Published in final edited form as:

J Psychiatr Res. 2009 January ; 43(3): 181–188. doi:10.1016/j.jpsychires.2008.04.015.

Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder

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Abstract

This study explored whether cerebral metabolic changes seen in treatment resistant and rapid cycling bipolar depression inpatients are also found in an outpatient sample not specifically selected for treatment resistance or rapid cycling. We assessed 15 depressed outpatients with bipolar disorder (six type I and nine type II) who were medication-free for at least 2 weeks and were not predominantly rapid cycling. The average 28-item Hamilton Depression Scale (HAM-D) total score was 33.9. The healthy control group comprised 19 age-matched subjects. All participants received a resting quantitative ¹⁸F-fluoro-deoxyglucose positron emission tomography scan. Data analyses were performed with Statistical Parametric Mapping (SPM5). Analyses revealed that depressed patients exhibited similar global metabolism, but decreased absolute regional metabolism in the left much more than right dorsolateral prefrontal cortex, bilateral (left

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Contributions Dr. Brooks conceived the study, performed the analyses and drafted the manuscript. Dr. Wang collected data and edited the manuscript. Dr. Bonner collected data, assisted with data analyses, and edited the manuscript. Dr. Rosen assisted with data analyses and edited the manuscript. Dr. Hoblyn assisted with the literature search and edited the manuscript. Ms. Hill collected data and assisted with editing the manuscript. Dr. Ketter collected data, contributed to study design, and edited the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Drs. Hoblyn, Rosen, and Bonner declare that they have no conflicts of interest. Ms. Hill declares no conflict of interest. Dr. Brooks is on the speaker's bureau of Eli Lilly and Company, Pfizer and AstraZeneca.

Here is Dr. Wang's full conflict of interest disclosure: Grant/Research Support: Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Eisai Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Novartis Pharmaceuticals Corporation, Repligen Corporation, Shire Pharmaceuticals Group plc., Solvay Pharmaceuticals, Inc., Wyeth Pharmaceuticals, Consultant: Abbott Laboratories, Corcept Therapeutics, Pfizer, Sanofi-Aventis, Lecture Honoraria, Abbott Laboratories, AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Pfizer, Sanofi-Aventis.

Here is Dr. Ketter's complete conflict of interest disclosure: Grant/Research Support: Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eisai Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Novartis Pharmaceuticals Corporation, Pfizer Inc., Repligen Corporation, Shire Pharmaceuticals Group plc., Solvay Pharmaceuticals, Inc., Wyeth Pharmaceuticals, Consultant: Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Cephalon Inc., Corcept Therapeutics, Elan Pharmaceuticals, Inc., Eli Lilly and Company, Forest Laboratories, Inc., GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Jazz Pharmaceuticals, Inc., Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Repligen Corporation, Shire Pharmaceuticals Group plc., Solvay Pharmaceuticals, Inc., UCB Pharmaceuticals, Wyeth Pharmaceuticals. Lecture Honoraria: Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceutica Products, LP, Novartis Pharmaceuticals Corporation, Pfizer Inc., Shire Pharmaceuticals Group plc., Employee (Nzeera Ketter, MD, Spouse): Johnson & Johnson.

Role of funding source

No sponsor had any role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

greater than right) insula, bilateral subgenual prefrontal cortex, anterior cingulate, medial prefrontal cortex, ventral striatum, and right precuneus. No region exhibited absolute hypermetabolism. Moreover, HAM-D scores inversely correlated with absolute global metabolism and regional metabolism in the bilateral medial prefrontal gyrus, postcentral gyrus, and middle temporal gyrus. Analysis of relative cerebral metabolism yielded a similar, but less robust pattern of findings. Our findings confirm prefrontal and anterior paralimbic metabolic decreases in cerebral metabolism outside of inpatients specifically selected for treatment resistant and rapid cycling bipolar disorder. Prefrontal metabolic rates were inversely related to severity of depression. There was no evidence of regional hypermetabolism, perhaps because this phenomenon is less robust or more variable than prefrontal hypometabolism.

Keywords

Bipolar disorder; Bipolar depression; Tomography; Emission-computed depression; Cortex; Prefrontal; Frontal lobes

1. Introduction

Neuroimaging studies of bipolar depression have provided variable results, although decreased activity in the prefrontal cortex of depressed bipolar patients relative to healthy controls appears to be one of the most consistent findings. In particular, the dorsolateral prefrontal cortex (DLPFC) appears to exhibit decreased activity in bipolar and unipolar depression relative to healthy controls (Buchsbbaum et al., 1986; Buchsbbaum et al., 1997; Ketter et al., 2001; Kimbrell et al., 2002; Baxter et al., 1985; 1989). Ketter et al. (2001) found that, relative to control subjects, moderately to severely depressed, unmedicated, treatment resistant, predominantly rapid cycling bipolar disorder inpatients had decreased absolute metabolism in prefrontal (including inferior, middle, and superior frontal gyri) and anterior paralimbic regions. Prefrontal activity decreases often appear bilaterally (Martinot et al., 1990; Ketter et al., 2001; Baxter et al., 1989), though some researchers have reported distinct unilateral changes, in either the left or right hemisphere (Buchsbbaum et al., 1997; Cohen et al., 1989). However, some investigators have failed to detect differences between depressed patients with bipolar disorder and healthy controls (Cohen et al., 1992; Goyer et al., 1992; Tutus et al., 1998).

Though decreased prefrontal metabolism has been more consistently found in bipolar depression, some studies have reported increased prefrontal metabolism. One report noted that in mildly depressed unmedicated predominantly rapid cycling bipolar inpatients with treatment resistance compared to healthy controls relative metabolic activity was increased in left prefrontal cortex, including ventrolateral structures such as the inferior frontal gyrus (Ketter et al., 2001). Increased prefrontal metabolism has also been reported in some studies of unmedicated depressed patients with major depressive disorder imaged in the resting condition (Baxter et al., 1987; Cohen et al., 1992; Drevets et al., 1992; Biver et al., 1994; Ketter and Drevets, 2002; Drevets et al., 2002).

Findings of metabolic changes associated with depression in other regions have been variable, but have implicated anterior paralimbic structures (anterior cingulate, amygdala, insula, and ventral striatum) connected to prefrontal areas and implicated in the neurocircuitry of emotion processing. For example, in depressed patients with bipolar disorder, Drevets et al. (Drevets et al., 1997) reported subgenual prefrontal cortex (SGPFC) hypometabolism. Subsequent work suggested an inverse correlation between SGPFC metabolism and the number of depressive episodes among patients with unipolar depression,

in that increasing numbers of episodes were associated with decreasing metabolism (Kimbrell et al., 2002).

Unfortunately, the findings of previous cerebral metabolic studies cannot be readily generalized to common clinical populations. For example, previous studies have usually relied on specific subpopulations of bipolar disorder, which may have lead to findings that are unique to such groups. It is vital to understand cerebral metabolic changes in more typical outpatient populations that are not specifically selected for rapid cycling or treatment resistance. Thus, although our patients were referred to a tertiary care center, they were not selected based on having characteristics of specific bipolar disorder subgroups. We assessed cerebral metabolism in such patients while they were medication free using quantitative resting positron emission tomography with ^{18}F Fluorodeoxyglucose (FDG-PET) scans.

2. Methods

2.1. Participants

The Stanford University Administrative Panel on Human Subjects approved this study; all participants provided verbal and written informed consent prior to enrollment.

The 15 outpatients with bipolar disorder were recruited from the Stanford Bipolar Disorders Clinic. To be eligible for inclusion, patients had to exhibit clinically significant depressive symptoms at the time of testing (as evaluated through a semi-structured interview with a psychiatrist) and meet DSM-IV criteria for Bipolar Disorder Type I or II, current episode depressed. At the times of the PET scans all patients were free of psychiatric medications for at least 2 weeks. Patients were allowed to take other non-psychiatric medications, as long as they were allowed by the exclusion criteria. Demographic information for the group of patients with bipolar disorder is provided in Table 1.

The 19 participants in the healthy control group were volunteers recruited from the community through newspaper advertisements and flyers. The control participants were eligible for inclusion if they did not meet criteria for any psychiatric or substance abuse disorder as determined through a semi-structured interview with a psychiatrist. In addition, first-degree relatives of the healthy controls did not meet have any history of psychiatric or substance use disorders. Demographic information for healthy controls is provided in Table 1.

Both patients with bipolar disorder and healthy controls were excluded from the study if they had or received any of the following: seizure disorder; progressive neurological and/or systemic disorder; any implanted metal; significant unstable concurrent medical illness (history of hypo- or hyperthyroidism was permissible if treated and participant had normal blood thyroid stimulating hormone concentration); administration of concomitant medication treatment that could alter mood or cerebral metabolism (e.g., benzodiazepines, antidepressants, mood stabilizers, antipsychotics, stimulants, steroids); hormone replacement therapy; electroconvulsive or light therapy; administration of any investigational drug within 30 days prior to screening; alcohol abuse within the 2 weeks prior to screening; drug abuse less than 6 months prior to screening or a significant past history of substance abuse/dependence; any major Axis I disorder (except for bipolar disorder for the patient group); pregnancy (as determined by a urine pregnancy test) or breastfeeding; incapacity to consent to study procedures.

2.2. Materials

The 28-item Hamilton Rating Scale for Depression (HAM28-D) (Zitman et al., 1990; Rosenthal and Heffeman, 1986), which better reflects reversed vegetative features (e.g.

hypersomnia and hyperphagia) common in bipolar depression than the 17-item version, and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were administered on the day of the PET scan by two of the authors (TK and PW). In Table 1 we include the 17-item Hamilton score for the purpose of cross-study comparison.

2.3. PET acquisition

PET scans were acquired on a Siemens Exact 921 scanner, which obtains 69 tomographic slices with an in-plane full-width half-maximum resolution of 7 mm, and an axial resolution (slice thickness) of 5 mm at the center of the gantry. Subjects were scanned after fasting at least 4 h to increase FDG uptake by the brain and reduce intrascan blood glucose variability. Intrascan head movement was restricted by use of foam headrests and light restraints placed upon the chin and forehead. Subjects' eyes were covered, and the PET gantry was aligned to the canthomeatal line. A ^{68}Ga rotating pin source was used to obtain a 20-minute transmission scan to correct for photon attenuation of emission data. Three mCi FDG was injected intravenously after subjects were instructed to relax and to avoid any active mental processes, aside from passively attending to their current emotional and sensory experiences during the 30-min FDG uptake period. Emission data were obtained for 30 min following uptake.

Intravenous catheters were placed for tracer administration and radial arterial catheters were placed for arterial blood sampling that occurred every 20 s for the first 5 min, every minute for the next 10 min, and every 15 min for the remaining 45 min. Conversion of image pixel values from nanocuries per cubic centimeter to milligrams of glucose per hundred grams of tissue was performed using procedures previously described by Kumar et al. (Kumar et al., 1992).

2.4. Data analysis

Image processing was performed using Statistical Parametric Mapping (SPM5) software (Medical Research Council, London, UK). All images were stereotactically normalized to the Montreal Neurological Institute template provided with SPM5 with an isotropic voxel size of $2 \times 2 \times 2$ mm. After normalization, images were smoothed with a 12 mm Gaussian kernel.

We compared absolute global and regional cerebral metabolism in depressed bipolar disorder patients and healthy controls. For our analyses of regional absolute cerebral metabolic data, no adjustment was made for global metabolic activity, but intra-group variability was controlled through analysis of covariance. In order to decrease interindividual variability related to differences in global metabolism (which could limit statistical power), and to provide data comparable to those of other studies that did not assess absolute metabolism, we also assessed relative (globally normalized) cerebral metabolism. For our analyses of regional relative cerebral metabolic data, an adjustment was made for global metabolic activity, and intra-group variability was controlled through analysis of covariance.

We used SPM5 (www.fil.ion.ucl.ac.uk/spm/) to compare bipolar patients and healthy controls using two-sample *t*-tests. The threshold for grey matter was set to at least 80% of each subject's average whole brain activity. Initial probability levels were set at $p < .005$ (uncorrected) and a corresponding *t* threshold of 3.65. Cluster thresholds were set at 200 voxels (1600 mm^3). For correlational analyses with the HAM28-D, we used a probability level of $p < .01$ (corresponding to a *t* threshold of 2.65). Cluster thresholds were set at 200 voxels. For presentation purposes, Montreal Neurological Institute (MNI) coordinates

reported by SPM5 were converted to Talairach space with the Talairach demon provided with Wake Forest University PickAtlas (www.fmri.sfu.bc.ca).

3. Results

3.1. Cerebral metabolic differences

Analysis of global cerebral metabolism revealed that depressed bipolar disorder patients exhibited a mean metabolic rate of 5.16 mg/hg/min and control subjects a mean rate of 5.38 mg/hg/min. These rates were not significantly different ($p > .05$).

Analyses of absolute regional cerebral metabolic rates revealed areas of decreased metabolism in patients with bipolar disorder compared to healthy controls. Fig. 1 illustrates that bipolar patients exhibited decreased regional absolute metabolism in: left much more than right DLPFC (BA 46) (Fig. 1 – left); left greater than right insula, bilateral ventral striatum and prefrontal cortices (BA 10/11) (Fig. 1 – middle); anterior cingulate (BA 24/32), prefrontal (BA 10/11) and subgenual prefrontal cortex (BA 25) (Fig. 1 – right); and right precuneus (not illustrated) (all $p < .005$). Talairach coordinates of statistically significant clusters in Fig. 1 are provided in Table 2.

The analyses of absolute data did not reveal any areas of hypermetabolism in bipolar patients compared to healthy controls at the $p < .01$ level.

Analysis of relative cerebral metabolism yielded a similar, but less robust pattern of findings.

3.2. Relations with severity of depression

To evaluate the relation between the hypometabolism observed in bipolar depression and the degree of depression, we assessed the correlation between global and absolute and relative regional metabolic rates and HAM-D total scores among the bipolar patients. Global metabolic rates in the depressed patients were inversely related to scores on the HAM-D, $r = -.62$, $p < .05$, as shown in Fig. 2.

The absolute regional analysis, illustrated in Fig. 3, revealed statistically significant correlations between HAM-D scores and decreased metabolism in the bilateral middle frontal gyrus (BA 9), postcentral gyrus (BA 3), the paracentral lobule, the middle temporal gyrus (BA 20), and the fusiform gyrus (BA 20), $p < .01$. Coordinates of statistically significant clusters are provided in Table 3. There were no statistically significant associations between increased absolute regional metabolism and HAM-D scores. Analysis of relative cerebral metabolism yielded a similar, but less robust pattern of findings.

3.3. Subtype analyses

We performed SPM analyses to check for differences between patients diagnosed with Bipolar Disorder Type I and II and did not find any statistically significant differences at the .005 level. However, our sample sizes in the two groups (six and nine, respectively) likely did not afford sufficient power to detect a difference should one exist. Consequently, based on our data we are not able to draw conclusions regarding differences in bipolar depression across these subtypes.

4. Discussion

Our findings demonstrate that prefrontal, anterior paralimbic, and ventral striatal hypometabolism is present in bipolar depression. This network of structures has been consistently implicated in contributing to affective processing in health and having

dysfunction in patients with mood disorders. This study demonstrates cerebral metabolic changes in a sample of bipolar disorder outpatients that more closely resembles those seen in clinical practice as opposed to inpatients with rapid cycling having only more treatment-resistant forms of the disorder. In Ketter et al.'s (2001) study, participants were treatment-resistant and predominantly (81%) rapid cycling inpatients, and thus may have exhibited changes some of which were unique to such a population. Although some findings may be confined to treatment resistant and/or rapid cycling inpatient populations, our findings indicate that hypometabolism in the DLPFC (BA 9, 10, 46) that extended into the inferior (BA 44), middle (BA 10), and superior aspects of the prefrontal cortex apply in a sample of outpatients not specifically selected for rapid cycling or treatment resistance.

Our study provides evidence of an association between bipolar depression and absolute hypometabolism extended into the prefrontal cortex (BA 10/11), anterior cingulate cortex (BA 24/32), and the SGPFC (BA 25). Our findings regarding the SGPFC replicate those of Drevets et al. (Drevets et al., 1997), who also reported decreased SGPFC metabolism in depressed bipolar patients relative to healthy controls. In the present study, the difference in metabolic rates between bipolar depressed patients and controls was more robust than that reported by Drevets et al., perhaps because of increased statistical power related to larger sample size or more severe depression in our sample.

Ketter et al. (2001) reported that in their full sample of bipolar patients with a wide range of severity of depression, regions with inverse correlations between HAM-D scores and absolute metabolism that overlapped the middle frontal gyrus finding noted in the current study, but were more widespread. They also found direct correlations between HAM-D scores and relative metabolism in subcortical structures that were not seen in the current study. The more extensive correlational findings in Ketter et al.'s study could be related to their larger sample size and a greater range of severity of depression. However, it is also possible that the differences between our findings and those of Ketter et al. could reflect either pathological or compensatory changes associated with a more chronic, treatment-resistant course. Again, in view of our preliminary data regarding this issue, an adequately powered study comparing these distinct subgroups of bipolar disorder patients is needed to address these differences.

The present study partially replicated the findings of Kimbrell et al. (2002), who obtained FDG-PET scans from a sample of inpatients and outpatients diagnosed with varying degrees of severity of unipolar depression. A subsample of their more depressed (HAM-D ≥ 22) unipolar patients compared to healthy controls had decreased absolute metabolism in right DLPFC and bilateral medial prefrontal cortex and anterior paralimbic areas (around and encompassing the amygdala), bilateral temporal lobes (right more so than left) following the Sylvian fissure, and the insula.

Previous work employed various imaging conditions, subject populations, and provided variable results. We provide a tabular summary of previous cerebral metabolic studies of bipolar depression in Table 4. Most (Baxter et al., 1985, 1989; Buchsbaum et al., 1986, 1997; Martinot et al., 1990), but not all (Tutus et al., 1998), studies have demonstrated decreased prefrontal metabolism in bipolar depression. Of note however, Tutus et al. (1998) employed a different radiotracer (^{99m}Tc -HMPAO) than used in all the remaining studies (FDG), which may have contributed to their failure to detect prefrontal hypometabolism. We did not find evidence of relative hypermetabolism in the left amygdala as reported in some (Drevets, 1999; Drevets et al., 2002, 1992) but not all (Abercrombie et al., 1998) prior studies of unipolar major depressive disorder. Ketter et al. found relative but not absolute increases in amygdala metabolism in treatment-resistant primarily rapid-cycling bipolar inpatients. It is possible that our sample size did not afford sufficient power to detect differences in

amygdala metabolism, but our sample size was twice that of one study that reported increased amygdala metabolism (Drevets et al., 2002) and less than that of another (Siegle et al., 2006). Perhaps hypermetabolism in the amygdala is more common in unipolar depression than in bipolar depression or not as robust a finding as prefrontal hypometabolism.

In addition to the above-mentioned metabolic changes in structures implicated in affective processing, we also found absolute hypometabolism in the right precuneus. Appreciation of the functions of this region of association cortex is only beginning to emerge, but its high resting metabolic rate that decreases during non-self-referential goal-directed actions suggests it may contribute to self-consciousness, and self-related mental representations during rest (Cavanna and Trimble, 2006). Thus, dysfunction in this region could be related to negativistic distortions of self that are observed in depressed bipolar disorder patients.

4.1. Limitations

There are some factors that limit the generalizability of our findings. Resting FDG-PET is advantageous because it is unlikely to perturb cerebral metabolism as would task performance. However, resting scans have the drawback that subjects may engage in variable mental activities while resting. Though our sample size is larger than some prior imaging studies of depression, it is possible that it was not sufficiently large to enable us to detect more subtle regional differences. Similarly, the extent of some of the regions of differential metabolism might differ somewhat with a larger sample.

4.2. Conclusions

The present study provides additional evidence of decreased cerebral metabolism in bipolar depression in the bilateral DLPFC, with the left side exhibiting a greater decrease relative to control subjects than the right. Moreover, we found that hypometabolism in bipolar depression extended to the bilateral insula, prefrontal cortices, anterior cingulate, and subgenual prefrontal cortex, and had regional correlations with degree of depression. In contrast, we failed to detect subcortical anterior paralimbic relative metabolic increases seen in some other studies. The absence of the latter finding could be related to sample size limitations in our study or differences in clinical features across studies. The patients in our sample were medication-free for at least 2 weeks, which lessens the possibility that our findings reflect treatment effects. Because our sample had a more varied composition than previous ones, our findings are not restricted to particular subpopulations of bipolar disorder. In summary, our data support the hypothesis that decreased prefrontal hypometabolism is a crucial and relatively robust finding in bipolar depression that is evident across different clinical samples, and even in samples such as the current study that include outpatients not specifically selected for treatment resistance or rapid cycling.

Acknowledgments

This research was supported in part by the Stanley Foundation Research Awards Program (T.A.K., P.W.W.), the National Alliance for Research in Schizophrenia And Depression (T.A.K., P.W.W., S.J.H.), Abbott Laboratories (T.A.K., P.W.W., S.J.H.), the National Institutes of Health (J.C.B., AR, T.A.K.), the Medical Research Service of the Veterans Affairs Palo Alto Health Care System (J.O.B., AR), and by the Department of Veterans Affairs Sierra-Pacific Mental Illness Research, Education, and Clinical Center (J.O.B., AR).

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Fig. 1. Rendered depictions showing decreased absolute metabolism (in blue) in bipolar patients relative to healthy controls ($p < .005$) in (A) left DLPFC, (B) left more than right insula and bilateral ventral striatum and prefrontal cortex, (C) anterior cingulate (BA 24/32), prefrontal (10/11), and subgenual prefrontal (BA 25) cortices.

Fig. 2.
Relation between global cerebral metabolic rates and scores on the HAM-D in depressed bipolar patients. $r = -.62$, $p < .05$.

Fig. 3. Anterior cut-out image showing in green the regions in bilateral middle prefrontal gyrus in which absolute metabolism inversely correlated (lower metabolism was associated with higher depression ratings) with HAM-D scores, $p < .01$.

Table 1

Demographic and clinical variables

	Depressed bipolar <i>n</i> = 15	Healthy control <i>n</i> = 19
Age (years)	36.1 (10.4; 19–53)	34.0 (13.3; 21–65)
Male/Female (N)	7/8	12/7
Proportion Type I	0.4	–
Proportion Type II	0.6	–
Proportion rapid cycling	0.33	–
YMRS (mean ± SD)	4.1 (3.4)	0.1 (0.5)
HAM-D ₁₇ (mean ± SD)	22.1 (7.7)	0.5 (0.8)
HAM-D ₂₈ (mean ± SD)	33.8 (8.7)	0.8 (1.0)

Note: Standard deviations and ranges are in parentheses. HAM-D₁₇, 17-item Hamilton Rating Scale for Depression. HAM-D₂₈, 28-item Hamilton Rating Scale for Depression. YMRS, Young Mania Rating Scale.

Table 2

Coordinates for regions of statistically significant absolute hypometabolism in depressed patients relative to healthy controls

Region	Brodmann's Area	Hemisphere	Talairach coordinates			Cluster size	<i>t</i>
			<i>x</i>	<i>y</i>	<i>z</i>		
Middle frontal gyrus, SGPFC	10, 11, 24, 25,	Bilateral	40	40	15	9,901	6.62
Anterior cingulate	32, 46						
Middle temporal gyrus, insula	13	Left	-54	-16	-6	*	6.05
Insula	NA	Left	-34	-15	-6	*	5.65
Precuneus	7	Right	10	-76	42	247	5.55

Note: $p < .005$.

* contiguous with preceding cluster. NA, not applicable.

Table 3

Coordinates for statistically significant correlations between HAM28-D and decreased absolute cerebral metabolism

Region	Brodmann's Area	Hemisphere	Talairach coordinates			Cluster size	<i>t</i>
			<i>x</i>	<i>y</i>	<i>z</i>		
Middle frontal gyrus	9	Right	28	0	42	498	4.31
Middle frontal gyrus	9	Left	-35	4	40	352	3.51
Post-central gyrus	3	Bilateral	12	-38	68	912	3.23
Paracentral lobule	NA	Right	16	-32	57	*	3.07
Middle temporal gyrus	20	Right	40	0	-34	*	2.98
Fusiform gyrus	20	Right	42	-15	-24	*	2.90

Note: All $p < .01$.

* contiguous with preceding cluster. NA, not applicable.

Table 4

Summary of cerebral metabolic studies of bipolar depression

Author	Sample composition	Type I/II	Radiotracer	Medication state	Scanning task	Rapid-cycling/Treatment resistant
<i>Prefrontal hypometabolism</i>						
Baxter et al. (1985)	5 BDd, 3 BDm, 9 Cntl	ns	FDG	Assorted medications	Resting	3/Unknown
Baxter et al. (1989)	10 BDd, 12 Cntl	10/0	FDG	No medications ≥ 1 week	Resting	Unknown
Buchsbaum et al. (1997)	9 BDd, 36 UDd, 20 Cntl	ns	FDG	No medications ≥ 2 weeks	Resting	Unknown
Ketter et al. (2001)	17 BDd, 43 Cntl	14/29	FDG	No medications ≥ 2 weeks	Resting	14/17
Martinot et al. (1990)	7BDd, 3UDd	ns	FDG	Assorted medications	Resting	Unknown
<i>No change in prefrontal metabolism</i>						
Tutus et al. (1998)	7 BDd, 9 Cntl	ns	^{99m} Tc-HMPAO	No medications ≥ 1 week	Resting	Unknown
<i>Amygdala hypermetabolism</i>						
Drevets et al. (2002)	7 BDd, 12 UDd, 12 Cntl	ns	FDG	No medications ≥ 3 weeks	Resting	Unknown
Ketter et al. (2001)	17 BDd, 43 Cntl	14/29	FDG	No medications ≥ 2 weeks	Resting	14/17

Note: BDd, bipolar, depressed episode; BDm, bipolar, mixed episode; UDd, unipolar depressed; Cntl, control. Ns, not specified. ^{99m}Tc-HMPAO, Technetium-99m-hexamethyl propylene amine oxime. No studies have reported prefrontal metabolic increases.