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ORIGINAL PAPER

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Changes in regional cerebral blood flow demonstrated by ^{99m}Tc-HMPAO SPECT in euthymic bipolar patients

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Abstract Single photon emission computed tomography (SPECT) with ^{99m}Tc-HMPAO was used to compare regional cerebral blood flow (rCBF) in patients with bipolar disorder and in healthy controls. The sample of this study consisted of 16 euthymic bipolar patients who met the DSM-IV criteria and 10 healthy control subjects. The mean regional cerebral blood flow values of the bipolar euthymic patients were significantly lower than those of the controls in the bilateral medial-basal temporal, occipital; medial frontal; parietal regions and in the cingulate gyrus; the hypoperfusion in the cingulate had the highest significant *P* value (.001, Bonferroni correction). No significant differences in rCBF emerged between right and left-brain regions. The most important findings of the current study are the presence of regional cerebral perfusion alterations, particularly in the cingulate gyrus in the euthymic bipolar patients. Our results imply that underlying brain dysfunction may be independent from manic or depressive episodes in bipolar disorder. Because of the small number of subjects, however, this finding should be viewed as preliminary.

Key words brain imaging · cerebral perfusion · cingulate gyrus · euthymic bipolar disorder

Introduction

Bipolar disorder appears to be one of the most important and common psychiatric illness. However, the specific neurophysiologic basis of this disorder is still unknown. One of the leading hypotheses concerning the pathophysiology of bipolar disorder suggests that a limbic/paralimbic, including a temporal lobe abnormality that has been implicated in the modulation of mood, affect and behavioral facilitation may underlie the disease [1]. Some studies have suggested that the pathophysiology of bipolar disorder may be related to abnormalities in the frontal lobe, subcortical structures and limbic system. These structures include the neuroanatomic circuits that are involved in mood regulation [2–4].

Researchers have recently reached the potential to examine specific brain regions of interest in bipolar disorder by using the new generation of brain imaging technology. This new technology allows them to understand the pathophysiological mechanism, which produces the affective symptomatology. Single photon emission computed tomography (SPECT), which is one of the neuro-imaging techniques, appears to be a suitable method to examine the direct in vivo characterization of cerebral abnormalities by identifying abnormal patterns of regional cerebral blood flow (rCBF) [5, 6].

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Table 1 Demographic and clinical characteristics

Variables	Patients group (n = 16)	Control group (n = 10)	Statistics significantly
Demographic characteristics			
Gender (female/male)	10/6	6/4	$x^2 = 0.16$, $P > 0.05$
Age (years)	31.93 ± 8.79	34.00 ± 8.86	$z = -0.741$, $P > 0.05$*
Education (years)	10.00 ± 4.17	10.20 ± 4.73	$z = -0.111$, $P > 0.05$*
Clinical characteristics			
Age of onset (years)	23.18 ± 6.02		
Length of illness (years)	9.18 ± 6.94		
Total episode number	5.12 ± 5.08		
manic/depressive episodes	3.93 ± 4.38/0.75 ± 1.18		
GAF	70.62 ± 5.71		
HRSD−17	1.56 ± 1.20		
BRMAS	1.37 ± 1.66		

GAF: Global Assessment Functioning, HRSD-17: Hamilton Rating Scale for Depression, BRMAS: Bech- Rafaelsen Mania Scale
* Mann Whitney U test

Previous studies have demonstrated that bipolar patients show distinct alterations of CBF during the different states of their disease [7–9]. For example, a number of studies have described decreased perfusion in the cerebral region in depressed bipolar patients, whereas others have found increased cerebral blood flow during mania [3, 4, 7, 8]. State-related confounds are avoided in euthymic bipolar patients and the abnormalities observed in the euthymic state seem to reflect the dysfunctional neurophysiology of bipolar disorder. However, we have limited information about bipolar patients' cerebral perfusion, especially during their euthymic state [9], even though euthymic bipolar patients are usually better functioning than acute stage bipolar patients. To address this question, we used Tc-99m HMPAO single photon emission computed tomography to compare regional cerebral blood flow in euthymic bipolar patients and in the healthy control group. We have strictly defined the euthymic state, in order to avoid state-related alterations, and our expectations are that the abnormalities uncovered in the euthymic state are more likely to reflect the underlying diathesis in bipolar disorder pathophysiology.

Materials and methods

Subjects and clinical evaluations

A total of 16 euthymic patients (10 female, 6 male) in this study were diagnosed with bipolar disorder according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria [10]. These subjects were recruited from a patient sample routinely followed at the Mood Disorder Clinic of the Department of Psychiatry in Pamukkale University Hospital [11]. The healthy controls were 10 subjects (6 female, 4 male) chosen among the hospital staff working in clinical and administrative areas. All of the controls were physically healthy and free of all medication. Mental health was ascertained by clinical interview. All control subjects were free of psychopathology as were all their first-degree relatives. Subjects with bipolar disorder were observed in the outpatient setting for 2 months to ensure euthymia before the experimental procedures were administered. All patients who met the inclusion criteria and gave consent were enrolled into the study. Subjects were included in the study if they: (1) met the diagnostic criteria for DSM IV bipolar disorder euthymic phase; (euthymia was defined as having a Hamilton Depression Scale score below 7 and a Bech-Rafaelsen Mania Scale score below 6 for two consecutive monthly assessments) [12, 13]; (2) had not received ECT within the last year; (3) showed no systemic or neurological illnesses; (4) had no present alcohol or drug abuse or history. All the subjects were right-handed, according to the Turkish version of the Edinburgh Handedness Inventory [14]. Co-morbid psychiatric disorders (i.e. anxiety or substance abuse) were not present in the patient group at the time of testing, as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders [10]. Psychological functioning was assessed according to DSM-IV GAF (Global Assessment of Functioning) scale with 0–100 scores.

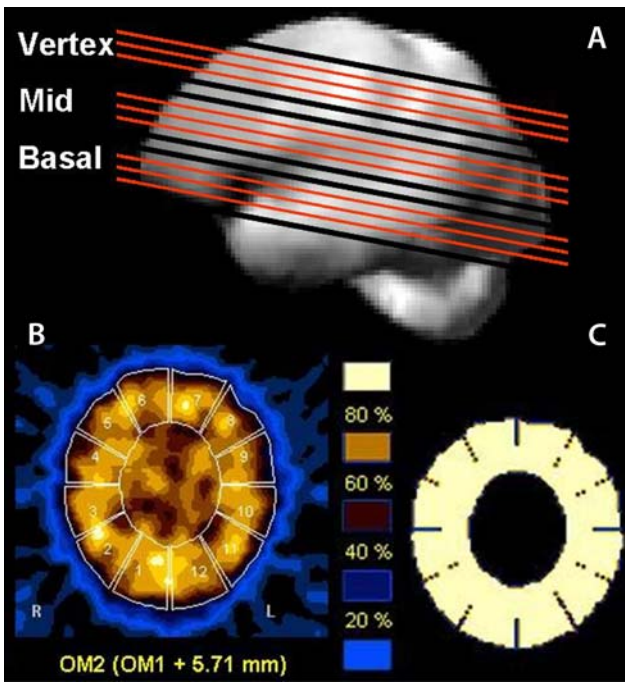

Fig. 1 (**a**) Twelve sequential transverse slices (thickness: 5.71 mm) of aligned parallel to the orbitomeatal line (OM) and (**b**) 12 ROIs placed on each brain slice from base to vertex. (**c**) The graphic image showing rCBF % which was obtained by using the cerebellar ratio method

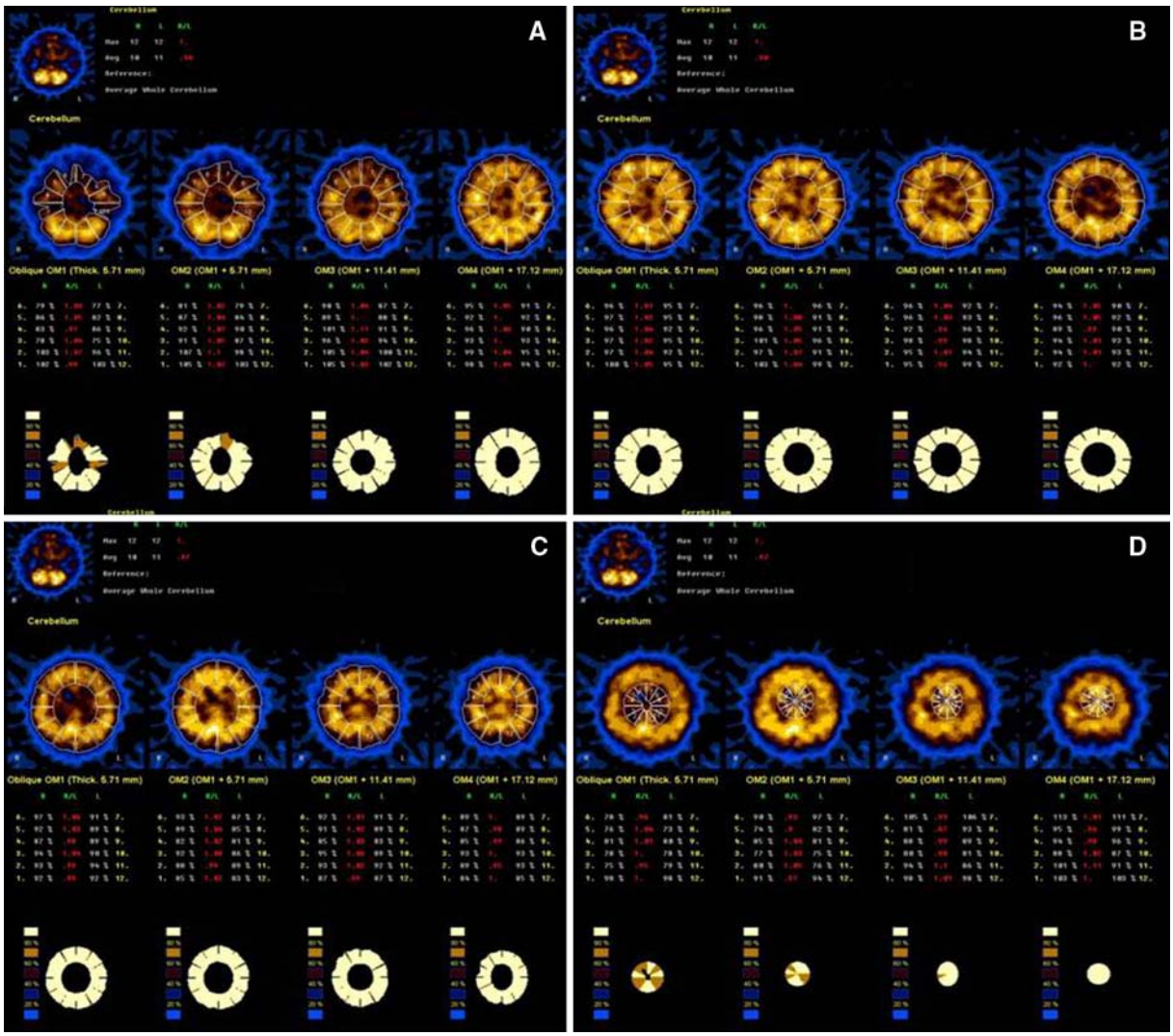

Fig. 2 Segmental analysis for regions of basal level (**a**), mid level (**b**), vertex (**c**) and cingulate gyrus (**d**) in the control case. In the image of each level, it is being seen cerebellar slice and it's ROIs localisation (left top), 12 ROIs placed on brain cortical slices (upper line), numerical value as percentage of the ratio of brain region to cerebellum and R/L ratio (middle line), and demonstration in colour scale of semiquantitative analysis (bottom line). Colour scale of graphic image has been divided to five sections in the level of 20%. Brilliant yellow shows that the rCBF of cerebral segment is in 80–100% of cerebellar rCBF. Other colors show hypoperfuse regions

All of the patients were receiving pharmacological treatment at the time of the study. Medications included mood stabilizers (lithium [n:8], valproate [n:6]) and combination with mood stabilizers and atypical antipsychotics (lithium + olanzapine [n:1], valproate + risperidone [n:1]). About 10 patients had a history of previous antipsychotic use, while 6 patients had no such history. About 7 of the 16 patients had a family history of mood disorders in a first-degree relative. Additional clinical information such as age of onset, length of illness and number of episodes were also recorded (Table 1).

The study protocol was approved by the Local Ethical Committee of the Medical Faculty of Pamukkale University, and was conducted in accordance with the Declaration of Helsinki (1996) [15]. All subjects gave written informed consent to participate.

Brain perfusion SPECT imaging and semiquantitative analysis

Because of the sensitivity of brain perfusion SPECT in detecting rCBF changes coupled with neuronal activity, sensorial and cognitive stimuli must be kept at a minimum level during tracer injection and uptake. Visual or auditory stimuli changes blood flow especially to the frontal, occipital and temporal regions, and results in change of radiotracer uptake in the brain tissue [16, 17]. Therefore, all subjects had been taken a rest in the supine position with closed eyes within a silent and darkened room approximately 20 min before radiopharmaceutical injection. ^{99m}Tc-HMPAO was prepared according to the manufacturer's instructions. A total of 555 MBq of ^{99m}Tc-HMPAO was injected through IV canula inserted into vena brachialis of the patient. The Brain SPECT study was performed 30 min after injection [18]. A single-head 360° rotating CamStar AC/T gamma camera (GE, Milwaukee, Wisc., USA) equipped with a LEAP collimator and GenieAcq acquisition module was used for SPECT acquisition. Each patient's head was fixed in a plastic head holder apparatus to minimize motion artefact during acquisition. Data were obtained in 128 × 128 matrix, 1.6 zoom and at 3° intervals for 20 s/frame. A GE Entegra Process Unit was used in the postacquisition processing procedure. A Butterworth filter (0.5:10) was used for the reconstruction of the SPECT data and then OSEM processing was applied 10 times in segmental analysis. Attenuation correction was not applied. Segmental analysis was performed on the sequential transvers slices (slice thickness = 5.71 mm) of 12 aligned regions parallel to the orbitomeatal line (OM). Each slice was divided

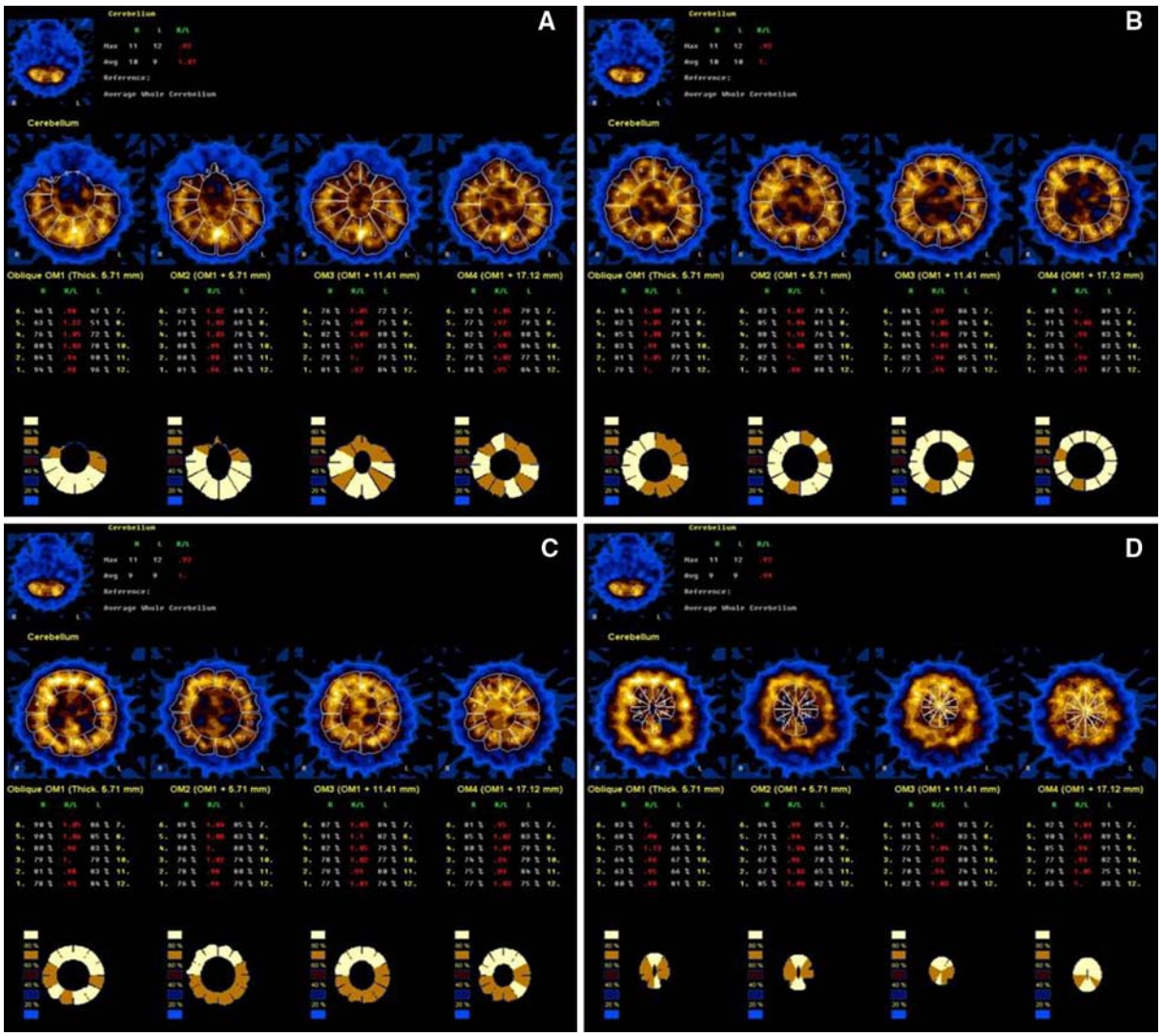

Fig. 3 Segmental analysis of the regions of basal (**a**), mid (**b**), vertex (**c**) and cyngulate gyrus (**d**) in the euthymic bipolar patient. The regional cerebral blood flow decreased in following regions: (**a**) Bilateral gyrus temporalis superior, left gyrus temporalis medialis, bilateral gyrus temporalis inferior, left gyrus frontalis superior and left gyrus frontalis medialis in basal brain slices; (**b**) Left gyrus frontalis superior, medialis and inferior, bilateral gyrus temporalis superior, bilateral gyrus temporalis inferior and gyrus occipitalis in medial brain slices; (**c**) Bilateral precentral gyrus, postcentral gyrus, lobus parietali, gyrus temporalis superior, gyrus temporalis inferior, gyrus occipitalis and additionally cuneus in superior (vertex) slices; (**d**) The rCBF of gyrus cinguli almost equals to the rCBF of cerebellum

into a total of 12 (as 6 right and 6 left) regions of interest (ROI) (Fig. 1). Cerebral segments were defined based on the neuroanatomic cross sections illustrated in an atlas depicting the relevant slice levels [19]. The mean regional cerebral blood flow (rCBF) was determined by using the cerebellar ratio method. Cerebellum ROIs did not include vermis, they, only covered the hemispheres. An average count in each of the cerebellar hemisphere ROIs was used for calculating the ratio of each cerebral segment located in the basal, medial and vertex levels of brain to cerebellum (Fig. 2).

Statistical analysis

Descriptive statistics for continuous variables including mean ± SD, number and percentage for categorical variables were computed. The difference between the means of continuous variables in the two groups was compared using the Independent Samples *t*-test where the data fulfilled the assumptions of this test. Where the data did not, they were compared using the Mann Whitney U test. Significance was set at 5% ($P < .05$). *P* values were also adjusted by the Bonferroni correction when a large number of comparisons were made.

To examine possible group differences in laterality we computed the ratio between the regional blood flow values of the left and right side regions, respectively for each patient and control, and thus we obtained a single left/right ratio value for each region and each participant. The differences between the groups regarding left/right ratio values were compared by Mann Whitney U test. The Spearman Correlation Coefficient was used to examine the relationship between the continuous variables. The statistical analysis was performed with the statistical package program SPSS (version 13.0) for Windows.

Results

The socio-demographic and clinical variables and the psychometric scores of the subjects are presented in Table 1. There were no significant differences in demographic variables of age, gender composition

Table 2 Comparison of regional ^{99m}Tc- HMPAO uptake ratios, in euthymic patients and normal controls (mean ± standard error)

Slice	Region	Right hemisphere Euthymic patients (*n*:16)	Controls (*n*:10)	Test statistic	*P*	Left hemisphere Euthymic patients (*n*:16)	Controls (*n*:10)	Test statistic	*P*
Vertex	Temporal medial	0.84 ± 0.24	0.96 ± 6.90	−1.74[a]	0.82	0.81 ± 0.23	0.95 ± 7.2	−2.26[a]	0.2
	Temporal inferior	0.82 ± 0.24	0.75 ± 0.40	−1.03[a]	0.30	0.82 ± 0.24	0.77 ± 0.40	−0.87[a]	0.3
	Occipital	0.82 ± 0.23	0.93 ± 6.53	−1.79[a]	0.73	1.39 ± 2.29	0.94 ± 6.00	−1.58[a]	0.1
	Frontal superior	0.90 ± 0.10	0.97 ± 7.22	1.92	0.06	0.88 ± 0.11	0.95 ± 7.40	1.67	0.1
	Frontal medial	0.89 ± 0.10	0.95 ± 6.40	1.64	0.11	0.86 ± 0.10	0.92 ± 6.70	1.67	0.1
	Presentral	0.86 ± 7.50	0.93 ± 6.30	1.95	0.06	0.84 ± 1.15	0.90 ± 6.30	1.77	0.08
	Postsentral	0.87 ± 0.10	0.95 ± 7.50	2.05	0.50	0.85 ± 0.10	0.94 ± 7.70	2.28	0.03*
	Parietal	0.85 ± 0.10	0.94 ± 5.00	2.75	0.01*	0.85 ± 0.11	0.94 ± 6.70	2.32	0.02*
Medial	Temporal superior	0.91 ± 0.10	1.03 ± 1.15	2.65	0.01*	0.88 ± 0.10	0.98 ± 0.10	2.27	0.03*
	Temporal medial	0.91 ± 0.11	1.04 ± 0.10	2.93	0.007*	0.89 ± 0.10	1.01 ± 1.10	2.75	0.01*
	Temporal inferior	0.85 ± 0.20	0.98 ± 0.10	−2.08[a]	0.03*	0.88 ± 0.10	0.98 ± 0.10	2.39	0.02*
	Occipital	0.92 ± 0.11	1.03 ± 0.12	2.24	0.03*	0.92 ± 0.11	1.03 ± 0.12	2.37	0.02*
	Frontal superior	0.94 ± 0.11	1.03 ± 0.10	2.02	0.05*	0.92 ± 0.12	1.01 ± 9.83	2.05	0.05*
	Frontal medial	0.94 ± 0.12	1.03 ± 9.21	2.00	0.05*	0.89 ± 0.11	0.99 ± 9.80	2.11	0.04*
	Frontal inferior	0.89 ± 0.10	1.00 ± 0.10	2.44	0.02*	0.86 ± 0.10	0.97 ± 0.10	2.57	0.01*
Basal	Temporal superior	0.86 ± 8.72	0.92 ± 7.88	1.75	0.09*	0.83 ± 8.48	0.90 ± 7.17	−2.24[a]	0.02*
	Temporal medial	0.90 ± 0.10	0.98 ± 9.13	2.18	0.03*	0.86 ± 1.00	0.95 ± 8.56	−2.24[a]	0.02*
	Temporal inferior	0.90 ± 0.11	0.99 ± 9.04	1.98	0.05*	0.86 ± 0.11	0.96 ± 8.85	−2.21[a]	0.02*
	Occipital	0.95 ± 0.11	1.05 ± 0.11	2.31	0.02*	0.94 ± 0.11	1.04 ± 9.20	−2.42[a]	0.01*
	Frontal superior	0.88 ± 0.12	0.88 ± 0.32	−1.45[a]	0.14	0.86 ± 0.11	0.87 ± 0.31	−1.58[a]	0.11
	Frontal medial	0.86 ± 0.11	0.87 ± 0.31	−1.63[a]	0.10	0.83 ± 0.10	0.84 ± 0.31	−1.69[a]	0.09
Other Regions	Cuneus	0.84 ± 0.10	0.91 ± 6.57	1.84	0.07	0.84 ± 0.11	0.91 ± 6.67	1.90	0.06
	Cingulate gyrus	0.91 ± 7.05	1.04 ± 7.50	4.48	0.000**	0.92 ± 7.09	1.05 ± 8.67	4.28	0.000**

[a] Refer to Mann–Whitney-U test U values, all others refer to student *t*-test, *t* values
* $P < .05$
** $P < .001$ (Denotes that significance level survived Bonferroni correction for multiple testing)

and educational level between patients and healthy controls ($P > .05$).

Table 2 shows the comparison of the mean values relative to perfusion in bipolar euthymic patients and healthy controls. The mean rCBF values of the bipolar euthymic patients were significantly lower than those of the controls in bilateral medial-basal temporal, occipital, medial frontal and cingulate regions. In addition, the bilateral parietal and left postcentral vertex regions showed hipoperfusion compared to the controls ($P < .05$). For example, Fig. 3 has demonstrated hypoperfused brain regions in the euthymic patient. This patient had prominently low rCBFs in the temporal, frontal, parietal and occipital lobe gyruses. When the *P* value was Bonferroni-corrected, so that a *P* value of 0.0010 (0.05/46, number of ROIs) was considered significant, only the differences involving the cingulate gyrus remained statistically significant. Left to right perfusion ratios did not show significant differences between the patient and control groups in any brain slice ($P < .05$).

The mean rCBF values showed no significant differences between female and male patients. The mean rCBF values were not significantly correlated with total episode number and length of illness.

Discussion

Although SPECT studies have described patterns of abnormality in cerebral blood flow during different mood states or mixed patient groups in unipolar and bipolar patients, to our knowledge there is no SPECT report during euthymia in affectively ill patients [3, 5, 20]. The importance of the present study is that it is a first detailed study performed on a sample entirely comprised of euthymic bipolar patients.

The major finding in this study is a highly significantly decreased perfusion in a large brain region in the bipolar patients during euthymia when compared with healthy subjects. However, the hypoperfusion in the cingulate gyrus was the most prominent finding in the euthymic patients. Because of a lack of studies conducted during euthymia we cannot directly compare our results with any others. Several studies in bipolar subjects have also demonstrated regional alterations in cerebral perfusion and metabolism, particularly in the anterior cingulate cortex, during manic and depressive episodes [21, 22]. More recently, the possibly key role of the cingulate gyrus, which has extensive connections with limbic regions, has attracted attention in bipolar disorder [23, 24]. In a recent study Kaur et al. [23] proposed that decreased cingulate volumes in children and adolescents with bipolar disorder could possibly be related to neurodevolepmental abnormalities. Our finding indicating a more severe hypoperfusion in the cingulate gyrus may be interpreted as an evidence of that region playing an important role in the pathophysiology of bipolar disorder.

The results of the present study indicated significantly decreased cerebral blood flow not only in the

cingulate gyrus but also in bilateral medial temporal, frontal, parietal, and occipital regions in eutyhmic bipolar patients when compared to healthy controls. A decreased regional blood flow in temporal lobes has been frequently reported in both unipolar and bipolar depression [9, 25]. Previously published studies using HMPAO-SPECT discovered a lower cerebral blood flow in a number of brain regions including the left superior temporal gyrus, the occipital cortex bilaterally, and the right parietal cortex as well as in the superior and middle frontal cortex, and the right anterior cingulate in depressed bipolar subjects when compared with healthy volunteers [5, 26]. Findings are more varied in manic bipolar patients. Rubin et al. [27] found decreased temporal and frontal blood flow in manic bipolar patients compared with healthy subjects. In contrast, some blood-flow studies suggest that manic patients exhibit increased baseline blood flow as temporal, frontal and basal ganglia in different brain regions [28, 29]. Thus, perfusion studies do not provide a clear conclusion regarding the changes of cerebral blood flow that accompany mania [3]. In our euthymic patients group, we found significantly decreased cerebral blood flow in brain regions including all bilateral medial fronto temporal and basal temporal regions. Our data are consistent with the previously found evidence of the role of frontal temporal structures in the pathogenesis of bipolar disorder.

Another considerable finding of the present study is that patients with euthymic bipolar disorder did not show significant differences in hemispheric asymmetry in brain regional blood flow compared to healthy subjects. The existence of a hemispheric lateralization has also been linked to different mood states. Several SPECT studies suggest that depressed bipolar patients exhibit lower baseline blood flow in frontal and temporal cortical regions, particularly in the left hemisphere [4, 20, 26]. The left frontal cerebral perfusion, which has been observed in both unipolar and bipolar depressive disorders, appears to be state dependent [3]. Studies have reported that these abnormalities tend to disappear and to be reversible with effective pharmacotherapy, and in these cases there were no significant differences in uptake between controls and depressed patients in remission. However, abnormality was found to be persistent when recently remitted patients were studied again when they were off medication [30–32]. On the other hand, several studies performed during the manic phase indicate left-right asymmetry, with less perfusion in the right and basal temporal cortex than in the left and dorsal regions [29, 33]. Gyulai et al. [9] found that in 12 rapid cycling bipolar patients, radiodrug distribution was asymmetric in the anterior part of the temporal lobes in both the depressive/dsysphoric phases as well as in the manic/hypomanic phases, being symmetric in the euthymic phases. Our results, indicating no asymmetry in the euthymic phase, support Gyulai's [9] finding on asymmetry being related to state in bipolar patients. These findings are consistent with the hypothesis that certain neuroanatomic regions of the central nervous system may be functionally and reversibly involved during depressive and manic episodes [3, 34]. Taken together, all of these results have suggested that asymmetric brain dysfunction is more related to acute affective episodes in both depression and mania, although non-asymmetric but still abnormal dysfunction in temporal and frontal structures is more likely to reflect an underlying and ongoing disease process. Nevertheless, it should be borne in mind that these observations are hypothetical and should be used with caution until they are confirmed with future studies on a larger number of patients.

It is well known that duration of illness and number of episodes influences the prognosis of bipolar illness. Altshuler et al. [35] initially reported a decreased temporal volume in male bipolar patients that was associated with longer duration of illness. However, in many SPECT studies the relationship between more chronic illness and altered regional blood flow is not clearly defined. In our study group, we also did not find any relationship between brain blood flow and duration of illness or number of episodes.

The findings here are preliminary and require replication, as this study has several limitations. First, the overall number of subjects is relatively small, and the patients received variable treatment. However, for ethical reasons, we could not keep the patients medication-free. The influence of psychotropic medication on brain functions has been investigated in a number of studies [30, 36–38]. Goodwin et al. [30] reports that after the withdrawal of lithium, anterior cingulate and right caudate CBF decrease, whereas development of mania on lithium withdrawal is associated with increased anterior cingulate CBF. There is some evidence indicating that antipsychotics increase caudate activity and cerebral blood flow [36, 37]. In a study which used functional magnetic resonance imaging, it was found that there is no significant difference between the brain activation in any of the brain region of the medicated and medication free euthymic bipolar patients [38]. Patients in our study receiving medications were being treated with different mood stabilizers or a combination with mood stabilizer and atypical antipsychotics, so that specific medication effects could not be completely excluded on regional blood flow. However, the nature and extent of the effects of medication are difficult to determine. Future studies should ideally examine drug-free bipolar patients, although this is clearly difficult in this patient population. Second, the limited number of patients in the study may decrease the statistical analysis power. Another limitation, because we don't have fan-beam collimator or HR collimator we could not evaluate the deep cerebral structures.

The results of our study provide strong evidence about the role of cingulate gyrus abnormalities in

bipolar patients. This decreased CBF of cingulate region may underlie the vulnerability to mood episodes present in bipolar patients. The present study may also point at a decreased cerebral blood flow of the bilateral medial fronto temporal and basal temporal regions in euthymic phases. However hemispheric asymmetry of rCBFs was not present in the eutymic bipolar patients. These findings have suggested that underlying brain dysfunctions tend to show a continuum during euthymic phase. To our knowledge, this is the first SPECT study examining the rCBF in euthymic bipolar patients. Longitudinal studies with larger numbers of patients are needed in order to understand brain abnormalities in bipolar mood disorders.

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References

1. Ketter TA, George MS, Ring HA, Pazzaglia P, Marangell L, Krimbell TA, Post RM (1994) Primary mood disorder: structural and resting functional studies. Psychiatr Ann 24:637–642
2. Soares JC, Mann JJ (1997) The functional neuroanatomy of mood disorders. J Psychiatr Res 31:393–432
3. Strakowski SM, DelBello MP, Adler C, Cecil KM, Sax KW (2000) Neuroimaging in bipolar disorder. Bipolar Disord 2:148–164
4. Drevets WC, Price JL, Simpson JR, Tood RD, Reich T, Vannier M, Raichlem F (1997) Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386:824–827
5. Bonne O, Krausz Y, Gorfine M, Karger H ,Gelfin Y, Shapira B, Chisin R, Lere B (1996) Cerebral hypoperfusion in medication resistant depressed patients assessed by Tc99m HMPAO SPECT. J Affect Disord 41:163–171
6. Bearden CE, Hoffman KM, Cannon TD (2001) The neuropsychology and neuroanatomy of bipolar disorder: a critical rewiew. Bipolar Disord 3:106–150
7. Videbech P (2000) PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. Acta Psychiatr Scand 1:11–20
8. Strakowski SM, Delbello MP, Adler CM (2005) The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry 10:105–116
9. Gyulai L, Alavi A, Broich K, Reilley J, Ball WB, Whybrow PC (1997) I-123 Iofetamine single-photon compudet emission tomography in rapid cycling bipolar disorder: a clinical study. Biol Psychiatry 41:152–161
10. First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured clinical interview for DSM-IV clinical version (SCID-I/CD). American Psychiatric Press, Washington DC
11. American Psychiatric Association (1994). DSM IV: diagnostic and statistical manual of mental disorders IV. American Psychiatric Press, Washington, DC
12. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
13. Bech P, Bolwig TG, Kramp P, Rafaelsen OJ (1979) The Bech-Rafaelsen mania scale and the Hamilton depression scale. Acta Psychiatr Scand 59:420–430
14. Tan U (1988) The distribution of hand preference in normal men and women. Int J Neurosci 42:85–105
15. Declaration of Helsinki (1996) World medical organization. Br Med J 313:1448–1449
16. Camargo EE (2001) Brain SPECT in neurology and psychiatry. J Nucl Med 42:611–623
17. Catafau A (2001) Brain SPECT in clinical practice. Part I: perfusion. J Nucl Med 42:259–271
18. Tatsch K, Asenbaum S, Bartenstein P, Catafau A, Haldin C, Pilowsky LS, Pupi A (2002) European Association of Nuclear Medicine. European Association of Nuclear Medicine procedure guidelines for brain perfusion SPET using (99m) Tc-labelled radiopharmaceuticals. Eur J Nucl Med Mol Imaging 29:BP36–BP42
19. Guerra UP (ed) (1998). Brain SPECT: a normal brain morphofunctional atlas. Gruppoimmagine, Roma
20. Delvenne V, Delecluse F, Hubain P, Schoustens A, De Maertelaer V, Mendlewicz J (1990) Regional cerebral blood flow in patients with affective disorders. Br J Psychiatry 157:359–365
21. George MS Ketter TA Post RM (1993) SPECT and PET imaging in mood disorders. J Clin Psychiatry 54 (suppl):6–13
22. Kennedy SH, Javanmard M, Vaccarino FJ (1997) A revive of functional neuroimaging in mood disorder; positron emission tomography and depression. Can J Psychiatry 42:467–475
23. Kaur S, Sassi RB, Axelson D (2005) Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. Am J Psychiatry 162:1637–1643
24. Zimmerman ME, DelBello MP, Getz GE, Shear PK, Strakowski SM (2006) Anterior cingulate subregion volumes and executive function in bipolar disorder. Bipolar Disord 8:281–288
25. Benabarre A, Vieta E, Martinez-Aran A, Garcia MG, Martin F, Lomena F, Torrent C, Moreno JS, Colom F, Reinares M, Esteve B, Valdes M (2005) Neuropsychological disturbances and cerebral blood flow in bipolar disorder. Aust N Z J Psychiatry 39:227–234
26. Ito H, Kawashima R, Awata S, Ono S, Sato K, Goto R, Koyama M, Sato M, Fukada H (1996) Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. J Nucl Med 37:410–414
27. Rubin E, Sackeim HA, Prohovnik I, Moeller JR, Schnur DB, Mukherjee S (1995) Regional cerebral blood flow in mood disorders: IV. Comparison of mania and depression. Psychiatry Res 61:1–10
28. Rush AJ, Schlesser MA, Stokely E, Bonte FR, Altshuller KZ (1982) Cerebral blood flow in depression and mania. Psychopharmacol Bull 18:6–7
29. O'Connell RA, Van Heertum RL, Luck D, Yudd AP, Cueva JE, Billick SB, Cordon DJ, Gersh RJ, Masdeu JC (1995) Single photon emission computed tomography of the brain in acute mania and schizophrenia. J Neuroimaging 5:101–104
30. Goodwin GM, Cavanagh JTO, Glabus MF, Kehoe F, O'carroll RE, Ebmeir KP (1997) Uptake of 99mTc-exametazime shown by single photon emission computed tomography before and after lithium withdrawal in bipolar patients: associations with mania. Br J Psychiatry 170:426–430
31. Tutus A, Simsek A, Sofuoglu S, Nardali M, Kugu N, Karaaslan F, Gonul AS (1998) Changes in regional cerebral blood flow demonstrated by single photon emission computed tomography in depressive disorders: comparison of unipolar vs. bipolar subtypes. Psychiatry Res 83:169–177
32. Navarro V, Gasto C Lomena F, Mateos JJ, Marcos T, Portella MJ (2002) Normalization of frontal cerebral perfusion in remitted elderly major depression: a 12-month follow-up SPECT study. NeuroImage 16:781–787
33. Migliorelli R, Sarkstein SE, Teson A (1993) SPECT findings in patients with primer mania. J Neuropsychiatry Clin Neurosci 5:379–387
34. Stoll AL, Renshaw PF, Yurgelun-Todd A, Cohen BM (2000) Neuroimaging in bipolar disorder: What have we learned? Biol Psychiatry 48:505–517
35. Altshuler LL, Conrad A, Hauser P, Li X, Guze BH, Denikoff K, Troutellotte W, Post R (1991) Reduction of temporal lobe volume in bipolar disorder: a preliminary report of magnetic resonance imaging. Arch Gen Psychiatry 48:482–483
36. Holcomb HH, Cascella NG, Thaker GK, Medoff DR, Dannals RF, Tamminga CA (1996) Functional sites of neuroleptic drug action in the human brain: PET/FDG studies with and without haloperidol. Am J Psychiatry 153:41–49

37. Miller DD, Rezai K, Alliger R, Andreasen NC (1997) The effect of antipsychotic medication on relative cerebral perfusion in schizophrenia: assessment with technetium-99m hexamethyl-propyleneamine oxium single photon emission computed tomography. Biol Psychiatry 41:550–559

38. Strakowski SM, Adler CM, Holland SK, Mills NP, DelBello MP, Eliassen JC (2005) Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting stroop interference task. Am J Psychiatry 162:1697–1705