Effects of Mood and Subtype on Cerebral Glucose Metabolism in Treatment-Resistant Bipolar Disorder

Terence A. Ketter, Tim A. Kimbrell, Mark S. George, Robert T. Dunn, Andrew M. Speer, Brenda E. Benson, Mark W. Willis, Aimee Danielson, Mark A. Frye, Peter Herscovitch, and Robert M. Post

Background: Functional brain imaging studies in unipolar and secondary depression have generally found decreased prefrontal cortical activity, but in bipolar disorders findings have been more variable.

Methods: Forty-three medication-free, treatment-resistant, predominantly rapid-cycling bipolar disorder patients and 43 age- and gender-matched healthy control subjects had cerebral glucose metabolism assessed using positron emission tomography and fluorine-18-deoxyglucose.

Results: Depressed bipolar disorder patients compared to control subjects had decreased global, absolute prefrontal and anterior paralimbic cortical, and increased normalized subcortical (ventral striatum, thalamus, right amygdala) metabolism. Degree of depression correlated negatively with absolute prefrontal and paralimbic cortical, and positively with normalized anterior paralimbic subcortical metabolism. Increased normalized cerebello-posterior cortical metabolism was seen in all patient subgroups compared to control subjects, independent of mood state, disorder subtype, or cycle frequency.

Conclusions: In bipolar depression, we observed a pattern of prefrontal hypometabolism, consistent with observations in primary unipolar and secondary depression, suggesting this is part of a common neural substrate for depression independent of etiology. In contrast, the cerebello-posterior cortical normalized hypermetabolism seen in all bipolar subgroups (including euthymic) suggests a possible congenital or acquired trait abnormality. The degree to which these findings in treatment-resistant, predominantly rapid-cycling patients pertain to community samples remains to be established.

Key Words: PET, cerebral metabolism, bipolar disorders, depression, rapid cycling

Introduction

A substantial series of investigations using positron emission tomography (PET) and single photon emission computed tomography (SPECT) to assess regional cerebral flow (rCBF) and glucose metabolism (CMRglu) have most consistently found decreased prefrontal cerebral activity (hypofrontality) in unipolar depressed patients compared to control subjects (for a review see Ketter et al 1996b).

A small number of studies in bipolar depressed patients have also found decreased prefrontal CMRglu (Baxter et al 1989; Buchsbaum et al 1984, 1986; Cohen et al 1989, 1992; Goyer et al 1992; Martinot et al 1990; Schwartz et al 1987) and CBF (Ebert et al 1993; Ketter et al 1996b) compared to control subjects; however, some studies indicated that certain prefrontal and temporal areas had increased CMRglu (Cohen et al 1992; Goyer et al 1992; Ketter et al 1994). Global CMRglu in depressed bipolar disorder patients has commonly been decreased (Baxter et al 1985, 1989; Cohen et al 1992; Goyer et al 1992; Martinot et al 1990; Schwartz et al 1987), but has also been noted to be increased (Buchsbaum et al 1986). This heterogeneity could be related to methodologic differences, illness subtypes, state-trait differences, or degree of responsiveness to treatment (Ketter et al 1999).

In a recent study, Drevets and associates (Drevets et al 1997) found decreased rCMRglu and rCBF in the prefrontal cortex ventral to the genu of the corpus callosum (subgenual prefrontal) in both familial bipolar depressives and familial unipolar depressives. Decreased activity was accompanied by corresponding substantial reductions in gray matter volume in this area of 39% in unipolar and 48% in bipolar patients. Decreased CMRglu in the temporal lobes (Goyer et al 1992; Ketter et al 1996b; Martinot et al 1990; Post et al 1987) and basal ganglia (Buchsbaum et al 1986; Cohen et al 1989) has also been reported.
In view of these varying findings in bipolar disorders, we obtained fluorine-18-deoxyglucose (\(^{18}\)FDG) PET scans in a substantial series of medication-free bipolar disorder patients compared with age- and gender-matched control subjects while performing an auditory continuous performance task, to better understand how changes in prefrontal and anterior paralimbic \(r\text{CMRGlucose}\) relate to clinical parameters, such as mood state, degree of depression, disorder subtype, and cycle frequency.

**Methods and Materials**

**Subjects, Medications, and Mood Ratings**

The study was approved by the National Institute of Mental Health (NIMH) Institutional Review Board, and written informed consent was obtained from all subjects before participation. We studied 43 inpatients (age range, 21–65 years) with DSM-IV bipolar disorders that were resistant to standard treatments in the community and referred to the NIMH (Table 1). This highly treatment-resistant group of bipolar disorder patients had medians of 19 years of illness duration, 16 manic/hypomanic episodes, 24 depressive episodes, and 4 hospitalizations per patient. Medical and neurologic histories and physical examinations were obtained to rule out medical illnesses in patients and in age- and gender-matched healthy control subjects. Both diagnoses in patients and the absence of mental illness in 43 paid healthy control subjects (age range, 20–65 years) were confirmed by the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). Episodes and hospitalizations as well as the presence of a current rapid cycling pattern (four or more affective episodes in the year before the PET scan) were determined by examination of retrospective lifecharts assessed by the NIMH-Life Chart Methodology (NIMH-LCM) (Leverich and Post 1996, 1998).

Trained clinical research nurses blind to medication status and scans obtained twice-daily global Bunney-Hamburg depression (BH-D) (Bunney and Hamburg 1963), weekly 28-item Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), Mood Analog, and global Bunney-Hamburg mood ratings, and in 30 patients day-of-scan HRSD and Young Mania Rating Scale (Young et al 1978) ratings. Self-rated Beck Depression Inventory (Beck et al 1961) scores were also obtained weekly.

The patient sample was subdivided using three clinical phenomenologic parameters: mood state (depressed, mildly depressed, euthymic), bipolar subtype (bipolar I, bipolar II), and rapid-cycling status (currently rapid cycling, non–rapid cycling). No patient had a full acute manic syndrome (mean Young Mania rapid-cycling status (currently rapid cycling, non–rapid cycling). pressed, euthymic), bipolar subtype (bipolar I, bipolar II), and nomenologic parameters: mood state (depressed, mildly depressed, euthymic), bipolar subtype (bipolar I, bipolar II), and cycle frequency.

![Table 1. Sample description](https://example.com/table1.png)

- **Depressed**, **Mildly depressed**, **Euthymic**
- **Bipolar I (BPI)**, **Bipolar II (BPII)**
- **Rapid cycle**, **Nonrapid cycle**
- **HRSD**, **Duration (years)**, **Episodes (per year)**, **Onset (years)**
- **Gender**, **Subtype**, **Episode**
- **Control subjects**
- **p < .05 vs. nonrapid. All other subgroup comparisons nonsignificant.**

The patient sample was subdivided using three clinical phenomenologic parameters: mood state (depressed, mildly depressed, euthymic), bipolar subtype (bipolar I, bipolar II), and rapid-cycling status (currently rapid cycling, non–rapid cycling). No patient had a full acute manic syndrome (mean Young Mania Rating Scale score 3.1 ± 3.2, range 0–13). Patients were classified as euthymic if they had no or only mild symptoms on prospective NIMH-LCM and thus no functional impairment, HRSD scores of 10 or less, and BH-D scores of 3 or less. Those with HRSD scores of 18 or greater and BH-D scores of 7 or greater were considered depressed, and those with HRSD scores ranging from 11 to 17 and BH-D scores ranging from 4 to 6 were classified as mildly depressed. The four instances of disagreement between HRSD and BH-D were dealt with by referring to...
appropriate, mood. Results were displayed as transverse statistical maps with significant voxels color coded to correspond to decreasing p-values (starting at p = .05, not initially corrected for multiple comparisons). Correction for multiple comparisons was applied by only displaying voxels within clusters deemed significant by particle analysis using a Z-threshold of 1.96 and cluster probability <.05 (Friston et al 1994).

Demographic and clinical patient data were analyzed using unpaired t-tests for between-group comparisons. Categorical data were analyzed by χ² tests. Means (± standard deviations) are reported, and significance thresholds were set at p = .05, unless noted otherwise.

**Results**

Among subjects with complete CPT data, 29 patients compared to 34 control subjects had slower mean reaction time [0.90 ± 0.18 vs. 0.75 ± 0.21 sec, t(61) = 2.98, p = .004], but did not otherwise differ significantly on CPT performance parameters.

**Mood State Subgroups**

The 17 depressed bipolar patients with HRSD scores greater than 17, compared to 17 age- and gender-matched control subjects had 7.7% lower global metabolism [7.15 ± 0.89 vs. 7.75 ± 0.80, t(32) = 2.07, p < .05; Figure 1]. Decreased absolute (but not normalized) regional metabolism was seen in widespread prefrontal and anterior paralimic cortical regions, including inferior (Brodmann areas [BAs] 44, 45, 46), middle (BAs 8, 9, 10, 46), and superior (BAs 9, 10) frontal gyri; superior (BAs 22, 39, 40, 42), middle (BAs 21, 39, 40), and transverse (BA 41) temporal gyri; as well as in inferior parietal lobule (BAs 39, 40), and bilateral lateral cerebellum (Figure 2, top, and Table 2). Decreased absolute (and to a lesser extent, normalized) CMRglu was observed in temporal white matter and anterior cingulate, as well as in subgenual and anterior cingulate gray matter. Significant differences were also noted for the nondepressed bipolar patients, with 7.2% lower global CMRglu compared to age- and gender-matched control subjects (Figure 2, bottom, and Table 2). Decreased absolute (and to a lesser
degree normalized) metabolism was also seen in fascicular (BA 19) and lingular (BAs 18, 19) gyri (Figure 2 and Table 2).

In contrast, increased normalized (but not absolute) metabolism was noted in subcortical regions, including right amygdala, bilateral accumbens, and ventral caudate and putamen, as well as in right anterior superior longitudinal fasciculus, bilateral medioposterior thalamus (dorsomedial nucleus, pulvinar), and bilateral medial cerebellum (Figure 2, bottom). Thus, in depressed bipolar disorder patients there were three main components to the pattern of differences compared to control subjects, namely 1) widespread prefrontal and anterior paralimbic cortical absolute decreases; 2) subcortical (ventral striatum, thalamus, right amygdala) normalized increases; and 3) cerebellar and posterior cortical normalized increases.

The 16 mildly depressed patients with HRSD scores ranging from 11 to 17, compared with 16 control subjects, did not differ significantly in global metabolism (7.31 ± 0.94 vs. 7.37 ± 1.11; Figure 1) or in the absolute regional analysis. Increased normalized (but not absolute) metabolism was noted in bilateral cerebellum (sparsely), lingual gyrus (BAs 18, 19), cuneus (BAs 18, 31), and hippocampus; left postcentral gyrus (BAs 1, 2, 3); left insula and left transverse temporal gyrus (BA 41); and left inferior (BAs 44, 45, 47), middle (BAs 9, 10, 46), and superior (BAs 8, 9) frontal gyri. In contrast, decreased normalized (but not absolute) metabolism was noted in right inferior (BAs 20, 37) and middle (BAs 20, 21) temporal gyri (Table 2).

The 10 euthymic patients, compared with 10 control subjects, did not differ significantly in global metabolism (7.73 ± 1.21 vs. 7.63 ± 1.00; Figure 1) or in the absolute regional analysis (Figure 3, top). Increased normalized (but not absolute) metabolism was noted in bilateral cerebellum, lingual gyrus (BA 18), cuneus (BAs 18, 19, 31), and precuneus (BA 7); as well as right inferior frontal gyrus (BA 44), right superior longitudinal fasciculus, right insula, and right inferior parietal lobule (BA 40; Figure 3, bottom, and Table 2).

Direct comparison of the 17 depressed versus 10 euthymic patients (covarying for age and gender) revealed no significant global difference but decreased (lower in depressed) both absolute and normalized metabolism in left postcentral gyrus (BAs 40, 43), left inferior parietal lobule (BAs 39, 40), and left supramarginal gyrus (BA 40). Also, decreased normalized (but not absolute) metabolism was noted in left precentral (BA 6), left middle frontal (BA 9), and left inferior frontal (BA 44) gyri; bilateral lingual gyrus (BA 18), and cuneus (BA 18). In contrast, increased (higher in depressed) normalized (but not absolute) metabolism was seen in right inferior (BAs 45, 46, 47), middle (BAs 8, 9, 10, 46), and superior (BA 9) frontal gyri, bilateral accumbens, and ventral caudate and putamen (Table 3).

Direct comparison of the 17 depressed versus 16 mildly depressed patients and of the of the 16 mildly depressed versus 10 euthymic patients (covarying for age and gender) revealed no global or cerebellar differences but some regional differences (Table 3).

Thus, the metabolic difference patterns obtained from comparing depressed with both euthymic and mildly depressed patients appeared to be attenuated forms of the pattern seen comparing depressed patients with healthy control subjects, in that they included two main components, namely 1) cortical absolute decreases, and 2) paralimbic subcortical normalized increases, but they lacked the cerebellar, posterior cortical, and posterior thalamic normalized increases seen when comparing depressed patients to healthy control subjects.

Severity of Depression Correlation

On the day of the scan, HRSD (mean ± SD 21.5 ± 11.0; n = 30) covarying for age and gender was not significantly correlated with global metabolism but correlated inversely with absolute (but not normalized) metabolism in prefrontal and anterior paralimbic cortical regions, including left inferior (BAs 44, 45) and middle (BA 9) frontal gyri, left temporal pole (BA 22), and left middle temporal gyrus (BA 21), as well as left hippocampus (Figure 4). On the day of the scan, HRSD also correlated inversely with absolute (and to a lesser extent normalized) metabolism in left inferior parietal lobule (BAs 39, 40), bilateral cuneus (BAs 17, 18), fascicular (BAs 19, 20) and lingual (BAs 18, 19) gyri, and right posteromedial cerebellum.
Conversely, degree of depression correlated positively with normalized metabolism in subcortical anterior paralimbic regions, including basal forebrain and ventral caudate and putamen, as well as in subgenual and pregenual anterior cingulate (BAs 24, 32), medial (BAs 10, 11) and right inferior (BAs 45, 46, 47) frontal gyri, and right middle (BAs 20, 21) and inferior (BA 20) temporal gyri. The overall pattern thus largely overlapped the prefrontal and anterior paralimbic cortical absolute decreases and subcortical normalized increases seen in depressed patients compared to control subjects.

**Bipolar I and Bipolar II Subgroups**

The 14 bipolar I patients compared with 14 healthy control subjects did not significantly differ in global metabolism (7.35 ± 0.84 vs. 7.16 ± 1.13; Figure 1) and had increased normalized metabolism in bilateral cerebellum (cerebellum also had increased absolute metabolism), lingual gyrus (BAs 18, 19), and cuneus (BAs 29, 30, 31; Table 2).

The 29 bipolar II patients compared with 29 healthy control subjects tended to have 5.8% lower global metabolism [7.34 ± 1.07 vs. 7.78 ± 0.64, \( t(56) = 1.78, p < .08 \); Figure 1], and had decreased absolute (but not normalized) metabolism in right lateral prefrontal cortex, including superior (BAs 9, 10), middle (BAs 9, 10, 46), and inferior (BAs 44, 45, 46) frontal gyri, as well as right insula and right temporal pole. In contrast, increased normalized (but not absolute) metabolism was noted in left cerebellum (sparse), left lingual gyrus (BAs 18, 19), left cuneus (BAs 29, 30, 31), and bilateral medioposterior thalamus (dorsomedial nucleus, pulvinar; Table 2). This pattern appeared to be an attenuated form of the pattern seen comparing depressed patients to healthy control subjects in that it included two main components, namely 1) anterior paralimbic and prefrontal cortical absolute decreases, and 2) cerebellar, posterior cortical, and posterior thalamic normalized increases.

Direct comparison of the 14 bipolar I with the 29 bipolar II patients (covarying for age and gender) lacked significant differences in global or absolute regional metabolism but showed increased (higher in bipolar I) normalized metabolism in supragenual anterior cingulate (BA 32), right middle frontal gyrus (BA 9), and right inferior parietal lobule (BA 40) in the bipolar I patients (Table 3). Thus, comparison of bipolar I and II subgroups with one another lacked the cerebellar-posterior cortical normalized metabolic increases seen when comparing these patient subgroups to healthy control subjects.

**Table 2. Summary of rCMRglu in Bipolar Subgroups Compared to Healthy Control Subjects**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Cerebellum</th>
<th>Lingual gyrus</th>
<th>Cuneus</th>
<th>Thalamus (DM, Pulv)</th>
<th>Basal ganglia</th>
<th>Temporal lobe</th>
<th>Frontal lobe</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 BPdep</td>
<td>↑ Med; ↓ Lat</td>
<td>↑; ↓ a</td>
<td>—</td>
<td>↑</td>
<td>↑ NA,Cd,Pu</td>
<td>↑ R Am; ↓ Cx</td>
<td>↑ L Cx</td>
<td>↑ L Ins</td>
</tr>
<tr>
<td>16 BpMild</td>
<td>± ↑</td>
<td>↑ ↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑ R IFG</td>
</tr>
<tr>
<td>10 BPeu</td>
<td>↑ ↑ ↑</td>
<td>↑ ↑ ↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑ R IFG</td>
</tr>
<tr>
<td>14 BP1</td>
<td>↑; ↓ a</td>
<td>↑ ↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>29 BP2</td>
<td>± ↑</td>
<td>↑</td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↓ R TP a</td>
<td>↓ R Cx a</td>
</tr>
<tr>
<td>35 Rapid</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8 Nonrapid</td>
<td>—</td>
<td>↓</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑ R Hi</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>43 All BP</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>—</td>
<td>↑ L TP, L Cx</td>
<td>↑ L IFG</td>
</tr>
</tbody>
</table>

All data globally normalized except "absolute. Note that all patient subgroups compared to control subjects have cerebello-posterior cortical normalized increases. DM, dorsomedial nucleus; Pulv, pulvinar; Med, medial; Lat, lateral; BPdep, BpMild, BPeu, bipolar depressed, mildly depressed, euthymic; NA, accumbens; Cd, caudate; Pu, putamen; R, right; L, left; Am, amygdala; Cx, cortex; IPL, inferior parietal lobe; Hi, hippocampus; TTG, transverse temporal gyrus; Ins, insula; IFG, inferior frontal gyrus; TP, temporal pole.

**Table 3. Summary of rCMRglu in Bipolar Subgroups Compared to One Another**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Cerebellum</th>
<th>Lingual gyrus</th>
<th>Cuneus</th>
<th>Thalamus (DM, Pulv)</th>
<th>Basal ganglia</th>
<th>Temporal lobe</th>
<th>Frontal lobe</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 BPdep vs. 10 BPeu</td>
<td>—</td>
<td>↓</td>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>↓</td>
<td>L MI FG, L IFG</td>
<td>↓ L IPL, ↓ L IPL a</td>
</tr>
<tr>
<td>17 BPdep vs. 16 BpMild</td>
<td>—</td>
<td>↓; ↓ a</td>
<td>↓</td>
<td>—</td>
<td>↑</td>
<td>L Cd, L Pu</td>
<td>↓ L Hi, L TP</td>
<td>↑</td>
</tr>
<tr>
<td>16 BPmild vs. 10 BPeu</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14 BP1 vs. 29 BP2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑ R MI FG, AC</td>
</tr>
<tr>
<td>35 Rapid vs. 8 Nonrapid</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>↑ Me FG, AC</td>
</tr>
</tbody>
</table>
Rapid-Cycling and Non–Rapid-Cycling Subgroups

The 35 rapid cycling patients, compared with 35 control subjects, had nonsignificantly (3.6%) lower global metabolism (7.26 ± 0.92 vs. 7.53 ± 1.03; Figure 1) and no differences in absolute but increased normalized (but not absolute) metabolism in bilateral cerebellum, lingular gyrus (BAs 18, 19), cuneus (BAs 29, 30, 31), and medioposterior thalamus (dorsomedial nucleus, pulvinar; Table 2).

The eight non–rapid-cycling patients, compared with eight control subjects, had similar global metabolism (7.70 ± 1.26 vs. 7.78 ± 0.72; Figure 1) and no differences in absolute but increased normalized (but not absolute) metabolism in bilateral cerebellum and right hippocampus (Table 2).

Direct comparison of the 35 rapid cycling and eight non–rapid-cycling patients (covarying for age and gender) revealed no significant global difference but increased (higher in rapid cycling) normalized (but not absolute) metabolism in right greater than left medial frontal gyrus (BAs 8, 9, 10), and supragenual and pregenual anterior cingulate (BAs 24, 32; Table 3). Thus, comparison of rapid and non–rapid-cycling subgroups with one another lacked the cerebello-posterior cortical normalized metabolic increases seen when comparing these patient subgroups to healthy control subjects.

All Patients

The heterogeneous group of all 43 bipolar patients, compared with 43 healthy control subjects, had nonsignificantly (3.2%) lower global metabolism (7.34 ± 0.99 vs. 7.58 ± 0.96; Figure 1) and no significant absolute rCMRglu differences but increased normalized metabolism in bilateral cerebellum, lingular gyrus (BAs 18, 19), cuneus

Figure 4. Correlation between degree of depression and regional cerebral metabolism (rCMRglu). Pearson r maps of the relationship between degree of depression and baseline absolute and normalized regional cerebral metabolism in 30 bipolar disorder patients. Color bar indicates two-tailed p thresholds. This pattern of absolute cortical negative and normalized subcortical positive correlations overlaps that of Figure 2, excluding normalized cerebello-posterior cortical increases, which may be a trait marker. HamD, Hamilton Rating Scale for Depression; L, left.
(BAs 29, 30, 31), and medioposterior thalamus (dorsomedial nucleus, pulvinar), as well as left temporal pole (BA 38), left middle (BA 21) and left inferior (BA 20) temporal gyri, and left inferior frontal gyrus (BAs 45, 46, 47; Table 2). Thus, comparison of all patients to healthy control subjects yielded cerebello-posterior cortical normalized metabolic increases seen with all comparisons of patient subgroups with healthy control subjects, but not with comparisons of patients subgroups with one another.

Discussion

We found that bipolar disorder patients in the depressed phase compared to healthy control subjects (and to a lesser extent compared to mildly depressed or euthymic patients) had decreased global and prefrontal and anterior paralimbic cortical absolute (but not normalized) metabolism, and increased normalized metabolism in subcortical structures, including ventral striatum, thalamus, and right amygdala. This pattern was also evident in bipolar II patients compared to control subjects (Table 2, right) and in the degree of depression correlation but not in other patient subgroup versus control subject (Table 2, right) or patient versus patient subgroup (Table 3, right) comparisons, suggesting some specificity of this pattern to the depressed state.

Euthymic patients compared to control subjects had increased cerebello-posterior cortical (cerebellum, lingual gyrus, cuneus) normalized metabolism, with similar patterns (in some comparisons also involving thalamic increases) present in all patient subgroup versus control subject comparisons (Table 2, left) but not in patient versus patient subgroup comparisons (Table 3, left) or the degree of depression correlation. This is consistent with the notion that such cerebello-posterior cortical relative metabolic increases could represent a trait marker, which might be congenital, or a “scar” acquired over the course of many episodes. Unipolar patients may display this pattern in the depressed but not euthymic state, more consistent with a state marker (Kimbrell et al, unpublished data).

Our finding that global cerebral metabolism in bipolar disorder patients is decreased when depressed, but not when euthymic, is consistent with prior reports. Global cerebral metabolism was decreased in six reports of bipolar depression (Baxter et al 1985, 1989; Cohen et al 1992; Goyer et al 1992; Martinot et al 1990; Schwartz et al 1987), and in four studies (Kishimoto et al 1987; Kumar et al 1993; Raichle et al 1985; Schlegel et al 1989) of unipolar depression. One study reported increased global metabolism in bipolar depressed patients (Buchsbaum et al 1986). Also, global cerebral metabolism in hypomanic or euthymic bipolar patients did not differ from healthy control subjects but was increased compared to bipolar patients in depressed or mixed states (Schwartz et al 1987). In rapid-cycling bipolar patients, global cerebral metabolism (Baxter et al 1985) and blood flow (Speer et al 1997) oscillated as mood state changed. Taken together, these data are consistent with global cerebral metabolism being decreased in bipolar depression and varying across mood states; however, many factors could contribute to such a phenomenon. For example, plasma thyroid stimulating hormone levels may correlate inversely with global cerebral blood flow and metabolism in mood disorder patients (Marangell et al 1997).

The observed decrease in global cerebral metabolism in bipolar depression could confound findings in the normalized analysis, particularly for the subcortical normalized increases, which could merely represent areas that failed to be decreased to the same extent as the global decrease. This is less of a concern for the finding of increased normalized cerebello-posterior cerebral metabolic increases, as these were evident in other subgroup comparisons in which there was no significant global difference between patients and control subjects; however, even in the absence of global differences, increased normalized posterior activity in patients could be related to decreased anterior–posterior gradients.

The metabolic pattern we observed in depressed bipolar disorder patients compared to control subjects (and to a lesser extent compared to mildly depressed or euthymic patients, and in the correlation with degree of depression) of decreased prefrontal and anterior paralimbic cortical absolute metabolism, and increased subcortical (ventral striatum, thalamus, right amygdala) normalized metabolism implicates some of the classic neural substrates hypothesized to be involved in affective modulation in general, and bipolar illness in particular. Dysregulated function of basal ganglia–corticothalamic loops as described by Alexander and colleagues (Alexander et al 1986, 1990) could account for such complementary absolute cortical decreases and relative subcortical increases. Activation of the right amygdala has been associated with affective arousal, with increased activity occurring with both euphoric and dysphoric affects, as opposed to the left amygdala, in which activity tends to increase with sadness or fear and decrease with happiness or euphoria (George et al 1995; Ketter et al 1996a). In bipolar depression, we have thus observed relative activation of anterior paralimbic subcortical regions classically linked to affective modulation (Ketter et al 1996b), such as amygdala, accumbens, and ventral striatum.

We also observed relative activation of bilateral medio-posterior thalamus. This is consistent with altered thalamic relay and gating function with respect to communication between subcortical and cortical regions. We noted increased basal ganglia normalized activity, similar to that seen in obsessive-compulsive disorder (Baxter et al 1987).
a condition often considered more treatment-resistant than depressive disorders; however, decreased normalized basal ganglia and thalamic activity has been reported in some studies of bipolar disorder patients (Baxter et al 1985; Buchsbaum et al 1986, 1997; Cohen et al 1989) Variability in findings could be due to methodological differences, such as normalizing activity to posterior structures (Buchsbaum et al 1986), partial volume effects in view of the small size of these structures compared to cortical regions, the type of task performed during scan acquisition, or the highly treatment-resistant nature of our patient sample.

In contrast, depressed bipolar patients had absolute deactivation of prefrontal and anterior paralimbic cortical regions, including inferior, middle, superior, and medial frontal gyri, anterior and midcingulate, and superior, middle, and transverse temporal gyri. This is consistent with reports of decreased activity in such regions not only in bipolar depression (Baxter et al 1989; Buchsbaum et al 1984, 1986, 1997; Cohen et al 1989, 1992; Drevets et al 1997; Ebert et al 1993; Goyer et al 1992; Ketter et al 1996b; Martinot et al 1990; Post et al 1987; Schwartz et al 1987) but also in many studies of unipolar depression (Austin et al 1992; Baxter et al 1989; Bench et al 1992; Biver et al 1994; Curran et al 1993; Drevets et al 1997; Ebert et al 1991; Edmonstone et al 1994; Hagman et al 1990; Hurwitz et al 1990; Kanaya and Yonekawa 1990; Kimbrell et al, unpublished data; Kishimoto et al 1987; Kuhl et al 1985; Kumar et al 1993; Lesser et al 1994; Mayberg et al 1994; O’Connell et al 1989; Pillay et al 1997 or Yates et al 1987) studies of bipolar, two of four (Escalona et al 1993 but not Coffman et al 1990, Dewan et al 1988 or Yates et al 1987) studies; however, the consistent increases we observed in these normalized posterior increases are not merely secondary to absolute anterior cortical decreases.

The cerebellum, through limbic and brain stem connections, may have a role in mood regulation (Berntson and Torello 1982; Haines et al 1984; Snider and Maiti 1976). Case reports and case series have noted affective symptoms in patients with cerebellar pathology (Cutting 1976; Lauterbach 1996; Schmahmann and Sherman 1998; Starkstein et al 1988; Yadalam et al 1985). Cerebellar electrode implantation and subsequent chronic cerebellar stimulation for neurologic disorders can yield decreased anxiety and improved mood (Riklan et al 1977) and has also been reported helpful in some patients with psychiatric (especially depressive) disorders, although methodologic problems have limited the utility of this approach (Heath et al 1981). Hence, a “cerebellar cognitive affective syndrome” due to disrupted cerebellar modulation of cerebello-parieto-temporo-limbic-prefrontal circuits has been proposed (Schmahmann and Sherman 1998).

In healthy volunteers, resting cerebellar (and brainstem) rCBF correlated with harm-avoidance (George et al 1994), and lateral cerebellar (and occipito-temporo-parietal) CBF increases appeared related to emotional responses to exteroceptive sensory (film) stimuli (Reiman et al 1997).

Cerebellar atrophy has been reported in mood disorders. Thus, in four of seven (DelBello et al 1999, Heath et al 1982, Lippmann et al 1982, and Nasrallah et al 1982 but not Coffman et al 1990, Dewan et al 1988 or Yates et al 1987) studies of bipolar, two of four (Escalona et al 1993 and Shah et al 1992 but not Pillay et al 1997 or Yates et al 1987) studies of unipolar, and one study (Weinberger et al 1982) of mood disorder patients, vermian or cerebellar atrophy tended to occur compared to healthy control subjects. Such changes could confound our functional cerebellar findings; however, such a confound would be expected to yield decreased activity due to the decreased volume, rather than the increased activity which we observed.

Increased cerebellar vermis (and decreased left anterior medial prefrontal) rCBF has been seen in depressed patients with cognitive impairment compared to those without (Dolan et al 1992), whereas decreased cerebellar blood volume was reported in mood disorder patients compared to control subjects (Looer et al 1999). In unipolar depression, venlafaxine response was accompanied by decreases in cerebellar (and occipital and anterior paralimbic) normalized rCBF (Little et al 1997). Manic
compared to euthymic patients had attenuated cognitive task-related rCBF changes in left cerebellum (and right orbitofrontal, right brainstem, and right medial thalamus) (Blumbberg et al 1999).

The practice of normalizing regional data to activity in cerebellum (rather than in hemisphere, slice, or whole brain) in brain imaging studies of mood disorder patients (Amsterdam and Mozley 1992; Bonne et al 1996, 1999; Dubé et al 1993; Jaracz et al 1996; Kanaya and Yonekawa 1990; Kocmur et al 1998; Mozley et al 1996; Vasile et al 1997) may thus need to be reconsidered. If cerebellar activity is increased in mood (and particularly in bipolar) disorder patients compared to healthy control subjects, then this referencing technique could exaggerate the degree of perceived hypofrontality in patients.

Bipolar II compared to bipolar I patients had somewhat greater CMRglu deficits. This could be related to multiple factors, such as bipolar II patients having numerically (but not statistically) higher proportions of subjects who were depressed (13/29 [45%] versus 4/14 [29%]) and rapid cycling (25/29 [86%] vs. 10/14 [71%]), and numerically (but not statistically) higher HRSD, duration, and number of medications failed. In addition, comparisons with control subjects involving the 29 bipolar II patients had greater power than those involving the 14 bipolar I patients, owing to the larger sample size.

The data presented have a number of important limitations. Our sample is a highly treatment-resistant group of predominantly rapid-cycling (81%) bipolar disorder patients who were referred to the NIMH, a tertiary center for clinical research studies, because of resistance to agents generally utilized in the community, including lithium and, more recently, carbamazepine and valproate (Frye et al 2000). As such, the abnormalities outlined could relate primarily to relatively late-stage, treatment-resistant, rapid-cycling bipolar disorder patients, and determination whether these same abnormalities are evident earlier in illness course, in non–treatment-resistant, or in non–rapid-cycling patients requires further investigation. In addition, structural abnormalities in bipolar disorder patients, such as lateral ventricular enlargement and cerebellar atrophy, the use of stereotactic and global normalization, and partial volume effects could have confounded our findings.

Patients and control subjects were engaged in an auditory continuous performance task, which has the asset of occupying both patient and healthy control subjects with a similar set of mental operations, but may distract patients from negative affects or ruminations that are important components of the disorder, or introduce spurious metabolic changes in neural substrates not central to affective modulation or other aspects of cognitive–somatic function in bipolar illness.

Conversely, the data presented in this article have certain strengths. We have studied a relatively substantial number of bipolar disorder patients who have been medication-free for at least 2 weeks and monitored in a highly controlled environment. In contrast to some other reports, we assessed not only normalized but also absolute regional cerebral glucose utilization through the use of arterial cannulation. Depressed, mildly depressed, and euthymic patients were included in the analysis, giving preliminary insights into possible alterations related to both state and trait phenomena in these treatment-resistant bipolar disorder patients.

In summary, in bipolar depression we found widespread anterior (prefrontal and temporal) cortical absolute hypometabolism, consistent with previous observations in primary unipolar and secondary depression, suggesting a relationship to the depressed state, and a common pathway to depressive symptoms independent of illness etiology (primary vs. secondary) and subtype (unipolar vs. bipolar). Moreover, depressed bipolar disorder patients also had increased normalized subcortical (amygdala, accumbens, and ventral striatum) metabolism, consistent with a limbic–cortical dysregulation model of depression. In contrast to the findings related to depression, we also observed normalized cerebello-posterior cortical hypermetabolism in all (including euthymic) patient subgroups compared to control subjects, but not in comparisons of patient subgroups with one another, suggesting a possible trait abnormality for bipolar disorders. In addition, we noted increased thalamic normalized metabolism in several patient versus control subject but no patient versus patient subgroup comparisons, suggesting basal ganglia–thalamic circuit dysfunction as a possible trait abnormality. Thus, depressed state and bipolar disorder trait may be the clinical phenomena with the greatest impact on scan patterns, appearing more robust than the effects of cycling pattern or bipolar subtype. Further studies are required to determine whether these putative state and trait patterns are replicated in bipolar disorder patients with shorter duration and less treatment-resistant illness, and using other behavioral and methodologic paradigms.

Support was received from the Stanley Foundation (TAKe, TAKi, MWW, AD).

References
Alexander GE, DeLong MR, Strick PL (1986): Parallel organi-
zation of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9:357–381.


