate	R	31	4	−54	12	10	−74	36	4.0/5.1	Rem/Dep	
	L	23/31	−12	−38	42				4.3	Rem	
	L	23/31	−2	−70	8				4.5	Rem	

Coordinates are in MNI space (SPM99).

[a] Z values > 3.0, $p < .001$.

[b] Areas identified in interaction analysis: remitted (sad-rest) versus depressed (sad-rest); precise coordinates not provided.

BA, Brodmann's area; BP, bipolar; Rem, remitted; Dep, depressed; x,y,z, three dimensional coordinates by which a pixel is determined; rCBF, regional cerebral bloodflow; R, right; L, left; C, control (reanalyzed in SPM99 for post hoc comparison with bipolar patient); I, interaction.

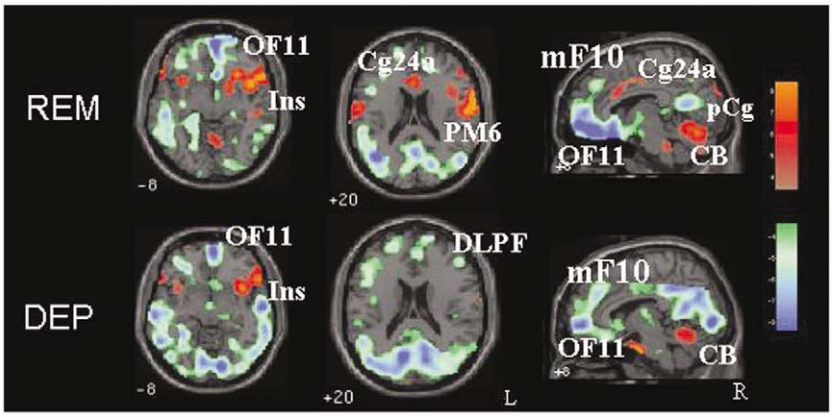

Figure 1. Significant regional blood flow (rCBF) increases (in red/yellow) and decreases (in green-blue) after sad mood provocation overlayed on a magnetic resonance imaging template. Top row: remitted bipolar group; bottom row: acutely depressed bipolar group. REM, remitted; DEP, depressed; CB, cerebellar vermis; Cg24a, pregenual cingulate (BA 24a); PM6, premotor (BA 6); DLPF, dorsolateral prefrontal; mF10, medial prefrontal (BA 10); OF11, orbitofrontal (BA 11); Ins, insula; pCg, posterior cingulate; L, left; R, right.

DEPRESSED SUBJECTS. An overall similar pattern of rCBF changes was seen in the depressed group. The most significant changes again involved widespread rCBF decreases in dorsal and ventral medial frontal cortices, although without orbitofrontal changes (BA11). rCBF increases were also seen in anterior insula and cerebellum, and similar decreases were observed in posterior cingulate, inferior parietal, and inferior temporal cortices. Unique to depressed subjects were rCBF decreases in dorsolateral prefrontal cortex (BA9). Absent were the rCBF increases in dorsal anterior cingulate and premotor regions seen in remitted subjects. (Table 3, Figure 1 bottom).

The direct contrast of the group change patterns identified two areas of double dissociation: unique prefrontal cortex (BA9) decreases in the depressed group and unique orbitofrontal cortex (BA11) decreases in the remitted group (Table 3, images not shown). In neither group were there differences between men and women at baseline or with mood induction, nor were there trial order effects ([rest 1 vs. sad 1] versus [rest 2 vs. sad 2]).

Post Hoc Analyses

BASELINE ABNORMALITIES. Comparison of remitted to depressed subjects with BP at baseline revealed no significant rCBF differences despite obvious differences in clinical state. Post hoc analyses of each group relative to the comparison sample identified prefrontal (BA9) hypoperfusion in both groups, but to a greater, although not significant, degree in depressed relative to remitted subjects. On the other hand, remitted subjects showed unique rCBF increases in dorsal anterior cingulate relative to control subjects, which was not seen at any threshold in the depressed group. Both groups compared with control subjects also showed similar significant rCBF decreases in prefrontal medial frontal orbitofrontal and parietal cortices as well as increased rCBF in cerebellum and insula. No further significant differences between depressed and remitted subjects at the preset statistical threshold were observed, suggesting that the identified abnormalities were trait rather than state abnormalities. Only with the induction of transient sadness were the two groups further differentiated.

CHANGES WITH SADNESS. In examining BD-specific change effects, there were several regions of significant difference between patients and the healthy comparison group. Again, a double dissociation was identified. Medial frontal rCBF decreases (BA 9/10/11) were seen only in the subject groups, suggesting a possible BD trait marker. rCBF increases in subgenual cingulate (BA 25) were seen uniquely in the comparison group. No changes in this region were seen in either patient group, similar to the findings reported in MDD (Liotti et al 2002). Increased rCBF in cerebellum and insula and decreased rCBF and lateral prefrontal and parietal cortices were similar for patients and healthy volunteers.

Discussion

With mood induction, regional brain changes previously identified in both healthy subjects and subjects with MDD were demonstrated in two groups of subjects with BD. These changes include rCBF increases in insular cortex, cerebellar vermis, motor and premotor cortex and rCBF decreases in parietal cortex, posterior cingulate cortex, and posterior inferior temporal cortex; changes may reflect shared circuitry in mood regulation in health and disease.

A major finding was the common pattern of brain activity following sad mood precipitation in fully remitted and acutely depressed BD subjects, in contrast to the pattern observed in healthy subjects. More specifically changes in BD subjects included increased rCBF in anterior insula, cerebellum and decreases in dorsal and ventral medial frontal cortex, posterior cingulate, inferior parietal and temporal cortex. Remitted subjects had more robust rCBF decreases in medial frontal cortex than depressed and had unique increases in dorsal anterior

cingulate and premotor cortex, while prefrontal decreases were unique to depressed subjects. Comparison of remitted to depressed subjects at baseline revealed a rCBF increase in remitted subjects in dorsal anterior cingulate and orbitofrontal cortex, but prefrontal cortex rCBF comparable to healthy control subjects.

Medial Frontal Cortex

The sadness-related rCBF decreases in medial frontal cortex seen in both BD groups is almost identical to that seen in remitted and depressed unipolar patients (Liotti et al 2002). These frontal changes have also been reported in a case of Parkinson's disease with remitted depression following right-sided subthalamic nucleus stimulation for treatment of refractory motor symptoms (Stefurak et al 2001), as well as following tryptophan depletion in SSRI-treated depressed patients (Bremner et al 1995; Smith et al 1999). These changes are not seen in healthy subjects at any significance threshold, suggesting a critical role for medial frontal cortex during mood challenge paradigms across depression diagnoses.

Previous functional brain imaging studies in humans with PET and functional magnetic resonance imaging have demonstrated consistent reductions in medial frontal cortex blood flow during the performance of a wide range of cognitive tasks, which may, in part, represent an attenuation or inactivation of elements of a functionally active, baseline, or default state of brain activity (Simpson et al 2001). It has been hypothesized that the observed changes reflect a dynamic interplay between ongoing cognitive processes and the emotional state of the subject.

Activation of medial prefrontal cortex has been previously associated with emotional processing tasks in nondepressed control subjects including the active rethinking and reappraisal of emotional feelings. Exaggerated activity in this region has been similarly reported in depressed patients in response to sad words, supporting the previously recognized negative emotional bias in this patient population. Selective changes in medial frontal cortex may reflect a reduced bias toward the processing of negative information in the recovered state, with implications for future relapse risk (Craik et al 1999; Elliott et al 2000; Fossati et al, in press; Kelley et al 2002).

Regional cerebral blood flow in medial frontal cortex has further been reported to be decreased during anticipatory anxiety and has been inversely correlated to the anxiety state itself (Simpson et al 2001).

The resting state abnormalities in these ventral medial frontal regions seen in both bipolar groups are not the typical pattern seen in other patient groups, suggesting perhaps some specificity for BD (Mayberg 1994).

These apparent "subtype"-specific effects are pertinent, given structural MRI and postmortem studies demonstrating abnormalities in both medial prefrontal and ventral medial frontal cortex in familial depressions and in specific studies of BD (Burnet and Harrison 2000; Drevets et al 1997; Ongur 1998; Rajkowska 2000). Volumetric measurements were not performed in this study to examine potential confounding effects of atrophy on baseline measurements that may have introduced an apparent but spurious flow defect. The findings here are, however, much more widespread than the relatively focal structural abnormalities previously reported.

The presence of comparable baseline ventral medial abnormalities in both remitted and depressed state in subjects with BD therefore might be better interpreted as potential trait abnormalities. This is consistent with previous reports of orbitofrontal dysfunction in BD patients with either depressed or manic states (Biver et al 1994; Blumberg et al 2000b; Drevets et al 1997). The regions described here, however, are more widespread, extending rostrally and superiorly to include other regions of medial frontal cortex.

The greater magnitude of change with mood provocation in orbitofrontal cortex in patients with remitted BP combined with a unique increase in anterior cingulate and premotor regions may be linked to the reported increased affective reactivity of these patients (including "interepisodic switching"; Silberman et al 1985), which has been recognized as one of the classic hallmarks of BD (Bräunig 1995a, 1995b; Kraepelin 1916; Leonhard 1957). Anecdotally, this is also consistent with several patients' self report of being emotionally overwhelmed at the conclusion of this experiment.

The link between orbitofrontal abnormalities and propensity for rapid shifts in mood state is also consistent with clinical observations of orbitofrontal cortex lesions where affective lability, impulsivity, and sudden changes between euphoric and dysphoric mood states are commonly seen (Angrilli et al 1999; Grafman et al 1986; Joseph 1999). Contiguous but more dorsal and rostral medial frontal regions are additionally involved in mediating self-referential processing of emotionally salient stimuli (Elliott et al 2000; Murphy and Sahakian 2001) and in reward assessment (Bechara et al 2000; Rolls 2000; Schultz 1999, 2001), which may further explain the observed abnormalities in these domains, particularly during acute depressive episodes.

These converging findings might therefore suggest that medial frontal regions are involved in preventing uncontrolled or exaggerated responses to external stimuli and in maintaining emotional and behavioral homeostasis.

Dorsolateral Prefrontal Cortex

Dorsolateral prefrontal hypoperfusion at rest was present in both remitted and depressed subjects. Dorsolateral prefrontal hypoperfusion has been one of the most consistent findings in imaging studies of major depression, whether unipolar, bipolar, or neurologic (Baxter et al 1989; Buchsbaum 1986, Buchsbaum et al 1997; Dolan et al 1992; Kennedy et al 2001; Mayberg 1994). This pattern has been shown to correlate with psychomotor speed and frontal cognitive impairment (Bench et al 1993; Mayberg 1994; Videbech 2000). Deactivation of predominantly dorsal prefrontal cortex has also been reported during memory-driven emotional states in healthy subjects (Damasio 1996; Gemar et al 1996; Ketter et al 1999; Mayberg et al 1999), although not in patients with active MDD, where there is also baseline prefrontal hypoperfusion. This differs from the findings in the depressed subjects with BD, suggesting another difference between the two depression subtypes.

Absence of further changes (decreases) in prefrontal cortex in remitted subjects with emotional stress may, however, be a marker of preserved integrity of these pathways when in remission. Known connections between prefrontal and anterior cingulate may together serve a protective function in remitted patients. This would be consistent with the absence of dorsal cingulate baseline abnormalities or change effects in the depressed BD group.

Dorsal Anterior Cingulate (BA 24a)

Increased rCBF in dorsal anterior cingulate (BA 24a/32) occurred uniquely in the remitted group both at rest and after mood induction. Cingulate changes may be linked to the decrease in orbitofrontal cortex, because these regions have strong reciprocal connections (Vogt and Pandya 1987). That said, one might have expected changes in the depressed subjects as well. Multivariate analyses are likely needed to address the apparent complex relationships between prefrontal anterior cingulate and medial frontal cortex with and without mood provocation in the various patient groups (Mayberg 2002).

Nonetheless, dorsal anterior cingulate has been implicated in attention to emotional salience (Bush et al 1998; Lane et al 1997a, 1997b; Whalen et al 1998) and in emotion-attention interaction tapped by the Emotional Stroop Task (Whalen et al 1998). In MDD, BA 24a resting metabolism has been previously identified as a predictor of future antidepressant response (Mayberg et al 2000). Increased activity above baseline in the remitted bipolar group may reflect a basal hyperactivity of this emotion-vigilance system, explaining the remitted subjects' tendency to react faster to the mood provocation paradigm and to feel emotionally overwhelmed by the sad stimulus. In combination with orbitofrontal hypometabolism, this finding might explain the exaggerated emotional reactivity of subjects with BD observed in the clinically euthymic state.

Subgenual Cingulate (BA 25)

Despite previous studies demonstrating robust and reproducible activity of subgenual cingulate with negative mood change in healthy subjects (Damasio 1996; George et al 1995; Liotti et al 2000) as well as its role in SSRI antidepressant response (Mayberg et al 1999, 2000), no significant changes were identified in either the remitted or acutely depressed group. A similar finding was seen in patients with an acute major depressive episode and recovered from depression, on maintenance SSRI antidepressants or drug free (Liotti et al 2002). To further explore the role of this area in BD, we conducted a secondary analysis, addressing the comparison of rCBF in this region during the resting state across groups. Resting rCBF in BA 25 was increased, albeit not significantly, in both remitted and depressed subjects with BD relative to the healthy control group, suggesting a subtle, ongoing tonic activation of this region. This is different from that seen in remitted subjects with MDD, in whom tonic rCBF decreases in this region relative to control subjects were demonstrated (Liotti et al 2002). This finding may be another disease-specific marker differentiating BD from MDD. That said, relative resting state hyperactivity in this region is also seen in healthy subjects with high self-ratings of negative affect (Zald et al 2002), perhaps reflecting a personality trait maker rather than a BD-specific effect.

Absence of change in this region with mood provocation may alternatively reflect long-standing functional reorganization of limbic-cortical pathways that normally mediate acute shifts in mood state and participate in selection of emotional targets, whether happy or sad (Elliott et al 2000). This absence of change in either bipolar group is similar to that previously reported in subjects with recurrent MDD (Liotti et al 2002), again suggesting a depression-specific, albeit not a syndrome-specific marker.

Some studies of mood provocation show changes in the amygdala. These were not seen in this study, nor are they present in other studies using a pure personal memory provocation paradigm. When seen, it is generally using novel emotional stimuli, such as faces, pictures, or film (Levesque et al 2003; Phillips et al 1998, 2001). In this study, both the timing of scan acquisition (minutes after first provoking the emotional state, rather than during evaluation of the stimulus itself) and the nature of the

provocation stimulus (a familiar, personal sad memory rather than a novel stimulus) likely account for these apparent differences across studies.

Caveats

A first potential confounding factor in considering the interpretation of these data are the ongoing treatment of all subjects with valproic acid. Studying patients in a drug-free state was not considered an ethical option for an experiment of this type. Moreover, medication treatment was comparable for the two groups, and the group patterns were similar to those demonstrated in subjects with recurrent MDD, who were studied with the same provocation method, but who were not on mood stabilizers. Although it is certainly a possibility that the baseline abnormalities may include medication effects, the change pattern with mood induction likely does not.

Data are limited as to known effects of anticonvulsants in either actively depressed or remitted subjects with BD. Valproic acid has been reported to cause a 22% reduction in overall glucose metabolism in patients with epilepsy (Leiderman et al 1991) and a 15% decrease in global rCBF in healthy volunteers (Gaillard et al 1996). In a baboon model of epilepsy, a similar global rCBF decrease has been reported (Oliver and Dormehl 1998). These findings are inconsistent with the resting state pattern seen here.

Furthermore, rCBF increases in the insula have also been reported in patients with treatment resistant depression before treatment with carbamazepine (Ketter et al 1999). Treatment with carbamazepine resulted in a widespread metabolic decrease, with the degree of insular decrease correlating with treatment response. Further inferences from this study cannot be drawn as remitted patients were not reported. Taken together, there is no clear link between the reported abnormalities seen commonly in the remitted and depressed BD groups that is best explained by chronic exposure to valproic acid.

Secondly, it might be assumed that rCBF baseline changes observed in remitted subjects may be due to residual depressive symptoms rather than to an underlying disease marker; however, the HAM-D scores of our remitted subjects were below 4, and all patients were assessed to be clinically euthymic by experienced psychiatrists in a tertiary care bipolar clinic.

Thirdly, it is possible that subtle technical differences may be present, confounding what we believe are trait effects, because scans from the comparison control group were not acquired with the same PET camera as that used for the subjects with BD but with a like-generation scanner made by the same manufacturer. To reduce the potential contribution of hardware differences, the control raw data were reprocessed and reanalyzed in SPM99 to match all variables used for the bipolar analyses. Also notable are the similarities between the bipolar findings and those seen in unipolar patients scanned on the same camera as that used for the control subjects (Liotti et al 2002), suggesting that differences between PET cameras are unlikely to account for apparent disease-specific effects reported here.

Finally, this experiment addresses only vulnerability to the depressive pole of BD of potential relevance to understanding potential mechanisms mediating depression relapse in patients with remitted BD. These findings cannot be extrapolated to either pathways mediating hypomanic or manic switches or triggers of such switches, because methods for the experimental induction of switches into hypomania, mania, or lability per se are untested.

Conclusions and Clinical Implications

This study complements the results of a previous study of mood induction in subjects with MDD, highlighting differences specific to BD. Unique to remitted subjects with BD is increased rCBF in dorsal anterior cingulate with mood induction, the reverse of what is reported in remitted subjects with MDD (Liotti et al 2002). Common to both, subjects with MDD and with BD, independent of clinical state and in clear distinction to healthy volunteers, are widespread rCBF decreases in medial frontal cortex (BA 9/10). More specific to subjects with BD regardless of state are resting abnormalities in the same regions. The additional characterization of the functional interactions between medial frontal (BA 10), anterior cingulate (BA 24), orbital cortex (BA 11), and prefrontal (BA 9) regions using multivariate analyses may provide a more mechanistic understanding of the euthymic bipolar state. As well, future studies in which at risk subjects (e.g., family members of subjects with BD) are subjected to the same mood induction protocol will be needed to test whether this mood induction paradigm can determine vulnerability for disease.

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